TECHNICAL SPECIFICATION

ISO/TS 19844

Third edition
2018-07

Health informatics — Identification of medicinal products (IDMP) — Implementation guidelines for ISO 11238 for data elements and structures for the unique identification and exchange of regulated information on substances

Informatique de santé — Identification des médicaments — Lignes directrices pour la mise en oeuvre de l'ISO 11238 relative aux éléments de données et structures pour l'identification unique et l'échange d'informations réglementées sur les substances

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Reference number
ISO/TS 19844:2018(E)

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Published in Switzerland

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 215, *Health informatics*.

This third edition cancels and replaces the second edition (ISO/TS 19844:2016), which has been technically revised.

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Introduction

This document provides guidelines for implementing ISO 11238. This document is developed in response to a worldwide demand for guidance on the implementation of internationally harmonized specifications for medicinal products. It is one of a group of four implementation guides for a total of five ISO standards which together provide the basis for the unique identification of medicinal products. The other standards in this group are:

— ISO 11615, *Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated medicinal product information*;

— ISO 11616, *Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated pharmaceutical product information*;

— ISO 11239[2], *Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging*;

— ISO 11240, *Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of units of measurement*.

The standards for the Identification of Medicinal Products (IDMP) support the activities of medicines regulatory agencies worldwide by jurisdiction. These include a variety of regulatory activities related to development, registration and life cycle management of medicinal products as well as pharmacovigilance and risk management.

The business objective of this implementation guide is to provide a means for exchanging regulatory substance information. To meet the primary objectives of the regulation of medicines and pharmacovigilance, it is necessary to exchange medicinal product information in a robust and reliable manner.

For the purposes of this document, all conditions (e.g. mandatory, conditional, optional) correspond to the necessary requirements to uniquely and unambiguously identify a substance. Implementation of the ISO IDMP standards may dictate that mandatory elements for identification be tagged as conditional or optional, based on regional requirements. If a subclause is identified as 'optional' but is implemented in a specific region, conformance described within that subclause is applicable. The scope of this document is to identify the scientifically necessary elements for the unique identification of Substances/Specified Substances.

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Health informatics — Identification of medicinal products (IDMP) — Implementation guidelines for ISO 11238 for data elements and structures for the unique identification and exchange of regulated information on substances

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CAUTION — This document uses colour. This should be taken into consideration when printing.

1 Scope

This document is used in the implementation of ISO 11238. This document defines substances based on their scientific identity (i.e. what they are) rather than on their use or method of production.

ISO 11238 provides the conceptual framework for defining Substances and Specified Substances and for assigning unique identifiers in the context of the ISO IDMP standards. ISO 11238 describes general concepts for defining and distinguishing substances and a high-level model for the structuring of information for substances. This document provides detailed explanations of each type or grouping of substance information, an element-by-element description for implementation of ISO 11238, and examples for a variety of Substances and Specified Substances.

This third edition of the document addresses Substances Groups 1 to 3 of the Specified Substances as defined in ISO 11238 and Annexes A, B, C, D, E, F, G, H, I, J and K. It is anticipated that Specified Substances Group 4, as defined in ISO 11238, will be addressed in a subsequent edition of this document. Some information that would typically fall under Specified Substances Group 4 is covered in the Annexes of this document. This information, although not defining of either a Substance or a Specified Substance Group 1, might be essential to distinguishing substances. This document addresses the following:

— data elements necessary for defining Substances and Specified Substances Groups 1 to 3;

— the logical use of data elements as defined in ISO 11238;

— Substances and Specified Substances Groups 1 to 3 business rules for:

  — determining necessary data elements,

  — distinguishing and defining materials according to ISO 11238,

  — triggering the assignment of identifiers.

This document does not address the following:

— business processes for data management;

— implementation of a specific data information system (e.g. a relational database schema);

— normative messaging standards for substances;

— the maintenance of controlled vocabularies;

— the specific global identifier system that should be used;

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— nomenclature standards for substances.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 639-1, *Codes for the representation of names of languages — Part 1: Alpha-2 code*

ISO 3166-1:2013, *Codes for the representation of names of countries and their subdivisions — Part 1: Country codes*

ISO 8601, *Data elements and interchange formats — Information interchange — Representation of dates and times*

ISO 11238, *Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on substances*

ISO 11240, *Health informatics — Identification of Medicinal Products — Data elements and structures for the unique identification and exchange of units of measurement*

ISO 11615, *Health informatics — Identification of Medicinal Products — Data elements and structures for the unique identification and exchange of regulated Medicinal Product information*

ISO 11616, *Health informatics — Identification of Medicinal Products — Data elements and structures for the unique identification and exchange of regulated pharmaceutical product information*

ISO/TS 20443, *Health informatics — Identification of Medicinal Products — Implementation guide for ISO 11615 data elements and structures for the unique identification and exchange of regulated Medicinal Product information*

ISO/TS 20451, *Health informatics — Identification of Medicinal Products — Implementation guide for ISO 11616 data elements and structures for the unique identification and exchange of regulated pharmaceutical product information*

3 Terms and definitions

No terms and definitions are listed in this document.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

4 Symbols and abbreviated terms

NOTE The abbreviations are listed are either used within ISO 11238 or ISO/TS 19844 since they are regarded as inseparable documents.

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4.1
ACS
American Chemical Society[1]

4.2
ASK Number
ID of a substance in German “Arzneistoffkatalog” (Pharmaceutical Substance Dictionary)

4.3
BAN
British Approved Name[127]

4.4
COL
Catalogue of Life[2]

4.5
DCF
Dénominations Communes Françaises (French approved drug name)[128]

4.6
EVcode
EudraVigilance Code (Unique Identifier) used for a substance in the Extended EudraVigilance Medicinal Product Dictionary (XEVMPD)[3]

4.7
ExPASy
SIB (Swiss Institute of Bioinformatics) Bioinformatics Resource Portal[4]

4.8
HAB
Homöopathisches Arzneibuch, Amtliche Ausgabe

4.9
HTS
high-throughput sequencing

4.10
INCI
International Nomenclature of Cosmetic Ingredients[5]

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[1] https://www.acs.org/content/acs/en.html

[2] http://www.catalogueoflife.org/

[3] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000596.jsp

[4] https://www.expasy.org/

[5] http://www.cirs-reach.com/Cosmetic_Inventory/International_Nomenclature_of_Cosmetic_Ingredients_INCI.html

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4.11
INN
International Nonproprietary Name [also consider as rINN (recommended International Nonproprietary Name) or pINN (proposed International Nonproprietary Name)][6]

4.12
iPSCs
induced pluripotent stem cells

4.13
ITIS
Integrated Taxonomic Information System[7]

4.14
JAN
Japanese Approved Name[8]

4.15
JP
Japanese Pharmacopoeia[129]

4.16
NCBI
National Center for Biotechnology Information

4.17
NDF-RT
National Drug File - Reference Terminology, produced by the U.S. Department of Veterans Affairs, Veterans Health Administration (VHA)[130]

4.18
NLT
not less than

4.19
NMT
not more than

4.20
OMG
Object Management Group[9]

4.21
PBMCs
Peripheral Blood Mononuclear cells

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[6] http://www.who.int/medicines/services/inn/en/

[7] https://www.itis.gov/

[8] http://jpdb.nihs.go.jp/jan/index.aspx

[9] http://www.omg.org/

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4.22
Ph.Eur.
European Pharmacopoeia (Pharmacopée Européenne)[131]

4.23
UCUM
Unified Code for Units of Measure[10]

4.24
UML
Unified Modeling Language[11]

4.25
UNII
Unique Ingredient Identifier. Identifier of a substance in the FDA Global Substance Registration System (G-SRS)[12]

4.26
UniProt
Universal Protein Resource[13]

4.27
USAN
United States Adopted Name[14]

4.28
USP
United States Pharmacopeia [132]

4.29
WHO-ATC
World Health Organization – Anatomical Therapeutic Chemical Classification System[133]

5 General background and history

Due to the lack of a common and harmonized approach to define substances, regulators and pharmaceutical industry are faced with the inability to:

1) effectively exchange medicinal substance information in a structured and efficient way;

2) ensure data consistency and evaluate/compare information across regions, which especially impairs pharmacovigilance and compliance activities;

3) develop consistent terminology for use throughout the healthcare community.

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[10] http://unitsofmeasure.org/trac

[11] http://www.uml.org/

[12] https://www.fda.gov/forindustry/datastandards/substanceregistrationsystem-uniqueingredientidentifierunii/

[13] http://www.uniprot.org/

[14] https://www.ama-assn.org/about/united-states-adopted-names-council

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The objectives of the IDMP standards are to address the issues outlined above by developing harmonized standards that build on the regulatory and technical processes already established and to support the population and maintenance of existing systems/applications with fully reliable regulatory medicinal product information.

Harmonized standards will stimulate vendors to develop "off-the-shelf" tools (that are interoperable due to the standard itself). Harmonized standards will also help to maximize forward compatibility of data and minimize the complexities of backward compatibility.

This implementation guide is intended to assist reporters (including pharmaceutical companies, regulatory authorities and non-commercial sponsors) in constructing messages or transmitting information that allows substances to be defined unambiguously and assigned unique IDs. It also provides guidance to help choose the correct Substance ID from a public data source that provides unique Substance and Specified Substance identifiers. It is anticipated that an extensive list of substance identifiers, as well as the definitional elements upon which the ID was based, will be provided. This document is not intended to be a guide for a maintenance organization. The maintenance organization may also create alternative methods to submit information consistent with the ISO model.

Table 1 is an example table for class and elements description.

Table 1 — Example table for class and element description

User Guidance	
Example(s)	
Conformance	
Data Type	
Values Allowed	
Business Rule(s)	

In contrast to other parts of the guide, conformance refers to whether an element is required for a given substance type or a Specified Substance Group. Conformance is not meant to be applied globally to all types of messages.

Definition: Conformance will be expressed based on the following terminology: Mandatory, Conditional and Optional.

Mandatory: refers to data elements that are required and shall therefore be implemented.

Conditional: refers to data elements that are subject to business rules and may become required by:

— data rules;

— process rules;

— regional rules.

Optional: refers to data elements that are informative but not definitional.

The description on whether a data element is conditional by data, by process or by regional rule is out of scope of this document and will be defined within regional implementation guides.

The information provided in the table refers to the global guidance. When there is no information in the conformance table row (e.g. information on business rule is not provided), please refer to the regional implementation guide.

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6 Substance (Mandatory)

6.1 General

All medicinal products consist of substances; these substances can be active ingredients, excipients, or packaging materials. There are two fundamental levels of information described in ISO 11238, a “Substance level" and a “Specified Substance level”. Both levels are included in the more generic concept of an ingredient. At the Substance level, substances are defined based on inherent attributes rather than use or method of manufacture. At the Specified Substance level, four separate groups of elements provide additional information.

In order to define or distinguish material either at a Substance or Specified Substance level, a number of attributes should be taken into consideration.

— For chemicals, the molecular structure is captured at the substance level.

— For proteins, the amino acid sequence, sites and type of glycosylation, and the presence and position of disulfide bonds are captured at the substance level.

— For nucleic acids, the sequence, type of sugar and linkage are captured at the Substance level.

— For other polymers, the monomers used to synthesize the polymer, the structural repeat units, the molecular weight and/or a property related to molecular weight (e.g. viscosity), the source of naturally derived polymers and any modifications that irreversibly alter the molecular structure are captured at the substance level.

— For structurally diverse material, taxonomic, anatomical and fractionation information, properties related to the underlying molecular structure of the material, and modifications that alter the underlying molecular structure are captured at the substance level.

— A Mixture consists of a simple combination of Single Substances that are either isolated together or are the result of the same synthetic process. This applies also to a homologous group of structurally diverse single substances used to prepare an allergen extract. The biological source of the mixture is also captured where relevant at the substance level. Proportions are not captured at the Substance level. It should be noted that a Mixture description should only include the substances that are generally or consistently present in the material. This excludes impurities and degradants.

Other attributes will be specific to the Specified Substance levels:

— Constituent substances in a multi-substance material;

— Proportions of constituent substances in a multi-substance material;

— Physical state;

— Grade or purity of material;

— Manufacturing information;

— Analytical data, Specifications and Tests.

There are four groups of elements that are used to further define and specify Substances. Specified Substances are always composed of at least one substance.

Specified Substance Group 1 is typically used to define:

— multi-substance materials consisting of multiple substances, which are not defined as mixture;

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— defining information regarding homeopathic-, plasma derived-, vaccines substances, herbal and allergenic extracts;

— physical state, including polymorphic forms;

— detailed glycosylation information.

Specified Substance Group 2 is typically used to define:

— Manufacturer, manufacturing process and critical process version number as well as in some cases extended manufacturing information are used to provide information regarding herbal and allergenic extracts when multiple extraction methods with different solvent compositions are used or a stepwise manufacturing process is in place describing an extraction method followed by a general modification process of the extract e.g. modified allergen extract, modified vaccines by multiple modification processes.

Specified Substance Group 3 is typically used to define:

— Grade or level of purity (Pharmacopoeial Specifications) and In-house specification used to cover a set of specifications of all approved manufacturers for the substance.

Specified Substance Group 4 is typically used to define:

— Detailed specification information including analytical information to be used in tests;

— Detailed manufacturing information.

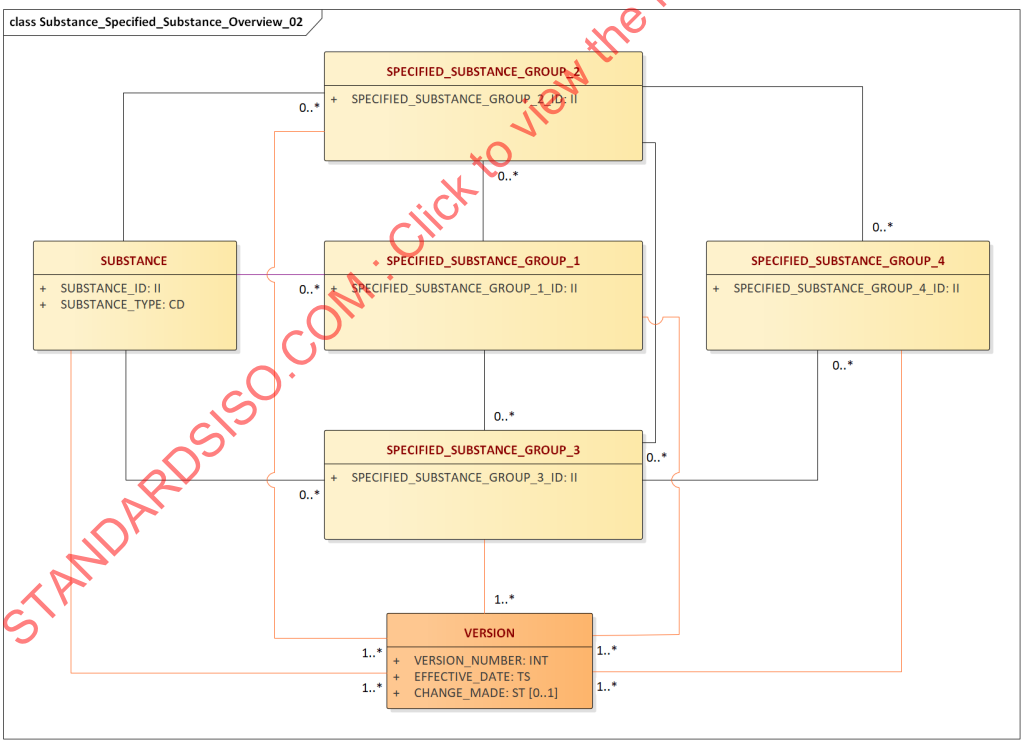


Figure 1 — High-level Substance-Specified Substance information model

EXAMPLE In Figure 1, the Substance class is parent of the classes Specified Substance Group 1 (SSG1), Specified Substance Group 2 (SSG2) and Specified Substance Group 3 (SSG3). Similarly, SSG1 is a parent of SSG2 and SSG3. For Triamcinolone acetonide, Figure 2 shows the relationships of Substance and Specified Substance Groups.

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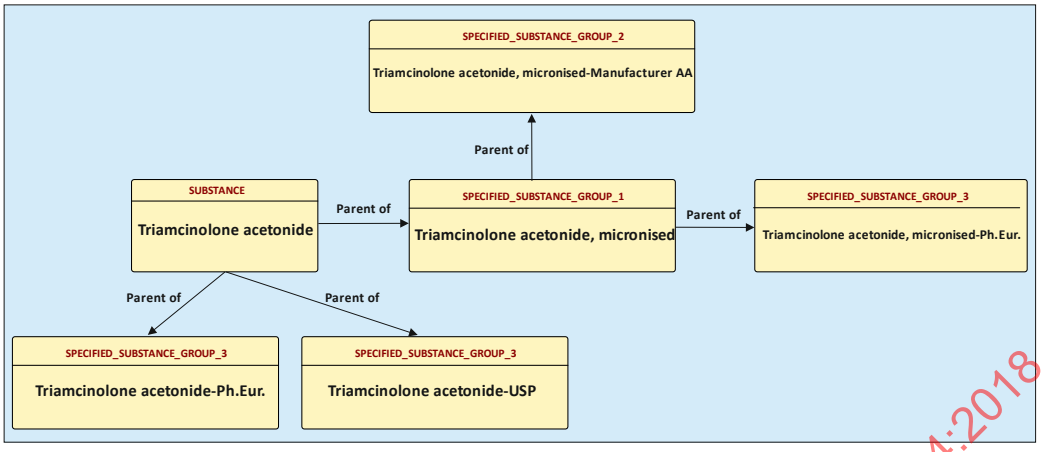


Figure 2 — Parent Substance and Specified Substances Groups relationships of Triamcinolone acetonide

6.2 Defining substances

A substance is any matter of defined composition that has discrete existence, whose origin may be biological, mineral or chemical. Substances can be single well-defined chemical entities containing a definite molecular structure, synthetic (e.g. isomeric mixtures) or naturally-occurring (e.g. conjugated oestrogens) mixtures of chemicals, or materials derived from plants, animals, micro-organisms or inorganic matrices that are not definable by a single or limited number of molecular structures. Substances may contain active moieties, salts, solvates, stoichiometric complexes or mixtures of compounds that are isolated or synthesized/obtained or produced in a process together. Materials that are combined from multiple sources to form a product are not considered to be substances.

A substance is generally defined by what it is, and not by how it is made or used. Substance definitions are typically based on the immutable properties of a given material. These properties include the molecular structure, or structures of a given material, taxonomic, anatomical or fractionation information for material that cannot be represented by molecular structures. Purity, physical form, and method of production are typically not considered when defining substances.

In addition to defining information there is also information that is essential to validate the defining information and this information should be submitted if available. Validation may be performed based on relevant provided documents (e.g. regulatory dossier) or information available in recognized source (e.g. pharmacopoeias).

The primary goal of ISO 11238 is to define unambiguously all substances present in regulated products. Once a substance has been defined, a unique identifier will be assigned that is permanently associated with that substance. This document describes the necessary information for this registration process. Reference information, names, codes and IDs that can be associated with a substance are also described. The document is not comprehensive in regards to reference and definitional information. Other substance attributes may be associated for both reference and definitional information as new scientific standards or information becomes available.

Substances that are mixed together to form a product, even if there are physical interactions between the Substances will be described as a Specified Substance or a product.

EXAMPLE 1 FD&C Blue No. 1 Aluminium Lake is not defined as a mixture substance but rather as two separate substances FD&C Blue No. 1 and aluminium oxide. Also, simethicone is not a substance because it contains two substances, namely dimethicone and silicon dioxide. These materials would be described as Group 1 Specified Substances.

Conversely, if new covalent bonds and/or simple salts or solvates are formed, separate Substance IDs for each molecular entity are assigned.

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EXAMPLE 2 Fluticasone propionate would have a separate ID from fluticasone; atorvastatin calcium trihydrate would have a separate ID from atorvastatin calcium anhydrous.

Differences at the Specified Substance level should trigger a new Specified Substance ID.

EXAMPLE 3 Insulin Human Crystalline and Insulin Human Amorphous have different Specified Substances Group 1 IDs and map to the substance Human Insulin.

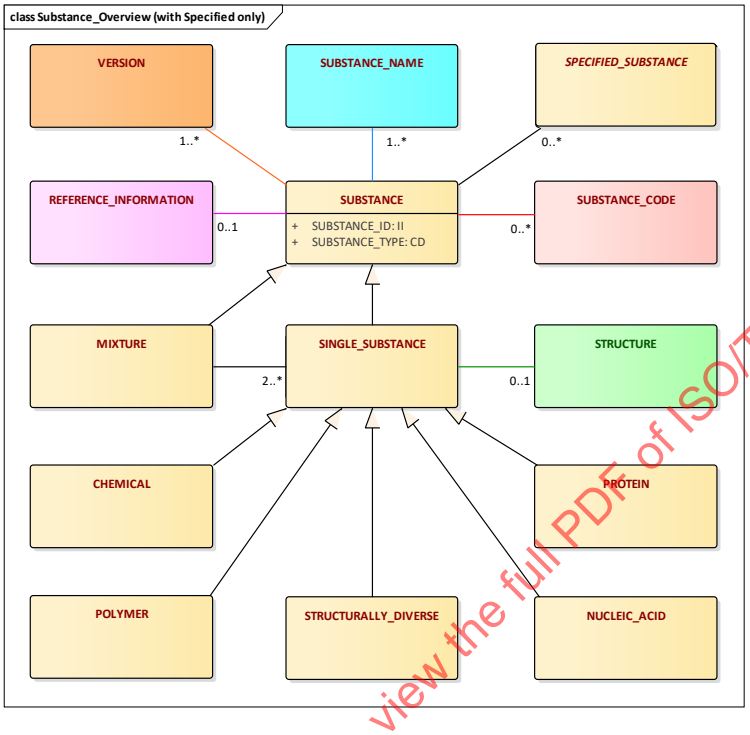


Figure 3 — High-level information model for Substances

6.2.1 Substance type (Mandatory)

At the basic level, all material present in medicinal products will either be described as a Substance and/or a Specified Substance Group 1. Additional information, such as manufacturer, grade and manufacturing information on a given material will be associated with Specified Substance Groups 2 to 4.

Substances shall be defined using one or more of the five types of single substances or a mixture. Mixtures consist of a combination of related single substances where the source material and essential properties are also captured but proportions are not. Mixtures also describe extracts of homologous groups of substances and in this case the proportions of the multi-substance starting materials are captured. For the purposes of definition, all single substances are of one of the following types:

— (simple) chemical;

— protein;

— nucleic acid;

— polymer;

— structurally diverse.

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Each of these different types of single substances has distinct elements essential for definition. Substances can also be a mixture of single substances. Some materials may appear to have elements from multiple types of single substances e.g. PEGylated proteins, drugs covalently linked to polymeric matrices or proteins, etc., to fully define the substance. Each of these substances will be described as a single type, although it is possible for the same substance to be defined by using two or more substance types of which one is the predominant one.

EXAMPLE 1 Proteins modified with a polymer or drug will be described as a protein with the polymer or drug captured as a modification. Drugs covalently linked to a polymer will be described as a polymer with the drug either captured as an end-group or as structural modification. Another example can be structurally diverse substances such as vaccines containing a protein fraction, which should also be described using elements from the protein model. Detailed examples will be provided in the Annex to address these complex materials. Although every substance definition will be defined with a single type it is possible that an alternative definition of a substance will be of a different type.

Mixtures consist of a combination of related single substances where the source material and essential properties are also captured as are proportions, if applicable. At the Specified Substance Group 1 level proportions can be captured.

Additional information, such as manufacturer, grade, and manufacturing information on a given material will be associated with Specified Substances Groups 2-4. The first step in defining a material is to determine whether the material can be defined as a Single Substance, a Mixture or a Specified Substance Group 1. A mixture is a substance that cannot be defined using a single set of substance elements or structural representations. Racemic mixtures, most polymers and structurally diverse substances, although inherently mixtures, can be defined using a single set of elements and therefore are not described as mixtures. Material that contains multiple substances that are not synthesized or isolated together and are not related or not derived from homologous groups of substances will be described as Specified Substance Group 1. Specified Substance Group 1 would also include crystalline polymorphs, substances in varied physical states along with the capture of additional properties regarding sterility or the presence of endotoxin.

Examples of Specified Substance Group 1 include simethicone, adjuvanted vaccine antigens, isophane insulins and additional herbal and allergenic extract information not captured at the Substance level. Sterile water, water for injection, ice, and steam would be different Specified Substances Group 1 that would map to the substance water.

Mixtures are substances like Gentamicin sulfate, USP or Gentamicin sulfate, Ph.Eur. which consists of mixtures of distinct but related individual aminoglycosides. In USP Gentamicin sulfate is described as a mixture of Gentamicin C1A sulfate, Gentamicin C1 sulfate, and Gentamicin C2 sulfate. In Ph.Eur. it is described as a mixture of five components Gentamicin C1, C1a, C2, C2a, and C2b respectively which are typically isolated together from a bacterial culture. At the substance level, all related substances typically present at a level greater than 1 % would be listed as components of the mixture regardless of whether the substance is listed in a given pharmacopoeia. Mixture is defined in the ISO 11238 standard as a type of polydisperse substance that is a combination of single substances isolated together or produced in the same synthetic process.

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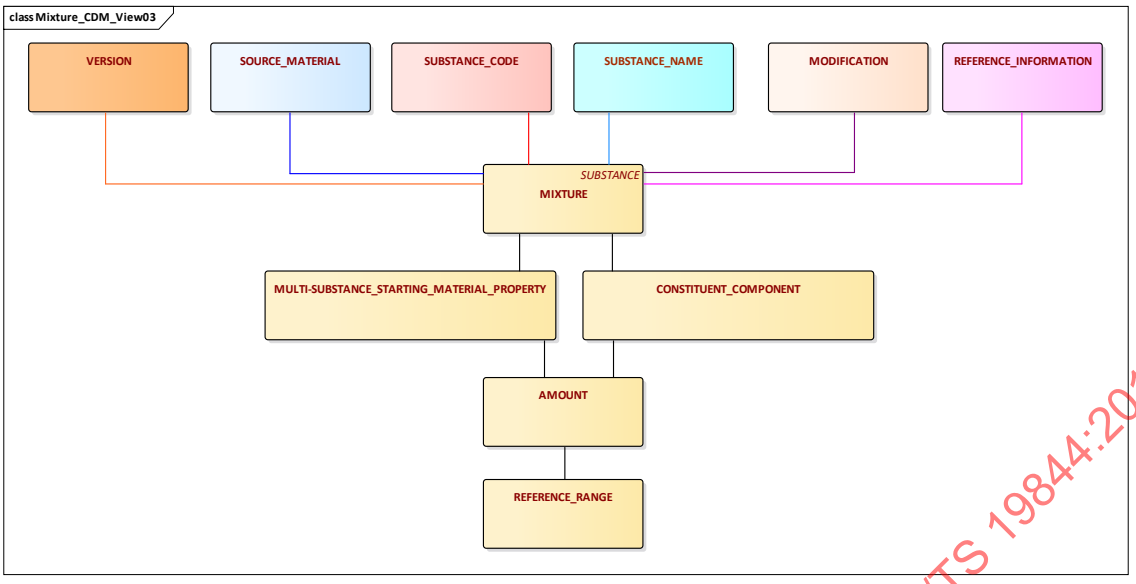


Figure 4 — High-level information model for Mixture

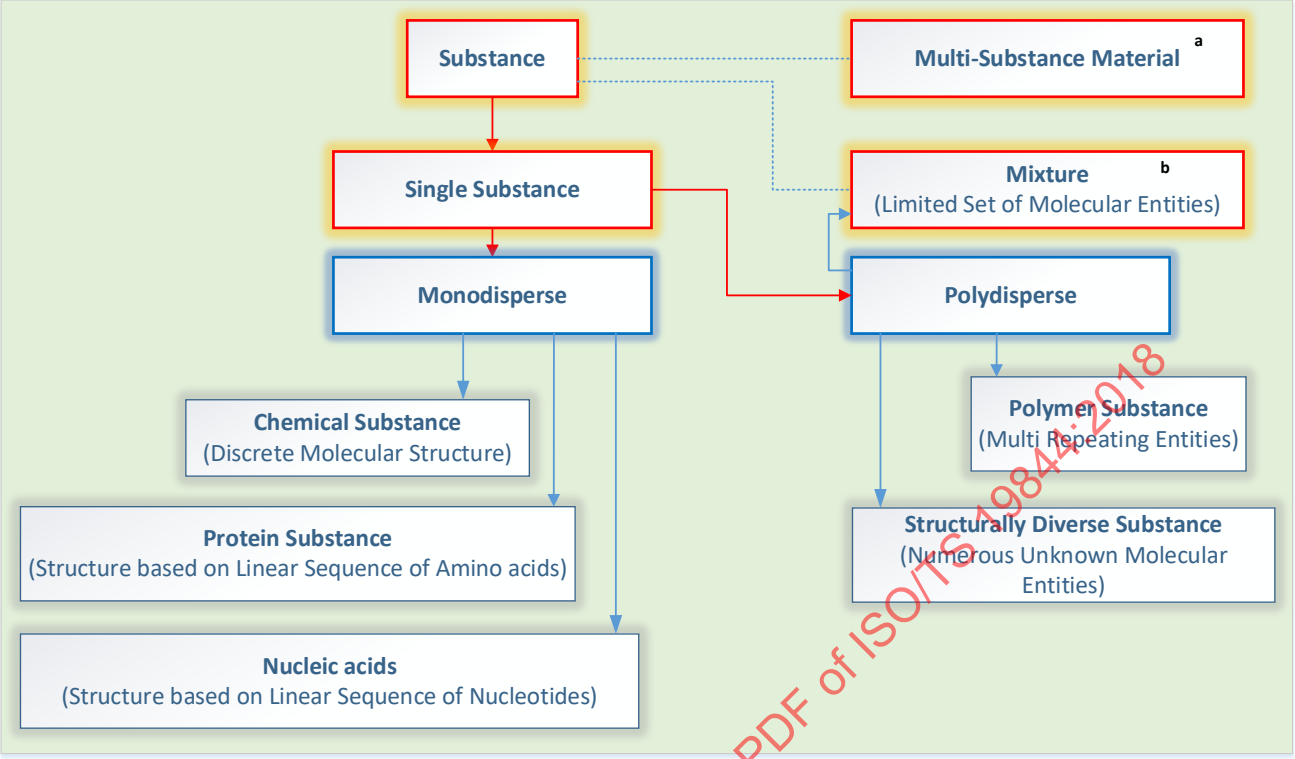
For mixtures in which multiple related substances are isolated together from a single source, the source will be a defining element. Starches are typically a mixture of the two distinct polymers amylose and amylopectin. Corn, wheat, potato and tapioca starches are all distinct substances distinguished by the source.

Most other polymers will be described as single substances with the definition based on the structural repeat unit and a representation of the average molecular weight of the polymer as well as the biological source for biopolymers or polymers derived from biological matrices.

Figure 5 represents a decision tree or process by which the type of substance is determined. Monodisperse substances are substances that can be described as a single molecular entity. Polydisperse substances are substances that typically have multiple molecular entities that are too numerous or too diverse to be captured as a mixture (e.g. cells or tissues) or where the production of the substance inherently results in polydispersity (e.g. polymers).

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[a] Multi-substance material: Multiple-Substances and/or Specified Substances of diverse origin.

[b] Mixture: Type of polydisperse substance that is either a combination of single substances isolated together or synthesized/obtained or produced in the same process or an extract of a homologous group of substances (multi-substance starting material) resulting from the same synthetic process.

Figure 5 — Decision tree or process by which the type of substance is determined

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Table 2 — Substance type

User Guidance	Information about the substance type as described in and in accordance with ISO 11238 definitions
Example(s)	Chemical, Protein, Nucleic acid, Polymer, Structurally Diverse, Mixture
Conformance	MANDATORY
Data Type	CD
Values Allowed	Chemical, Protein, Nucleic Acid, Polymer, Structurally Diverse, Mixture, Specified Substance Group 1, Specified Substance Group 2, Specified Substance Group 3, Specified Substance Group 4
Business Rules	For each substance type, a qualification is possible, e.g. Structuraly Diverse (Plasma-derived), Structurally Diverse (Herbal Substance), Structurally Diverse (Herbal Drug), Structurally Diverse (Allergen Substance), Polymer (Biopolymer), Protein (Recombinant), Protein (Naturally-derived), Protein (Allergen, Naturally-derived), Chemical (Mineral, naturally occurring substance), Mixture (Homologous Group of Allergen Source Material), etc. In these cases, the qualifier shall also be captured at the Substance Name Type attribute described in and shall always coupled with the substance name. Example: Substance Type: Structurally Diverse Substance Name Type: Plasma-derived Substance Name: Human Albumin, Plasma-derived (see also) In all these cases, a new ID shall be issued, that is, 'Human Albumin, Plasma-derived' shall have a distinct identifier from 'Human Albumin, Recombinant'.

6.2.2 Substance ID (Mandatory)

Every substance shall be identified by an ID. An ID will be generated following the initial submission of substance data. The ID should be unique to each substance, non-semantic, non-chronological, and of fixed length with an integrity check. Once an ID is assigned to a given physical or conceptual material the ID will not change. Changes or additions to defining information result in a new version of the substance definition but would not result in a new Substance ID. Although an effort should always be made to obtain complete information prior to assignment there will be instances when additional definitional information on a given substance is transmitted after assignment. When incorrect or incomplete information may be transmitted and used to define a substance, the information will be changed or added but the ID will not change. In rare cases when the same substance is found to have two IDs one of the IDs will remain a primary ID and the use of the other ID will be deprecated and captured in the Substance Code class. For some materials, there may be multiple IDs that a material could map to. The maintenance organization shall always issue the ID on the material that is the most descriptive of the material.

EXAMPLE Glucose, when a solid crystalline material, can exist with an alpha or beta pyranose structure in an anhydrous state, or as a monohydrate with an alpha pyranose structure. If a solid crystalline form of glucose exists in a medicinal product the ID specific to the structure should be used. Glucose in a liquid or an amorphous solid state would use the Substance ID that does not specify the specific form.

Both Substances and Specified Substances shall be identified with an ID. IDs will be released to the public if the substance is in a licensed medicinal product. The IDs for substances in the investigational stage will only be released if an official name exists or a company code is associated with defining information and is found together in at least one single reference that is from a reputable source in the public domain (i.e. scientific journal, presentations or posters at scientific conferences, company publication, patent or published patent application, public databases such as STN from CAS). Substance IDs shall always be issued to the requester if sufficient information is provided to unambiguously define the substance.

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Table 3 — Substance ID

User Guidance	ID to be used in all electronic submissions to identify a substance. Generated when sufficient information is available to unambiguously define a substance. ID will be permanently associated with a given substance and each substance at the substance level shall have one and only one ID. NOTE If a unique "Substance ID" has been assigned, this "Substance ID" is specified based on the Substance Name controlled vocabulary. In the absence of a unique "Substance ID", *e.g.* for the initial submission of the substance, this data element is not mandatory.
Example(s)	UNII Code, EV-Code, Global Substance ID[15] (DEVTYS543H)
Conformance	MANDATORY
Data Type	II
Values Allowed	Value could be a code associated with a preferred term, or a specific type of data. If a code is transmitted the preferred term associated with that code should also be transmitted.
Business Rule(s)	All substances shall be identified by a single ID. The conformance is Mandatory in all cases. The only exception is at the very first submission when the ID is requested. NOTE The ID will only be released to the public if the defining information is in the public domain or if a company that provides the defining information requests public release or releases the code in public marketing materials. An ID will always be issued to an organization that requests an ID and supplies the information necessary to define a substance. A flag to control the release of the ID to the general public is part of the Reference Source information . Defining information found in patents will usually not be sufficient to release the ID to the public.

6.3 Substance names (Mandatory)

Although ISO 11238 does not provide any guidance on substance nomenclature, it does provide a structure for the capture of names and codes that are used to refer to a substance. For the purpose of ISO 11238 there are at the moment sixteen types of names, e.g. Official names, systematic names, other names, brand names, company codes, homeopathic names, specified homeopathic names, plasma-derived names, Specified Substance Group 1, 2 and 3 names.

At least one name or company code should be associated with each substance. Names for a given substance and/or standardized names submitted by another party may be available in the substance terminology. Indication that a name is the preferred name or term by which a substance will be referred to in a given jurisdiction and domain may be presented in the terminology. This preferred term may vary depending on jurisdiction or domain or the state of development of a given substance.

EXAMPLE During the early stages of clinical development, the preferred term for a substance can be its company code. In later stages, an INN can be associated with the substance and become the preferred term for that substance.

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[15] Global Substance ID is corresponding to the ISO IDMP identifier of a Substance intended to be used globally.

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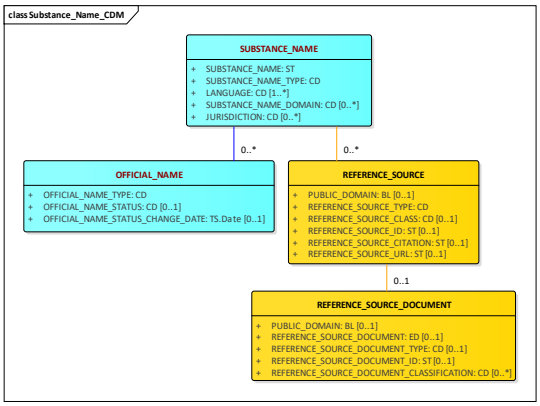


Figure 6 — Information model for Substance Name

6.3.1 Substance name (Mandatory)

When requesting an ID, a submitter should submit all names and company codes which have been associated with the substance. A submitter may also want to add a name to a substance that is already in the database. Defining information for a given substance should also be transmitted when requesting that a name is added to the database to ensure the correct substance identity. A submitter may also submit names in multiple languages. Although there is no requirement that names are unique, other or common names should also explicitly distinguish related substances from one another. Distinguishing characteristics for many polymers, such as molecular weight, degree of polymerization, and viscosity, should be indicated in the names of these substances. Standardization on such names to facilitate searching and identification of substances may be adopted within regions.

EXAMPLE Polyethylene glycol is a name for a family of polymers, so it would not be an acceptable name for an individual substance. Polyethylene Glycol 1000 is an official name in the US for a polyethylene glycol polymer with an average molecular weight of 1000. In the European Union, the INN Macrogol 1000 would be an official name for the same substance. In the personal care products domain PEG-20 is the official name for the same substance and 20 refers to the average degree of polymerization.

Table 4 — Substance name

User Guidance	The name or company code associated with the Substance shall be specified. For substances originated from Plants the Substance is always a single species, or intraspecies, or is occasionally a single genus. It will have a Name which is composed of: [Scientific genus/binomial/trinomial with Author] [Part(s)] The scientific element of the name is usually a binomial, but may be a trinomial or a genus, as appropriate, together with the author of the name. The Name is not an official name in any pharmacopoeia or other legislation, and the inclusion of the author is to ensure that it is not confused with the official names for specified substances that are derived from a single species substance. It can be written in any language and its jurisdiction can be restricted using Official Name Status.
Example(s)	Amoxicillin; Harpagophytum procumbens (Burch.) DC. ex Meisn., Root
Conformance	MANDATORY
Data Type	ST
Values Allowed	Free text, multiple names allowed, each in its own <asNamedEntity> element.
Business Rule(s)	Mandatory all substances shall have at least one name or company code (also considered to be a Substance Name) associated with the substance.

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6.3.2 Substance name type (Mandatory)

Every substance name shall have one name type. When a Substance has the Substance Name Type e.g. Other Name, but also an official name exists, which will be used then the Substance Name element group should be repeated with the Name referring to the Official Name and the Substance Name Type should be 'Official', see Table B.1. Official names are typically nonproprietary names used in a given jurisdiction and domain to refer to a specific substance. The domain, jurisdiction, and authority that assigned the name (USAN, INN, JAN etc.) and the language of the name are also captured.

Systematic names will typically be used for simple chemicals and structurally diverse materials where the definitions are based on a chemical structure or systematic taxonomic information. For chemicals, these names are typically derived from IUPAC or CAS systems of nomenclature. From the systematic names of chemicals, a molecular structure can typically be derived and the name can be checked by a number of chemical drawing programmes that convert a given name to a molecular structure. Brand names are names by which a company identifies a given substance typically for marketing purposes. Other names associated with a given substance are for instance common names. Company codes (also known as lab/laboratory codes or clinical trial codes) are also treated as names. They are assigned by a given company to substances in clinical or preclinical development.

Table 5 — Substance name type

User Guidance	Each name shall be associated with one type.
Example(s)	Official Name; Systematic Name; Scientific Name; Company Code; Other Name; Brand Name; Herbal Name; Homeopathic Name; Specified Homeopathic Name; Plasma-Derived Name; Preferred Name; Specified Substance Group 1 Name; Specified Substance Group 2 Name; Specified Substance Group 3 Name; Display Name, Common Name; Specified Substance Group 1, Display Name; Specified Substance Group 2, Display Name; Specified Substance Group 3, Display Name; Specified Substance Group 4, Display Name
Conformance	MANDATORY
Data Type	CD
Values Allowed	Official Name, Systematic Name, Scientific Name, Company Code, Other Name, Brand Name, Herbal Name, Homeopathic Name, Specified Homeopathic Name, Plasma-Derived Name, Preferred Name, Specified Substance Group 1 Name, Specified Substance Group 2 Name, Specified Substance Group 3 Name, Display Name, Common Name
Business Rule(s)	A Substance Name shall always correspond to at least one and only one Substance Name Type. The Preferred Name is the name that describes at least all moieties of a substance and shall be used in all EU languages, e.g. Benzathine Benzylpenicillin tetrahydrate (Dutch: Benzathinebenzylpenicillinetetrahydraat). For the Substance (fresh) (e.g. Harpagophytum procumbens (Burch.) DC. ex Meisn., Root) the Substance Name Type shall be 'Other'. Specified Substance Group 1, 2 and 3 name types are used to guide the user with regards to which level the substance name belongs to e.g. water for injection – Ph.Eur. is a name having the substance name type: Specified Substance Group 3.

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6.3.3 Language (Mandatory)

All names shall be associated with at least one language. Often the name, particularly INN, will be identical in multiple languages. The language for company codes that use a Latin character set shall be described as English (en). The language for the systematic name of plant, micro-organism or animal derived substances shall also be described as English since many of these will be a hybrid of a Latin Name for the species and an English name for the part and/or the subspecies information.

EXAMPLE The INN alisertib is identical in English, French and Spanish.

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Table 6 — Language

User Guidance	The language used to provide the structured substance information shall be specified according to the XML standard's xml:lang attribute specification, which is based on ISO 639-1, alpha-2 codes
Example(s)	en – English, de – German, fr –French
Conformance	MANDATORY
Data Type	CD
Values Allowed	ISO 639-1, alpha-2 codes
Business Rule(s)	While xml:lang allows country-specification of language, e.g. en_US vs. en_UK or pt_PT vs. pt_BR, such specificity is to be avoided except if the country variant of the language exceptionally does give rise to an alternative spelling. In that case, only the exceptional spelling needs to be tagged with the country-specific language code, not the regular spelling for that language in all other countries. If the same name spelling exists for multiple languages of interest, each language shall be specified.

6.3.4 Substance name domain (Conditional)

Substance names will also be associated with a domain. The domain and the actual name of a domain will vary according to jurisdiction.

EXAMPLE The terms DRUG and BIOLOGIC could be used in Japan and the US as official name domain. In the EU the term MEDICINE may cover the name of many substances that would be either DRUG or BIOLOGIC in the US and Japan.

Table 7 — Substance name domain

User Guidance	Specifies when and for what purpose the name is to be used. All substance names can have at least one domain. This is useful to differentiate different names for the same substance as used for a drug active ingredient as opposed to a food colour additive.
Example(s)	Biologic, cosmetic, drug, food, medicine, dietary supplement, homeopathic, mineral, zoological, allergen, botanical, vegetable oil, bacterial
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	Used if different names exist that are not appropriate to be used across all domains.

6.3.5 Jurisdiction (Conditional)

When a product is on the market and contains pharmaceutically active substances at least one jurisdiction should be associated with the name of the active substance. For inactive substances or excipients, the jurisdiction may not be apparent or captured. Pharmacopoeias will often be consulted to determine the jurisdiction of an official name. For Official Names, the Jurisdiction element is optional; when necessary the following conformances apply.

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Table 8 — Jurisdiction

User Guidance	The jurisdiction of the official name should be provided.
Example(s)	US, EU, JP
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	ISO 3166-1 alpha-2 codes. For the European Union EU shall be used.
Business Rule(s)	All the jurisdictions in which the Official Name is to be used should be indicated.

6.3.6 Official name (Conditional)

Each official name should have one or more official name types. The official name type reflects the organization that assigns or recognizes the name associated with the substance. These names are typically nonproprietary names that are used in the labelling of pharmaceuticals. The domains and jurisdictions in which the official name is used are also captured, tracked and maintained within the terminology. Although most official names will refer to material at the substance level there will be instances where an official name will refer to material at the Specified Substances Group 1 level [e.g. Simeticone (BAN, INN) or Simethicone (USAN)]. The official name class is conditional and shall be repeated as necessary.

6.3.6.1 Official name type (Mandatory)

Any authority which assigns official names shall typically do so in a publication, and as such, referencing the publication is sufficient indication for the name being "official" and sufficient representation for the "official name type". When new official names are issued by official naming bodies, the naming bodies will be reflected in this terminology.

Table 9 — Official name type

User Guidance	Designation of which authority assigned the Offficial Name of the Substance or Specified Substance. All official names need to have at least one such designation. The name type is the name of the authority or authorities that have assigned or have adopted the name.
Example(s)	BAN, COSING, Ph.Eur., FCC, INCI, INN, JAN, JECFA, MARTINDALE, USAN, USP, PHF, HAB, PhF (Pharmacopée française), IUIS
Conformance	MANDATORY — all official names require a designation of the naming authority
Data Type	CD
Values Allowed	All values in the name assigning authority identifier system.
Business Rule(s)	All official names shall have a naming authority designated. If multiple authorities have assigned the same name.

6.3.6.2 Official name status (Conditional)

The status of the official name is associated with a given jurisdiction. It is possible that an official name could be official in one jurisdiction and superseded in another. With some official name types an initial name will be proposed and the name will later become recommended. Recommended INN would be considered to be the Official name in many jurisdictions.

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Table 10 — Official name status

User Guidance	The status of the official name.
Example(s)	Current, Alternate, Superseded, Proposed, Primary
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	Current, Alternate, Superseded, Proposed, Primary
Business Rule(s)	Each official name shall have a single status. The fact that a name is alternate is evident by having more than one name assigned to the same substance by the same authority for the same language, domain, etc.

6.3.6.3 Official name status change date (Conditional)

The change date of the status of the official name shall be specified according to the ISO 8601 date format (the variant without any delimiters).

Table 11 — Official name status change date

User Guidance	Date of official name change if known.
Example(s)	20110601
Conformance	CONDITIONAL
Data Type	TS.DATE
Business Rule(s)	If official name status changes the date of the official change should be captured if known.

6.4 Reference source (Conditional)

All data elements associated with a Substance or Specified Substance should have a reference source. These sources could be regulatory submissions, publications by naming authorities such as INN or USAN, pharmacopoeias, books, journals, web sites, meeting materials or public databases such as Chemical Abstracts. A source can refer to multiple data elements and a given element can have multiple sources.

NOTE Elements of 'Reference Source" class are provided in Figure 6.

6.4.1 Public domain (Conditional)

Most reference sources other than regulatory submissions will be in the public domain. All regulatory submissions will typically be considered to not be in the public domain. If the reference source is in the public domain, the data elements referenced by the source could be made public. There may be a separate determination whether any portion of the record can be made public. This determination may vary depending on type of substance. Regardless, submitters of information should always explicitly indicate whether data should be considered confidential.

EXAMPLE Particular care is advised in the release of company codes. Although the company codes are frequently mentioned in the public domain the release of a company code associated with a Substance ID and the defining information should only be made if all of the defining elements are associated with the company code in a single source in the public domain. For chemicals, the chemical structure should be associated with the company code in the public domain. For proteins, such as monoclonal antibodies, names or company codes could be released to the public only if the target of the antibody is mentioned in the same public source as the name or code. A separate determination will be made as to whether the protein sequence is in the public domain.

Table 12 — Public domain

User Guidance	Indication of whether the source is in the public domain. Company codes will only be released if the defining information is associated with the code in a public source such as

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	Chemical Abstracts (CAS), a journal article, or a poster at scientific meeting attributable to the company.
Example(s)	Yes, No
Conformance	CONDITIONAL
Data Type	BL
Values Allowed	Yes, No
Business Rule(s)	All regulatory submissions are considered not to be in the public domain. There may be an additional flag that determines whether any information can be released on a given substance.

6.4.2 Reference source type (Mandatory)

All reference sources shall be associated with a type. The type shall actually identify the source of the information if it is a public database or naming authority. For official names and defining information, the primary source should be used if available. A single source can be used for many data elements. Public databases particularly those of official naming bodies, regulatory submissions, manufacturer's technical specifications, scientific journal articles and pharmacopoeias are all sources that can be used.

Table 13 — Reference source type

User Guidance	The reference source type in which the data elements were actually found.
Example(s)	BP, ChemID (NLM), Ph.Eur., USP/NF, IND (Investigational New Drug), Recommended INN List, ITIS, JAN, Journal, JP, KEGG, Martindale, NDA, Personal Care Products Council (PCPC), PubChem, USAN, USP, Web Page, CAS Registry, FDA Global Substance Registration System (FDA GSRS), WHO Collaborating Centre for Drug Statistics Methodology (WHOCC), Chemical Book, Orange Book, Marketing Authorization Application (MAA), WHO/IUIS Allergen Nomenclature, UniProt, Plasma Master File, Homeopathic Pharmacopoeia
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	All names should have at least one source and hence source type. When the Reference Source Type is a Pharmacopoeial monograph, no reference has to be made to the version. The reference made (for example to Ph.Eur., USP, or JP) shall comply with the latest (current) and valid edition.

6.4.3 Reference source class (Optional)

Each reference information type should be associated with a class. The class will be automatically associated with each type of information.

Table 14 — Reference source class

User Guidance	Useful for classification of sources.
Example(s)	Regulatory submission, Public Database
Conformance	OPTIONAL
Data Type	CD
Values Allowed	Literature, Official Name Source, Other Name Source, Regulatory Submission, Public Database, Web
Business Rule(s)	Need not be entered as the value is dependent on the Reference Source Type.

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6.4.4 Reference source ID (Conditional)

Many sources such as regulatory submissions, INN lists and others should be associated with a number or ID. The ID should be captured.

Table 15 — Reference source ID

User Guidance	An ID associated with reference source.
Example(s)	IND number, Recommended INN list; PMID (PubMed Identifier)
Conformance	CONDITIONAL
Data Type	ST

6.4.5 Reference source citation (Conditional)

A citation should be captured for a literature reference. The specific format for a given citation may be defined at regional level.

Table 16 — Reference source citation

User Guidance	The actual reference source or citation in which the name was found.
Example(s)	Literature reference: Encycl. 3: 429 (1792) WHO Drug Information Vol. 25, no 3, 2011 Recommend INN: list 66
Conformance	CONDITIONAL
Data Type	ST

6.4.6 Reference source URL (Conditional)

In case the Reference source citation is a Web Page or Public Database, the URL should be provided.

Table 17 — Reference source URL

User Guidance	The reference source URL in which the citation was found. The URL should be captured here.
Example(s)	http://www.who.int/medicines/publications/druginformation/issues/RL_66.pdf
Conformance	CONDITIONAL
Data Type	ST

6.4.7 Reference source document (Conditional)

The elements of the 'Reference Source Document" class are provided in Figure 5.

6.4.7.1 Public domain (Conditional)

Most sources other than regulatory submissions should be in the public domain. All regulatory submissions will typically be considered to not be in the public domain. If the reference source is in the public domain, the data elements referenced by the source could be made public. There may be a separate determination whether any portion of the record can be made public. This determination may vary depending on type of substance. Regardless submitters of information should always explicitly indicate whether data should be considered confidential.

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Table 18 — Public domain

User Guidance	Indication of whether the source is in the public domain.
Example(s)	Yes, No
Conformance	CONDITIONAL
Data Type	BL
Values Allowed	Yes, No
Business Rule(s)	All regulatory submissions are considered not to be in the public domain. This flag determines whether any information can be released on a given substance.

6.4.7.2 Reference source document (Optional)

The document should be concise and contain information specific for given data elements.

Table 19 — Reference source document

User Guidance	Documents that contain relevant information on data elements and are referenced should be stored if available.
Example(s)	PDF, TEXT
Conformance	OPTIONAL
Data Type	ED
Values Allowed	The documents can be saved as PDF files or TEXT files. If the documents or data source contains structured data such as spectra, it can be transmitted in a standard format that can be visualized and searched.

6.4.7.3 Reference source document type (Optional)

Table 20 — Reference source document type

User Guidance	The type of the document
Example(s)	Pharmacopoeial monograph, Regulatory submission, Journal article, Release specification, In-house specification, Text file
Conformance	OPTIONAL
Data Type	CD

6.4.7.4 Reference source document ID (Optional)

Table 21 — Reference source document ID

User Guidance	An ID associated with reference source document.
Example(s)	FR4563 (Artificial ID)
Conformance	OPTIONAL
Data Type	ST

6.4.7.5 Reference source document classification (Optional)

A classification system will be also developed for documents. The classification system will indicate the type of information contained within the reference document based on a terminology for the classification of reference source documents.

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Table 22 — Reference source document classification

User Guidance	The reference document should be classified according to the information contained within
Example(s)	Chemical structure, NMR spectra, Mass Spectra, In-house/Batch release specification, Plasma Master File (PMF)
Conformance	OPTIONAL
Data Type	CD

6.5 Substance code (Conditional)

This subclause of reference information allows the capture of codes that are typically associated with a substance. The capture of these codes typically facilitates the defining and mapping of substances and linking of substances to a variety of information sources. Codes should be communicated if known but are not necessary or mandatory. The terminology should have the ability to capture, store and distribute codes as necessary. All the codes that are captured should be associated with a publicly recognized code system and map directly to a given substance. It should be noted that company codes are not captured in this subclause but are considered a type of name for a given substance. Commonly used public codes such as CAS Registry numbers with a given substance should be provided and associated to the substance.

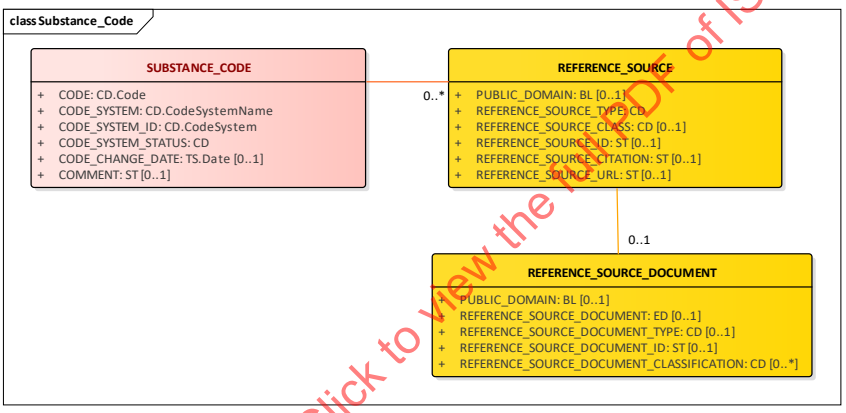


Figure 7 — Information model for Substance Codes

6.5.1 Code (Mandatory)

The actual code shall be captured using the same format that is used in the code system. Only codes associated with a code system shall be captured. The code shall be specifically associated with a given substance. Many public and non-public databases identify substances with a code and these codes can be very helpful in mapping substances to various systems. Codes shall always be verified against the source system. Different jurisdictions may require a code from a code system or multiple code systems to be associated and submitted with a substance.

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Table 23 — Code

User Guidance	The specific code (the value) with regard to a referenced code system. NOTE InChI is not considered a code and is specified within the structure description.
Example(s)	11-22-356; ab02sh
Conformance	MANDATORY
Data Type	CD.Code
Business Rule(s)	Only codes from recognized code systems will be captured. The code should specifically link to a substance but need not uniquely link to substance. This code can also be a deprecated Substance ID generated based on ISO 11238.

6.5.2 Code system (Mandatory)

Every code shall be associated with a code system and a list of names of code systems expected to be submitted shall be maintained by the maintenance organization.

EXAMPLES CAS Registry numbers, EC numbers, FDA UNII codes, EMA XEVMPD codes, ASK numbers, EPA Pesticide codes.

Table 24 — Code system

User Guidance	Name of the code system.
Example(s)	CAS, EINECS, NSC, ASK, RX-CUI, INN BQ
Conformance	MANDATORY
Data Type	CD.CodeSystemName
Business Rule(s)	If the Code class applies, the code system name is implicit and derived from the Code System ID.

6.5.3 Code system ID (Mandatory)

The code system ID shall be an OID or an ID as applicable.

Table 25 — Code system ID

User Guidance	The ID of the code system.
Example(s)	CAS Registry code: 0049; FDA GSRS (UNII) 0050; INN Biological Qualifier (INN BQ) code: 0051
Conformance	MANDATORY
Data Type	CD.CodeSystem
Business Rule(s)	The code system ID is required as all codes shall be linked to a code system.

6.5.4 Code system status (Mandatory)

The code system status is typically the status provided by the system for a given code. Many code systems can end up with multiple codes representing the same substance. Often one code will be the preferred code and others will either be deleted or deprecated. Ad hoc terms may also be developed to indicate a code status.

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Table 26 — Code system status

User Guidance	The status of the code assignment
Example(s)	Current, Alternate, Superseded, Proposed, Active, Migrated
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	The values allowed are those of the code systems being referred to. The examples above are typical examples of statuses used in code systems.

6.5.5 Code change date (Optional)

Table 27 — Code change date

User Guidance	The date at which the code status is changed as part of the terminology maintenance.
Example(s)	20110601
Conformance	OPTIONAL
Data Type	TS.DATE

6.5.6 Comment (Optional)

Table 28 — Comment

User Guidance	Any comment can be provided in this field, if necessary.
Example(s)	20110601
Conformance	OPTIONAL
Data Type	ST

6.5.7 Reference source (Conditional)

The reference source information should be captured as described in 5.4.

6.5.7.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7.

6.6 Reference information (Conditional)

Reference information should be captured for all types of substances and Group 1 Specified Substances. According to ISO 11238, this subclause captures additional types of informative reference information for each type of substance. This information shall not affect the generation of a new unique identifier; it may include both classification and target information for active substances but it does not provide any guidance on the classification of pharmacological effects or the determination of the putative targets for any Substance or Specified Substance.

NOTE Genes from which proteins are derived, target information and codes from code systems also constitute reference information to capture and link to a substance. Classification systems such as the WHO ATC and NDF-RT, which code classification information to substances, are particularly important. Target information is important for monoclonal and polyclonal antibodies and small molecules directed against specific molecular targets.

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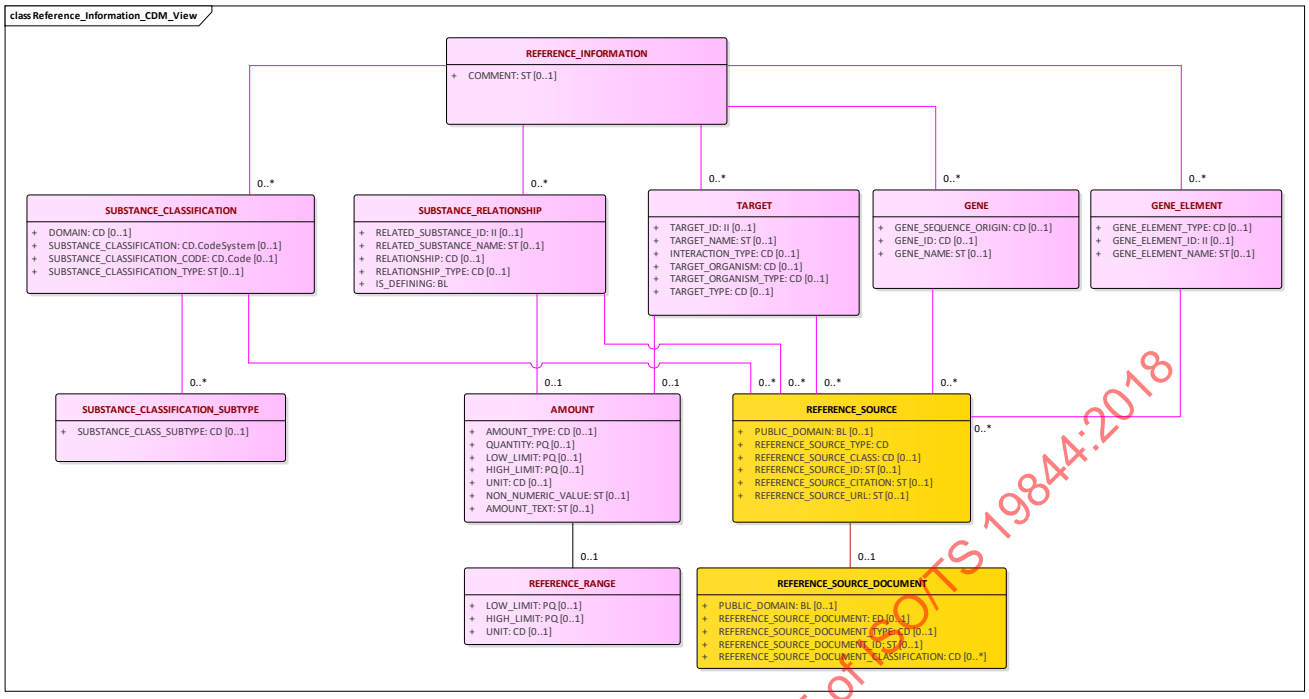


Figure 8 — Information model for Reference Information

6.6.1 Comment (Optional)

Table 29 — Comment

User Guidance	Any comment can be provided in this field, if necessary.
Conformance	OPTIONAL
Data Type	ST

6.6.2 Substance classification (Conditional)

The standard should have the ability to capture a variety of classification systems. Classification systems are typically based on molecular structure, chemical properties, pharmacological effects, mechanism of action, therapeutic targets or indication.

The standard should have the ability to capture multiple classifications and variable levels of classification. Although most classifications will be associated with an external classification system, ad hoc classification of substances may be developed within this terminology as needed.

The information should be captured as shown in Figure 9 — Information model for substance classification.

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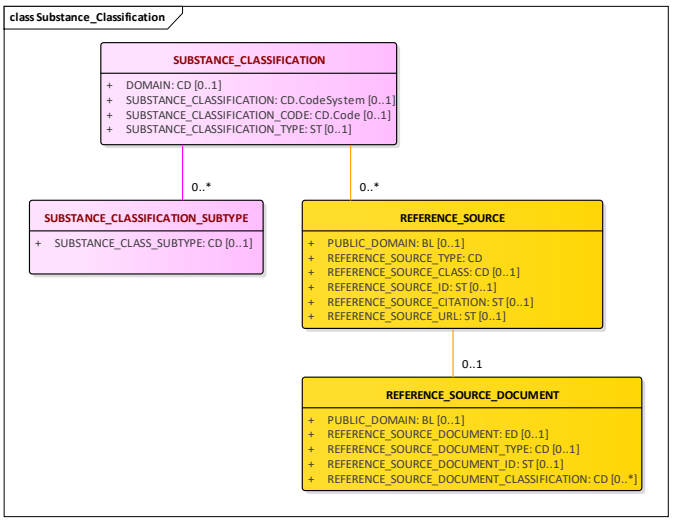


Figure 9 — Information model for Substance Classification

6.6.2.1 Domain (Optional)

Classification systems will often only be used within a specific domain. The domain will be associated with the classification system.

Table 30 — Domain

User Guidance	The domain of the substance classification shall be provided.
Example(s)	Human pharmaceutical, human vaccine, animal drug, animal vaccine, food, food additive, colourant, pesticide, tobacco additive, flavour, excipient
Conformance	OPTIONAL
Data Type	CD

6.6.2.2 Substance classification (Optional)

There are a number of systems that classify substances based on chemical structure, pharmacological effect, organ system affected, mechanism of action or molecular targets. These classification systems are useful and this information, if available, should be provided and maintained as applicable.

Table 31 — Substance classification

User Guidance	Substance Classification terms based on a controlled vocabulary that is controlled by the system or type of substance classification. The system should be capable of capturing a variety of classification systems and each system should be identified. All active ingredients are typically classified in multiple systems. Ad hoc classification may be created as necessary.
Example(s)	ATC, NDF-RT (National Drug File – Reference Terminology), NCI, AHPA, MESH; Therapeutic Category of Drugs in Japan
Conformance	OPTIONAL
Data Type	CD.CodeSystem

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6.6.2.3 Substance classification code (Optional)

Classification code which maps to the active moiety of a given substance.

Table 32 — Substance classification code

User Guidance	Code from the classifying code system. The code should be tied to the substance.
Example(s)	N0000175684 NDF-RT code for Oxycodone that maps to the mechanism of action classification. N02AA05 ATC code that maps to Oxycodone.
Conformance	OPTIONAL
Data Type	CD.Code
Business Rule(s)	The classification code shall be part of an internationally recognized classification system.

6.6.2.4 Substance classification type (Optional)

Nearly all classification systems contain multiple levels. Type is the highest level or the initial level of the classification system.

Table 33 — Substance classification type

User Guidance	The appropriate type or level within a classification system.
Example(s)	'lower' level in ATC
Conformance	OPTIONAL
Data Type	ST
Business Rule(s)	The value is IMPLICIT and can be derived by the “Substance Classification — Subtype “if available. Jurisdictional requirements should further define the appropriate level within a code system that should be used.

6.6.2.5 Substance classification subtype (Optional)

6.6.2.5.1 Substance class subtype (Optional)

Table 34 — Substance class subtype

User Guidance	Many classification systems will have multiple subtypes of classification. This field will attempt to capture this information.
Example(s)	NDF-RT Mechanism of Action (MOA) or Physiological Effect.
Conformance	OPTIONAL
Data Type	CD

6.6.2.6 Reference source (Conditional)

The reference source information should be captured as described in 5.4.

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6.6.3 Substance relationship (Conditional)

Table 35 — Substance Relationship

User Guidance	Relationships between substances such as the relationship between a salt form and its active moiety or parent substance should be captured. These relationships are often essential to the description of medicinal products, the basis of strength and the classification of substances. These relationships are often obvious and rules will be developed for specifying substances involved in each type of relationship. For example, the active moiety of all sodium salts would be the free acid, conversely the active moiety of a hydrochloride salt would be a free base. Example: the active moiety of the salt amlodipine besilate hydrate (1:1:1) is the related substance amlodipine. The salt amlodipine besilate hydrate contains 69.8 % w/w of amlodipine. Therefore, the equivalence factor is 0,698, meaning 10 mg amlodipine besilate hydrate salt corresponds to 6,98 (approx to 7 mg) amlodipine active moiety. The Equivalence Factor is captured by the element group Amount in combination with the element group Substance Relationship as Amount Text.
Example(s)	N/A
Conformance	CONDITIONAL
Data Type	N/A
Business Rule(s)	The Equivalence Factor shall be ≤1,00. It is formed by dividing the molecular weight of the (parent) substance (active moiety)/molecular weight of the corresponding salt or salt hydrate or hydrate .

6.6.3.1 Related substance ID (Conditional)

Table 36 — Related substance ID

User Guidance	Substance ID associated with the related substance. All related substances should have a Substance ID.
Conformance	CONDITIONAL
Data Type	II
Values Allowed	ISO 11238 Substance ID

6.6.3.2 Related substance name (Conditional)

Table 37 — Related substance name

User Guidance	Preferred term or primary name of related substance.
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	Based on ISO 11238 substance name
Business Rule(s)	The preferred term of the related substance is captured; this information is required when there is a “Substance Relationship”; The substance name is implicit and derived from the Substance ID.

6.6.3.3 Relationship (Conditional)

The relationship is not a mere code but the actual connection between the two substances which may be different for different kinds of relationships.

There are a variety of different relationships that are possible but for the identification of medicinal products the most important relationships are between a substance, its active moieties, the basis of

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strength and constituents in herbal and other complex substances. Parent and salt-solvate relationships and relationship of drug substance to its metabolites and impurities are also important although not essential for the description of a medicinal product. If there are known relationships between substances the relationships should be provided and maintained. The parent-active moiety relationship may be essential in describing medicinal products.

Table 38 — Relationship

User Guidance	Relationship between substances. NOTE Target and gene elements are not to be specified in this subclause.
Example(s)	Parent, active moiety, salt, parent molecule to salt/solvate, parent molecule to co-crystal, salt to parent, hydrate to parent, parent substance to salt-hydrate, radiolabelled, prodrug, metabolite, impurity, enantiomer, starting material, processing material, resultant material, polymer to polymer, protein to polymer, polymer to protein, protein to protein, parent polymer to polymer
Conformance	CONDITIONAL
Data Type	CD

6.6.3.4 Relationship type (Optional)

Table 39 — Relationship type

User Guidance	The Type of interaction between the substances.
Example(s)	Ionic, Van der Waals interaction, adjuvant absorption agent, sized polymer, hydrolysis, covalent attachment
Conformance	OPTIONAL
Data Type	CD

6.6.3.5 Is Defining (Mandatory)

Table 40 — Is Defining

User Guidance	There are cases that the substance relationship is a defining element for the substance's pharmacodynamic action. For example, if an enzyme has a strong binding with Substance A, then the relationship of Substance A with the enzyme (Related Substance) is defining information.
Example(s)	Yes, No
Conformance	MANDATORY
Data Type	BL

6.6.3.6 Amount (Conditional)

For some substance relationships, it may be desirable to capture a quantitative or semi-quantitative amount that may further define the relationship (i.e. major metabolite, degradants etc.). Amount should be captured according to 5.8.

Substance Relationships which refer to reactions (e.g. metabolism, prodrug) are quantified by specifying the quantity of the reactants.

6.6.3.6.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

6.6.3.7 Reference source (Optional)

The reference source information should be captured as described in 5.4.

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6.6.3.7.1 Reference source document (Optional)

The reference source document information should be captured as described in 5.4.7.

6.6.4 Target (Conditional)

The target subclause allows the capture of information related to the targets that a substance is known to interact with and the interaction results in a biological effect or transformation. These targets can be therapeutic, metabolic, interactions postulated to result in toxicity or interactions of unknown effect. Targets are typically proteins, or complexes of proteins. The target may be a substance in its own right and ID shall be assigned and/or existing ID of a known system used (i.e. GenBank, UniProt) to refer to a target.

For monoclonal antibodies, the target shall always be provided. For other types substances, the target may be provided if known. Ideally the target is a substance with its own Substance ID. However, in specific circumstances, the target may be handled as a relationship between two substances.

6.6.4.1 Target ID (Conditional)

Typically, the Target ID is either a Substance or Specified Substance ID.

Table 41 — Target ID

User Guidance	ID of the target relation molecular entity upon which the substance acts. One Target ID should be specified. The target should be a molecular entity or a family of molecular entities. The target is usually a protein entity that the drug actually interacts with. Both therapeutic and metabolic targets and targets associated with toxicity should be captured.
Conformance	CONDITIONAL
Data Type	II
Values Allowed	ISO 11238 Substance ID
Business Rule(s)	The ISO 11238 Substance ID shall be referenced.

6.6.4.2 Target name (Conditional)

At least one name of the target shall be provided when target information is submitted. Target names will not be handled any differently than other substance names. If an active ingredient targets more than one target each target should be listed. In addition to names a list of codes associated with the target may also be used. GenBank and UniProt codes can be particularly useful for identifying and tracking targets.

Table 42 — Target name

User Guidance	Name of the target molecular entity upon which the substance acts. Each target should be associated with a target name.
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	ISO 11238 substance name
Business Rule(s)	ISO 11238 substance name implicitly derived from Target ID. A variety of names can be captured. A single name will be a preferred name and associated with the Target ID. At least one name of the target should be provided when target information is submitted.

6.6.4.3 Interaction type (Conditional)

The type of interactions between a substance and its target should also be captured. A controlled vocabulary should be developed to capture these types of interactions.

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Table 43 — Interaction type

User Guidance	Type of interaction between the substance and the target. The interaction type should be captured for all substrate-target interactions. A substance can have multiple types of interactions.
Example(s)	AGONIST, INDUCER, INHIBITOR, PARTIAL ANTAGONIST, SUBSTRATE, PRODUCT
Conformance	CONDITIONAL
Data Type	CD

6.6.4.4 Target organism (Conditional)

When drugs are targeted against a specific organism the organism should be captured. For antivirals and antibacterials there is typically no need to give the strain level unless the organism is resistant to more commonly used drugs.

Table 44 — Target organism

User Guidance	The organism for which the active substance is targeted.
Example(s)	*Homo Sapiens*, M. TB, HIV-1
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	At least one organism type should be associated.

6.6.4.5 Target organism type (Conditional)

Every organism should have a type that is maintained within this terminology. The organism type may also be used independent of the organism particularly for substances such as antibacterial which may be targeted against a wide range of organisms.

Table 45 — Target organism type

User Guidance	Every target organism should have a type associated with the organism.
Example(s)	human, viral, bacterial, fungal, insect, helminth, malarial
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	At least one organism type should be associated.

6.6.4.6 Target type (Optional)

Each target-substance interaction should be assigned a type. The type is dependent on the substance and also to some extent the use of the substance. A given target-substance interaction can be of more than one type.

EXAMPLE The therapeutic target would be HIV-1 protease when ritonavir is used in HIV-related therapy. The metabolic target is Cyp 3A4 and ritonavir is an inhibitor of this target. Ritonavir is also an inhibitor of P-glycoprotein, a drug transporter. In many combination products ritonavir is used strictly to inhibit Cyp 3A4/5 and transporter enzymes.

Table 46 — Target type

User Guidance	Type is a limited form of classification associated with a target of an active substance. Some targets can be both toxic and therapeutic; the choice is dependent on the dose (Km value) of a given substance.
Example(s)	therapeutic, metabolic, toxic, transporter

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Conformance	OPTIONAL
Data Type	CD
Business Rule(s)	Each target should be associated with a target type when the target can be classified.

6.6.4.7 Amount (Conditional)

Amount should be captured as described in 5.8.

6.6.4.7.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

6.6.4.8 Reference source (Optional)

The reference source information should be captured as described in 5.4.

6.6.4.8.1 Reference source document (Optional)

The reference source document information should be captured as described in 5.4.7.

6.6.5 Gene (Conditional)

The gene subclause should only be captured for proteins and nucleic acids. It does not apply for chemicals, polymers or structurally diverse substances. It is only used as reference information and refers to the gene that is the origin of the substance (typically a protein). Genes may also be substances and would be described as nucleic acids.

6.6.5.1 Gene sequence origin (Conditional)

For monoclonal antibodies, the gene sequence origin should be used to capture species from which the antibody was derived.

Table 47 — Gene sequence origin

User Guidance	Common name for the organism from which the final gene sequence originated.
Example(s)	Human, Bovine, Human, Humanized, Mouse-Human Chimeric, Mouse, Bacterial, Viral, Plant, Arachnid
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	Typically, from the NCBI Gene database.
Business Rule(s)	The provision of a Gene Sequence Origin applies primarily to proteins.

6.6.5.2 Gene ID (Conditional)

Table 48 — Gene ID

User Guidance	ID associated with the gene of origin
Example(s)	YP_299723.1
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	Typically, from the NCBI Gene database.

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6.6.5.3 Gene name (Conditional)

Table 49 — Gene name

User Guidance	Complete name given for a gene. Every gene which has an ID should also have a name.
Example(s)	hIL-10 gene
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	Implicit from the Gene ID from the applicable Gene database.

6.6.5.4 Reference source (Conditional)

The reference source information should be captured as described in 5.4.

6.6.5.4.1 Reference source document (Optional)

The reference source document information should be captured as described in 5.4.7.

6.6.6 Gene element (Conditional)

Gene elements should be captured for genes that are used in gene therapy. When the gene element subclause applies, the following information shall be provided.

6.6.6.1 Gene element type (Conditional)

Table 50 — Gene element type

User Guidance	Type of the gene element. This should be captured for all genes that are transduced into cells and are intended to be expressed.
Example(s)	enhancer, promoter, silencer, terminator, repressor, epimerase, polymerase linker, transferase, capsule transporter, synthase, synthetase
Conformance	CONDITIONAL
Data Type	CD

6.6.6.2 Gene element ID (Conditional)

Table 51 — Gene element ID

User Guidance	Unique identifier for gene element.
Conformance	CONDITIONAL
Data Type	II
Values Allowed	A unique identifier will be associated with each gene element.

6.6.6.3 Gene element name (Conditional)

Table 52 — Gene element name

User Guidance	Specific gene element name.
Example(s)	SV40 Enhancer
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	A unique name will be associated with each gene element.
Business Rule(s)	Implicit from the Gene Element ID from the applicable Gene element controlled vocabulary.

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6.6.6.4 Reference source (Conditional)

The reference source and related information should be captured according to 5.4. One or more reference sources could be cited.

6.6.6.4.1 Reference source document (Optional)

The reference source document information should be captured as described in 5.4.7.

6.7 Structure (Conditional)

Structural information of a substance should be provided as discribed in Figure 10.

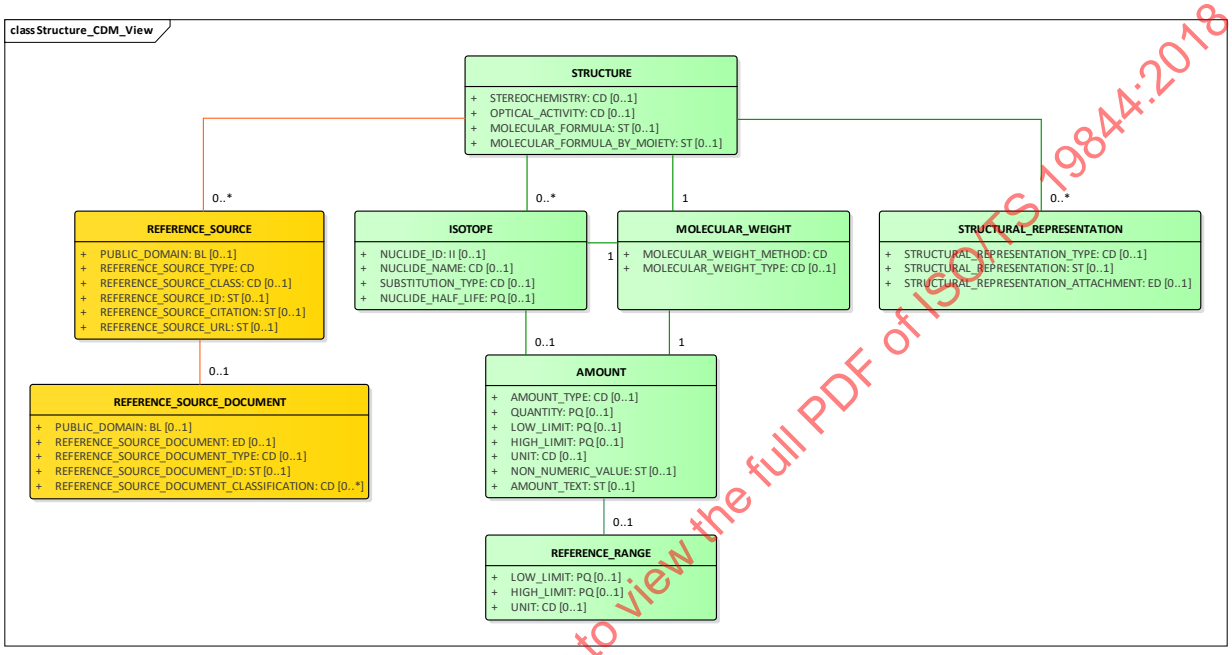


Figure 10 — Information model for Structure and Isotope

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6.7.1 Stereochemistry (Conditional)

The overall stereochemistry of the substance should be indicated in this field.

Table 53 — Stereochemistry

User Guidance	The stereochemistry of the substance should be indicated in the structure and is captured here. Special cases of stereochemistry that can't be indicated in the structure shall be described based on a controlled vocabulary. Mixtures of stereoisomers shall be represented explicitly as a mixture of substances with absolute stereochemistry. In case the absolute stereochemistry is unknown the substance definition should be marked as "Incomplete".
Example(s)	Absolute, axial r, axial s, square planar 1, square planar 2, square planar 3, square planar 4, tetrahedral, octahedral 12, octahedral 22, octahedral 21, chiral, geometric, achiral, racemic, mixed
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	ABSOLUTE, AXIAL R, AXIAL S, SQUARE PLANAR 1, SQUARE PLANAR 2, SQUARE PLANAR 3, SQUARE PLANAR 4, TETRAHEDRAL, OCTAHEDRAL 12, OCTAHEDRAL 22, OCTAHEDRAL 21; RACEMIC, MIXED, CHIRAL, ACHIRAL, ABSOLUTE, AXIAL, EPIMERIC, MESO, UNKNOWN, CIS, TRANS
Business Rule(s)	When the Substance type, as defined in is either chemical or polymer, this class is MANDATORY; for all other cases this class is CONDITIONAL.

6.7.2 Optical activity (Conditional)

The optical activity of a chiral substance should be captured if known. The extent of optical rotation is not mandatory at the substance level.

Table 54 — Optical activity

User Guidance	The optical activity should be described based on a controlled vocabulary.
Example(s)	(+/-), (+), (-), None, N/A, Unknown
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	(+/-), (+), (-), None, N/A
Business Rule(s)	Shall be entered if known for substances that have at least one moiety with stereochemistry defined as chiral. Can be a defining element when the absolute stereo configuration is not known.

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6.7.3 Molecular Formula (Conditional)

Table 55 — Molecular formula

User Guidance	Molecular formula is written as a sequence of pairs of atom symbol and stoichiometric number (see example below). This formal notation is essentially a code system. Specified according to the Hill system, i.e. first C, then H, then alphabetical. NOTE The messaging requirements can dictate a specific electronic format for the molecular formula and the molecular formula by moiety.
Example(s)	$C_{26}H_{33}ClN_2O_9S$
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	Can be implicitly derived from the structure; Validity check for identity and structural representation Molecular formula is not mandatory in the case of a large protein (e.g. more than 10k Da), a large nucleic acid or a large polymer For small molecules up to molecular weight of 5 000 the unit should be g/mol; above that the Da/kDa is to be used.

6.7.4 Molecular Formula by Moiety (Conditional)

Table 56 — Molecular formula by moiety

User Guidance	Specified per moiety according to the Hill system, i.e. first C, then H, then alphabetical and each moiety separated by a dot. NOTE The messaging requirements can dictate a specific electronic format for the molecular formula and the molecular formula by moiety.
Example(s)	$C_{20}H_{25}ClN_2O_5.C_6H_6O_3S.H_2O$ (amlodipine besilate monohydrate)
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	Can be implicitly derived from the structure; Validity check for identity and structural representation For a salt/hydrate the molecular formula of the base or the acid and the salt/hydrate part are separated by a dot per moiety, e.g. Desmopressin Monoacetate Trihydrate: Molecular formula by moiety: $C_{46}H_{64}N_{14}O_{12}S_2.C_2H_4O_2.3H_2O$.

6.7.5 Molecular weight (Mandatory)

This information shall be captured as described in 6.2.7.

6.7.6 Structural Representation (Conditional)

Structural information is an essential element for all chemical substances, polymers and for other types of substances that have structurally definable elements or modifications. The representation should contain structural information in one or more of the standardized formats as indicated below. A graphical image of the molecular structure should also be provided if available. A complete representation of the structure should be provided and is usually sufficient to define chemical substances. Structural representations can be in a variety of formats or even multiple formats. The commonly used formats include molfile, SMILES, InChI, and cdx. Indication of a preferred structural representation may be defined at regional level. Although most chemical substances may be represented by a single unambiguous structural representation, there are also many substances that can be represented by multiple structural representations or as a mixture of single substances. For the initial implementation

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and the transmittal of data for substance definitions, an approach that limits submissions to a single or a limited number of unambiguous structural representations is recommended. There are several examples below that illustrate the process in choosing a defining structural representation to submit. A more detailed structural representation guide is provided as part of the Annex B.

For Amine Salts, with the exception of ammonium and quarternium, salts shall be represented as a free base.

EXAMPLE Difloxacin Hydrochloride

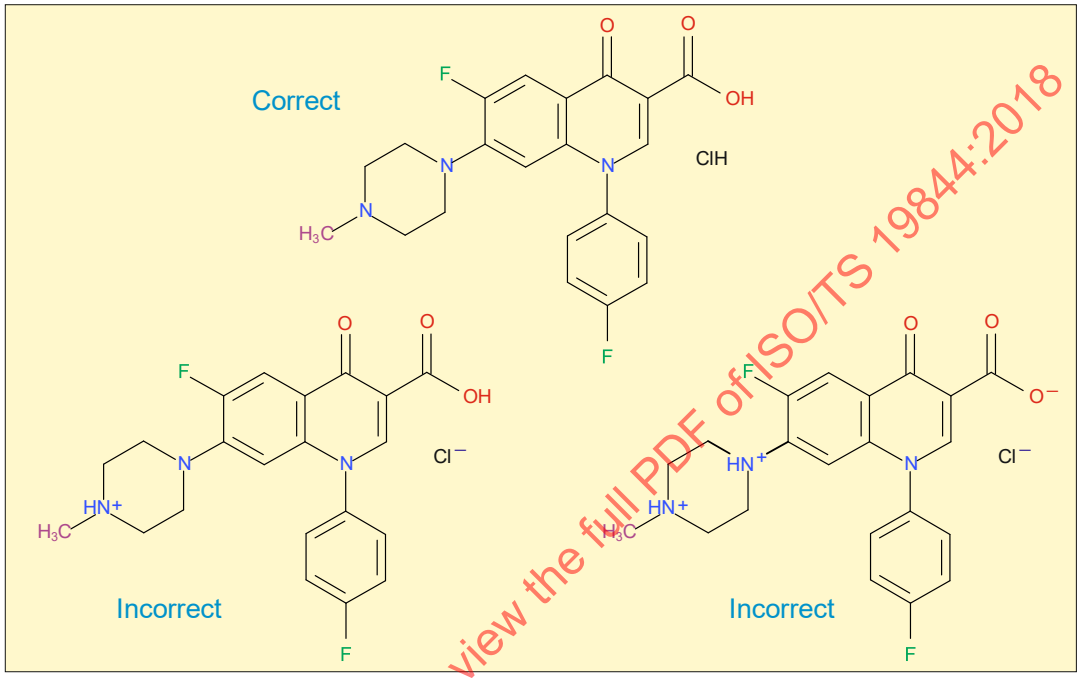


Figure 11 — Correct and incorrect graphical images of the molecular structure of difloxacin hydrochloride

Metal and ammonium salts: All metal and ammonium salts (NH_4^+) shall be represented in a charged configuration with all equivalent functional groups ionized. Charge balance will be achieved when necessary by adding hydrogen ions (protons).

EXAMPLE Monosodium Citrate.

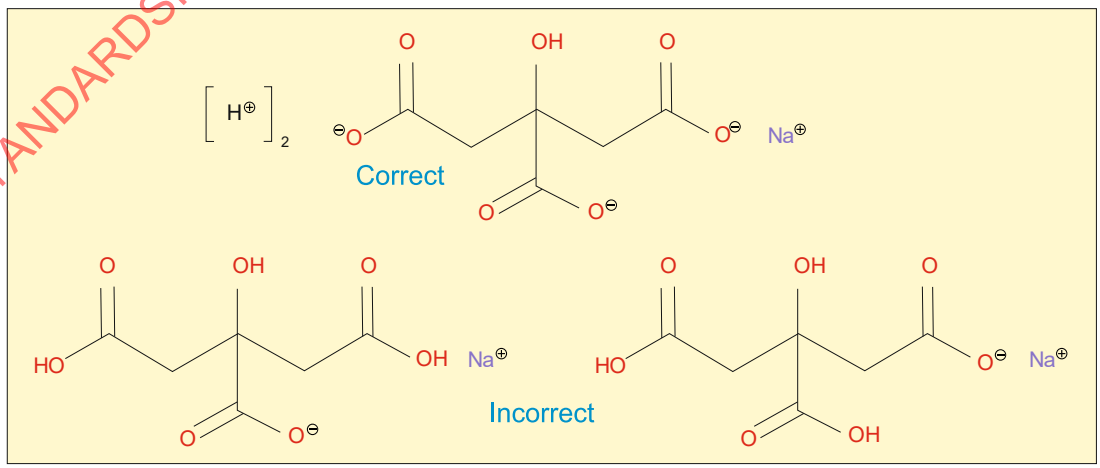


Figure 12 — Correct and incorrect graphical images of the molecular structure of monosodium citrate

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Racemic mixtures can be represented as mixtures of enantiomers or by a single structural representation. When using a single structural representation and the substance only contains one chiral centre, a single structure will be drawn that does not contain a chiral bond. If more than one chiral centre exists, relative stereochemistry shall be indicated. The stereochemistry of each moiety of a given substance will be captured separately. An example of this is Ofloxacin, see Figure 13.

A racemic mixture of the R and S isomers. A single structural representation can be used in this case.

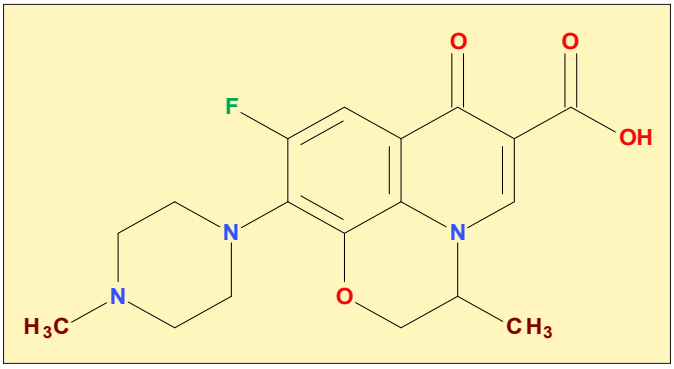


Figure 13 — Graphical image of the molecular structure of Ofloxacin

There are also substances that are mixtures of multiple enantiomers. These substances can also be transmitted in a single structural representation.

Substances can exist in interconverting forms or with a different defined structure depending on the physical state. In cases where the actual structure is a single configuration in a solid physical state, that structure should be captured. When a substance exists in a liquid state and can interconvert to a variety of structures, the least ambiguous single structure should be chosen.

EXAMPLE DEXTROSE (GLUCOSE): Exists as three separate substances in the crystalline state. For a crystalline substance one of the following representations should be chosen.

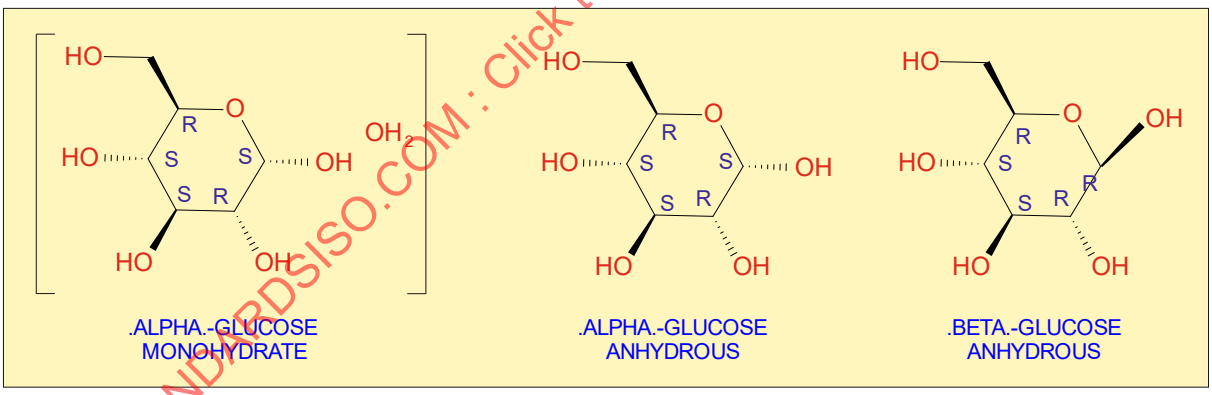


Figure 14 — Graphical images of the molecular structure of the three crystalline states of dextrose

In the liquid state dextrose and many other monosaccharides, disaccharides and higher homologs that end in an aldehyde are often referred to as reducing sugars and exist as mixtures of interconverting substances as illustrated in the structures of glucose below.

In this case the linear single representative structure is chosen to represent dextrose in the liquid or amorphous state. If pyranose or furanose forms were chosen, the representative structure would have one site of stereochemical ambiguity. One general rule is that if there are multiple interconverting structural representations for a substance the preferred representation is the one with the least ambiguity. In Figure 15, the pyranose and furanose structures have one site of stereochemical ambiguity.

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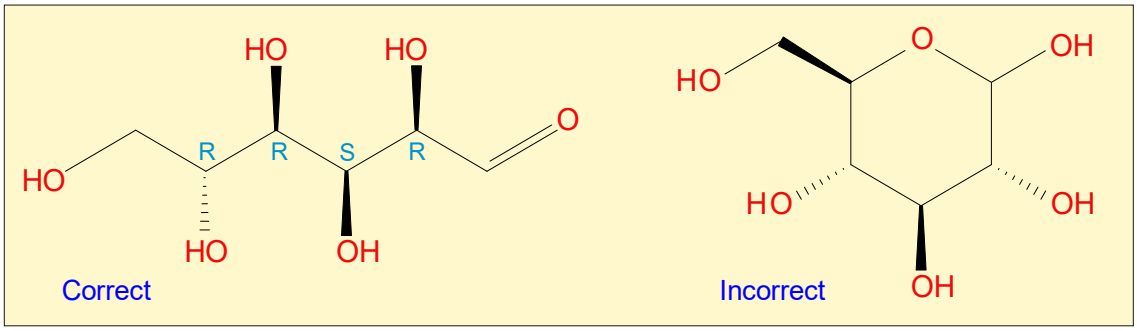


Figure 15 — Correct and incorrect graphical images of the molecular structure of (liquid) dextrose

Structural representations will also be used to represent fragments of molecules. Fragments will be used in describing partially modified polymers and are typically generated to describe partially acylated polymers, proteins or even nucleic acids. In order to consistently describe substances a fragment will be generated in a defined manner. Ester and amides will always be broken up so that the oxygen or nitrogen stays with the alcohol or amine. Ethers will be broken so that the oxygen stays with polymeric or larger structural unit.

EXAMPLE Cellulose Acetate.

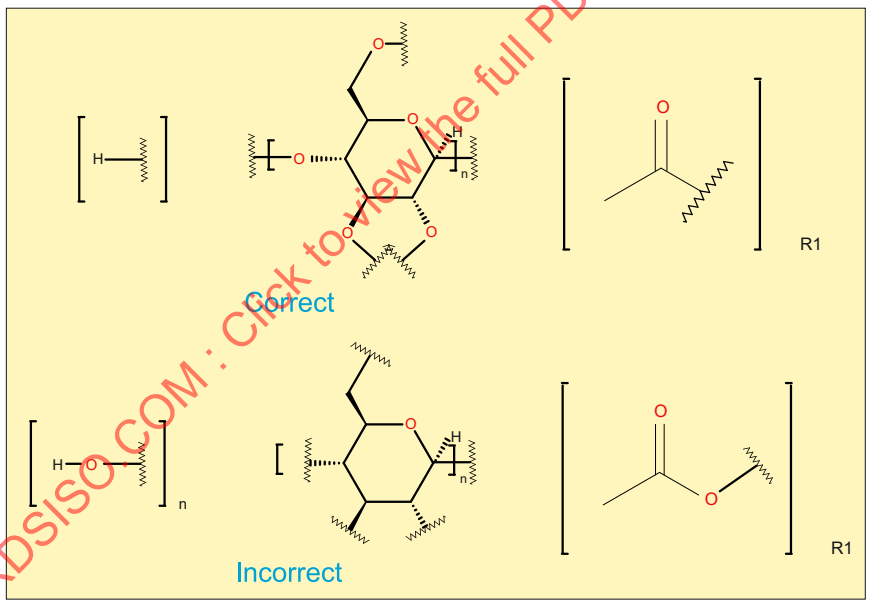
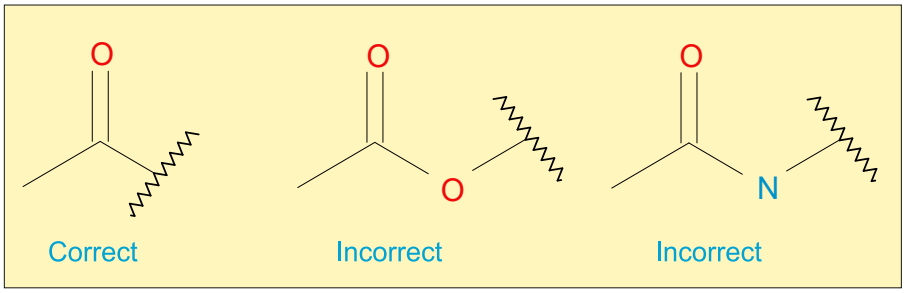


Figure 16 — Correct and incorrect graphical images of the molecular structure of cellulose acetate

The acetyl fragment is represented in Figure 17.



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Figure 17 — Correct and incorrect graphical images of the molecular structure of the acetyl fragment

In fragments derived from ethers, the oxygen will be retained by the polymer or largest portion of a molecule.

EXAMPLE Hypromelloses.

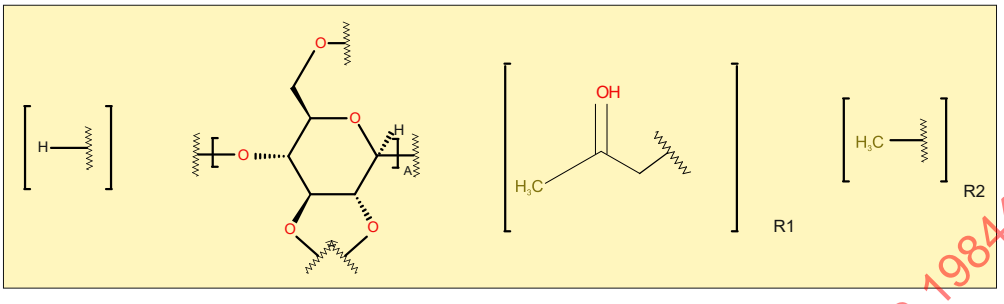


Figure 18 — Graphical images of the molecular structure of hypromelloses

Figure 17 provides the high-level information for the Class Structure.

In the class 'Structure' the Element 'Molecular Formula' is represented by molecular formula by moiety and by the total of moieties in accordance with the Hill system captured by the term molecular formula. In addition, the Element Group 'Molecular Weight' is connected to the class 'Structure' also for stoichiometric substances.

See also the high-level information at the substance type Chemical.

A structural representation is an essential element for defining chemical substances and is often sufficient for defining most chemical substances.

Four common structural representation types are listed below. Each of the types can unambiguously describe substances with a definite molecular structure. Stereochemistry should be completely defined in each structural representation. Formats like MOLFILES and CDX have the ability to describe polymeric repeating units and molecular fragments. There are a number of tools available, both free and commercial, that allow the creation of molecular structural representations. Multiple structural representation types can be submitted.

This class is CONDITIONAL. When the Substance type, as defined in 5.2.1, is either chemical or polymer this class becomes MANDATORY and the following data elements should be described:

6.7.6.1 Structural representation type (Conditional)

Table 57 — Structural representation type

User Guidance	This field indicates the type of structure. A FULL structure is a structure in which the complete connectivity of the substance is known and the substance is monodisperse. A PARTIAL structure is a structure in which either complete connectivity or stereochemistry is not defined. A REPRESENTATIVE structure is used when the connectivity of the underlying material is diverse and a single structure is needed to represent that material
Example(s)	Full; partial; representative; fragment; ionic moiety; structural repeat unit; the formats InChI, MOLFILE, SMILES, HELM
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	A structure can only be of one type. Field is mandatory when structural elements are present.

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	When the Substance type, as defined in is either chemical or polymer this element becomes MANDATORY

Structural representation type is specified as a MIME Media Type code:

Type	MIME Media Type
InChI	chemical/x-InChI
MOLFILE	chemical/x-mdl-molfile
SMILES, SMI	chemical/x-daylight-smiles
HELM	chemical/x-helm
XHELM	chemical/x-xhelm
CDX	chemical/x-cdx

6.7.6.2 Structural representation (Conditional)

Table 58 — Structural representation

User Guidance	The structural representation should be provided as text string, the following formats are acceptable: InChI, SMILES, MOLFILE, CDX.
Example(s)	InChI, Molfile, SMILES, CDX, HELM
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	Each structural representation will have one and only one type. When the Substance type, as defined in is either chemical or polymer, this element becomes MANDATORY. The preferred representation type is MOLFILE v 2000.

6.7.6.3 Structural representation attachment (Optional)

Table 59 — Structural representation attachment

User Guidance	An attached file that may contain the structural representation should be provided for complex data formats, e.g. CDX, MOLFILE.
Conformance	OPTIONAL
Data Type	ED

6.7.7 Isotope (Conditional)

Applicable for single substances that contain a radionuclide or a non-natural isotopic ratio, e.g. ^{13}C enriched material. All radionuclide and non-natural isotopes will also be represented in the structural representation for chemical substances. For other types of substances, a structural representation could be created to indicate the position of substitution.

6.7.7.1 Nuclide ID (Conditional)

Table 60 — Nuclide ID

User Guidance	A Substance ID for each non-natural or radioisotope is created. The ID is linked to a single atom zero valence element.
Conformance	CONDITIONAL
Data Type	II
Values Allowed	ISO 11238 Substance ID
Business Rule(s)	Mandatory when substance contains non-natural or radioisotope.

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6.7.7.2 Nuclide name (Conditional)

Table 61 — Nuclide name

User Guidance	The name for each isotope should be provided.
Example(s)	CARBON ^{13}C
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	ISO 11238 Substance names
Business Rule(s)	This element is Mandatory when substance contains non-natural or radioisotope. Implicitly derived from Nuclide ID.

6.7.7.3 Substitution type (Conditional)

Applicable for single substances that contain a radionuclide or a non-natural isotopic ratio, e.g. ^{13}C enriched material. All radionuclide and non-natural isotopes will also be represented in the structural representation.

Table 62 — Substitution type

User Guidance	The type of isotopic substitution present in a single substance: — specific if the site of attachment/substitution indicated in structure; — non-specific if the nuclide is distributed throughout molecule or substance; — unknown if site unknown. Substitution refers to the relationship between the nuclide and the rest of the substance.
Example(s)	specific; non-specific; unknown
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	Mandatory when substance contains non-natural or radioisotope.

6.7.7.4 Nuclide Half Life (Optional)

Table 63 — Nuclide Half Life

User Guidance	The half life of a non-natural nuclide.
Example(s)	109,77 min (^{18}F)
Conformance	OPTIONAL
Data Type	PQ
Business Rule(s)	This field can be calculated from the Isotopes table.

6.7.7.5 Amount (Conditional)

Amount should be captured as described in 5.8.

6.7.7.5.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

6.7.7.6 Molecular weight (Mandatory)

This information shall be captured as described in 6.2.7.

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6.7.8 Reference Source (Conditional)

The reference source information should be captured as described in 5.4.

6.7.8.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7.

6.8 Amount (Conditional)

The amount subclause serves to provide the quantitative or qualitative values that are associated with a variety of elements. The same format will be used for all quantitative, semi-quantitative and qualitative values. Amounts may be a single value or a range (with low or high limits or both). An 'amount type' may be associated with an amount to state if the value needs to be interpreted as an average or an exact or approximate quantity. The attribute 'Non-numeric Value' is used to carry a value that is purely textual, with no numeric component. The 'Amount Text' is used for additional text to explain a numeric value.

6.8.1 Amount type (Conditional)

Table 64 — Amount type

User Guidance	This attribute may be used to state how a numeric amount is to be interpreted.
Example(s)	Exact (the default, when not specified); Approximate; NLT; NMT
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	

6.8.2 Quantity (Conditional)

Table 65 — Quantity

User Guidance	Used to capture a quantitative value for a variety of elements.
Conformance	CONDITIONAL
Data Type	PQ
Values Allowed	Exact or approximate quantitative value or an average value for a given element. NOTE The element 'Amount Type' is used to distinguish.
Business Rule(s)	Quantity not to be used with Low Limit or High Limit, or Non-numeric value

6.8.3 Low limit (Conditional)

It should be noted that there can be two types of low limit, one is a limit on actual values and the other is the lower limit of the average of values ('Amount Type' is used to distinguish). The low limit can be used alone to express one-sided ranges greater than or equal to this limit (NLT). It can also be used to express NLT (not less than) values.

Table 66 — Low limit

User Guidance	To be used to express the lower limit of a range of values, if applicable
Conformance	CONDITIONAL
Data Type	PQ
Business Rule(s)	Not to be used with Quantity or Non-numeric Value. Both limits must have the same dimension and units.

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6.8.4 High limit (Conditional)

Similar to the low limit, Amount Type is used to state if the high limit refers to a range of values or a range of averages. The high limit can also be used to express one-sided limits. It can also be used to express NMT (not more than) values.

Table 67 — High limit

User Guidance	To be used to express the higher limit of a range of quantitative values, if applicable.
Conformance	CONDITIONAL
Data Type	PQ
Business Rule(s)	Not to be used with Quantity or Non-numeric Value. Both limits must have the same dimension and units.

6.8.5 Unit (Conditional)

Most units should be consistent with those described in UCUM. There may be a need for additional units to describe particular properties and the maintenance organization should maintain them. Units may be dependent on the method of measurement or calculation to determine the property.

Table 68 — Unit

User Guidance	The unit of measure. There is only one unit for the single quantity, or for both parts of a range.
Example(s)	1, g, mg, mol, mmol, L, [IU], mg/L, mol/L, g/mol, [IU]/g, DH (decimal), %{w/w}, %{v/v}, $\log_{10}$, ln
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	The units shall be specified in accordance with ISO 11240 and the resulting terminology. NOTE Other specific units can be required by jurisdictional guidelines.
Business Rule(s)	The unit is mandatory for amount expressed as numeric value, except where the value has no unit (dimensionless). It is not to be used with Non-numeric Value. Units should be restricted to the actual physical units of the numeric value, and not be used to restate what property the value is for, nor comments about the value (see amount text).

6.8.6 Non-numeric Value (Conditional)

Table 69 — Non-numeric value

User Guidance	Qualitative value or general description to capture information related to a characteristic attribute or constituent.
Example(s)	'June – August, ' Shock frozen directly after harvesting', 'Provinces Shandong, Jiangsu, Sichuan'
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	Not to be used with a numeric value, or unit, or amount text or amount type.

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6.8.7 Amount text (Conditional)

Table 70 — Amount text

User Guidance	To capture additional explanatory text for a numeric value.
Example(s)	For a Quantity of "71,9" and a Unit "% {w/w}" the Amount text could be: "Equivalence Factor: 0,72" Killing by cold shock at -20^0 C, Microscopic inspection, and dried in a fluid bed dryer and controlled air temperature and moister
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	Not to be used with a non-numeric value

6.8.8 Reference range (Conditional)

This element group is used to capture a specification range as specified in a reference document, e.g. Note for Guidance, Pharmacopoeial monograph, which can be used to interpret the measured value, or range, in an Amount.

6.8.8.1 Low limit (Conditional)

Table 71 — Low limit

User Guidance	The lower limit of a specification range.
Example(s)	
Conformance	CONDITIONAL
Data Type	PQ

6.8.8.2 High limit (Conditional)

Table 72 — High limit

User Guidance	The upper limit of a specification range.
Conformance	CONDITIONAL
Data Type	PQ

6.8.8.3 Unit (Conditional)

Table 73 — Unit

User Guidance	The unit for both limits of a specification range.
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	The units shall be specified in accordance with ISO 11240 and the resulting terminology. NOTE Other specific units can be required by jurisdictional guidelines.
Business Rule(s)	The Unit is mandatory except where the value has no unit (dimensionless).

6.9 Source material (Conditional)

Source material shall capture information on the taxonomic and anatomical origins as well as the fraction of a material that can result in or can be modified to form a substance. This set of data elements shall be used to define proteins and polymer substances isolated from biological matrices. Taxonomic and anatomical origins shall be described using a controlled vocabulary as required. This information is

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captured for naturally derived proteins and polymers (e.g. starch) and structurally diverse substances. For Organisms belonging to the Kingdom Plantae the Substance level defines the fresh material of a single species or intraspecies, the Herbal Drug and the Herbal preparation. For Herbal preparations, the fraction information will be captured at the Substance information level and additional information for herbal extracts will be captured at the Specified Substance Group 1 information level. See for further explanation the Substance Class: Structurally Diverse and the herbal Annex E.

The information model for the source material is shown in Figure 19.

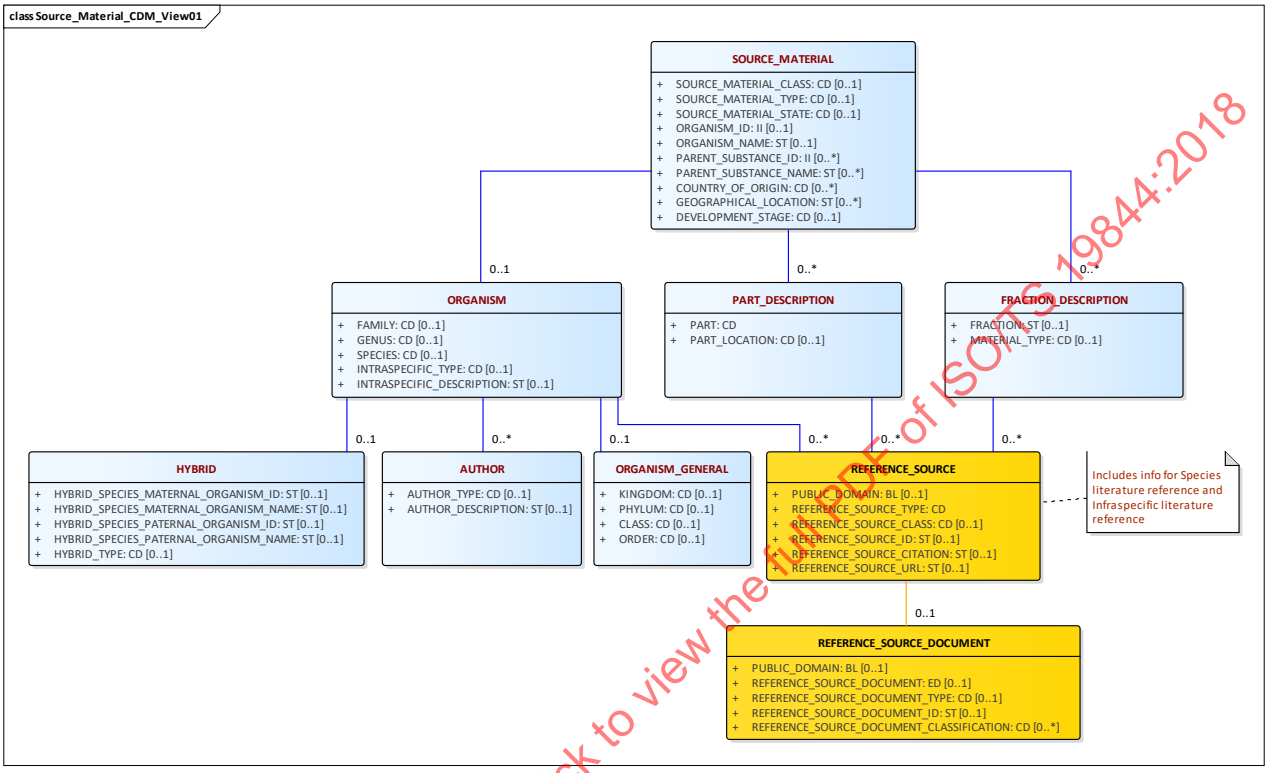


Figure 19 — Information model for Source Material

Specifically, the information on the source material shall be provided by means of the following set of data elements.

6.9.1 Source material class (Conditional)

Table 74 — Source material class

User Guidance	General high-level classification of the source material specific to the origin of the material.
Example(s)	mineral, biologic, organic, botanical
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	For Structurally Diverse substances, this class shall be Mandatory.

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6.9.2 Source material type (Conditional)

Table 75 — Source material type

User Guidance	The type of the source material shall be specified based on a controlled vocabulary. For vaccines, this subclause refers to the class of infectious agent.
Example(s)	bacteria, human, mammal, fungus, virus, plant, animal, grass pollen, arachnid, porcine
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	The "Source Material Type" values are presented based on the "Source Material Class" values above. Because organic/inorganic is just a class best captured in terminology of the source material types, only one data element is needed for Type which implies Class. For Herbals, this class shall be Mandatory.

6.9.3 Source material state (Conditional)

Table 76 — Source material state

User Guidance	The state of the source material when extracted.
Example(s)	Live; activated; inactivated; attenuated; conjugated; live (attenuated); cultured (killed); polysaccharide, natural-derived.
Conformance	CONDITIONAL
Data Type	CD

6.9.4 Organism ID (Conditional)

Table 77 — Organism ID

User Guidance	The unique identifier associated with the source material parent organism should be specified. NOTE This ID might or might not be the parent ID of the substance. EXAMPLE The substance *Ginkgo biloba* L. Leaf has an Organism ID belonging to the Organism *Ginkgo biloba* L.
Conformance	CONDITIONAL
Data Type	II
Business Rule(s)	For Herbals, this element shall be Mandatory.

6.9.5 Organism name (Conditional)

Table 78 — Organism name

User Guidance	The organism accepted Scientific name should be provided based on the organism taxonomy.
Example(s)	*Ginkgo biloba* L.; *Harpagophytum procumbens* (Burch.) DC. ex Meisn.
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	For Herbals, this element shall be Mandatory. The accepted scientific name for plants is provided by Kew Gardens' Medicinal Plant Names Services (MPNS). The names for other organisms will be provided by other authoritative sources.

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6.9.6 Parent substance ID (Conditional)

Table 79 — Parent substance ID

User Guidance	The Parent substance ID of the herbal drug Ginkgo biloba, Leaf is the substance ID of the substance (fresh) of *Ginkgo biloba* L. or *Ginkgo biloba* L. (Whole plant).
Example(s)	The substance ID of *Ginkgo biloba* L., Leaf
Conformance	CONDITIONAL
Data Type	II
Business Rule(s)	For Herbal Drugs, Herbal preparations and Vaccines this element shall be Mandatory.

6.9.7 Parent substance name (Conditional)

Table 80 — Parent substance name

User Guidance	The parent substance of the Herbal Drug, or Herbal preparation.
Example(s)	The parent substance of the Herbal Drug Ginkgo biloba, Leaf is the substance (fresh): *Ginkgo biloba* L., or *Ginkgo biloba* L. (Whole plant). The parent substance of Influenza A virus A/Christchurch/16/2010 (H1N1), NIB-74xp is Influenza A virus A/Christchurch/16/2010 (H1N1).
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	For Herbal Drugs, Herbal preparations and Vaccines this element shall be Mandatory.

6.9.8 Country of origin (Conditional)

Table 81 — Country of Origin

User Guidance	The country where the plant material is harvested or the countries where the plasma is sourced from as laid down in accordance with the Plasma Master File. For "Plasma-derived substances" the attribute country of origin provides information about the countries used for the manufacturing of the Cryopoor plama or Cryoprecipitate.
Example(s)	NL, DE, FR, ES, US. This is in line with Table G1 of the Annex G and it is the largest collection of countries
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	This attribute is mandatory when the substance name type is Herbal or Plasma-derived. When the information for Herbals is provided at the substance level it is not necessary to provide the same information again at the Specified Group 1 information level.

6.9.9 Geographical location (Conditional)

Table 82 — Geographical location

User Guidance	The place/region where the plant is harvested or the places/regions where the animal source material has its habitat.
Example(s)	Shaanxi Province, China
Conformance	CONDITIONAL
Data Type	ST

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Business Rule(s)	This element is not applicable for blood/plasma-derived substances.

6.9.10 Development stage (Conditional)

Table 83 — Development stage

User Guidance	Stage of life for animals, plants, insects and micro-organisms. This information should be provided only when the substance is significantly different in these stages (e.g. foetal bovine serum).
Example(s)	foetus, infant, juvenile, adult, senescent, leafing, pre-flowering, flowering, fruiting, mature development stage, mature animal
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	If it is a distinguishing factor for the production of the substance then the Development Stage should be provided.

6.9.11 Part Description (Conditional)

Information of the part of the material used to produce the substance should be provided by means of the following data elements.

6.9.11.1 Part (Mandatory)

Table 84 — Part

User Guidance	Entity of anatomical origin of source material within an organism.
Example(s)	Cartilage, Root and Stolon, whole plant is considered as a part, Aerial part of the plant, Leaf, Tuberous Root, whole animal, venom, intestinal mucosa
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	Depending on the Source Material Type values (e.g. human/mammalian or plant) the relevant controlled vocabulary applies (e.g. organism or plant). A controlled vocabulary for plant parts is maintained by Kew Gardens Medicinal Plant Names Services.

6.9.11.2 Part location (Conditional)

Table 85 — Part location

User Guidance	The detailed anatomic location when the part can be extracted from different anatomical locations of the organism. When multiple alternative locations may apply, the Part Description class will be repeated for each value.
Example(s)	For cartilage: knee, elbow, stomach, shoulder
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	Applicable only if 'Source Material Type' is human or mammalian. Not applicable for Herbals.

6.9.11.3 Reference source (Conditional)

The reference source information should be captured as described in 5.4.

6.9.11.3.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7.

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6.9.12 Fraction description (Conditional)

Many complex materials are fractions of parts of plants, animals, or minerals. Fraction elements are often necessary to define both Substances and Specified Group 1 Substances. For substances derived from Plants, fraction information will be captured at the Substance information level (e.g. Oils, Juices and Exudates). Additional information for Extracts, such as extraction solvent composition, will be captured at the Specified Substance Group 1 information level. For plasma-derived products fraction information will be captured at the Substance and the Specified Substance Group 1 levels. If there is a fraction, the class Fraction Description is mandatory.

6.9.12.1 Fraction (Conditional)

Table 86 — Fraction

User Guidance	This element is capturing information about the fraction of a plant part, or human plasma for fractionation.
Example(s)	oils; juice; exudates; liquid or dry extract; polyclonal antibodies; serum; Cryopoor plasma; Cryoprecipitate, faecal fraction, body fraction; water soluble freeze-dried extract; water soluble extract; process flow 'N'
Conformance	CONDITIONAL
Data Type	ST

6.9.12.2 Material type (Conditional)

Table 87 — Material type

User Guidance	The specific type of the material constituting the component. For Herbal preparations, the particulars of the extracts (liquid/dry) are described in Specified Substance Group 1.
Example(s)	Lipid; Phospholipid; Protein; Nucleic acid; Herbal; Liquid/Dry Herbal extract; Herbal part; Biological fluid; Herbal extract; Liquid Herbal Extract; Dry Ethanolic Extract; Herbal, Leaf; Botanical, Herbal, Polysaccharide
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	When the herbal substance is derived from a fraction of the plant, the description of the fraction is required.

6.9.12.3 Reference Source (Conditional)

The reference source information should be captured as described in 5.4.

6.9.12.3.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7.

6.9.13 Organism (Conditional)

This subclause describes the organism which the substance is derived from. For vaccines, the parent organism shall be specified based on these subclause elements. As an example, full taxonomy will be described for the Substance Name: *Ginkgo biloba* L., Leaf.

Organism Taxonomy

Substances of organic origin, such as plants and animals, should be defined simply by taxonomic information and the organism part. Taxonomic information, particularly the scientific name of an organism (usually a species, but may be a genus or an intraspecies), is essential for defining such substances in medicinal products.

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The Kew Gardens Medicinal Plant Names Services (MPNS) should be the authoritative source for all scientific names of plants (see E.2.2 for further details). The expert opinion for fungi should be obtained from Species Fungorum (http://www.speciesfungorum.org/) which is managed and maintained by Kew Gardens. Taxonomic information for most other organisms is available through Catalogue of Life (COL, currently 1,600,000+ organsims, http://www.catalogueoflife.org/col/) and its 151 contributing source databases. The most notable contributors are Kew Gardens and the Integrated Taxonomic Information System (www.itis.gov). COL has integrated the source datasets into a common seven level taxonomic tree using an eight-kingdom model and includes intraspecifics where relevant. For organisms omitted in the above sources, NCBI taxonomy (http://www.ncbi.nlm.nih.gov/taxonomy) is the most useful source database.

The higher levels of taxonomy are useful but all levels above family are not required for organism definition. The primary definition of organism is the combination of genus and species together with the describing author and family in that order providing validation. Intraspecific type, description and hybrid characteristics are also definitional where appropriate. The organism should be described as whole with no other characteristics. Because taxonomy is continuously changing, new organism identifiers should only be generated after analysing potential collisions with existing identifiers using the above public datasets and/or conferring with appropriate taxonomic experts. Developmental stage, part and viral strain characteristics should be associated with separate identifiers that refer back to the whole organism parent substance.

6.9.13.1 Family (Conditional)

Table 88 — Family

User Guidance	The family of an organism should be specified.
Example(s)	Ginkgoaceae
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	This is implied by the species and is referenced from an appropriate terminology/taxonomy, e.g. Kew Gardens Medicinal Plant Names Services for plants. Catalogue of Life typically captures complete taxonomy in a manner consistent with this standard.

6.9.13.2 Genus (Conditional)

Table 89 — Genus

User Guidance	The genus of an organism should be specified; refers to the Latin epithet of the genus element of the plant/animal scientific name; it is present in names for genera, species and intraspecies.
Example(s)	*Ginkgo; Harpagophytum*
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	

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6.9.13.3 Species (Conditional)

Table 90 — Species

User Guidance	The species of an organism should be specified; refers to the Latin epithet of the species of the plant/animal; it is present in names for species and intraspecies.
Example(s)	*Biloba; procumbens*
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	For Herbals, this element shall be Mandatory. They shall be specified as a code from an appropriate taxonomy terminology (e.g., the Catalogue of Life, Kew Gardens Medicinal Plant Names Services for plants or NCBI Taxonomy ID).

6.9.13.4 Intraspecific type (Optional)

Table 91 — Intraspecific type

User Guidance	The Intraspecific type of an organism should be specified.
Example(s)	cv. (cultivar), var. (variety), serotype, strain, subsp. (subspecies); cell line; year of isolation
Conformance	OPTIONAL
Data Type	CD
Business Rule(s)	

6.9.13.5 Intraspecific description (Conditional)

Intraspecific information should be used to describe strains, serotypes, varieties, cultivars and cell lines. Often there is not a naming or taxonomic authority for this information. Standardized formats for this information may be developed. The actual intraspecific information should also be captured in the naming of these substances and synonyms should be maintained to help to identify intraspecific information and avoid duplication. For plants, the intraspecific description will be the variety or subspecies name from the Medicinal Plant Names Services portal, and for other organisms, such as animals, the appropriate taxonomy will be used.

Table 92 — Intraspecific description

User Guidance	The intraspecific description of an organism should be specified based on a controlled vocabulary. For Influenza Vaccine, the intraspecific description shall contain the syntax of the antigen in line with the WHO convention.
Example(s)	A/BRISBANE/59/2007(H1N1)
Conformance	CONDITIONAL
Data Type	ST

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6.9.13.6 Author (Conditional)

This class captures information of the author of an organism species.

6.9.13.6.1 Author type (Conditional)

Table 93 — Author type

User Guidance	The type of author of an organism species should be specified. The parenthetical author of an organism species refers to the first author who published the plant/animal name (of any rank). The primary author of an organism species refers to the first author(s), who validly published the plant/animal name.
Example(s)	Species parenthetical author, Species primary author
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	All names should have a primary author to avoid ambiguity, but not every name will have a parenthetical author.

6.9.13.6.2 Author description (Conditional)

Table 94 — Author description

User Guidance	The author of an organism species should be specified. The author year of an organism shall also be specified when applicable; refers to the year in which the first author(s) published the intraspecific plant/animal name (of any rank).
Example(s)	L.; Sch.Bip; Linnaeus, 1766
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	

6.9.13.7 Organism general (Conditional)

6.9.13.7.1 Kingdom (Conditional)

Table 95 — Kingdom

User Guidance	The kingdom of an organism should be specified.
Example(s)	Plantae
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	This is derived from the species and is referenced from an appropriate terminology/taxonomy. Catalogue of Life typically captures complete taxonomy in a manner consistent with this standard.

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6.9.13.7.2 Phylum (Conditional)

Table 96 — Phylum

User Guidance	The phylum of an organism should be specified.
Example(s)	Tracheophyta
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	This is derived from the species and is referenced from an appropriate terminology/taxonomy. Catalogue of Life typically captures complete taxonomy in a manner consistent with this standard.

6.9.13.7.3 Class (Conditional)

Table 97 — Class

User Guidance	The class of an organism should be specified.
Example(s)	Mammalia, Maxillopoda, Sauropsida. Ginkgoopsida
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	This is implied by the species and is referenced from an appropriate terminology/taxonomy. Catalogue of Life typically captures complete taxonomy in a manner consistent with this standard.

6.9.13.7.4 Order (Conditional)

Table 98 — Order

User Guidance	The order of an organism should be specified,
Example(s)	Ginkgoales
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	This is implied by the species and is referenced from an appropriate terminology/taxonomy. Catalogue of Life typically captures complete taxonomy in a manner consistent with this standard.

6.9.13.8 Hybrid (Conditional)

6.9.13.8.1 Hybrid species maternal organism ID (Optional)

Table 99 — Hybrid species maternal organism ID

User Guidance	The identifier of the maternal species constituting the hybrid organism should be specified based on a controlled vocabulary. For plants, the parents aren't always known, and it is unlikely that it will be known which is maternal and which is paternal.
Conformance	OPTIONAL
Data Type	ST
Business Rule(s)	

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6.9.13.8.2 Hybrid species maternal organism name (Optional)

Table 100 — Hybrid species maternal organism name

User Guidance	The name of the maternal species constituting the hybrid organism should be specified. For plants, the parents aren't always known, and it is unlikely that it will be known which is maternal and which is paternal.
Conformance	OPTIONAL
Data Type	ST
Business Rule(s)	

6.9.13.8.3 Hybrid species paternal organism ID (Optional)

Table 101 — Hybrid species paternal organism ID

User Guidance	The identifier of the paternal species constituting the hybrid organism should be specified based on a controlled vocabulary. For plants, the parents aren't always known, and it is unlikely that it will be known which is maternal and which is paternal.
Conformance	OPTIONAL
Data Type	ST
Business Rule(s)	

6.9.13.8.4 Hybrid species paternal organism name (Optional)

Table 102 — Hybrid species paternal organism name

User Guidance	The name of the paternal species constituting the hybrid organism should be specified. For plants, the parents aren't always known, and it is unlikely that it will be known which is maternal and which is paternal.
Conformance	OPTIONAL
Data Type	ST
Business Rule(s)	

6.9.13.8.5 Hybrid type (Conditional)

Table 103 — Hybrid type

User Guidance	The hybrid type of an organism should be specified.
Example(s)	hybrid unknown lineage, hybrid known lineage
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	If the hybridization step is present, the type of hybridization should be provided.

6.10 Modification (Conditional)

The Modification subclause is to be used to describe irreversible modifications to material (e.g. PEGylation, phosphorylation, hydrogenation) or reversible modifications that may affect tertiary structure. The modifications may be physical, chemical, enzymatic, etc. Modifications may be described by their structural result (substitution of moieties to residues, etc.) or by the process, reagents, or processing time if a specific structural modification cannot be determined (e.g. aggregated albumin).

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A minimal description of the modification process shall be generated when a definitive structural modification cannot be determined.

This subclause applies to:

— Nucleic Acids;

— Proteins;

— Polymer;

— Structurally Diverse Substances;

— Mixture;

— Specified Substance Group 1.

This subclause shall be repeatable to describe each modification occurred on each residue modified.

The information model for the class modification group is shown in Figure 20 — Information model for modifications.

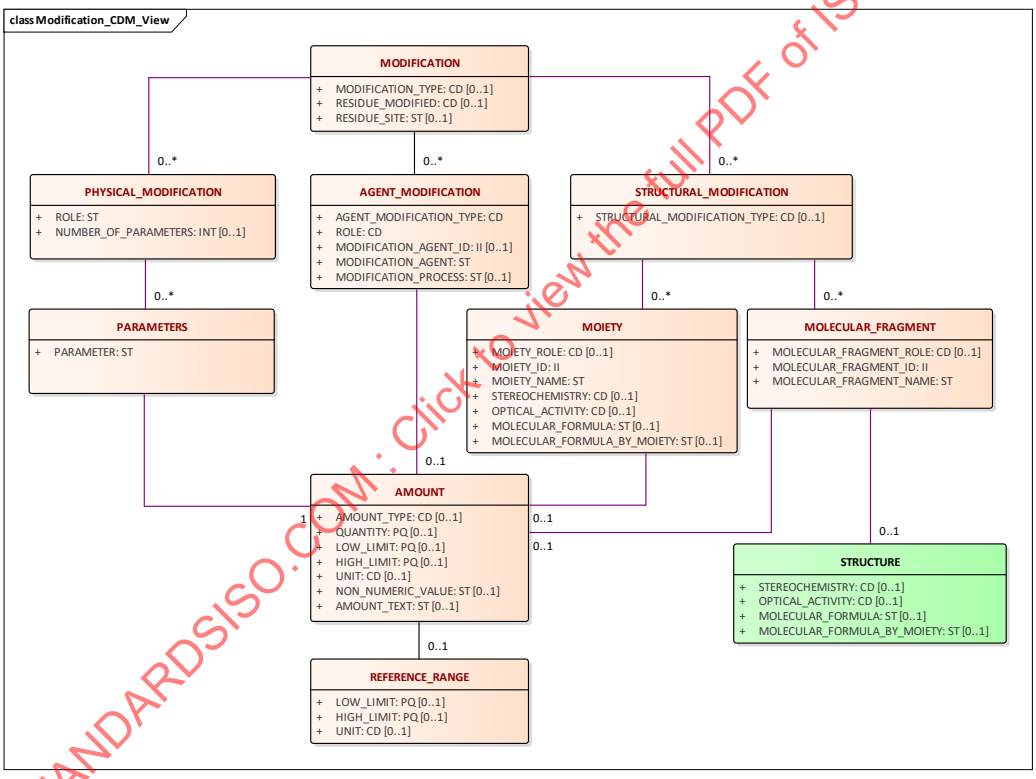


Figure 20 — Information model for Modifications

Modifications will be divided into structural modifications where the existing molecular structure is discretely modified (either covalent modification, ionic modification including salt and solvate formation or modification by chelate formation), physical modifications where no new covalent bonds are formed and agent modifications where the chemical modifications are diverse or unclear.

EXAMPLE Structural modifications are used to describe in principle covalent modifications or essential associations of moieties with a protein, nucleic acid, or structurally diverse material. Covalent modification for a protein, nucleic acid or structurally diverse material typically means an amino acid substitution, a C-/N-terminal modification of a protein or base or 5'-, 3'- modifications of nucleic acids. The tight and/or stoichiometric association of moieties to macromolecular material by ionic forces, chelate formation, van der Waals interactions, or dipole

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moment interactions are also considered structural modifications since they may affect the tertiary structure of the protein/peptide or are an essential element of the drug substance (e.g. a chelated radionuclide). When peptide or nucleic acid chains are tightly associated either through covalent bonds or strong non-covalent interactions (e.g. Factor VIII: Von-Willebrand Factor interactions, Watson-Crick base pairing) they will be described as subunits of the respective protein or nucleic acid.

In case of N-Terminal modification and C-Terminal modification of a Protein subunit, the Modification class is mandatory.

Specifically, information on the modification shall be provided by means of the following descriptors.

6.10.1 Modification type (Conditional)

The modification type becomes apparent by its description. Structural modification is described using the structural elements. Agent and physical modifications are described by a series of elements. Agents are also substances in their own right.

Table 104 — Modification type

User Guidance	The type of the modification should be specified. Modifications will be divided into structural modifications where the existing molecular structure is discretely modified, physical modifications where no new covalent bonds are formed and agent modifications where the chemical modifications are diverse or unclear.
Example(s)	structural modification, agent modification, physical modification
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	In case of N-Terminal modification and C-Terminal modification of a Protein subunit, the Modification class is mandatory.

6.10.2 Residue modified (Conditional)

Table 105 — Residue modified

User Guidance	The amino acid or nucleic acid base that is modified. It may be known that lysine residues are modified but the particular lysine in the sequence may not be known. It should be captured for both specific and non-specific modifications, e.g. sizing carbohydrate polymers by hydrolysis.
Example(s)	Lysine; non-specific modifications; Reducing end of Oligosaccharide; ε-amino, α-amino, guanidinyl, secondary amino, and hydroxyl groups (in decreasing order of reactivity) of amino acids residues of proteins.
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	In case of N-Terminal modification and C-Terminal modification of a Protein subunit, the Modification class is mandatory.

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6.10.3 Residue site (Conditional)

Table 106 — Residue site

User Guidance	The position of specific residue undergone to modifications shall be described.
Example(s)	1_20; Protein unit 1, amino acid at position 20; C-Terminal removal.
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	In case of N-Terminal modification and C-Terminal modification of a Protein subunit, the Modification class is mandatory.

6.10.4 Structural modification (Conditional)

All structurally specific post-translational modifications are expressed as amino acid substitutions. In order to limit ambiguity, all structural substitutions will be represented with a single structural element that contains the amino acid, a linker if present and the conjugate as a single entity. The substituted amino acid is assumed to connect through the alpha amino and the carboxylic acid group. If there is potential ambiguity or if the connectivity is not through the alpha amino acid groups, connection points or atoms should be used. The substituted amino acid will be a substance in its own right. For informational purposes, the linker and conjugate can also be indicated as separate elements. When the sites of modifications are known, they should be listed. For a modification that is not site specific, the extent of modification should be captured. New substances would be created if there are consistent differences in the extent of modification. For example, a monoclonal antibody with an average of two toxins conjugated to it would be a different substance than the same monoclonal antibody with an average of four toxin conjugates.

It should be noted that post-translational modifications, such as glycosylation, phosphorylation, or sulfation that result in microheterogeneity will not be described at the substance level, but could be described at the Specified Substance level. Microheterogeneity of proteins can be captured at the Specified Substance Group 1 level if the type of glycosylation is necessary to distinguish the material.

EXAMPLE Substitution of N terminal amino acid by pyroglutamic acid.

Structural modification is conditional and becomes mandatory when the type of modification as described in 5.10.1 refers to a structural modification, then the following specifications apply.

6.10.4.1 Structural modification type (Conditional)

Table 107 — Structural modification type

User Guidance	The Type of structural modification should be described.
Example(s)	Amino Acid Substitution of the peptide/protein, Salt, hydrate, solvate formation, chemical substitution, moiety, amino acid sulphation, nucleic acid base substitution, Reductive Amination
Conformance	CONDITIONAL
Data Type	CD

6.10.4.2 Moiety (Conditional)

For structural modifications, the moiety shall be provided based on the specifications provided in 6.1.6.

6.10.4.2.1 Amount (Conditional)

Amount should be captured as described in 5.8.

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6.10.4.2.1.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

6.10.4.3 Molecular fragment (Conditional)

For covalent modifications of proteins, nucleic acids, polymers or even structurally diverse material, fragments will be created and used to capture the extent of the modification.

6.10.4.3.1 Molecular fragment role (Conditional)

For modified proteins, covalent modifications should be captured as a fragment modification. For many protein modifications, the fragment will typically be a modified amino acid.

Table 108 — Molecular fragment role

User Guidance	The role of the fragment.
Example(s)	N-Terminal Pyroglu Formation; C-Terminal Modification; N-Terminal Modification; C-Terminal Lysine Removal; Post Translational Modification; Nucleotide Base Modification; Toxin Conjugation
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	

6.10.4.3.2 Molecular fragment ID (Mandatory)

Each fragment shall be identified with a Substance ID.

Table 109 — Molecular fragment ID

User Guidance	The unique identifier assigned to the substance representing the fragment based on the ISO 11238 substance controlled vocabulary.
Conformance	MANDATORY
Data Type	II
Values Allowed	ISO 11238 Substance ID
Business Rule(s)	If the Molecular Fragment ID is not available, a new ID shall be assigned with the submission.

6.10.4.3.3 Molecular fragment name (Mandatory)

Each fragment shall have at least one name associated with the fragment ID.

Table 110 — Molecular fragment name

User Guidance	The name of the moiety shall be provided.
Example(s)	Tyrosine O-sulfate; Cysteine-VC-MMAE; Glycinamide; 3-Mercaptopropionic acid; Prolinamide; Pyroglutamic acid (pE); Hydroxypropoxy Fragment; Methoxy Fragment
Conformance	MANDATORY
Data Type	ST
Values Allowed	ISO 11238 substance name.
Business Rule(s)	ISO 11238 substance preferred name is selected as default value. The substance name is implicit and derived from the Moiety ID described in .

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6.10.4.3.4 Amount (Conditional)

Amount shall be captured as described in 5.8. Typically, there will be an Amount Type relationship that indicates the degree of fragment substitution. Typically, a single moiety will be assigned the value 1 and ranges for moieties that are stoichiometric will be relative to.

6.10.4.3.5 Structure (Conditional)

Structure should be captured as described in 5.7.

For the use case of glycans, the structure of the molecular fragments of the monoclon antibody as described at the Specified Substance Group 1 level shall be provided since they are shall have been pre-registered.

6.10.5 Agent modification (Conditional)

This type describes modifications that do not result in the addition of a single well-defined chemical entity (i.e. formaldehyde, glutaraldehyde treatment, peroxide treatment). In the inactivation of vaccines or treatment of tissue matrices, agent modification is essential for the description of these materials. Agent modification is also used in describing the culturing of cells that result in phenotypic differentiation. The agent modification could also be used to capture the actual agent that reacts with a protein that results in the attachment of a well-defined chemical fragment or entity. The following descriptors would be used to define agent modifications.

6.10.5.1 Agent modification type (Mandatory)

Table 111 — Agent modification type

User Guidance	Refers to the type of the agent caused the modification.
Example(s)	Chemical, enzymatic, immunological, organism, UV radiation
Conformance	MANDATORY
Data Type	CD

6.10.5.2 Role (Mandatory)

Table 112 — Role

User Guidance	For proteins, agent (a chemical that results in non-specific modifications of a protein) or moiety (a specific moiety added to a protein molecule) are used to describe the function of the modification.
Example(s)	Antigen, linker, conjugate, inactivation, antigen priming, end-cap polymerization, sizing of Polysaccharide into Oligosaccharides, inactivation of antigen to reduce allergenicity
Conformance	MANDATORY
Data Type	CD

6.10.5.3 Modification agent ID (Conditional)

Table 113 — Modification agent ID

User Guidance	Unique identifier for modifying agent.
Example(s)	UNII code, Global Substance ID
Conformance	CONDITIONAL
Data Type	II
Values Allowed	ISO 11238 Substance ID

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6.10.5.4 Modification agent (Conditional)

Table 114 — Modification agent

User Guidance	Established or primary name of the modifying agent.
Example(s)	Formaldehyde; sodium hydroxide; glutaraldehyde, hydrochloric acid
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	ISO 11238 substance name
Business Rule(s)	Implicitly derived from the value of the Modification Agent ID.

6.10.5.5 Modification process (Conditional)

Table 115 — Modification process

User Guidance	Refers to the description of the modification process.
Example(s)	Cell culture, UV irradiation, Basic hydrolysis, Depolymerization of Carbohydrates
Conformance	CONDITIONAL
Data Type	ST

6.10.5.6 Amount (Conditional)

Amount should be captured as specified in Subclause 5.8.

6.10.5.6.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

6.10.6 Physical Modification (Conditional)

The physical modification is conditional; when applicable, the information shall be provided by means of the following descriptors.

6.10.6.1 Role (Mandatory)

Table 116 — Role

User Guidance	Shall be used to describe the function of the modification.
Example(s)	'Micronization', 'Isolation of Cryoprecipitate by Centrifugation', 'Removal of Cryoprecipitate by Centrifugation', 'Isolation of Cryopoor plasma process flow 'N' by Precipitation and absorption steps by the modified Cohn fractionation process', 'Micronization of animal part'
Conformance	MANDATORY
Data Type	ST

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6.10.6.2 Number of parameters (Conditional)

Table 117 — Number of parameters

User Guidance	The number of parameters that is going to be described as a result of the modification should be provided.
Example(s)	For thermal denaturation two parameters, temperature and time, are typically captured.
Conformance	CONDITIONAL
Data Type	INT
Business Rule(s)	This number can be counted and is never explicitly represented. This value is calculated implicitly.

6.10.6.3 Parameters (Conditional)

Primarily used for nonspecific modification, specifies how a modification is quantified or extent of physical treatment; when applicable, the information shall be provided by means of the following descriptors.

6.10.6.3.1 Parameter (Mandatory)

Table 118 — Parameter

User Guidance	Refers to the conditions under which the modification has been produced.
Example(s)	time, temperature, fractionation condition, centrigugation temperature, thaw temperature
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	Required parameter depend on process.

6.10.6.3.2 Amount (Mandatory)

Amount shall be captured as described in 5.8.

6.10.6.3.2.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

6.11 Property (Conditional)

The subclause serves to provide information related to biological, physical or chemical characteristics associated with a substance. This information can be essential for the definition of each type of substance when structural elements are not sufficient to distinguish between similar substances.

EXAMPLE The pH of magnesium aluminometasilicate is necessary to distinguish low and high pH substances.

EXAMPLE Viscosity is used to distinguish many polymers and should always be reported if known.

EXAMPLE The acid value of olive oil, refined is necessary to distinguish the substance from olive oil, virgin. The acid value of olive oil refined must be 10 times lower than the value of olive oil, virgin.

Properties can have values that are quantitative, semi-quantitative or qualitative. For semi-qualitative values, a consistent scale should be used.

EXAMPLE For chemical substances; elemental analysis, mass and NMR spectra can be very helpful in determining whether two materials are different chemical substances and also in verifying that the xxx. molecular

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structure is correct. Solubility information, melting, boiling and critical points, partition coefficients (logKow), and pKa values should also be supplied if known.

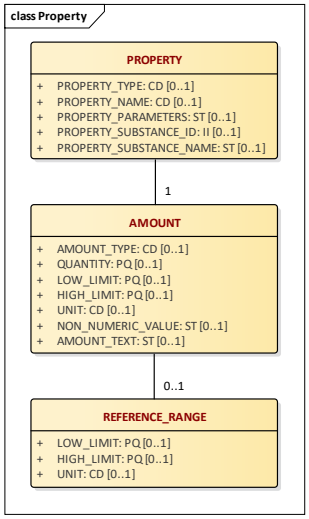


Figure 21 — Information model for Property

The property information shall be provided by means of the following data elements:

6.11.1 Property type (Conditional)

Each property will be associated with a single property type and the list of property types should be maintained.

Table 119 — Property type

User Guidance	Type of the property for which the information is provided.
Example(s)	physical, chemical, enzymatic, immunological
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	Each property shall be provided with a fully terminologically defined concept for measurements. Such definition would include any necessary "types" such as this.

6.11.2 Property name (Conditional)

Table 120 — Property name

User Guidance	The name of the property should be specified based on a controlled vocabulary.
Example(s)	viscosity, pH, cell surface antigen, spectra, pK_a, UV absorption maxima, isoelectric point, relative density, Percent MenA Polysaccharide eluted before K_D = 0,50
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	A fully defined coded concept shall always be provided.

6.11.3 Property parameters (Conditional)

Parameters are often associated with properties and should be captured. In order to compare or distinguish substances it is important that measurements are taken using the same parameters.

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Parameters are not elements that will typically be searchable, but standard formats for given property measurements may be defined.

Table 121 — Property parameters

User Guidance	A field that should be used to capture parameters that were used in the measurement of a property.
Example(s)	For Viscosity, solvent concentration and temperature should be captured as a single entity. Measured at pH range of 2,5 to 10,5 Measured at 20 °C and a pH of 7,1
Conformance	CONDITIONAL
Data Type	ST

6.11.4 Property substance ID (Conditional)

Table 122 — Property substance ID

User Guidance	Substance ID of a substance upon which a defining property depends; the identifier of the substance related to a defining property shall be described where applicable.
Example(s)	Solubility in Water, the Substance ID for Water shall be specified.
Conformance	CONDITIONAL
Data Type	II
Values Allowed	ISO 11238 Substance ID

6.11.5 Property substance name (Conditional)

Table 123 — Property substance name

User Guidance	To be used to identify a substance related to a defining property, for example: cell surface antigens (the Substance ID for CD4 would be captured to defined CD4 positive cells).
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	ISO 11238 substance name
Business Rule(s)	The preferred term will be the default value implicitly derived from the Substance ID ().

6.11.6 Amount (Mandatory)

The information related to the amount shall be provided as per specification described in 5.8. The non-numeric value in the case of spectra would be the actual spectra or a reference to the document containing the actual spectra.

6.11.6.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

6.12 Version (Mandatory)

This subclause shall provide information on the version of the substance. Where no “Version Number” and “Effective Date” have been assigned by an authority source, the version number shall be set as 0 with the date set as the date of initial submission of the substance. Any changes or updates to a given substance will result in a new version. This could include changes in the definition of the substance or the addition

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of names or codes. The version of substances should be tracked. Submitters should also indicate if it is a new version of a previous submission.

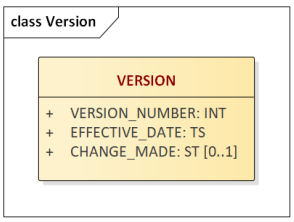


Figure 22 — Information model for Version

6.12.1 Version number (Mandatory)

Table 124 — Version number

User Guidance	The number of the version of the substance shall be provided.
Example(s)	1, 2, 3, 99
Conformance	MANDATORY
Data Type	INT
Business Rule(s)	If same document set exists, version shall be greater than the last submitted version. For maintainance purpose, the version number shall be updated after the effective date.

6.12.2 Effective date (Mandatory)

Table 125 — Effective date

User Guidance	The date when the substance was effective should be provided in line with the ISO 8601 date format. This shall be defined when the substance is generated or modified.
Example(s)	20110219
Conformance	MANDATORY
Data Type	TS
Business Rule(s)	The value may be implicitly derived.

6.12.3 Change made (Conditional)

Table 126 — Change made

User Guidance	The description of the updates or changes of the substance should be specified. The field will be left empty when first insert of substance.
Example(s)	Update to previous version to include additional translation.
Conformance	CONDITIONAL
Data Type	ST

7 Substance definitions

All material will be traced back to one of the five types of substances or a mixture as described below. All substances will be described as a single substance type or as a mixture. The Annexes give additional examples of how to choose the correct type of substance and what specific elements to submit.

If the Substance Type as defined in 5.2.1 is equal to Chemical substance, the following data elements and conformances apply.

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7.1 Chemical substance

Chemical substances are a single substance type whose primary defining element is the molecular structure. Chemical substances shall be defined on the basis of their complete covalent molecular structure; the presence of a salt (counter-ion) and/or solvates (water, alcohols) or co-crystal is also captured. Purity, grade, physical form or particle size are not taken into account in the definition of a chemical substance or in the assignment of a Substance ID.

EXAMPLE Purified Water, Water for Injection, Sterile Water for Injection USP, ice and steam all map to the same substance Water, but would be separate Specified Substances Group 1.

In order to assign a Substance ID for a chemical substance, a complete covalent structure with all stereochemistry (R or S and E or Z) defined shall be submitted. The stoichiometry (mole ratio) of counter-ions or solvates or co-crystals present in the material shall also be provided in the structural representation.

The molecular representation (molfile, SMILES, InChI, CDX) of the substance shall be provided with all stereochemistry assigned or sites of unknown stereochemistry identified. An actual image of the structure should be provided in an accompanying document.

The information typically provided to INN, USAN, BAN or JAN to assign a nonproprietary name is typically sufficient to define chemical substances. Active substances and excipients are typically defined in accordance with INN, JAN, or USAN definitions or European Pharmacopoeia (Ph.Eur.), Japanese Pharmacopoeia (JP), or United States Pharmacopoeia (USP/NF) monographs. The labelling requirements provided by monographs should be taken into account when defining and distinguishing substances. Information beyond monograph requirements may occasionally be necessary to distinguish substances.

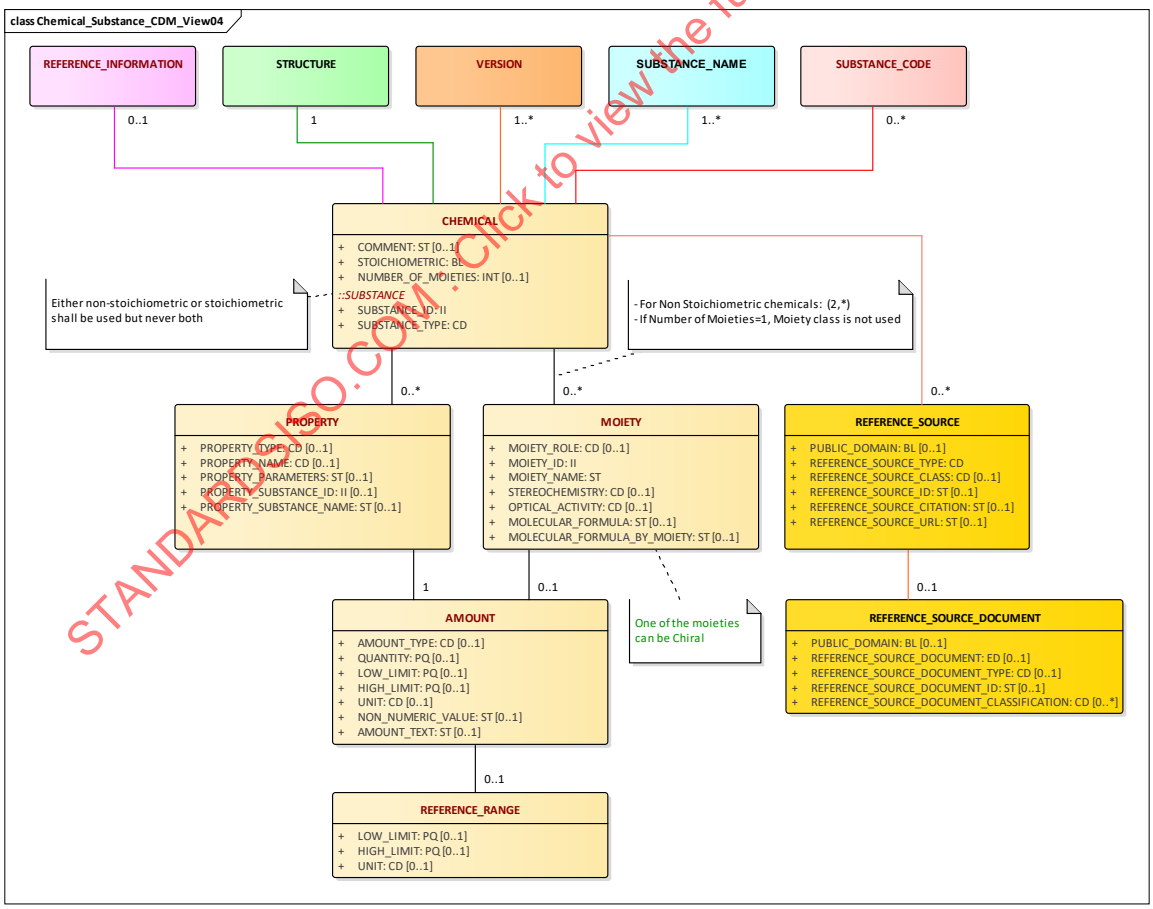


Figure 23 — Information model for the Chemical Substance

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The molecular structure, the molecular formula (molecular formula by moiety), the molecular weight and optical activity, together with the representation of the stereochemistry are mandatory elements to be provided. Although the molecular weight can be derived from the structure, this element should be presented at the substance level for chemical substances in order to substantiate the provided structural information (e.g. by mass spectrometry).

In addition, the molecular formula should be described according to the moieties even for stoichiometric substances. See above Molecular formula by moiety and Molecular formula, which is meant to be equal to the sum of molecular formula by moiety.

7.1.1 Structure (Mandatory)

The information related to the structure shall be provided as per the specification described in 5.7.

Chemical substances can either be stoichiometric or non-stoichiometric (i.e. substances with variable or unknown stoichiometry). Variable or unknown stoichiometry should be indicated by brackets without a number associated with the brackets around moieties where the stoichiometry is either variable or unknown.

For ingredients in drug products, a preferred format may be specified (molfile, SMILES, etc.) for the transmittal of information. Although most chemicals exist primarily with a single structural representation, there are a number of substances that have multiple structural representations in equilibrium. This is illustrated in the glucose (Dextrose) example above, see Figure 14.

7.1.2 Stoichiometric/Non-stoichiometric chemicals

Stoichiometric chemical substances are substances that contain complete chemical structures and definite stoichiometric ratios among moieties (see 6.1.2.1 for details). Non-stoichiometric chemical substances are substances that do not have defined stoichiometry (see 6.1.2.2 for further information).

Stoichiometry describes if a substance can be represented as single covalent structural moiety or a salt or solvate with a defined and constant ratio of ions or molecules and solvents.

In the case of a substance consisting of one moiety (e.g. base, acid, ester) there is (per definition) one compound. In this case only one moiety shall be provided.

7.1.2.1 Stoichiometric chemicals

As described above, stoichiometric chemical substances are substances that contain complete chemical structures and definite stoichiometric ratios among moieties. Stoichiometric ratios between moieties should be whole integers and not fractions. They can be defined by a single representation of the complete molecular structure and a stereochemistry descriptor. The representation can be of one of the four types listed above. The following examples of defining elements for various types of chemical substances help illustrate the information needed to define substances. There are a variety of drawing tools that can generate any of the formats described.

EXAMPLE Ethanol is an example of an achiral substance and can be completely defined by either one of the three following representations:

InChI Representation	STRUCTURAL REPRESENTATION TYPE: “InChI”
	STRUCTURAL REPRESENTATION: “INCHI=1/C2H6O/c1-2-3/h3H,2H2,1H3”
	STEREOCHEMISTRY: “ACHIRAL”
SMILES Representation	STRUCTURAL REPRESENTATION TYPE: “SMILES”
	STRUCTURAL REPRESENTATION: “CCO”
	STEREOCHEMISTRY: “ACHIRAL” (same as above)
Molfile representation	STRUCTURAL REPRESENTATION TYPE: “MOL”
	STRUCTURAL REPRESENTATION:

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```
 3  2  0  0  0  0  0  0  0  0999 V2000
  3.9063  -7.3125   0.0000 C  0  0  0  0  0  0  0  0  0  0  0  0
  4.6223  -6.8991   0.0000 C  0  0  0  0  0  0  0  0  0  0  0  0
  5.3383  -7.3125   0.0000 O  0  0  0  0  0  0  0  0  0  0  0  0
 1  2  1  0  0  0  0
 2  3  1  0  0  0  0
M  END
```

STEREOCHEMISTRY “ACHIRAL” (same as above)

Levofloxacin Sodium. This is an example of a chiral substance and salt. An InChI, SMILES or Molfile is sufficient to define this substance.

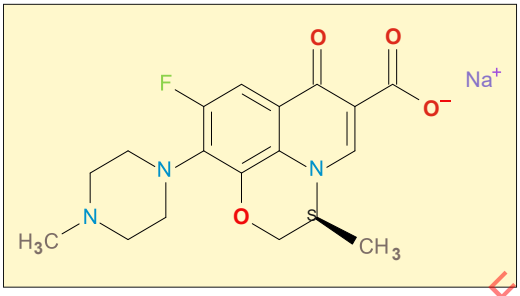


Figure 24 — Graphical representation of Levofloxacin Sodium

InChI Representation	STRUCTURAL REPRESENTATION TYPE: “INCHI”
	STRUCTURAL REPRESENTATION: “InChI=1S/C18H20FN3O4.Na/c1-10-9-26-17-14-11(16(23)12(18(24)25)8-22(10)14)7-13(19)15(17)21-5-3-20(2)4-6-21;/h7-8,10H,3-6,9H2,1-2H3,(H,24,25);/q;+1/p-1/t10-;/m0./s1”
	STEREOCHEMISTRY “CHIRAL”
SMILES Representation	
	STRUCTURAL REPRESENTATION TYPE: “SMILES”
	STRUCTURAL REPRESENTATION: “C[C@H] STEREOCHEMISTRY: “CHIRAL”1COc2c3n1cc(c(=O)c3cc(c2N4CCN(CC4)C)F)C(=O)[O-].[Na+]”
Molfile Representation	STRUCTURAL REPRESENTATION TYPE: “MOL”
	STRUCTURAL REPRESENTATION:

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```
27 29  0  0  1  0  0  0  0  0999 V2000
   14.5167   -9.0507    0.0000 N   0  0  0  0  0  0  0  0  0  0  0  0
   15.1250   -7.9548    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   13.8500   -8.7215    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   13.2625   -9.0840    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   13.8500   -8.0048    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   15.1250   -8.7048    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   14.4667   -7.6340    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   12.6334   -8.7673    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   13.2625   -9.8506    0.0000 O   0  0  0  0  0  0  0  0  0  0  0  0
   12.6334   -8.0048    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   13.2292   -7.6548    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   12.0167   -9.1298    0.0000 N   0  0  0  0  0  0  0  0  0  0  0  0
   15.8250   -7.6007    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   14.5167   -9.7840    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   10.7417   -9.8965    0.0000 N   0  0  0  0  0  0  0  0  0  0  0  0
   14.4667   -6.8965    0.0000 O   0  0  0  0  0  0  0  0  0  0  0  0
   13.9125  -10.1632    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   12.0167   -9.8798    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   11.3584   -8.7757    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   15.8250   -6.9548    0.0000 O   0  0  0  0  0  0  0  0  0  0  0  0
   11.9542   -7.7132    0.0000 F   0  0  0  0  0  0  0  0  0  0  0  0
   10.7417   -9.1340    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   11.4000  -10.2465    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   16.6458   -7.9631    0.0000 O   0  5  0  0  0  0  0  0  0  0  0  0
   10.0792  -10.1715    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   15.3500  -10.3215    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   17.3000   -7.9630    0.0000 Na  0  3  0  0  0  0  0  0  0  0  0  0
 21 10  1  0  0  0  0
 22 19  1  0  0  0  0
 23 18  1  0  0  0  0
 24 13  1  0  0  0  0
 25 15  1  0  0  0  0
 14 26  1  1  0  0  0
  4  9  1  0  0  0  0
  5  7  1  0  0  0  0
  8 10  2  0  0  0  0
 15 23  1  0  0  0  0
  2  6  2  0  0  0  0
  3  1  1  0  0  0  0
  4  3  2  0  0  0  0
  5  3  1  0  0  0  0
  6  1  1  0  0  0  0
  7  2  1  0  0  0  0
  8  4  1  0  0  0  0
  9 17  1  0  0  0  0
 10 11  1  0  0  0  0
 11  5  2  0  0  0  0
 12  8  1  0  0  0  0
 13  2  1  0  0  0  0
 14  1  1  0  0  0  0
 15 22  1  0  0  0  0
 16  7  2  0  0  0  0
 17 14  1  0  0  0  0
 18 12  1  0  0  0  0
 19 12  1  0  0  0  0
 20 13  2  0  0  0  0
M  CHG  2  24  -1  27   1
M  END
```

STEREOCHEMISTRY “CHIRAL”

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7.1.2.2 Non-stoichiometric

The subclause applies to chemical substances that do not have defined stoichiometry.

Every non-stoichiometric substance will have more than one moiety. Each moiety will be enclosed in brackets indicating stoichiometry where known and transmitted in a single structural representation. Every non-stoichiometric moiety will have a complete structural representation and also be described as a substance in its own right. If ranges of amounts for the non-stoichiometric moieties are known, they will be preferably captured as mole ratios or weight per cent if mole ratios cannot be determined.

If the substance type as defined in 5.2.1 is equal to *Chemical substance*, the following data elements and conformances apply in order to assign Substance IDs.

7.1.3 Stoichiometric (Mandatory)

Table 127 — Stoichiometric

User Guidance	This flag shall indicate if the chemical substance is stoichiometric or Non-stoichiometric.
Example(s)	Yes/No
Conformance	MANDATORY
Data Type	BL
Business Rule(s)	

7.1.4 Number of moieties (Conditional)

Table 128 — Number of moieties

User Guidance	The number of moieties specified should be provided. Non-stoichiometric chemical substances shall have at least two moieties. Each moiety shall be represented by a chemical structure.
Example(s)	2
Conformance	CONDITIONAL
Data Type	INT
Business Rule(s)	The numeric value shall be always ≥2; The value is automatically calculated (Implicit) based on the number of Moieties as described in); if the numeric value is equal to 1, the class Moiety shall not be used.

7.1.5 Comment (Optional)

Comments should be used sparingly to capture information that does not fit into other fields. They may be used to indicate that alternate structures exist.

Table 129 — Comment

User Guidance	Any comment can be provided in this field, if necessary.
Conformance	OPTIONAL
Data Type	ST

7.1.6 Moiety (Conditional)

The moiety subclause serves for the description of both the moiety and the other fragment constituting the substance, see Figure 25.

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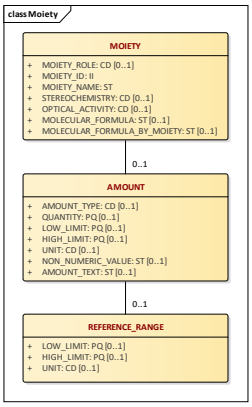


Figure 25 — Information model for Moiety

The Element Group Moiety is attached to the element class Chemical in order to describe a salt, solvates and co-crystals relationship to the active moiety in an unambiguous way with respect to the description of the molecular formula and sometimes the official names. The Element Group Amount is attached to Moiety. This will help to describe salts, solvates, hydrated substances and co-crystallising agents in a more unambiguous way with respect to the description of the molecular formula and sometimes official names.

EXAMPLE Aluminium Sesquichlorohydrex Propylene Glycol is defined by relationships between five moieties, the aluminium cation, chloride and hydroxide ions, propylene glycol and water; three of the five moieties have mole ratios to each other. The ratio of aluminium cation to chloride to hydroxide is 2:3:3. The amount of propylene glycol and water is variable and not stoichiometric.

Each moiety within the chemical substance is to be identified and the composition range of the moieties when known is to be provided by means of the following data elements:

If the numeric value of the element 'Number of Moieties' is equal to 1, the class Moiety should not be used; otherwise, the class shall always be mandatory.

7.1.6.1 Moiety role (Conditional)

In addition to the moiety role for chemicals, for many peptides, the moiety role of counter-ions such as acetate should be indicated.

Table 130 — Moiety role

User Guidance	The role of the moiety should be specified if there is a specific role the moiety is playing.
Example(s)	Counter-ion, solvate, hydrate, parent, base, acid, co-crystallising agent
Conformance	CONDITIONAL
Data Type	CD

7.1.6.2 Moiety ID (Mandatory)

Each moiety in a non-stoichiometric substance shall be identified with a Substance ID.

Table 131 — Moiety ID

User Guidance	The unique identifier assigned to the substance representing the moiety based on the ISO 11238 substance controlled vocabulary.
Conformance	MANDATORY
Data Type	II
Values Allowed	ISO 11238 Substance ID

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Business Rule(s)	If not available a new ID will be assigned with the submission.

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7.1.6.3 Moiety name (Mandatory)

Each moiety shall also have at least one name associated with the moiety.

Table 132 — Moiety name

User Guidance	The name of the moiety shall be provided.
Example(s)	Propylene glycol
Conformance	MANDATORY
Data Type	ST
Values Allowed	ISO 11238 substance name.
Business Rule(s)	ISO 11238 substance preferred name is selected as default value. The substance name is implicit and derived from the Moiety ID described in .

7.1.6.4 Stereochemistry (Conditional)

Stereochemistry should be captured as described in 5.7.1.

7.1.6.5 Optical activity (Conditional)

Optical activity should be captured as described in 5.7.2.

7.1.6.6 Molecular formula (Conditional)

Molecular formula should be captured as described in 5.7.3.

7.1.6.7 Molecular formula by moiety (Conditional)

Molecular formula by Moiety should be captured as described in 5.7.4

7.1.6.8 Amount (Conditional)

Typically, there should be an Amount Type relationship between the moieties. A single moiety will typically be assigned the value 1. Ranges of moieties that are stoichiometric will be assigned successive values. Amount should be captured as described in 5.8.

7.1.6.8.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

7.1.7 Property (Conditional)

Property should be captured as specified in 5.11.

7.1.7.1 Amount (Mandatory)

Amount shall be captured as described in 5.8.

7.1.7.1.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

7.1.8 Substance Name (Mandatory)

Names associated with a Specified Substance Group 1 shall be captured as described in 5.3. The name type shall be specified and, for Official Names, the same format should be followed 5.3.6.

7.1.9 Substance Code (Conditional)

Substance Code should be captured as described in 5.5.

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7.1.10 Version (Mandatory)

Version information shall be captured as described in 5.12.

7.1.11 Reference information (Conditional)

Reference information should be captured as described in 5.6.

7.1.12 Reference source (Conditional)

The reference source information should be captured as described in 5.4.

7.1.12.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7.

7.2 Proteins/peptides

A protein is defined as a single unit of a linear amino acid sequence, or a combination of subunits that are either covalently linked or have a defined invariant stoichiometric relationship. This includes all synthetic, recombinant and purified proteins of defined sequence, whether the use is therapeutic or prophylactic. This set of elements will be used to describe albumins, coagulation factors, cytokines, growth factors, peptide/protein hormones, enzymes, toxins, toxoids, recombinant vaccines, and immunomodulators.

Proteins and peptides are defined by their molecular structure based on the amino acid sequence, disulfide linkages, sites and a general type of glycosylation, based on the cell or organism type from which the protein was isolated from or produced (e.g. yeast, plant, mammalian, human). The method of production is generally not a defining element for proteins and peptides. For a given non-glycosylated peptide, whether naturally isolated, produced by recombinant technology, or chemically synthesized, it will be defined as the same substance when there are no resultant differences in the amino acid sequence and disulfide linkages.

EXAMPLE Recombinant and chemically synthesized salmon calcitonin are chemically identical and therefore considered to be the same substance with the same Substance ID.

Proteins that have consistently different types of glycosylation are assigned separate Substance IDs. Human and primate glycosylation differ from other mammalian glycosylation in that terminal sialic acid residues are only acetylated and not glycolated. Glycosylation in human and old-world monkeys also differ from other mammals in lacking the alpha, 1,3-galactose epitopes. Avian, insect, plant, fish and yeast also have consistently different glycosylation. Yeast, plant, insect and avian glycosylation are also significantly different from mammalian and human glycosylation and glycoproteins produced in such systems would each have a separate Substance ID even if the amino acid sequences and disulfide linkages are the same.

EXAMPLE Coagulation Factor VIII isolated from human blood versus that produced by recombinant technology in Chinese hamster ovary (CHO) cells are considered to be different substances even if they have the same amino acid sequence and disulfide linkages. The glycosylation type would distinguish these types.

In defining proteins, microheterogeneity is typically not taken into account in the assignment of a Substance ID. Microheterogeneity generally refers to slight differences in the structure of proteins. Most of these differences are due to post-translational modification. There can also be slight differences in the ends of molecules due to differential protease activity. Many of these differences are in the extent of occupancy and type of glycan present on a given site. Therefore, a given glycoprotein produced in different mammalian cell lines would have the same Substance ID. Post–translational modifications will be captured when they are both complete and non-variable or when they are essential for bioactivity.

EXAMPLE In many blood clotting factors, glutamate residues are converted to gamma-carboxyglutamate residues. These modifications are essential for activity and will be captured as a structural modification.

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7.2.1 Microheterogeneity

The ISO 11238 Substance Standard does not explicitly capture microheterogeneity. Microheterogeneity is typically caused by differential post-translational modifications that lead to differences in the type and extent of glycosylation, phosphorylation, sulphation and/or other modifications throughout the ensemble of molecules of a given protein. Recently, regulatory agencies are receiving more detailed information on the microheterogeneity of proteins in medicinal products. This information may be used to further distinguish proteins at the Specified Substance Group 1 level. Further guidelines on capturing this information may be given in subsequent editions of this document and Protein Annex, e.g. isoforms.

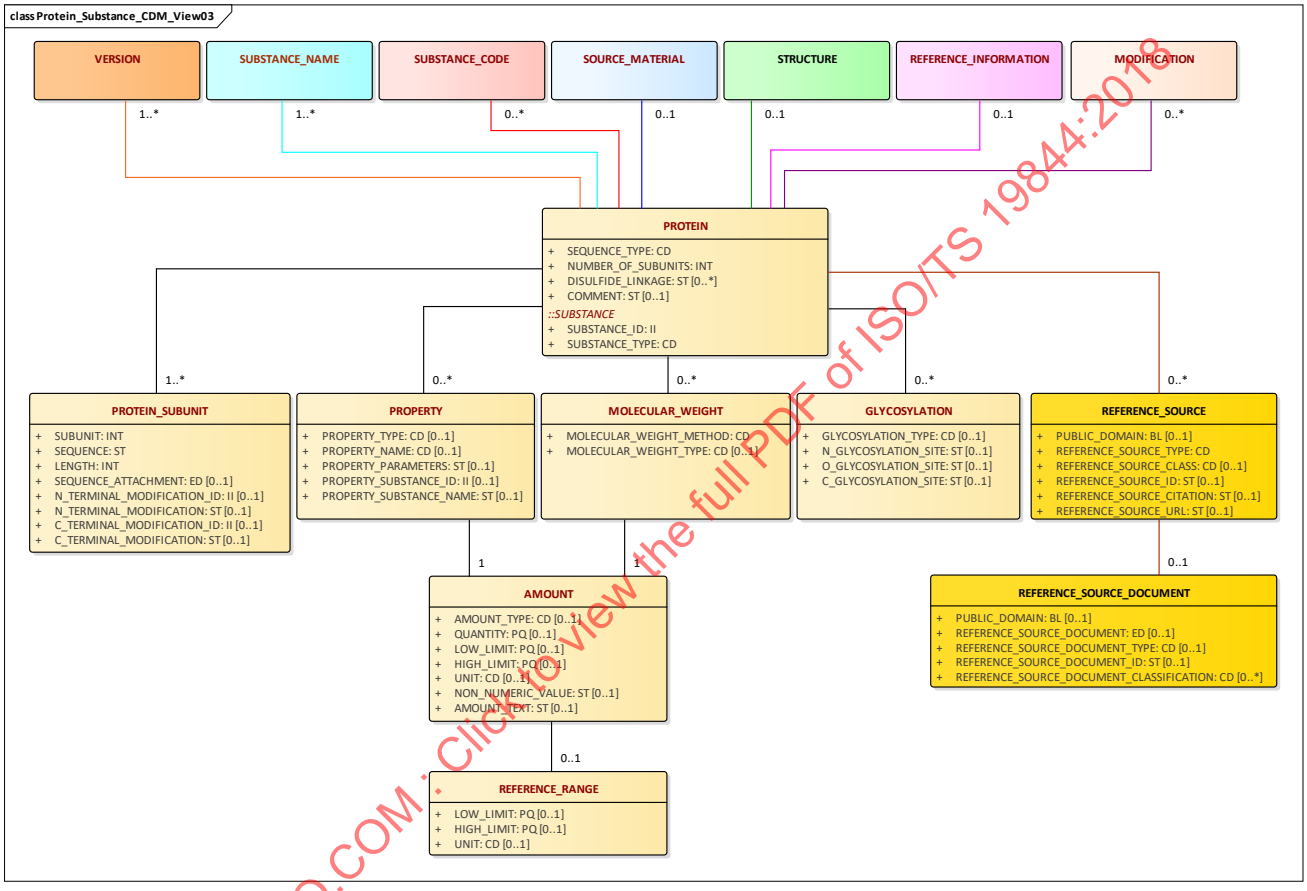


Figure 26 — Information model for the Protein Substance

If the substance type as defined in 5.2.1 is equal to *Protein substance*, the following data elements and conformances apply in order to assign Substance IDs.

7.2.2 Sequence type (Mandatory)

Table 133 — Sequence type

User Guidance	The protein descriptive elements will only be used when a complete or partial amino acid sequence is available or derivable from a nucleic acid sequence.
Example(s)	complete; partial
Conformance	MANDATORY
Data Type	CD

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7.2.3 Number of subunits (Mandatory)

Although many proteins form multimeric complexes, particularly at high concentrations, subunits are typically either connected through disulfide linkages or other covalent linkages or have strong non-covalent interactions with defined stoichiometry largely independent of concentration.

Table 134 — Number of subunits

User Guidance	Number of linear sequences of amino acids linked through peptide bonds. The number of subunits constituting the protein shall be described. It is possible that the number of subunits can be variable.
Example(s)	1
Conformance	MANDATORY
Data Type	INT
Business Rule(s)	This number is implicit and derived from number of protein subunits.

7.2.4 Disulfide linkage (Conditional)

Disulfide linkages imply that two cysteines connect forming a sulfur to sulfur linkage. There are also instances where disulfide linkages can be formed through other modified or substituted acids or amino acids containing a thiol (see Table C.3 — Desmopressin Acetate (USAN); Desmopressin Acetate Hydrate (JAN)).

Table 135 — Disulfide linkage

User Guidance	The disulfide bond between two cysteine residues either on the same subunit or on two different subunits shall be described. The position of the disulfide bonds in the protein shall be listed in increasing order of subunit number and position within subunit followed by the abbreviation of the amino acids involved. The disulfide linkage positions shall actually contain the amino acid Cysteine at the respective positions.
Example(s)	"Subunit 1 position 10 — Subunit 2 position 16" refers to a disulfide linkage between the residue of cysteine in the position 10 and 16 respectively of the first and second subunit. A convenient shorthand such as 1_10-2_16 could also be used.
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	The values have to be separated with semi-colons as defined in the examples in the .

7.2.5 Comment (Optional)

Table 136 — Comment

User Guidance	Any comment should be provided in this field, if necessary.
Conformance	OPTIONAL
Data Type	ST

7.2.6 Protein subunit (Mandatory)

This subclause refers to the description of each subunit constituting the protein. A subunit is a linear sequence of amino acids linked through peptide bonds. The Protein Subunit information shall be provided when the finished protein is a complex of multiple sequences; subunits are not used to delineate domains within a single sequence. Subunits are listed in order of decreasing length; sequences of the same length will be ordered by decreasing molecular weight; subunits that have identical sequences will be repeated multiple times.

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7.2.6.1 Subunit (Mandatory)

Table 137 — Subunit

User Guidance	Index of primary sequences of amino acids linked through peptide bonds in order of decreasing length. Sequences of the same length will be ordered by molecular weight. Subunits that have identical sequences will be repeated and have sequential subscripts.
Example(s)	1, 2, 3 (..)
Conformance	MANDATORY
Data Type	INT

7.2.6.2 Sequence (Mandatory)

Table 138 — Sequence

User Guidance	The sequence information shall be provided enumerating the amino acids from N- to C-terminal end using standard single-letter amino acid codes. Uppercase shall be used for L-amino acids and lowercase for D-amino acids. Transcribed proteins will always be described using the translated sequence; for synthetic peptide containing amino acids that are not represented with a single letter code an X should be used within the sequence. The modified amino acids will be distinguished by their position in the sequence.
Conformance	MANDATORY
Data Type	ST

7.2.6.3 Length (Mandatory)

Table 139 — Length

User Guidance	Length of linear sequences of amino acids contained in the subunit shall be provided.
Example(s)	25
Conformance	MANDATORY
Data Type	INT
Business Rule(s)	The sequence length is implicitly derived from the linear sequences of amino acids contained in the subunit.

7.2.6.4 Sequence attachment (Conditional)

Table 140 — Sequence attachment

User Guidance	An "enriched" string, a document or image representing the sequence should be provided.
Example(s)	See Sequence Attachment in See Sequence Attachment in Annex I, Vaccines, (CRM$_{197}$) See Sequence Attachment in Annex J, Allergen Substances, (nDer p 1); (Lol p 1)
Conformance	CONDITIONAL
Data Type	ED
Business Rule(s)	The element Sequence is always mandatory; the element Sequence Attachement may be provided based on jurisdinctional guidance. Either the sequence is provided as ST or/and as an attachment as ED.

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7.2.6.5 N_Terminal modification ID (Conditional)

Table 141 — N_Terminal modification ID

User Guidance	Unique identifier for molecular fragment modification based on the ISO 11238 Substance ID.
Example(s)	UNII code; SZB8301W42 (UNII)
Conformance	CONDITIONAL
Data Type	II
Values Allowed	ISO 11238 Substance ID
Business Rule(s)	If an N-terminal modification exists, this element becomes mandatory. The preferred name as specified in ISO 11238 is the default value. The value is implicit and derived based on the N_Terminal Modification ID.

7.2.6.6 N_Terminal modification (Conditional)

Table 142 — N_Terminal modification

User Guidance	The name of the fragment modified at the N-terminal of the protein should be specified.
Example(s)	Pyroglutamic acid (pE), 3-Mercaptopropionic acid
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	ISO 11238 substance names
Business Rule(s)	If an N-terminal modification exists, this element becomes mandatory. The preferred name as specified in ISO 11238 is the default value. The value is implicit and derived based on the N_Terminal Modification ID.

7.2.6.7 C_Terminal modification ID (Conditional)

Table 143 — C_Terminal modification ID

User Guidance	Unique identifier for molecular fragment modification based on the ISO 11238 Substance ID.
Example(s)	UNII code, K3Z4F99H6 (UNII), Lysine (K)
Conformance	CONDITIONAL
Data Type	II
Values Allowed	If a C-terminal modification exists, this element becomes mandatory. The preferred name as specified in ISO 11238 is the default value. The value is implicit and derived based on the C_Terminal Modification ID.

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7.2.6.8 C_Terminal modification (Conditional)

Table 144 — C_Terminal modification

User Guidance	The name of the fragment modified at the C-terminal of the protein should be specified
Example(s)	Glycinamid, Lysine
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	ISO 11238 substance names
Business Rule(s)	If a C-terminal modification exists, this element becomes mandatory. The preferred name as specified in ISO 11238 is the default value. The value is implicit and derived based on the C_Terminal Modification ID.

7.2.7 Molecular weight (Conditional)

The molecular weight or a molecular weight range for proteins, polymers or nucleic acids should be provided if known. Multiple molecular weights that either depend on the method or type should also be provided.

If the molecular weight is available, the following specifications apply.

7.2.7.1 Molecular weight method (Mandatory)

There are a variety of methods used to determine molecular weight. The method is often associated with the type of molecular weight. Each method shall be captured.

Table 145 — Molecular weight method

User Guidance	The method by which the molecular weight was determined.
Example(s)	SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis), calculated, light scattering, viscosity, gel permeation, end-group analysis, end-group titration, size-exclusion chromatography
Conformance	MANDATORY
Data Type	CD

7.2.7.2 Molecular weight type (Conditional)

There are basically four types of molecular weights associated with polymers, proteins and nucleic acids. The four types are number average, M_n; viscosity average, M_v; weight average, M_w; and Z-average, M_z. Polydispersity is an important property that will distinguish different polymers from one another. Polydispersity is typically defined as the ratio of weight average molecular weight to the number average molecular weight (M_w/M_n).

Table 146 — Molecular weight type

User Guidance	Type of molecular weight such as exact, average (also known as. number average), weight average
Example(s)	Number Average, Weight Average
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	number average, M_n; viscosity average, M_v; weight average, M_w; and Z-average, M_z
Business Rule(s)	If known, it shall be provided

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7.2.7.3 Amount (Mandatory)

Amount shall be captured as described in 5.8.

7.2.7.3.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

7.2.8 Glycosylation (Conditional)

Glycosylation is both variable and heterogeneous. Glycosylation sites typically have multiple glycans attached to them and even differ on the extent of glycosylation on a given site. For Glycosylated proteins, the type and sites of glycosylation should be provided. Glycosylation is applicable to both proteins and structurally diverse substances. Although sites of N-glycosylation can generally be predicted from the amino acid sequence, sites of O-glycosylation and C-glycosylation are usually determined experimentally and may not be completely known at the time of submission and can be added to a substance record when known. Generally, all sites that have occupancy greater than 5% should be submitted to define the glycoprotein. Although analytical techniques are evolving to better characterize the glycans attached to proteins this data will not be required to define a substance but could be captured at the Specified Substance Group 1 level. There can be substantial differences in glycosylation that are often dependent on the particular clone of a cell line that is used to produce a protein or even vary on a batch to batch basis.

7.2.8.1 Glycosylation type (Conditional)

The different glycosylation types are determined by the cell that either the protein or Specified Substance was synthesized in. The different types are based on consistent differences in the glycosylation. Human glycosylation differs from mammalian glycosylation in several ways. Human glycans do not contain glycolic acid residues on terminal sialic acid and they do not contain terminal .alpha.1-> 3-galactose. Old world monkeys also lack the ability to form .alpha. 1-> 3-galactose, but do have glycolic acid esters on terminal sialic acid residues. Other glycosylation types typically have substantial differences in both glycans used and the extent of site occupancy. Glycosylation type may also be captured for structurally diverse substances, particularly vaccines which may be produced in either human, mammalian or old-world monkey cells. The glycosylation type will often have substantial effects on the immunogenicity of the protein or vaccine.

Table 147 — Glycosylation type

User Guidance	The type of the glycan should be specified based on a controlled vocabulary.
Example(s)	Human, old world monkey, mammalian, avian, reptilian; fungal, bacterial, plant, insect, mammalian afucosylated, yeast humanized
Conformance	CONDITIONAL
Data Type	CD

7.2.8.2 N_Glycosylation site (Conditional)

N-linked glycosylation: The sites of N-glycosylation can typically be predicted from the amino acid sequence. The sequence NX(S/T) which indicates an asparagine followed any amino acid other than proline and then followed by either a serine or threonine will typically be a site of N-glycosylation.

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Table 148 — N-Glycosylation site

User Guidance	Information on the site of N-glycosylation (asparagine); N-glycosylation is to be listed according to the protein sequence.
Example(s)	Position 34 of this Subunit, an Asparagine; for a single subunit protein 1_34
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	The position of that subunit shall actually contain an amino acid that can have N-linked glycosylation.

7.2.8.3 O-Glycosylation site (Conditional)

O-linked glycosylation: The sites of O-glycosylation cannot typically be predicted from the sequence alone and are discovered through analytical methods. Sites may become identified at later stages in clinical development. The Substance ID typically should not change as new sites are identified but the version of the substance would.

Table 149 — O-Glycosylation site

User Guidance	Information on the site of O-glycosylation (serine, threonine, tyrosine, hydroxylysine, hydroxyproline) should be provided.
Example(s)	Position 34 of this Subunit, a Serine.
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	The position of that subunit shall actually contain an amino acid with an OH group (i.e. serine or threonine or tyrosine).

7.2.8.4 C-Glycosylation site (Conditional)

C-linked glycosylation: The consensus sequence for C-glycosylation is WxxW/F where the first tryptophan undergoes C-mannosylation.

Table 150 — C-Glycosylation site

User Guidance	Information on the C-glycosylation: site of C-glycosylation (tryptophan) should be provided.
Example(s)	Position 45 of this Subunit, a Tryptophan
Conformance	CONDITIONAL
Data Type	ST

7.2.9 Property (Conditional)

Property should be captured as specified in 5.11.

7.2.9.1 Amount (Mandatory)

Amount shall be captured as described in 5.8.

7.2.9.1.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

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7.2.10 Structure (Conditional)

The information related to the structure should be provided as per specification described in 5.7. The structural representation should include the first atom of the protein which is modified. For amino acid replacements and fragment additions a substance will be created in its own right. In addition, or in lieu of the data structure listed above, HELM notation can be a suitable format for transmitting definitive information on selected proteins and peptides[16].

7.2.11 Substance name (Mandatory)

Information shall be captured as described in 5.3.

7.2.12 Modification (Conditional)

The information should be captured as described in 5.10.

7.2.13 Substance code (Conditional)

Substance Code should be captured as described in 5.5.

7.2.14 Source material (Conditional)

Source Material should be captured as described in 5.9.

7.2.15 Version (Mandatory)

Version information shall be captured as described in 5.12.

7.2.16 Reference information (Conditional)

Reference information should be captured as described in 5.6.

7.2.17 Reference source (Conditional)

The reference source information should be captured as described in 5.4.

7.2.17.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7.

7.3 Nucleic acids

Nucleic acids are defined by three distinct elements: the base, sugar and linkage. Individual substance/moiety IDs will be created for each of these elements. The nucleotide sequence will be always entered in the 5'-3' direction.

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[16] See http://www.pistoiaalliance.org/projects/active-projects/hierarchical-editing-language-for-macromolecules-helm/

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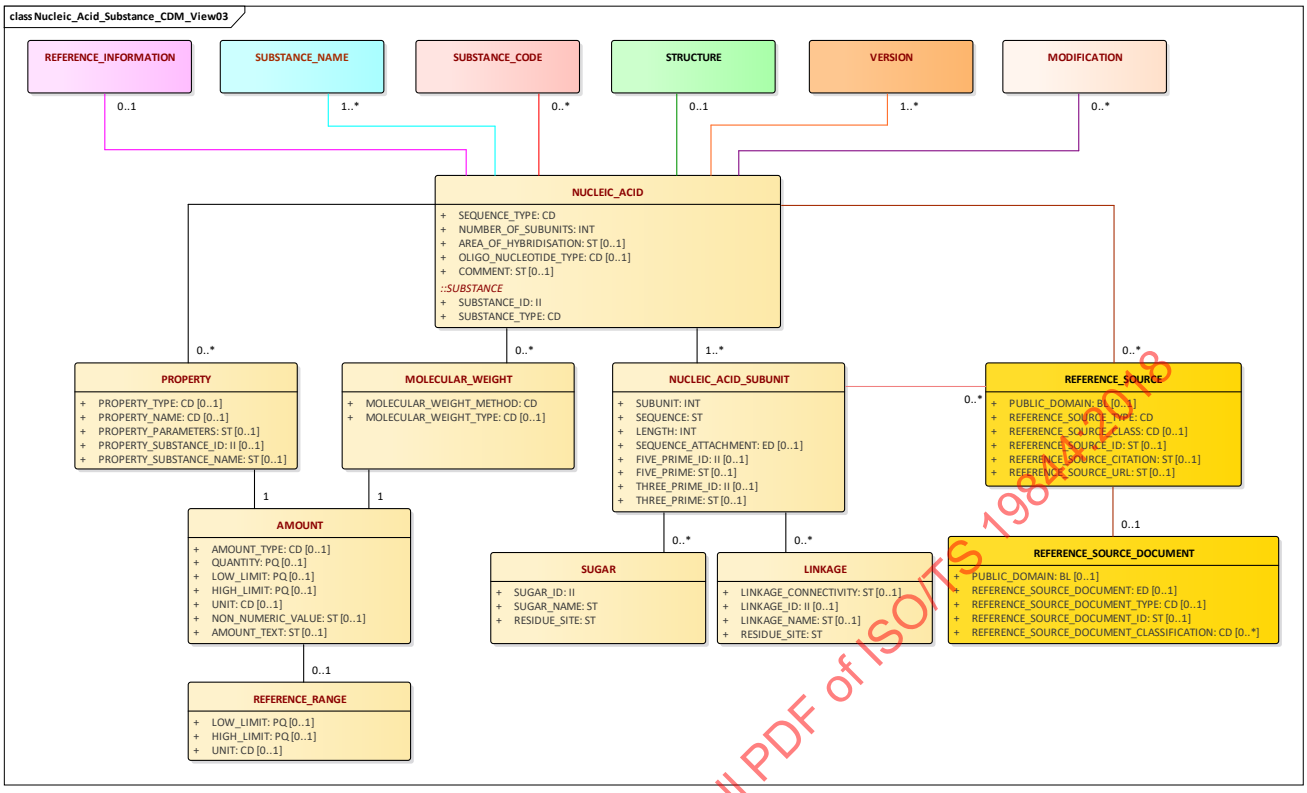


Figure 27 — Information model for the Nucleic Acid

The nucleic acid set of elements are only to be used to describe nucleic acids that have:

— A length greater than three bases or base pairs;

— Elements to be used for oligonucleotides;

— Genes used in gene therapy;

— Any nucleic acid aptamers.

For the description of nucleic acids, the following information can be used to assign Substance IDs:

— Nucleotide Sequence;

— Sugar or sugar-like entities;

— Linkage (typically phosphate);

— Nucleic Acid Type (RNA, DNA, plasmid, single or double stranded);

— Any Modifications to the substance either sequence specific (i.e. modified or unnatural base, sugar, phosphate linkage) or non-sequence specific modifications.

7.3.1 Structure (Conditional)

There are multiple alternative ways of representing the structure of nucleic acids. Figure 28 provides an example of one of the possible structural representations. While the sequence of nitrogenous bases is given as a single letter notation, the backbone structure is represented as a polymeric single repeat unit (see 6.4 “Polymers”). A structural representation can be provided for relatively short oligonucleotides but the textual fields illustrated below should be sufficient to describe nucleic acid based substances.

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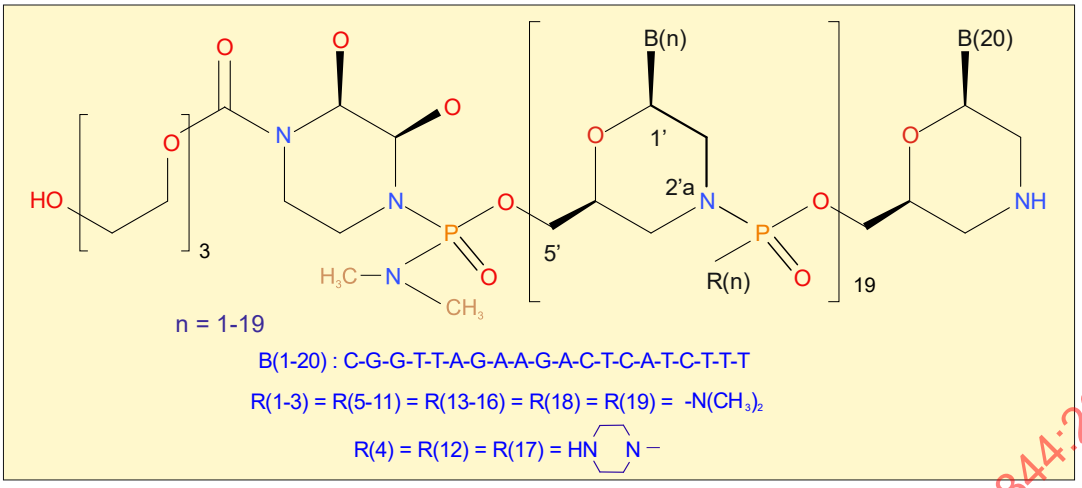


Figure 28 — Representative Structural Representation of nucleic acids

Information shall be captured as described in 5.7.

7.3.2 Sequence type (Mandatory)

Table 151 — Sequence type

User Guidance	The type of the sequence shall be specified based on a controlled vocabulary.
Example(s)	complete; partial
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	

7.3.3 Number of subunits (Mandatory)

Table 152 — Number of subunits

User Guidance	The number of linear sequences of nucleotides linked through phosphodiester bonds shall be described. Subunits would be strands of nucleic acids that are tightly associated typically through Watson-Crick base pairing. NOTE If not specified in the reference source, the assumption is that there is 1 subunit.
Example(s)	1, 2, or 3
Conformance	MANDATORY
Data Type	INT
Business Rule(s)	This number is implicit and derived from number of nucleic acid subunits.

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7.3.4 Area of hybridization (Conditional)

Table 153 — Area of hybridization

User Guidance	The area of hybridization should be described if applicable for double stranded RNA or DNA. The number associated with the subunit followed by the number associated to the residue shall be specified in increasing order. The underscore "_" shall be used as separator as follows: "Subunit_number Residue".
Example(s)	Each residue shall be specified followed by a comma and space.
Conformance	CONDITIONAL
Data Type	ST

7.3.5 Oligo nucleotide type (Conditional)

Table 154 — Oligo nucleotide type

User Guidance	This element distinguishes a single stranded oligo nucleotide from a double stranded gene or rDNA vaccine.
Example(s)	Single-stranded DNA; Double-stranded DNA.
Conformance	CONDITIONAL
Data Type	CD
Value(s) Allowed	Single-stranded DNA; Double-stranded DNA; Single-stranded RNA; Double-stranded RNA

7.3.6 Comment (Optional)

Table 155 — Comment

User Guidance	Any comment should be provided in this field, if necessary.
Conformance	OPTIONAL
Data Type	ST

7.3.7 Nucleic acid subunit (Mandatory)

Subunits are listed in order of decreasing length; sequences of the same length will be ordered by molecular weight; subunits that have identical sequences will be repeated multiple times.

7.3.7.1 Subunit (Mandatory)

Table 156 — Subunit

User Guidance	Index of linear sequences of nucleic acids in order of decreasing length. Sequences of the same length will be ordered by molecular weight. Subunits that have identical sequences will be repeated and have sequential subscripts.
Example(s)	1, 2, 3 (..)
Conformance	MANDATORY
Data Type	INT

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7.3.7.2 Sequence (Mandatory)

Table 157 — Sequence

User Guidance	Actual nucleotide sequence notation from 5' to 3' end using standard single letter codes. In addition to the base sequence, sugar and type of phosphate or non-phosphate linkage should also be captured.
Example(s)	GATTCA
Conformance	MANDATORY
Data Type	ST
Values Allowed	Sequence of the letters G, C, T, A, and U

7.3.7.3 Length (Mandatory)

Table 158 — Length

User Guidance	The length of the sequence shall be captured.
Example(s)	5
Conformance	MANDATORY
Data Type	INT
Business Rule(s)	The sequence length is implicitly derived by the sequence description.

7.3.7.4 Sequence attachment (Conditional)

Table 159 — Sequence attachment

User Guidance	An "enriched" string, a document or image representing the sequence should be provided.
Example(s)	See Sequence Attachment in Table D.1
Conformance	CONDITIONAL
Data Type	ED
Business Rule(s)	The element Sequence is always mandatory; the element Sequence Attachement may be provided based on jurisdinctional guidance. Either the sequence is provided as ST or/and as an attachment as ED.

7.3.7.5 Five prime ID (Conditional)

Table 160 — Five prime ID

User Guidance	The unique identifier of the five prime should be captured.
Example(s)	JKUHT76541 (Artificial ID)
Conformance	CONDITIONAL
Data Type	II
Values Allowed	ISO 11238 Substance ID
Business Rule(s)	

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7.3.7.6 Five prime (Conditional)

Table 161 — Five prime

User Guidance	The nucleotide present at the 5’ terminal should be specified based on a controlled vocabulary. Since the sequence is represented from the 5' to the 3' end, the 5’ prime nucleotide is the letter at the first position in the sequence. A separate representation would be redundant.
Example(s)	Tymidine (T)
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	ISO 11238 Substance Name
Business Rule(s)	Implicit If not specified in the available reference source this value shall be derived from the nucleic acid sequence.

7.3.7.7 Three prime ID (Conditional)

Table 162 — Three prime ID

User Guidance	The unique identifier of the three prime should be captured.
Example(s)	JKUHT76541 (Artificial ID)
Conformance	CONDITIONAL
Data Type	II
Values Allowed	ISO 11238 Substance ID
Business Rule(s)	

7.3.7.8 Three prime (Conditional)

Table 163 — Three prime

User Guidance	The nucleotide present at the 3’ terminal should be specified based on a controlled vocabulary. Since the sequence is represented from the 5' to the 3' end, the 5’ prime nucleotide is the letter at the last position in the sequence. A separate representation would be redundant.
Example(s)	Thymine (T)
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	ISO 11238 Substance Name
Business Rule(s)	NOTE If not specified in the available reference source this value is derived from the nucleic acid sequence.

7.3.7.9 Sugar (Conditional)

Sugar or sugar-like element is one of the three elements that define a nucleic acid.

7.3.7.9.1 Sugar ID (Mandatory)

The Substance ID for the type of sugar to which the base is connected. For naturally occurring nucleic acids the sugar is typically either .beta.-D-ribose or .beta.-D-deoxyribose. The actual configuration of the sugar shall be captured.

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Table 164 — Sugar ID

User Guidance	The Substance ID of the sugar or sugar-like component that makes up the nucleotide shall be provided.
Example(s)	UNII code for ribose:
Conformance	MANDATORY
Data Type	II
Values Allowed	ISO 11238 Substance ID

7.3.7.9.2 Sugar name (Mandatory)

The type of sugar to which the base is connected; for naturally occurring nucleic acids, the sugar is typically either .beta.-d-ribose or .beta.-d-deoxyribose.

Table 165 — Sugar name

User Guidance	The name of the sugar or sugar-like component that makes up the nucleotide shall be captured.
Example(s)	Ribose, deoxyribose, 2,5-dihydroxy-morphilino
Conformance	MANDATORY
Data Type	ST
Values Allowed	ISO 11238 substance name
Business Rule(s)	This is implicit and derived from the Sugar ID. The preferred name is the default value.

7.3.7.9.3 Residue site (Mandatory)

The residues that contain a given sugar entity shall be captured. Each sugar present in the nucleic acid will be represented.

Table 166 — Residue site

User Guidance	The residues that contain a given sugar shall be captured. The order of given residues will be captured in the 5‘-3‘direction consistent with the base sequences listed above.
Example(s)	1_1-1_20 would indicate that residues 1-20 of a given strand contain a particular sugar.
Conformance	MANDATORY
Data Type	ST

7.3.7.10 Linkage (Conditional)

The linkages between sugar residues should be captured.

7.3.7.10.1 Linkage connectivity (Conditional)

This element will indicate the orientation of the linkage. The 3‘-5‘ linkage is the most prevalent form.

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Table 167 — Linkage connectivity

User Guidance	The entity that links the sugar residues together should also be captured. For nearly all naturally occurring nucleic acid the linkage is a phosphate group. For many synthetic oligonucleotides phosphorothioate linkages are often seen. Linkage connectivity is assumed to be 3'→5'. If the linkage is either 3'→3' or 5'→5' this should be specified.
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	3'→5', 3'→3' or 5'→5' this should be specified.

7.3.7.10.2 Linkage ID (Conditional)

Table 168 — Linkage ID

User Guidance	Each linkage should be registered as a fragment and have an ID.
Conformance	CONDITIONAL
Data Type	II
Values Allowed	ISO 11238 Substance ID

7.3.7.10.3 Linkage name (Conditional)

Table 169 — Linkage name

User Guidance	Each linkage should be registered as a fragment and have at least one name. A single name should be assigned to each linkage.
Example(s)	Phosphothioate
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	ISO 11238 Substance Name

7.3.7.10.4 Residue site (Mandatory)

Residues shall be captured as described in 6.3.7.8.3.

7.3.7.11 Reference source (Conditional)

The reference source information should be captured as described in 5.4.

7.3.7.11.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7.

7.3.8 Modification (Conditional)

The information should be captured as described in 5.10.

7.3.9 Property (Conditional)

Property should be captured as specified in 5.11.

7.3.9.1 Amount (Mandatory)

Amount shall be captured as described in 5.8.

7.3.9.1.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

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7.3.10 Molecular weight (Conditional)

This information should be captured as described in 6.2.7.

7.3.10.1 Amount (Mandatory)

Amount shall be captured as described in 5.8.

7.3.10.1.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

7.3.11 Substance Name (Mandatory)

Information shall be captured as described in 5.3.

7.3.12 Substance Code (Conditional)

Substance Code should be captured as described in 5.5.

7.3.13 Version (Mandatory)

Version information shall be captured as described in 5.12.

7.3.14 Reference information (Conditional)

Reference information should be captured as described in 5.6.

7.3.15 Reference source (Conditional)

The reference source information should be captured as described in 5.4.

7.3.15.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7.

7.4 Polymers

Polymers are polydisperse molecular ensembles defined using a combination of structural and descriptive elements. The structural elements are the structural repeat units along with end-groups and salt forms. The number and/or weight average molecular weight, degree of polymerization, degree or extent of substitution of fragments and physical properties related to molecular weight are descriptive elements that may be required to assign a Substance ID. For synthetic polymers, the monomers used to prepare the polymer should also be provided. For copolymers, the type of copolymer (random, block, branched, etc.), along with the block/branch size and number of blocks or branches, should also be provided. A technical specification sheet and/or information sheet from a manufacturer is often sufficient to generate a Substance ID. For polymers derived from biological matrices, the source of the polymer should also be provided.

EXAMPLE Starch is a mixture of two polymers amylose and amylopectin. It is normally isolated from wheat, corn, rice, potato, or tapioca and source material elements should be used to capture the source.

For the description of polymer substances (see Annex H), a combination of the following elements should be submitted to assign Substance IDs:

— Structural Representations of the Structural Repeat Units and/or Monomers;

— Explicit Connectivity between Structural Repeat Units and End-groups;

— Number Average Molecular Weight and/or Limits;

— Weight Average Molecular Weight and/or Limits;

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— Degree of Polymerization;

— Physical Properties Related to Molecular Structure (i.e. Viscosity, Density, etc.);

— For Copolymers: Relative Amounts of Monomers;

— For Block Copolymers: Block Size and Block Number;

— For Substituted Polymers: Substituents and the Degree of Substitution;

— Any Process that Modifies the Chemical Structure.

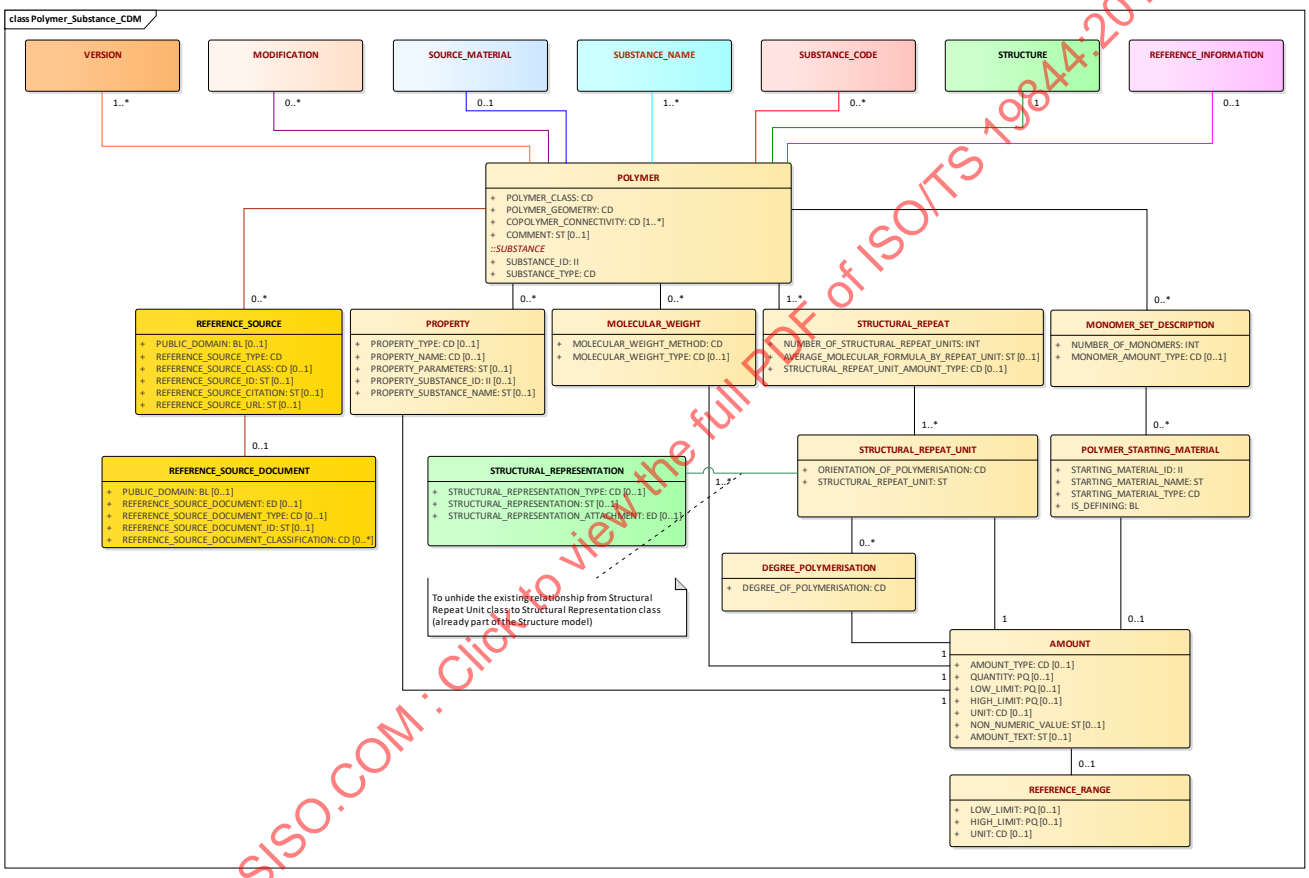


Figure 29 — Information model for the Polymer Substance

The general set of information shall be provided by means of the followings data elements.

7.4.1 Polymer class (Mandatory)

Table 170 — Polymer class

User Guidance	The type of polymer shall be captured.
Example(s)	homopolymer, copolymer
Conformance	MANDATORY
Data Type	CD

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7.4.2 Polymer geometry (Mandatory)

Table 171 — Polymer geometry

User Guidance	The geometry of the polymer shall be described.
Example(s)	linear, branched, cross-linked, network, dendritic, star, comb, brush
Conformance	MANDATORY
Data Type	CD

7.4.3 Copolymer connectivity (Mandatory)

Table 172 — Copolymer connectivity

User Guidance	The connectivity of the polymer, typically describing the manner in which the SRUs (Structural Repeat Units) connect to each other shall be specified.
Example(s)	random, alternating, block, graft, statistical, periodic, mixed, cross, N/A
Conformance	MANDATORY
Data Type	CD

7.4.4 Comment (Optional)

Table 173 — Comment

User Guidance	Any comment should be provided in this field, if necessary.
Conformance	OPTIONAL
Data Type	ST

7.4.5 Substance name (Mandatory)

The information related to the name of the substance shall be provided as as per the specification described in 5.3. The naming of polymers can be different from other types of substances. Official Names are typically given to classes of substances and not individual polymers. A naming convention to distinguish polymers within a class may be developed.

EXAMPLE POLYQUATERNIUM-47 is an INCI for an acrylate copolymer but it is necessary to indicate the relative amounts of the different acrylate Structural Repeat Units and the molecular weight. A specific name for a distinct polymer would be POLYQUATERNIUM-47 (METHACRYLAMIDOPROPYLTRIMETHYLAMMONIUM CHLORIDE-CO-METHYL ACRYLATE-CO-ACRYLIC ACID 45:10:45; 1200000 MW).

7.4.6 Structure (Mandatory)

The information related to the structure shall be provided as per specification described in 5.7. The structure wherever possible should be representative of the structural repeat units that make up the polymer. The structure should be contained within brackets. The end-groups or an asterisk indicating connectivity to another structural repeat unit should be drawn outside the brackets. For random copolymers, each structural repeat unit should be drawn in the same structural representation, but not directly connected to each other. For block copolymers, the structural repeating units will be directly connected to each other. End-groups, when known, should also be attached to the structural repeat units. MolFile are the preferred format for the molecular structure of the repeat unit.

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7.4.7 Monomer set description (Conditional)

For polymers, this set of descriptors intends to specify and quantify the monomers used for the synthesis of the polymer or copolymer. The information on the monomer should be provided by means of the following data elements.

7.4.7.1 Number of monomers (Mandatory)

Table 174 — Number of monomers

User Guidance	The number of diverse monomers used to synthesize the polymer shall be specified.
Example(s)	2
Conformance	MANDATORY
Data Type	INT
Business Rule(s)	This number can be implicitly derived from the number of polymer starting materials.

7.4.7.2 Monomer amount type (Conditional)

Table 175 — Monomer Amount type

User Guidance	This element should capture the ratio of the monomer or the Structural Repeat Unit (SRU) to the entire polymer.
Example(s)	Monomer/Polymer ratio, SRU/Polymer Ratio
Conformance	CONDITIONAL
Data Type	CD

7.4.7.3 Polymer Starting material (Conditional)

This subclause identifies and quantifies the starting materials, which are the monomer(s) used in the synthesis of the polymer.

7.4.7.3.1 Starting material ID (Mandatory)

Table 176 — Starting material ID

User Guidance	The unique identifier assigned to the monomer shall be captured.
Conformance	MANDATORY
Data Type	II
Values Allowed	ISO 11238 Substance ID

7.4.7.3.2 Starting material name (Mandatory)

Table 177 — Starting material name

User Guidance	The name of the starting material (monomer) shall be provided; established or primary name of starting material.
Example(s)	Ethylene Oxide; .BETA.-D-Glucopyranose; Propylene Oxide; .BETA.-L-Iduronic acid, Pyranose form; Deoxyguanosine 5'-Monophosphate; 5-*N*-acetyl-α-D-Neuraminic acid; Alpha.-D-Galactose
Conformance	MANDATORY
Data Type	ST
Values Allowed	ISO 11238 Substance Name

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7.4.7.3.3 Starting material type (Mandatory)

Table 178 — Starting material type

User Guidance	The type of the starting material shall be provided.
Example(s)	Chemical substance, Biological substance
Conformance	MANDATORY
Data Type	CD

7.4.7.3.4 Is defining (Mandatory)

Table 179 — Is defining

User Guidance	This attribute shall be used to specify whether the attribute described is a defining element for the unique identification of the Polymer.
Conformance	MANDATORY
Data Type	BL
Values Allowed	Yes/No

7.4.7.3.5 Amount (Conditional)

Amount should be captured as described in 5.8.

7.4.7.3.5.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

7.4.8 Structural repeat (Mandatory)

This subclause specifies and quantifies the repeated units and their configuration. A structural representation shall also be submitted. Information on the structural repeat unit shall be provided by means of the following data elements.

7.4.8.1 Number of structural repeat units (Mandatory)

Table 180 — Number of structural repeat units

User Guidance	The number of diverse structural repeated units represented in the structure of the polymer shall be specified.
Example(s)	Homopolymers will only have 1 Structural Repeat Unit; copolymers will typically have more than 1.
Conformance	MANDATORY
Data Type	INT
Business Rule(s)	Implicitly derived

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7.4.8.2 Average molecular formula by repeat unit (Conditional)

Table 181 — Average molecular formula by repeat unit

User Guidance	This element provides a representation of an (average) molecular formula from a polymer.
Example(s)	$HO(C_2H_4O)_{141}(C_3H_6O)_{44}(C2H_4O)_{141}H$
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	The element shall be captured for polymers only. The structural repeat unit shall have a distinct stoichiometric composition. When the substituents within SRU are variable the information may not be provided.

7.4.8.3 Structural repeat unit amount type (Conditional)

The information should be captured as described in 5.8.1. Indicate how the quantitative amount of Structural Repeat Units is captured (e.g. Exact, Numeric, Average).

7.4.8.4 Structural repeat unit (Mandatory)

For synthetic polymers, the structural repeat units are typically generated from the polymerization of monomers. The Structural Repeat Unit for polyethylene is ethylene and not methylene.

7.4.8.4.1 Orientation of polymerization (Mandatory)

This element is used to indicate how Structural Repeat Units connect to each other. In addition to the Orientation of Polymerization explicit connections between Structural Repeat Units can be indicated by connection points.

Table 182 — Orientation of polymerization

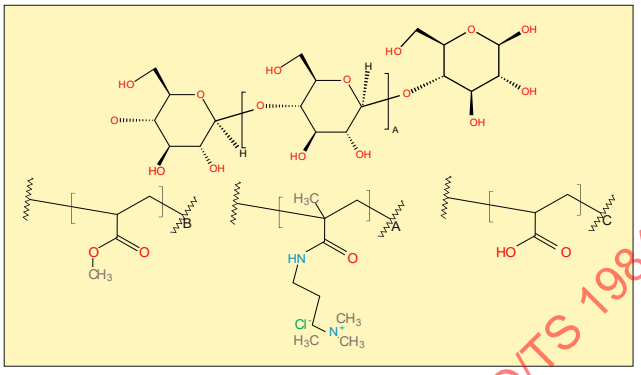
User Guidance	The orientation of the polymerization shall be described.
Example(s)	head-tail, head-head, random
Conformance	MANDATORY
Data Type	CD

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7.4.8.4.2 Structural repeat unit (Mandatory)

Table 183 — Structural repeat unit

User Guidance	Structural repeat units are essential elements for defining polymers. Specific guidance will be given in the /Polymer.
Example(s)	 **Figure 1 — Example of structural repeat units**
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	End-groups if defined can be attached to the Structural Repeat Unit. The Structural Repeat Unit shall be the largest repeating structural fragment

7.4.8.4.3 Amount (Mandatory)

Amount shall be captured as described in 5.8.

7.4.8.4.3.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

7.4.8.4.4 Structural representation (Mandatory)

Structural repeat unit representation information for each SRU should be captured as described in 5.7.6.

7.4.8.4.5 Degree of polymerization (Conditional)

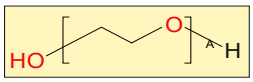
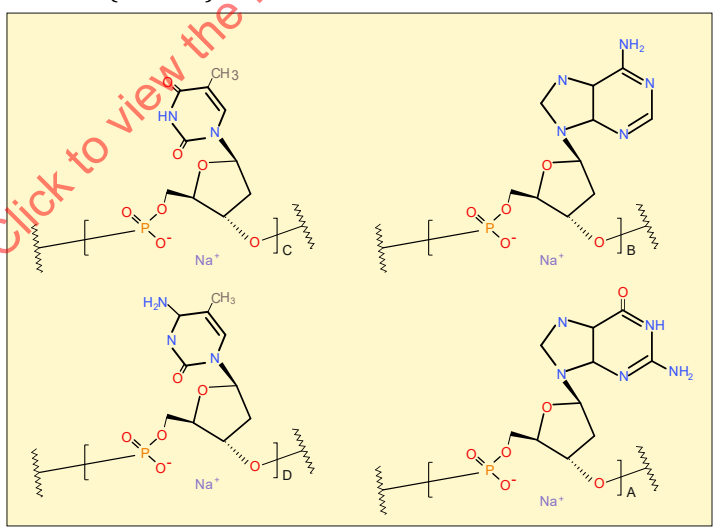
This subclause applies to homopolymers and block copolymers where the degree of polymerization within a block can be described. The following information should be provided where available.

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7.4.8.4.5.1 Degree of polymerization (Mandatory)

Table 184 — Degree of polymerization

User Guidance	The degree of polymerization shall be described through the identification of the SRU and its associated amounts.
Example(s)	"Structural Repeat Unit: <A><amount or number of SRU/per polymer ratio>", Example: Synthetic Polymer: Polyethylene Glycol 3350  A = Ethylene Oxide **Figure 2 — Degree of Polymerization = A** Example Biological Polymers: *N. meningitidis* group A polysaccharide: "<A = →6)-DMan*p*NAc(3/4OAc)-α-(1→OPO3)>", *N. meningitidis* group C polysaccharide: "<A = →9)-DNeu*p*5NAc(7/8OAc)-α-(2→>" *N. meningitidis* group W135 polysaccharide: "<A = →4)-DNeu*p*5NAc(7/9OAc)-α-(2→6)-D-Gal-α-(1→>", *N. meningitidis* group Y polysaccharide: "<A = →4)-DNeu*p*5NAc(7/9OAc)-α-(2→6)-D-Glc-α-(1→" EXAMPLE Defibrotide (Porcine).  **Figure 3 — Degree of Polymerization = A+B+C+D**
Conformance	MANDATORY
Data Type	CD

7.4.8.4.5.2 Amount (Mandatory)

Amount shall be captured as described in 5.8.

7.4.8.4.5.2.1 6.4.8.4.5.2.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

7.4.9 Molecular weight (Conditional)

This information should be captured as described in 6.2.7.

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7.4.9.1 Amount (Mandatory)

Amount shall be captured as described in 5.8.

7.4.9.1.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

7.4.10 Property (Conditional)

Property should be captured as specified in 5.11.

7.4.10.1 Amount (Mandatory)

Amount shall be captured as described in 5.8.

7.4.10.1.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

7.4.11 Substance code (Conditional)

Substance Code should be captured as described in 5.5.

7.4.12 Version (Mandatory)

Version information shall be captured as described in 5.12.

7.4.13 Reference information (Conditional)

Reference information should be captured as described in 5.6.

7.4.14 Modification (Conditional)

The information should be captured as described in 5.10.

7.4.15 Source material (Conditional)

This information should be captured as described in 5.9.

7.4.16 Reference source (Conditional)

The reference source information should be captured as described in 5.4.

7.4.16.1.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7.

7.5 Structurally diverse substances

There are a wide variety of substances described as structurally diverse substances. A Structurally diverse substance is a type of polydisperse substance isolated from a single source that is a complex combination which cannot be described as a mixture of a limited number of single substances. This category would be used to describe the following class of substances.

— Herbals — The Herbal preparation OIL is discussed in B.7.2 of the Chemical Annex B. The Herbal preparations, Extract and exudates as well as the (Herbal) Substance (fresh) and Herbal Drug are discussed in the Herbal Annex E.

— Homeopathic Substances are discussed in Annex F.

— Plasma-derived substances used in Blood products are discussed in Annex G.

— Vaccines — are discussed in Annex I.

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— Allergens — are discussed in Annex J.

— Polyclonal Immunoglobulins — to be addressed in the next edition of this document.

— Cells, tissues, complex animal derived products — to be addressed in the next edition of this document.

— Minerals —are discussed in the annexes where relevant.

For organism-based substances, the parent organism is essential defining information.

The majority of these substances will be derived from a biological organism, but they could be complex natural materials such as coal tar or mineral oil.

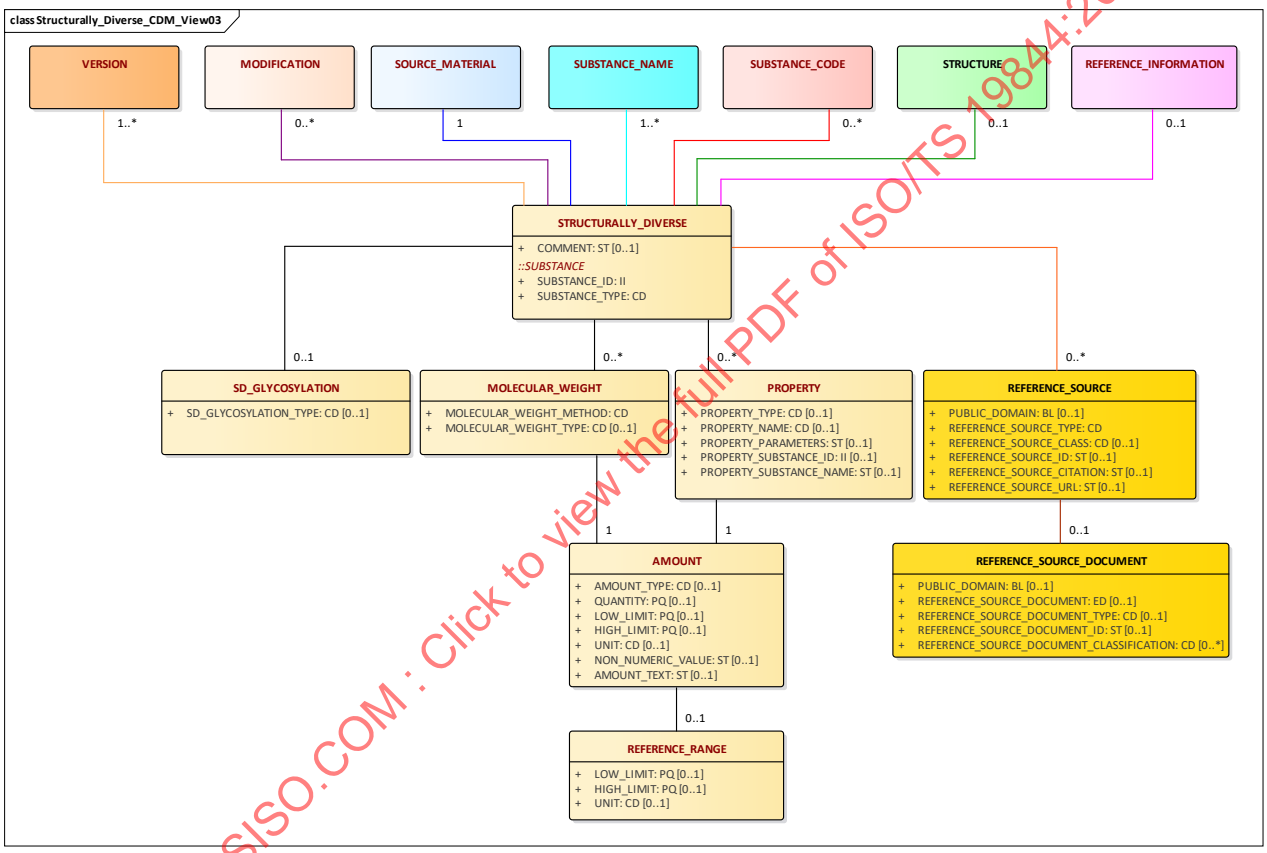


Figure 33 — Information model for the Structurally Diverse Substance

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The general set of information shall be provided by means of the followings data elements:

7.5.1 Comment (Optional)

Table 185 — Comment

User Guidance	Any comment should be provided in this field, if necessary.
Conformance	OPTIONAL
Data Type	ST

7.5.2 Substance name (Mandatory)

Information shall be captured as described in 5.3.

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7.5.3 Structure (Conditional)

If applicable, the information should be described based on specification provided in 5.7.

7.5.4 Property (Conditional)

Property should be captured as specified in 5.11.

7.5.4.1 Amount (Mandatory)

Amount shall be captured as described in 5.8.

7.5.4.1.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

7.5.5 Molecular weight (Conditional)

This information should be captured as described in 6.2.7.

7.5.5.1 Amount (Mandatory)

Amount shall be captured as described in 5.6.

7.5.5.1.1 Reference range (Conditional)

Reference range should be captured as described in 5.8.8.

7.5.6 SD glycosylation (Conditional)

SD glycosylation describes not-specific sites of glycosylation in structurally diverse material.

7.5.6.1 SD glycosylation type (Conditional)

Table 186 — SD glycosylation type

User Guidance	The type of the glycan should be specified based on a controlled vocabulary.
Example(s)	human, old world monkey, mammalian, avian, reptilian, fungal, bacterial, plant, insect, mammalian afucosylated, yeast humanized
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	

7.5.7 Modification (Conditional)

The information should be captured as described in 5.10.

7.5.8 Source material (Mandatory)

This information shall be captured as described in 5.9.

7.5.9 Substance code (Conditional)

Substance Code should be captured as described in 5.5.

7.5.10 Reference information (Conditional)

Reference information should be captured as described in 5.6.

7.5.11 Version (Mandatory)

Version information shall be captured as described in 5.12.

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7.5.12 Reference source (Conditional)

The reference source information should be captured as described in 5.4.

7.5.12.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7.

7.5.13 Herbals and substances used in the preparation of plant-based allergenic extracts

Substances in Herbal preparations and most substances in allergenic preparations shall be defined simply by taxonomic information and the plant part. Taxonomic information, particularly the scientific name of a medicinal plant, is essential for defining substances of herbal origin in medicinal products. The Kew Gardens Medicinal Plant Names Services (MPNS) should be the authoritative source for all scientific names and should also maintain a list of plant parts and fractions. A controlled vocabulary for medicinal plant taxonomy has been developed and will be maintained by the Kew Gardens Medicinal Plant Names Services. A submitter should choose the current accepted scientific name provided by MPNS. The MPNS Portal should be accessed via www.kew.org/mpns. The service should be contacted if the plant material cannot be mapped to records in the MPNS. It should be noted that many common and even pharmacopoeia names of herbs often map to more than one plant species, but it is important that the actual herbal plant (defined as a particular species) shall be used in defining a substance.

Although herbal products in some jurisdictions are not regulated as medicinal products, they are a major class of products covered by the IDMP standards. Many jurisdictions have a clear distinction between Herbal Drugs and Herbal preparations and that is what is followed in this implementation guide. Substances of herbal origin are defined by the taxonomic definition of the plant represented by the plant's scientific name which includes the genus, species and author. Additional taxonomy such as kingdom, phylum, class, order and family could also be captured to assist in the classification of substances. The part or parts of the plant that are used in the Herbal Drug or Herbal preparation are also included in the substance definition. Identification of a substance may also require an indication of the plant life cycle captured in the name of the plant part such as inflorescence or sprout.

EXAMPLE The common term chamomile typically refers to the flowers of two distinct plants identified by the accepted scientific names *Matricaria chamomilla* L. and *Chamaemelum nobile* (L.) All. The term chamomile is ambiguous and a submitter should refer to the specific species that is contained in the product.

Time and place of harvest, type of soil, the use of fertilizers, pesticides and herbicides, the amount of daylight and water, although important, are not captured as part of the substance definition. A cultivar or variety of a plant may be defined as a different substance if known differences in constituents exist (e.g. broccoli and cauliflower are defined as different substances even though they share the same genus and species). Fractions are Herbal preparations and will be captured at the substance (Herbal preparation) level for oils, and to some extent for extracts. Additional information for the extract will be defined at the Specified Substances Group 1 information level. Fractions of plant parts such as commodity oils, juices, and exudates such as acacia gum and herbal extracts such as teas and tinctures will always map to the parent organism and part or parts. A variety of examples of herbal Substances (fresh), Herbal Drugs and Herbal preparations are present in Annex E: Structurally Diverse Substance - Herbal Substance/Herbal Specified Substance.

The Herbal Annex E should be referred to for user guidance and business rules for the various elements of the source material for structurally diverse substances as they apply to herbals. Examples are given for herbals derived from plant material. Other types of natural materials, such as fungi, algea, animals and minerals are also treated as herbals in other systems of medicine and pharmacopoeias. Although Annex E doesn't include any examples of these algae and fungi would be treated as herbals and examples of animals and minerals are given in Annex F, Homeopathics.

7.5.13.1 Naming vegetable oils

The business rules for naming of vegetable oils are described in subclause Structurally Diverse Substance, Herbals, 6.5.13.1 and in the subclause Source Material (see 5.9).

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The terms Substance and Specified Substance are used as defined by ISO 11238. The terms Herbal Drug (Herbal Substance) and Herbal preparation are used as defined by pharmacopoeias, and will both be captured at the Substance level. In addition, a more basic unit, comprising unprocessed, fresh material of a single species or intraspecies (occasionally a genus) + part, with no affiliation to any particular pharmacopoeia, will also be captured at the Substance level; for clarity, these will be referred to as Substance (fresh). The information model also accommodates fraction information at the substance level. The element <Fraction> will be considered as two Herbal preparations: <Oil, Exudate, Juice> or <Extract>, each requiring different information.

Specified Substance Group 1 includes additional information for substances and multi-substance material. Additional information for Herbal Drugs and for Herbal preparations e.g. additional information for an extract such as extraction solvent composition, Herbal Drug/Herbal Extract ratio will be captured at this level along with the constituents and marker or signature substances.

7.5.13.1.1 Example: Olive Oil, Virgin

Olive Oil, Virgin Ph.Eur. is defined as a Herbal preparation (because it has been obtained by expression). There is no defined Herbal Drug for this Herbal preparation, but instead its source material is the ripe drupes (fruit) of *Olea europaea* L.

For the purposes of ISO 11238, the Herbal preparation referred to a Pharmacopoeia is defined as a Substance as [<Scientific genus/binomial/trinomial without Author>,<Part(s)>,<Fraction>], i.e. Olea *europaea*, Fruit, Oil.; Common name: Olive Oil, Virgin. The source material for such a Herbal preparation is a separate Substance (fresh) defined as [<Scientific genus/binomial/trinomial with Author>,<Part(s)>], i.e. *Olea europaea* L., Fruit. This Substance is the Parent Substance of *Olea europaea*, Fruit, Oil.

The name [<Scientific genus/binomial/trinomial **with Author**>,<Part(s)>] refers to a **Substance Name** in terms of ISO 11238 that is not an official name in any pharmacopoeia or other legislation. The inclusion of the author is to ensure that it is not confused with the official names for Herbal Drugs and Herbal preparations which are also defined as Substances by ISO 11238. The scientific element of the name is usually a binomial (species), but may be a trinomial (intraspecies such as a variety or subspecies) or a genus, as appropriate, together with the author of the name. The Part element of the name should be chosen from a CV consisting of a restricted number of terms.

The **name** [<Scientific genus/binomial/trinomial **without Author**>,<Part(s)>] refers to a **Substance Name** in terms of ISO 11238 and is the equivalent to a Herbal Drug Name. There is no such Substance Name for Olive Oil in this example from the Ph.Eur., although other pharmacopoeias might define a Herbal Drug for *Olea europaea*, Fruit.

The **name** [<Scientific genus/binomial/trinomial without Author>,<Part(s)>], [Fraction] refers to a **Substance Name** in terms of ISO 11238 and is **equivalent** to a **Herbal preparation Name**.

The Herbal preparation Name corresponds to two Herbal preparations; **one** for the Substance fraction: Oil, Exudate, Juice and one for the Substance fraction: Extract. This is done to differentiate between the cardinalities of the Herbal preparations.

The Herbal preparation relationship to the Substance (fresh) is a two-way relationship. The fraction <Oil, Exudate, Juice> is prepared from one Substance (fresh).

NOTE Several Herbal preparations, e.g. Juices, can be a mixture of separately obtained juices obtained from the herbal substances and mixed after expression. The final preparation is then a multi-substance material which is captured at the Specified Substance Group 1 level.

The fraction <Extract> can be prepared from one or more Herbal Drugs and by one or more extraction steps and by one or different extraction solvent compositions. Only the first extraction solvent composition is used in the element solvent. Further details of the Herbal preparation and Herbal Drug are described in the Annex E, Structurally Diverse substances, Herbals and for the Oils the information is provided in the Annex B/Chemical.

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For the Herbal preparation Olive Oil, Virgin the result of the information model will read:

Substance ID: HJFTE78543 (Artificial ID); (UNII: 6UYK2W1W1E)

Substance Name (Herbal preparation Name): *Olea europaea*, Fruit, Oil

Substance Name Type: Other

Fraction (Herbal preparation): Oil

Substance Name: Olive Oil, Virgin

Substance Name Type: Official (for further elements see tabular format in the Annex B)

Parent Substance ID: OLIJF5643S

Parent Substance Name: *Olea europaea* L., Fruit

7.5.14 Vaccines

Annex I provides guidance to describe the elements that are necessary to define vaccine antigens. Individual antigens in polyvalent vaccines shall be identified as separate substances. These substances could be any substance type but currently approved medicinal products include structurally diverse, protein, polymer (polysaccharide), and nucleic acid (veterinary) substances.

Vaccines for human use are preparations containing antigens capable of inducing a specific and active immunity in man against an infecting agent or the toxin or antigen elaborated by it. Immune responses include the induction of the innate and the adaptive (cellular, humoral) parts of the immune system. A vaccine typically contains an agent that resembles a disease-causing micro-organism and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins.

7.5.15 Plasma-derived substance for human blood products and polyclonal antibodies

See Annex G. Purified blood products (distinct clotting factors, human serum albumin) and monoclonal immunoglobulins are described as proteins. Polyclonal immunoglobulins are described as structurally diverse materials and require identification of the immunoglobulin type and targeted antigen if applicable.

7.5.16 Allergens

See Annex J. The active allergens are structurally diverse substance derived from biological matrices. In several instances, if the allergenic protein responsible for the allergenic response has been isolated and characterized in the majority of patients, then the substance is classified as protein, e.g. Fel d 1 in cat saliva.

7.5.17 Advanced Therapies and Advanced Vaccines (Genes, Modified Viruses, Cells and Tissues as Substances)

At this time, Annex K addresses these substance types. In this version of ISO TS/19844 high-level guidance to describe the elements that are necessary to define what are typically referred to as advanced therapies is provided. In a future version, it is intended to provide detailed examples of some substance types. The active substances will typically be defined as structurally diverse material and in a few instances nucleic acids when genes are directly injected into tissues.

Advanced therapies constitute a wide range of structurally diverse substances. They are predominantly consisting of modifications of viruses, bacteria, cells or tissues. The modifications can consist of genes inserted into autologous (from the patient's own body) or allogeneic cells (from a close relative of the patient or a donor) which result in either the expression of new protein or the silencing of an expressed protein. They can be gene modified lineage specific stem cells used to treat inherited metabolic disorders; antigen primed dendritic cells directed to provide an immune response against cancer cells; retroviruses designed to deliver specific genes to specific cell populations; viruses modified to express an antigenic protein of a human pathogen or acellular matrices to assist wound healing, bone or neural regeneration. Although only a handful of these substances are in approved products there are many in clinical development and they possess potential to treat or even cure a number of diseases that are currently untreatable.

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7.5.18 Minerals

Minerals will be described following the chemical substance information model and also, one example is described in the Homeopathic Annex F.

Structurally diverse substances not derived from organisms often require property descriptions as defining characteristics. In this way, light mineral oil is distinguished from mineral based on density or viscosity while petroleum distillates require a boiling range. These natural mixtures may be chemically, physically, or biologically modified prior to use so information about modifications may also be necessary to define them.

In order to assign a Substance ID for other structurally diverse substances (non-organism derived), the following information shall be provided:

— Source material (e.g. coal, petroleum);

— Physical properties related to molecular structure of the substance or ensemble of substances (i.e. viscosity, density, etc.);

— Any process that fractionates or modifies the source chemically.

7.6 Mixture

Material that contains multiple substances can be mixture if the substances are either isolated or synthesized together. Racemic mixtures or substances containing unknown or mixed stereochemistry will not be defined as mixtures, but will be represented as substances that contain impurities or degradants. Mixtures of mixtures will not be allowed. Each component of a mixture should be listed. Substances present in trace amounts will not be listed in a mixture unless they are known to have a specific effect. Mixtures are also used when substance ambiguity exists in authoritative sources (e.g. aloe).

NOTE There are three instances related to the information described above:

— component (part of a multi-substance material);

— constituent, single substance having a substance role (parent, marker, eluent etc);

— a particular case of Constituent Component used in a mixture having a relationship (part of a homologous group).

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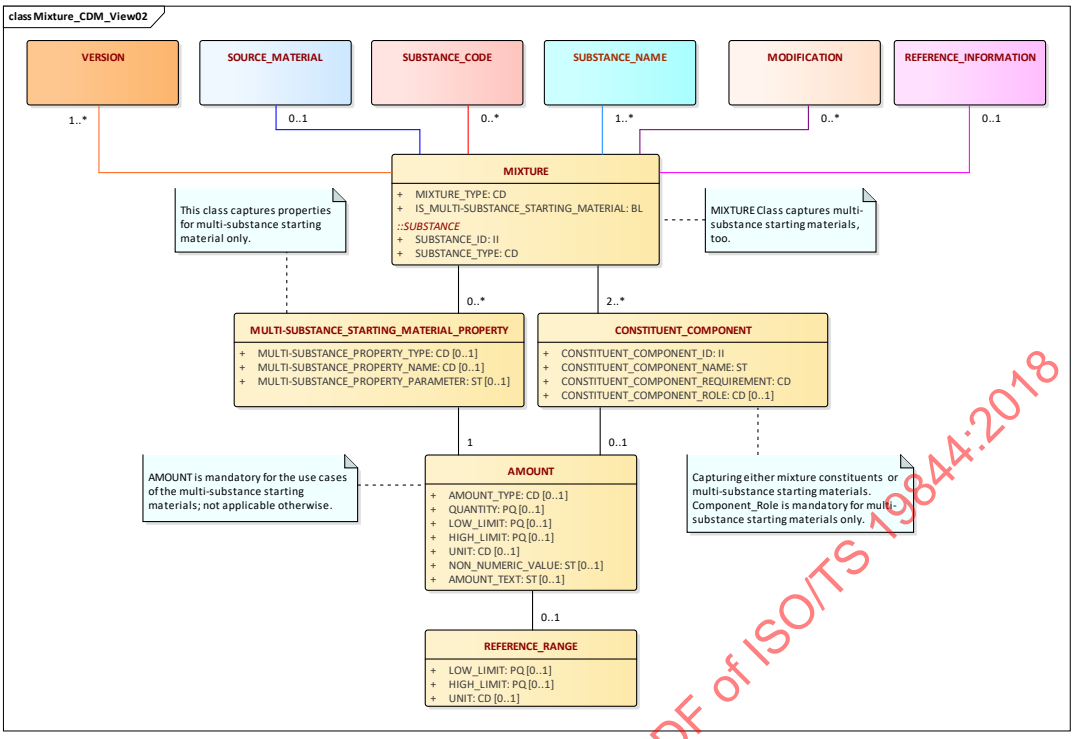


Figure 34 — Information Model for the Mixture

The following information on mixture shall be provided.

7.6.1 Mixture type (Mandatory)

Table 187 — Mixture type

User Guidance	There are basically three potential mixture types. Most mixtures will be “all of” mixtures meaning that all of the constituents are present in the mixture. The other two types of mixture are “one of” or “any of”. “Any of” mixtures will mean that at least one of the constituents shall be present but other constituents may or may not be present.
Example(s)	all of; one of; any of
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	

7.6.2 Is multi-substance starting material (Mandatory)

Table 188 — Is multi-substance starting material

User Guidance	In order to distinguish a mixture (a substance consisting of ‘closely related components’ as a result from the same synthetic process) from a mixture substance being an extract of a homologous group of substances as a result of the same synthetic process - which may have related (allergenic) components - the value ‘Yes’ shall be specified in the attribute ‘Is Multi-Substance Starting Material’.
Example(s)	Yes, No
Conformance	MANDATORY
Data Type	BL
Business Rule(s)	The value ‘Yes’ shall be specified to describe a mixture being an extract of a homologous group of substances.

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7.6.3 Constituent component (Mandatory)

The constituent component set of elements aims to describe either the constituents of the mixture or multi-substance starting materials as individual components, which are parents to a single substance manufactured via the same synthetic prossess e.g. allergen extract. Such information shall be provided by means of the following data elements.

7.6.3.1 Constituent component ID (Mandatory)

Table 189 — Constituent component ID

User Guidance	The unique identifier assigned to the constituent component substance. NOTE If a unique "Substance ID" has been assigned, this "Substance ID" is specified based on the Substance Name. In the absence of a unique "Substance ID" e.g. for the initial submission of the substance this data element is not required.
Example(s)	LOL1234567 (Artificial ID), ARRH123456 (Artificial ID)
Conformance	MANDATORY
Data Type	II
Values Allowed	ISO 11238 Substance ID

7.6.3.2 Constituent component name (Mandatory)

Table 190 — Constituent component name

User Guidance	The name of the constituent of the mixture shall be described or the name of each starting material; established or primary substance name. Teicoplanin A_{2-1} is one of the five constituents of the mixture of glycopeptides Teicoplanin produced by certain strains of *Actinoplanes teichomyceticus* sp.
Example(s)	Teicoplanin A_{2-1}
Conformance	MANDATORY
Data Type	ST
Values Allowed	ISO 11238 Substance Name
Business Rule(s)	

7.6.3.3 Constituent component requirement (Mandatory)

Table 191 — Constituent component requirement

User Guidance	An indication if this component is required.
Example(s)	Always present, may be present
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	

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7.6.3.4 Constituent component role (Conditional)

Table 192 — Constituent component role

User Guidance	The role of the constituent component shall be specified.
Example(s)	Parent substance
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	

7.6.3.5 Amount (Conditional)

Amount should be captured as described in 5.8.

7.6.4 Multi-substance starting material property (Conditional)

This class capture properties for multi-substance starting material only.

7.6.4.1 Multi-substance property type (Conditional)

Table 193 — Multi-substance property type

User Guidance	Type of the property for which the information is provided.
Example(s)	Physical, chemical, enzymatic, immunological
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	

7.6.4.2 Multi-substance property name (Conditional)

Table 194 — Multi-substance property name

User Guidance	The name of the property should be specified based on a controlled vocabulary.
Example(s)	Solubility, Appearance
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	

7.6.4.3 Multi-substance property parameter (Conditional)

Table 195 — Multi-Substance property parameter

User Guidance	A field that should be used to capture parameters that were used in the measurement of a property.
Example(s)	Temperature conditions determined during the time of solubility testing in different solvents.
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	

7.6.5 Modification (Conditional)

The information should be captured as described in 5.10.

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7.6.6 Source material (Conditional)

This information should be captured as described in 5.9.

7.6.7 Substance name (Mandatory)

Information shall be captured as described in 5.3.

7.6.8 Substance code (Conditional)

Substance Code should be captured as described in 5.5.

7.6.9 Reference information (Conditional)

Reference information should be captured as described in 5.6.

7.6.10 Version (Mandatory)

Version information shall be captured as described in 5.12.

8 Specified substance (Conditional)

There are a number of regulatory needs when defining materials in medicinal products. The globalization of supply chains, widespread contract manufacturing and the high value of many medicinal products places a much greater burden on both regulatory agencies and companies to ensure that the material used in medicinal products is correctly identified with known pedigree.

Although the substance model captures information essential to the description of materials in medicinal products there is often a strong regulatory need for additional information that is not captured at the substance level. The four groups of Specified Substance elements allow for the explicit capture of information essential for the evaluation and tracking of material used in medicinal products. Each of the four groups of elements provides information essential for these regulatory needs in a manner that should facilitate compliance. The implementation of the Specified Substance Groups is conditional depending on the condition that one of the elements used to describe the Specified Substance is defining. Should a region implement any of the Specified Substance Groups, the following conformances as described in this subclause are applicable.

8.1 Specified Substance Group 1 (Conditional)

Multiple substance materials (e.g. simethicone, aluminium lakes, and flavours), herbal extracts, juices, oils and tinctures and polymorphic forms of materials will be described and differentiated using Specified Substance Group 1 elements.

Specified Substances Group 1 always have at least one constituent; all constituents are either Substance or Specified Substance Group 1. The Modification Group elements and Fraction Description Group elements are also necessary to define many Specified Substances Group 1. For Herbal preparations, the drying process could be considered as a modification process. An extraction is a preparation. There can be a liquid extract or dry extract being made from the (herbal) Substance (fresh) or from the (herbal) Substance (dry) which is the Herbal Drug in terms of the Pharmacopoeia.

Single component substances that differ in physical form are defined as different Specified Substances Group 1. For example, crystalline insulin and amorphous insulin are two different Specified Substances Group 1. To avoid confusion, if substance information is sufficient for regulatory needs, the substance information and ID should be used to describe the medicinal product.

The Specified Substance Group 1 is associated with a set of Specified Substance particulars. These consist of information about Herbal substances (Herbal Substance Particulars), Homeopathic (Vehicle, Dilution and Potentization) etc.

The information model for Specified Substances Group 1 is listed in Figure 35.

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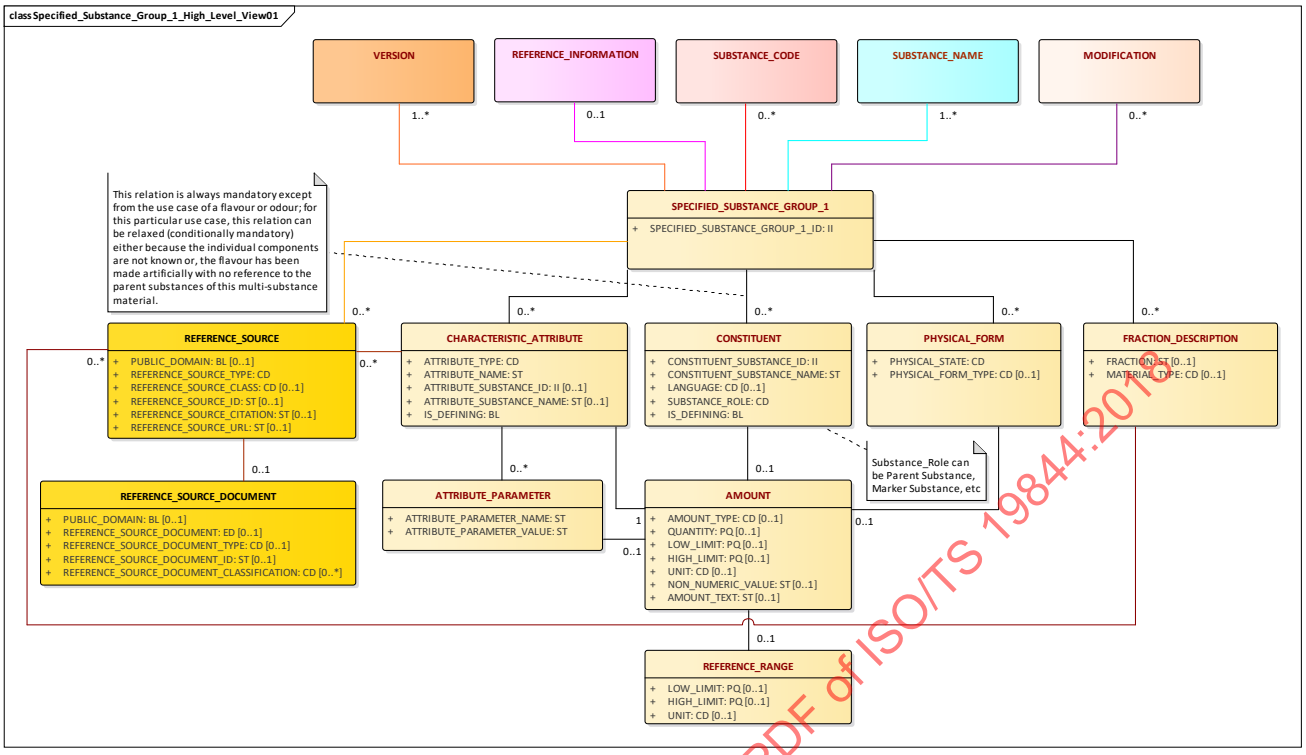


Figure 35 — Information model for the Specified Substance Group 1

8.1.1 Specified substance Group 1 ID (Mandatory)

Table 196 — Specified substance Group 1 ID

User Guidance	The unique identifier assigned to the Specified Substance Group 1 shall be specified. NOTE If a unique "Specified Substance ID" has been assigned, this "Specified Substance ID" is specified based on the Substance Name controlled vocabulary. In the absence of a unique "Specified Substance ID" e.g. for the initial submission of the substance this data element is not required.
Conformance	MANDATORY
Data Type	II
Business Rule(s)	The ID of the substance will be automatically assigned by the system once the message is processed. NOTE The Specified Substance ID is NOT SPECIFIED for Specified Substance ID Request.

8.1.2 Substance name (Mandatory)

Names associated with a Specified Substance Group 1 shall be captured as described in 5.3. For Herbal substances name conventions shall follow the pattern described in the E.2.3 of Annex E: [Scientific genus/binomial/trinomial **without** Author], [Part(s)], [Fraction],[Extraction solvent composition],[Herbal Drug/Native Herbal preparation(DER)].

EXAMPLE *Ginkgo biloba*, Leaf, Dry Extract Acetone-Water (60 – 40, w/w), (37 – 65 = 1).

EXAMPLE *Harpagophytum zeyheri*, Root, Dry Extract Ethanol-Water (60 – 40, v/v),(1,5 – 3,0 = 1).

For herbal substance names that follow the pattern described above, the Substance Name Type Specified Substance Group 1 shall be specified.

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8.1.3 Substance Code (Conditional)

Codes associated with a Specified Substance Group 1 should be captured as described in 5.5.

8.1.4 Version (Mandatory)

Version information associated with a Specified Substance Group 1 shall be captured as described in 5.12.

8.1.5 Reference source (Conditional)

The reference source information should be captured as described in 5.4.

8.1.5.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7.

8.1.6 Constituent (Conditional)

The Constituent group of elements serves several roles; each substance in multiple substance materials is captured as a constituent. Signature, active markers, and limit substances, extraction solvents, a vehicle, impurities and degradants are also captured. The amount of each constituent substance is captured too. A different Specified Substance Group 1 may be created if these amounts consistently vary.

EXAMPLE When the solvent composition quantitatively changes (ethanol 40 % to ethanol 50 %) a distinct Specified Substance Group 1 identifier will need to be created. When the amount of a marker substance (specification) is changed, this will not lead to a distinct Specified Substance Group 1 identifier.

EXAMPLE A change in the Drug Extract ratio (DER) will lead to a distinct Specified Substance Group 1 identifier.

Conclusion: The extraction solvent composition and the DER are defining elements.

At least one constituent is necessary for every Specified Substance Group 1 (i.e. the parent Substance ID). This relation is always mandatory with exception of use case of flavours and odours; for this particular use case, this relation can be relaxed (conditionally mandatory) to allow jurisdictional guidance define whether detailed composition has to be reported for all multi-component substances (either because the individual components are not known or, the flavour has been made artificially with no reference to the parent substances of this multi-substance material).

8.1.6.1 Constituent substance ID (Mandatory)

Each constituent should be identified by either a Substance ID or a Specified Substance ID.

Table 197 — Constituent substance ID

User Guidance	Every Specified Substance Group 1 shall have at least one constituent and the Substance ID for each constituent shall be captured.
Example(s)	ISO 11238 Substance or Specified Substance ID
Conformance	MANDATORY
Data Type	II
Values Allowed	ISO 11238 Substance or Specified Substance ID
Business Rule(s)	A constituent can be a Substance or a Specified Substance Group 1.

8.1.6.2 Contituent substance name (Mandatory)

Table 198 — Constituent substance name

User Guidance	The name of the substance which is the constituent of the Specified Substance Group 1 shall be described; Preferred or Official Name of the constituent.

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Conformance	MANDATORY
Data Type	ST
Values Allowed	ISO 11238 Substance or Specified Substance name
Business Rule(s)	This value is implicit and derived from the Substance ID. The Preferred name is the default value.

8.1.6.3 Language (Conditional)

Table 199 — Language

User Guidance	If the name is language dependent, that language shall be specified.
Example(s)	en – English, de – German, fr –French
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	ISO 639-1, alpha-2 codes
Business Rule(s)	

8.1.6.4 Substance role (Mandatory)

Table 200 — Substance role

User Guidance	The role of the substance in the Specified Substance shall be described based on a controlled vocabulary. An impurity component is not described in the Specified Substance Group 1. The parent substance ID of a Specified Substance Group 1 shall always be specified.
Example(s)	active marker, marker, analytical marker, component, degradant, impurity, metabolite, active moiety, parent substance, vehicle, major allergen, catalytic centre of a protein
Conformance	MANDATORY
Data Type	CD
Values Allowed	COMPONENT; EXTRACTION SOLVENT, SIGNATURE SUBSTANCE; MARKER; ACTIVE MARKER; ANALYTICAL MARKER; VEHICLE; IMPURITY; DEGRADANT; ACTIVE MOIETY; PARENT SUBSTANCE; CATALYTIC CENTRE OF A PROTEIN
Business Rule(s)	Markers and Extraction solvents for herbal Specified Substance are conditional, when available information on markers and extraction solvents shall be provided. In addition to marker substances additional constituents of each herbal extract should be captured and linked to the extract if significant biological activity has been attributed to them.

8.1.6.5 Is defining (Mandatory)

Table 201 — Is defining

User Guidance	This element is to specify if the Constituent described is considered defining for the Specified Substance.
Conformance	MANDATORY
Data Type	BL
Values Allowed	Yes, No
Business Rule(s)	In some cases, the Constituent Substance can be a defining element e.g. when the substance role is Parent Substance and in some cases the specification of a marker. Example: when a specification of a marker with significant therapeutic activity is not met either the solvent

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	composition of an extract or the DER must be adjusted (changed) in order to meet the specification of the marker, which leads to the generation of another SSG1 ID.

8.1.6.6 Amount (Conditional)

Amount should be captured as described in 5.8.

8.1.6.6.1 Reference range (Conditional)

Reference Range should be captured as described in 5.8.8

8.1.7 Characteristic attribute (Conditional)

The Element Group 'Characteristic Attribute' should be used to capture both definitional characteristics and characteristics that provide additional information about a Specified Substance Group 1.

At the Specified Substance Group 1 level, qualitative properties such as sterility are essential to distinguish materials from each other. Melting points and solubility that differ significantly for what is believed to be the same substance could either be indicative of purity or of polymorphism. Different polymorphs would be considered different Specified Substances at the Specified Substance Group 1 level. The melting point of a polymorphic substance or solubility or rate of dissolution of a crystalline material could be a defining property of a given Specified Substance Group 1 and be described with the Attribute Type Physical.

For the Herbal Specified Substance Group 1 substances, the Attribute Type 'Particular Herbal preparation' is used to capture additional information for Herbal substance/Herbal preparation Mass Ratio. For Plasma-derived Specified Substance Group 1, the Attribute Type Cryopoor Plasma Process Flow is used to capture the country of plasma origin, testing and safety information.

8.1.7.1 Attribute type (Mandatory)

Table 202 — Attribute type

User Guidance	Homeopathic substances are described using the Attribute Type 'Particular Homeopathic' and allergen substances the Attribute Type 'Particular Allergen'. The Attribute Types 'Particular Herbal' or 'Particular Herbal preparation' shall be used to further describe characteristics of the Substance (fresh) and Substance (Herbal Drug). The Attribute Type 'Cryopoor Plasma Process Flow' is used to describe plasma-derived substances. The Attribute Type 'Particular Vaccine' is used to describe vaccines. Physical attributes shall be used to describe Chemical, Protein, Nucleic acid and Polymer substances.
Example(s)	Particular Homeopathic; Particular Herbal; Particular Herbal preparation; Particular Allergen; Physical; Cryopoor Plasma Process Flow, Particular Vaccine
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	

8.1.7.2 Attribute name (Mandatory)

Each attribute type is connected to different attributes described in this subclause.

Table 203 — Attribute name

User Guidance	Examples of the attributes captured by each Attribute Type are described below. The Attribute Names that are captured for each Attribute Type may be further expanded. The Attribute Name for the Attribute Type 'Particular Homeopathic' is 'Substance dilution potentization grade'.

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	The Attribute Names to be captured by the Attribute Type 'Particular Herbal' are: Wild/Cultivated; Degree of comminution; Process state; Growth state; Harvesting time; Harvesting method; Decontamination process; Country of origin, Geographical location, Storage time and Storage temperature. The Attribute Name to be captured by the Attribute Type 'Particular Herbal preparation' is Drug Extract Ratio (DER), which describes the quantity of native Herbal Substance that is used to prepare 1 g Herbal extract. In this context, 'Herbal Substance' can be either a Substance (fresh) or a Herbal Drug. The Attribute Names to be captured by the Attribute Type 'Particular Allergen' are: Degree of Comminution, Process state, Wild/ Cultivated, Growth state, Feeding composition, Harvesting/killing process, Harvesting Ttme, Decontamination process, Country of origin, Geographical location, Storage time and Storage condition. The Attribute Names captured by the Attribute Type 'Cryopoor Plasma Process Flow' are: Country of origin; Pathogen test, testing strategy. The Country of origin is directly coupled to the plasma pool and the manufacturer. It shall include the subset of countries in which the collection organizations are located from which plasma for manufacturing of a specific plasma-derived product(s) is obtained.
	The Testing strategy is directly coupled to the plasma pool and the manufacturer. The manufacturer of a Cryoprecipitate sourced from a plasma pool is captured at the Specified Substance Group 2 information level. The Attribute Names captured by the Attribute Type 'Particular Vaccine' are: History of the strain; Passage of the master seed; Passage of the working seed lot; 'Cultured on Vero cell' e.g. Polio vaccines or 'Cultured on MDCK (Madin Darby canine kidney) cells; Cultured on embryonated fertilized hens' eggs. The Attribute Names captured by the Attribute Type 'Particular ATMP' is HEK293 cells for the adeno associated viruses used for gene therapy. The Attribute Names captured by the Attribute Type Physical are: melting point; boiling point; critical temperature; critical pressure; critical density; triple point; density; solubility; pKa; UV absorption maxima.
Example(s)	Substance dilution Grade; Drug Extract Ratio (DER); Wild/cultivated; Degree of comminution; Process state; Growth state; Harvesting time; Harvesting method; Harvesting/killing process; Decontamination process; Country of origin, Geographical location, Storage time; Storage temperature; Storage condition; Feeding composition, Particle size; Pathogen test, Testing strategy
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	

8.1.7.3 Attribute substance ID (Conditional)

Table 204 — Attribute substance ID

User Guidance	The unique identifier assigned to the Attribute Substance should be specified.
Example(s)	ISO 11238 Substance or Specified Substance ID
Conformance	CONDITIONAL
Data Type	II
Values Allowed	ISO 11238 Substance or Specified Substance ID
Business Rule(s)	

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8.1.7.4 Attribute substance name (Conditional)

Table 205 — Attribute substance name

User Guidance	The substance name of the attribute should be captured.
Example(s)	
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	ISO 11238 Substance or Specified Substance Name
Business Rule(s)	

8.1.7.5 Is defining (Mandatory)

Table 206 — Is defining

User Guidance	This attribute is used to specify whether the attribute described is a defining element for the unique identification of the Specified Substance Group 1 substance.
Example(s)	Yes, No
Conformance	MANDATORY
Data Type	BL
Business Rule(s)	In some cases, a Characteristic Attribute can be a defining element. Example: when a specification of a marker with significant therapeutic activity is not met either the solvent composition of an extract or the DER must be adjusted (changed) in order to meet the specification of the marker, which leads to the generation of another SSG1 ID.

8.1.7.6 Amount (Mandatory)

Amount shall be captured as described in 5.8.

8.1.7.6.1 Reference range (Conditional)

Reference Range should be captured as described in 5.8.8.

8.1.7.7 Attribute parameter (Conditional)

The Attribute Parameter class captures additional conditions related to the characteristic attribute.

8.1.7.7.1 Attribute parameter name (Mandatory)

Table 207 — Attribute parameter name

User Guidance	The name of the attribute parameter shall be captured.
Example(s)	Shock frozen condition; storage condition; harvesting condition; micronization temperature; melting point condition; boiling point condition; critical temperature condition; triple point condition; density condition; solubility condition; pH range
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	

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8.1.7.7.2 Attribute parameter value (Mandantory)

Table 208 — Attribute parameter value

User Guidance	The attribute parameter value shall be captured.
Example(s)	Protected from light at –20 °C to –24 °C; Stored protected from light at 0 °C, until processed; Plants are harvested during the whole year after they have been cultivated for at least two growth periods; Undamaged tubers and stored under dry conditions; measured under 101 kPa; Physical state: Liquid, at 0 °C, 31.29 atm at equilibrium; 1 Volume part 20 °C and at a pressure of 101 kPa; Measured at 20 °C; Measured at pH range of 2,5 to 10,5
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	

8.1.7.7.3 Amount (Mandatory)

Amount shall be captured as described in 5.8.

8.1.7.7.3.1 Reference range (Conditional)

Reference Range should be captured as described in 5.8.8.

8.1.8 Fraction description (Conditional)

As has been already described earlier in this document, many complex materials are fractions of parts of plants, animals, or minerals and Fraction elements are often necessary to define both Substances and Specified Group 1 Substances. For substances derived from plants, fraction information is captured at the Substance information level (see 5.9.12), (e.g. Oils, Juices and Exudates). Additional information for Extracts, such as extraction solvent composition, is captured at the Specified Substance Group 1 information level. For plasma-derived products, fraction information is captured both at the Substance level (see 5.9.12) and the Specified Substance Group 1 level (see 7.1.8.1 and 7.1.8.2).

8.1.8.1 Fraction (Conditional)

Table 209 — Fraction

User Guidance	The Fraction attribute at the Specified Substance Group 1 level should be captured as described in 5.9.12.
Example(s)	Extract; Liquid Extract (e.g. *Iberis amara*, Whole Plant, Liquid Extract); Ethanol-Water Liquid Extract (50 – 50 v/v)(1 = 1,5-2.5) (e.g. *Iberis amara*, Whole Plant, Ethanol-Water Liquid Extract (50 – 50 v/v) (1 = 1,5 -2,5)); Dry Extract (e.g. *Ginkgo biloba*, Leaf, Dry Extract); Dry Extract, Acetone-Water (60-40 w/w), (37-65 = 1) (e.g. *Ginkgo biloba*, Leaf, Extract); Dry Extract, Ethanol-Water (60-40 v/v), (1,5-3,0 = 1) (e.g. *Harpagophytum procumbens*, Root, Dry Extract, Ethanol-Water (60-40 v/v) (1,5–3,0=1)); Soft Extract; Dry or Viscous Aqueous Extract
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	When the herbal substance is derived from a fraction of the plant, the description of the fraction is required.

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8.1.8.2 Material type (Conditional)

The material should be captured as described in 5.9.12.2.

8.1.8.3 Reference Source (Conditional)

The reference source information should be captured as described in 5.4.

8.1.8.3.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7.

8.1.9 Modification (Conditional)

Modifications, particularly those involving Herbal preparations, should be captured at the Specified Substance Group 1 level when they are not captured at the substance level (see 5.10).

EXAMPLE The refinement of olive oil to remove or reduce free acids would be a modification captured at the Specified Substance Group 1 level. Partial or complete hydrogenation of given oil would also be captured at the Specified Substance Group 1 level (e.g. castor oil, hydrogenated).

8.1.10 Reference Information (Conditional)

Reference information should be captured as described in 5.6.

8.1.11 Physical form (Conditional)

This subclause is to capture information on the physical form of the Specified Substance (e.g. crystalline amorphous, tincture, dry extract), the state of matter, and slightly more detailed form of the final Specified Substance (e.g. solid, liquid, gas, or emulsion). Biphasic insulin is an example where a part of the insulin is dissolved in solution and the other part is present in a micro-crystalline form. There are also instances of substances being partially crystalline and partially amorphous which would be two different form types and a mixture of Specified Substances, different polymorphic crystalline types. Two polymorphs are distinguished by crystalline type e.g. form 1, form 2, amorphous etc.

The Physical Form is not always applicable (e.g. for multiple substances) and therefore is conditional; however, when it is applicable (e.g. Herbal preparation or when the form of the substance is available), the physical form is required to be provided in accordance with the following specifications.

8.1.11.1 Physical state (Mandatory)

Table 210 — Physical state

User Guidance	The actual state of the substance shall be catured.
Example(s)	Solid, Liquid
Conformance	MANDATORY
Data Type	CD
Values Allowed	Solid, Liquid, Gas, Emulsion, Gel
Business Rule(s)	

8.1.11.2 Physical form type (Conditional)

Table 211 — Physical form type

User Guidance	The type of the physical form should be captured.
Example(s)	Crystalline, Amorphous, Tincture, Dry extract
Conformance	CONDITIONAL

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Data Type	CD
Business Rule(s)	The element defines a new Specified Substance Group 1 ID.

8.1.11.3 Amount (Conditional)

Amount shall be captured as described in 5.8.

When there is an amount, it shall be specified as an observation with a quantifiable unit of measurement e.g. not a non-numeric value.

8.1.11.3.1 Reference range (Conditional)

Reference Range should be captured as described in 5.8.8

8.2 Specified substance Group 2 (Conditional)

Specified Substances Group 2 is used to capture the manufacturer of a given substance as well as limited manufacturing information. The defining elements are the parent substance which is either a Substance or a Specified Substance Group 1. Many biosimilar substances will be distinguished at this level. Any manufacturing information specific to the finished product is described based on the ISO 11615 standard and according to the specifications outlined in ISO/TS 20443 and ISO/TS 20451.

Each manufacturer shall be identified with a code, such as D.U.N.S. number (as ID), and a name. The Manufacturing Type can be Manufacturer. The description of the repackager or distributor is specified at the medicinal product level; it is based on the ISO 11615 standard and according to the specifications outlined in ISO/TS 20443 and ISO/TS 20451. It is also important to capture the Production Method Type (i.e. synthetic, extraction, biosynthetic), Production System Type and the Production System that describe the cell line or animal from which a given substance is isolated.

The manufacturer is not necessarily the entity that has market authorization, but the entity that manufactures the material. If a substantial change in a critical manufacturing process occurs, a new Specified Substance Group 2 ID shall be generated. This would result in a new version of the Specified Substance Group 2. The grade of a material as described for Specified Substance Group 3 can also be provided as a non-definitional field when relevant.

As shown in Figure 36, the Element Group 'Reference Source Document' is included. The attribute 'Reference Source Document Type' provides the manufacturer to submit the Release specification of the manufactured preparation.

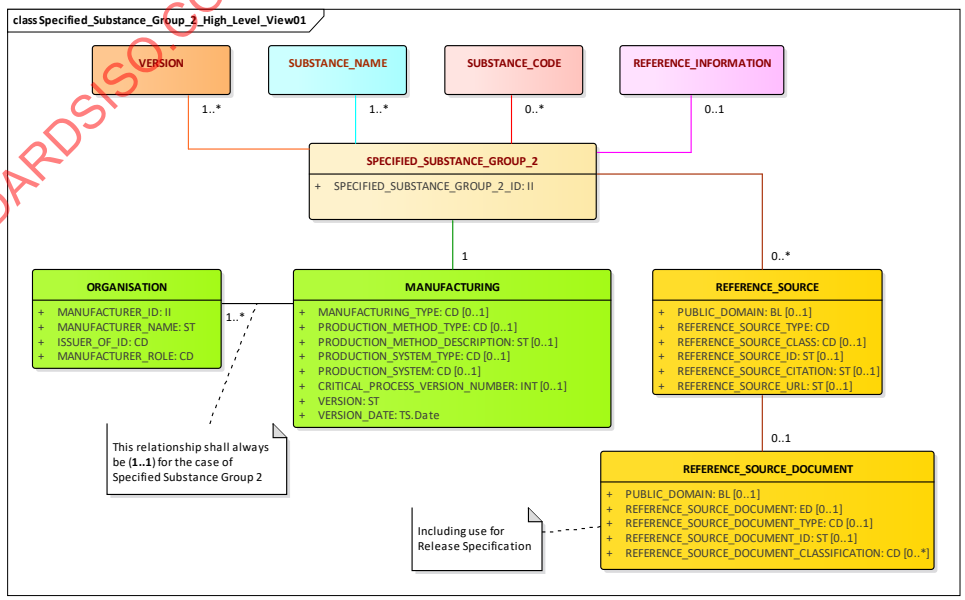


Figure 36 — Information model for the Specified Substance Group 2

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In this version of the ISO/TS 19844 Implementation Guidance, only the Element Group Manufacturing (classes in green colour in Figure 36) shall be implemented to include only the attributes within these classes. However, in this version of the document, the Manufacturing class shall be extended to cover extended manufacturing information, e.g. see Figure E.7 of the Herbal Annex to describe multiple extraction methods. This (extended) manufacturing information is also intended to capture the starting materials, impurities and the intended manufactured substance as shown in Figure 37 as part of the Specified Substance Group 4.

In Annex E, the model for a 'limited' extended information for Manufacturing (Figure E.7) is provided to serve the Herbal use cases for the Herbal preparation Extracts.

NOTE In the class 'Organization' in Figure 36, the elements 'Manufacturer ID' and 'Manufacturer Name' correspond to the information provided in accordance with the CTD[17] module M3, section 3.2.S.2.1 Manufacturer information. This means when the production method type is the same for different manufacturing sites of the same manufacturer, the SSG2 ID is the same in the case of limited manufacturer information. When differences exist according to the production method, the ID needs to be changed.

However, when conditions are fulfilled in accordance with the extended manufacturing model (see Figure E.7) the SSG2 ID will be site specific and trigger a different ID (also in the case when the same production method is used).

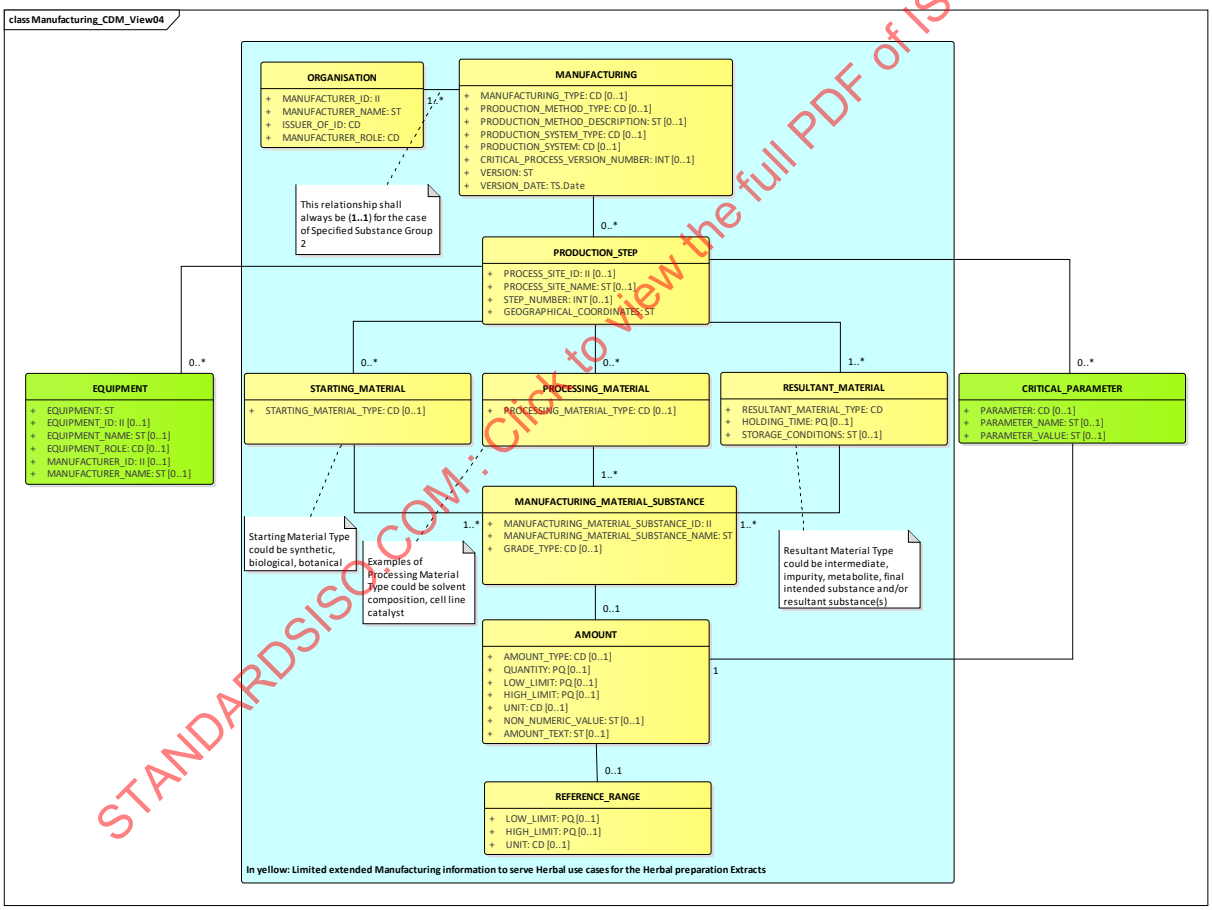


Figure 37 — Information Model for Manufacturing

17 The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q_R1_.pdf

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8.2.1 Specified Substance Group 2 ID (Mandatory)

Table 212 — Specified Substance Group 2 ID

User Guidance	The unique identifier assigned to the Specified Substance Group 2 shall be specified. NOTE If a unique "Specified Substance ID" has been assigned, this "Specified Substance ID" is specified based on the Substance Name controlled vocabulary. In the absence of a unique "Specified Substance ID" e.g. for the initial submission of the substance this data element is not required.
Example(s)	KHJTYD674R (Artificial ID)
Conformance	MANDATORY
Data Type	II
Business Rule(s)	NOTE The Specified Substance ID is NOT SPECIFIED for Specified Substance ID Request

8.2.2 Substance Name (Mandatory)

Names associated with a Specified Substance Group 2 shall be captured as described in 5.3. The name should be coined from a concatenation of the preferred term of the parent substance and the manufacturer (e.g. Human Insulin Drugco; Human Insulin Lilly). Trade names associated with the manufacturer will be captured at this level. Regions may provide additional guidance as the latest version of the Naming Conventions document (Ref. Doc.: EMA/720247/2011).

8.2.3 Substance code (Conditional)

Codes associated with a Specified Substance Group 2 should be captured as described in 5.5.

8.2.4 Reference source (Conditional)

The reference source information should be captured as described in 5.4.

8.2.4.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7.

8.2.5 Reference information (Conditional)

The reference source information should be captured as described in 5.6.

8.2.6 Version (Mandatory)

Version information associated with a Specified Substance Group 2 shall be captured as described in 5.12.

8.2.7 Manufacturing (Mandatory)

The manufacturing information shall be provided according to the specifications described below.

8.2.7.1 Manufacturing type (Conditional)

Table 213 — Manufacturing type

User Guidance	The type of operation performed by the entity associated with the substance.
Example(s)	Manufacturer (of Substance or Specified Substance), Harvester, Manufacturer/Grinder of bulk susbtance
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	For substance that are active ingredients intended to be used in the medicinal product, the element is always mandatory.

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	For excipients (non-active ingredients intended to be used in the medicinal product) the information is optional but for certain excipients that cause an intolerance or allergenic reaction (e.g. sesame oil) this information shall always be provided. NOTE In some cases, this element takes the same value as the 'Manufacturer Role' element (), e.g. when dealing with a Bulk Substance, but when dealing with the extended manufacturing model, these values could be different: a) Manufacturer (for the Bulk Substance) and Manufacturer/Grinder for a specialized company in making a specific particle size range.

8.2.7.2 Production method type (Conditional)

Table 214 — Production method type

User Guidance	The overall type of production system should be described e.g. synthetic, extraction, biosynthetic, extraction and potentization, chemical solubility and potentization, chemical mixing and potentization.
Example(s)	Synthetic, extraction, percolation, biosynthetic, semi-synthetic, extraction and potentization, chemical solubility and potentization, chemical mixing and potentization, harvesting, fractionation, fermentation and chemical synthesis, vaccine production
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	For substance that are active ingredients intended to be used in the medicinal product, the element is always mandatory. For excipients (non-active ingredients intended to be used in the medicinal product) the information is optional but for certain excipients that cause an intolerance or allergenic reaction (e.g. sesame oil) this information shall always be provided.

8.2.7.3 Production method description (Conditional)

Table 215 — Production method description

User Guidance	The production method description should be captured.
Example(s)	“Chemical synthesis from starting materials, purification steps and recrystallization to obtain crystalline form 1”. “Nuclide production by bombardment of [^{18}O] by accelerated protons in a Cyclotron: ^{18}O(p,n)^{18}F, followed by radiolabelling of a precursor substance by a chemical substitution on a radio synthesizer. The substance is not isolated during manufacturing”. “See, Document enclosed at Regulatory submission”. “Mother tinctures prepared according to Ph. Eur. Method 1.1.10 are prepared by maceration using 1 part of Herbal Drug and 10 parts of ethanol of the appropriate concentration. Generally used for Herbal Drugs (fresh or dried)”. “The preparation of a herbal extract’. “Cutting, fragmenting”. “Inoculation, Cultivation (including feeding composition), Harvesting and storing the mite culture and extraction”. “Continuous plasma fractionation from Human Plasma for Fractionation” “Fractionation, absorption, virus inactivation and depth filtration”
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	For substance that are active ingredients intended to be used in the medicinal product, the element is mandatory.

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	For excipients (non-active ingredients intended to be used in the medicinal product) the information is optional but for certain excipients that cause an intolerance or allergenic reaction (e.g. sesame oil) this information shall always be provided. The production method description shall be captured when the Substance Name Type is provided as Specified Homeopathic, or Herbal.

8.2.7.4 Production system type (Conditional)

Table 216 — Production system type

User Guidance	This element should capture information related to Production System Type.
Example(s)	Plant, animal, bacterial, fungal, insect cell line, yeast, mammalian cell line, human cell line, animal tissue, human tissue, solid phase chemistry, solution chemistry, condensation chemistry, chemical synthesis, nuclide production by bombardment of a parent substance followed by radiolabelling, continuous plasma fractionation from human plasma for fractionation, continuous plasma fractionation from Cryopoor plasma, continuous plasma fractionation from Cryopoor plasma process flow 'N', continuous plasma fractionation from Cryprecipitate, continuous thermal decomposition, fermentation harvesting and purification
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	For substance that are active ingredients intended to be used in the medicinal product, the element is mandatory. For excipients (non-active ingredients intended to be used in the medicinal product) the information is optional but for certain excipients that cause an intolerance or allergenic reaction (e.g. sesame oil) this information shall always be provided. The information shall be captured for all material derived from extractive or biosynthetic production methods and some synthetic peptides and nucleic acids. Versioning shall be tied to the element Production System Type.

8.2.7.5 Production system (Conditional)

Table 217 — Production system

User Guidance	The production system description should be provided when available. Should be captured for all material derived from extractive or biosynthetic production methods and some synthetic peptides and nucleic acids.
Example(s)	CHO cell, goat, bovine lungs, FMOC Chemistry, *Escherichia* coli AD494, Bacteria
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	For substance that are active ingredients intended to be used in the medicinal product, the element is mandatory. For excipients (non-active ingredients intended to be used in the medicinal product) the information is optional but for certain excipients that cause an intolerance or allergenic reaction (e.g. sesame oil) this information shall always be provided. Production System, Production System Type and Production Method Type are all to be represented in one terminology. When applicable and available it shall be provided. Versioning shall be tied to the element Production System (see also)

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8.2.7.6 Critical process version number (Conditional)

Table 218 — Critical process version number

User Guidance	Should be captured for material derived from both extractive and biosynthetic production method, for synthesized peptides and nucleic acids, chemical and polymer substances.
Example(s)	2
Conformance	CONDITIONAL
Data Type	INT
Values Allowed	Start at one and increase if a major change in a critical process step occurs (i.e. changes in master cell bank; elimination or addition of a chromatographic purification process).
Business Rule(s)	The critical process version number shall be tied to the Production System. For substances that are active ingredients intended to be used in the medicinal product, the element is mandatory. For excipients (non-active ingredients intented to be used in the medicinal product) the information is optional but for certain excipients that cause an intolerance or allergenic reaction (e.g. sesame oil) this information shall always be provided. Production System, Production System Type and Production Method Type are all to be represented in one terminology. When applicable and available it shall be provided.

NOTE The version is tied to the Production System Type and will change if a critical process changes.

8.2.7.7 Version (Mandatory)

Table 219 — Version

User Guidance	The version of a production process has an alpha numerical value. The version is tied to the Production System Type (as described in) and the critical production process.
Examples(s)	NITROUS-001, POTO-001, BBTH-001, FLORF18, CALSYN-001, CALREC-001, ManBCG002
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	

8.2.7.8 Version date (Mandatory)

Table 220 — Version date

User Guidance	The version date shall be provided.
Examples(s)	20110601
Conformance	MANDATORY
Data Type	TS.Date
Business Rule(s)	

8.2.7.9 Organization (Mandatory)

The manufacturer information shall be provided according to the specifications described below. For both active ingredients and excipients intended to be used in the medicinal product, the information shall be provided.

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8.2.7.9.1 Manufacturer ID (Mandatory)

Table 221 — Manufacturer ID

User Guidance	The unique code used to track manufacturers shall be provided.
Example(s)	DUNS86745HF (Artificial ID)
Conformance	MANDATORY
Data Type	II
Business Rule(s)	For both active ingredients and excipients intended to be used in the medicinal product the information shall be provided. A necessary condition for the Specified Substance Group 2 to exist is: either the Manufacturer ID, Manufacturer Name and Manufacturing Type is available AND/OR the production method type, product system type and production system exist. The manufacturer and Production Method Description can coexist, but at least one shall be provided. The Manufacturer ID for the Specified Substance Group 2 shall be linked to the actual Manufacturing site where the substance is manufactured. If necessary, bulk substance manufacturing site and further steps (e.g. micronization site) shall be provided. The Manufacturer ID is primarily linked to the bulk manufacturing of the substance. When other sites are needed to describe additional production steps this information shall be captured by the Reference Source Document class.

8.2.7.9.2 Manufacturer name (Mandatory)

Table 222 — Manufacturer name

User Guidance	The name of the manufacturer of the Specified Substance as provided in CTD 3.2.S.2.1
Example(s)	Company ABC, (Address, Geographical coordinates)
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	For both active ingredients and excipients intended to be used in the medicinal product the information shall be provided.

NOTE The process by which valid Manufacturer IDs are captured will be defined by Regional Guidance.

8.2.7.9.3 Issuer of ID (Mandatory)

Table 223 — Issuer of ID

User Guidance	The organization issuing the Manufacturer ID shall be specified
Example(s)	EMA OMS, DUNS
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	

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8.2.7.9.4 Manufacturer role (Mandatory)

Table 224 — Manufacturer role

User Guidance	The role of the manufacturer shall be specified.
Example(s)	Manufacturer; Manufacturer/Grinder of the bulk substance; Harvester and Manufacturer of Botanical Material; Harvester
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	

8.3 Specified Substance Group 2 Extended (Conditional)

8.3.1 Specified Substance Group 2 ID (Mandatory)

Table 225 — Specified substance Group 2 ID

User Guidance	The unique identifier assigned to the Specified Substance Group 2 shall be specified. NOTE If a unique "Specified Substance ID" has been assigned, this "Specified Substance ID" is specified based on the Substance Name controlled vocabulary. In the absence of a unique "Specified Substance ID" e.g. for the initial submission of the substance this data element is not required.
Example(s)	AGHFT4352E (Artificial ID)
Conformance	MANDATORY
Data Type	II
Business Rule(s)	NOTE The Specified Substance ID is NOT SPECIFIED for Specified Substance ID Request.

8.3.2 Substance Name (Mandatory)

Names associated with a Specified Substance Group 2 shall be captured as described in 5.3. The name should be coined from a concatenation of the preferred term of the parent substance and the manufacturer [e.g. *Harpagophytum procumbens*, Root, Dry Extract Ethanol-Water (60-40) (1.5–3.0 = 1 w/w) — Manufacturer Ex.]. Trade names associated with the manufacturer will be captured at this level. Regions may provide additional guidance.

8.3.3 Substance code (Conditional)

Codes associated with a Specified Substance Group 2 should be captured as described in 5.5.

8.3.4 Reference source (Conditional)

The reference source information should be captured as described in 5.4.

8.3.4.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7

8.3.5 Reference information (Conditional)

The reference source information should be captured as described in 5.6.

8.3.6 Version (Mandatory)

Version information associated with a Specified Substance Group 2 shall be captured as described in 5.12.

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8.3.7 Manufacturing (Mandatory)

The manufacturing information shall be provided according to the specifications described below.

8.3.7.1 Manufacturing type (Conditional)

The manufacturing type information should be captured as described in 7.2.7.1.

8.3.7.2 Production method type (Conditional)

The production method type type information should be captured as described in 7.2.7.2.

8.3.7.3 Production method description (Conditional)

The production method description information should be captured as described in 7.2.7.3.

8.3.7.4 Production system type (Conditional)

The production system type information should be captured as described in 7.2.7.4.

8.3.7.5 Production system (Conditional)

The production system information should be captured as described in 7.2.7.5.

8.3.7.6 Critical process version number (Conditional)

The critical process version number information should be captured as described in 7.2.7.6.

8.3.7.7 Version (Mandatory)

The version information shall be captured as described in 7.2.7.7.

8.3.7.8 Version date (Mandatory)

The version date information shall be captured as described in 7.2.7.8.

8.3.7.9 Organization (Mandatory)

The Organization information shall be captured as described in 7.2.7.9.

8.3.7.10 Production step (Conditional)

This class captures information about process site identifier, process site name, step number and geographical coordinates of the site location.

8.3.7.10.1 Process site ID (Conditional)

Table 226 — Process site ID

User Guidance	The unique identifier assigned to the process site shall be specified.
Example(s)	
Conformance	CONDITIONAL
Data Type	II
Business Rule(s)	

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8.3.7.10.2 Process site name (Conditional)

Table 227— Process site name

User Guidance	The process site name should be specified in accordance to CTD 3.2.S.2.1[18]
Example(s)	Company ABC, Germany (Address, Geographical coordinates)
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	

8.3.7.10.3 Step number (Conditional)

Table 228 — Step number

User Guidance	The number indicating the order of the step in the manuafacturing process should be specified.
Example(s)	
Conformance	CONDITIONAL
Data Type	INT
Business Rule(s)	

8.3.7.10.4 Geographical coordinates (Mandatory)

Table 229 — Geographical coordinates

User Guidance	The Geographic Coordinates of the site location shall be specified.
Example(s)	
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	

8.3.7.10.5 Starting material (Conditional)

This class should capture information of starting material(s) used in production step.

8.3.7.10.5.1 Starting material type (Conditional)

Table 230 — Starting material type

User Guidance	The type of the starting material(s) shall be provided for each production step.
Example(s)	Chemical substance, Protein Substance, Herbal Substance
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	

8.3.7.10.5.2 Manufacturing material substance (Mandatory)

Material to be used to manufacture a starting, processing or resultant material.

[18] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q__R1_.pdf

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8.3.7.10.5.2.1 Manufacturing material substance ID (Mandatory)

Table 231 — Manufacturing material substance ID

User Guidance	The unique identifier assigned to the substance that is described as a starting, processing or resultant material shall be specified.
Example(s)	Water67543 (Artificial ID)
Conformance	MANDATORY
Data Type	II
Values Allowed	ISO 11238 Substance ID
Business Rule(s)	

8.3.7.10.5.2.2 Manufacturing material substance name (Mandatory)

Table 232 — Manufacturing material substance name

User Guidance	The name of the substance that is described as a starting, processing or resultant material shall be specified.
Example(s)	Water (Buffer solution), Mixture of (*Lolium perenne*, Pollen; Arrhenatherum *elatius*, Pollen; *Dactylis glomerata*, Pollen; *Secale cereale*., Pollen; *Festuca rubra*, Pollen; *Agrostis stolonifera*, Pollen; *Phleum pratense*, Pollen; *Poa pratensis*, Pollen; *Anthoxanthum odoratum*, Pollen; *Holcus lanatus*, Pollen)
Conformance	MANDATORY
Data Type	ST
Values Allowed	ISO 11238 Substance Name
Business Rule(s)	

8.3.7.10.5.2.3 Grade type (Conditional)

Table 233 — Grade type

User Guidance	The Grade type should be specified of the Starting, Processing or Resultant Material
Example(s)	Compendial; Ph.Eur.; USP; JP; In-House
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	

8.3.7.10.5.2.4 Amount (Conditional)

Amount shall be captured as described in 5.8.

8.3.7.10.5.2.5 Reference range (Conditional)

Reference Range should be captured as described in 4.8.8.

8.3.7.10.6 Processing material (Conditional)

Material to be used in a manufacturing process step.

8.3.7.10.6.1 Processing material type (Conditional)

Table 234 — Processing material type

User Guidance	The type of the processing material(s) should be specified for each production step.

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Example(s)	solvent composition; cell line catalyst, modification agent, extraction solvent
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	

7.3.7.10.6.1.1 Manufacturing material substance (Mandatory)

Manufacturing material substance information shall be captured as described in subclause 7.3.7.10.5.2.

7.3.7.10.6.1.1.1 Amount (Conditional)

Amount should be captured as described in 5.8.

7.3.7.10.6.1.1.1.1 Reference range (Conditional)

Reference Range should be captured as described in 4.8.8.

8.3.7.10.7 Resultant material (Mandatory)

Material as a result of a manufacturing process step.

8.3.7.10.7.1 Resultant material type (Mandatory)

Table 235 — Resultant material type

User Guidance	The type of resultant material(s) shall be specified for each production step.
Example(s)	intermediate; impurity; metabolite; final intended substance; resultant substance(s); resultant substance (step 1)
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	

8.3.7.10.7.2 Holding time (Conditional)

Table 236 — Holding time

User Guidance	The holding time of the resultant material should be specified for each subsequent production step.
Example(s)	5 days NOTE 5 days in this example means the time between two production steps.
Conformance	CONDITIONAL
Data Type	PQ
Business Rule(s)	

8.3.7.10.7.3 Storage conditions (Conditional)

Table 237 — Storage conditions

User Guidance	The storage conditions of the resultant material should be specified.
Example(s)	Store at 25 °C, 60 % RH, protected from light, in double LDPE bags in a fibre drum
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	

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8.3.7.10.7.3.1 7.3.7.10.7.3.1 Manufacturing material substance (Mandatory)

Manufacturing material substance information shall be captured as described in subclause 7.3.7.10.5.2.

7.3.7.10.7.3.1.1 Amount (Conditional)

Amount should be captured as described in 5.8.

7.3.7.10.7.3.1.1.1 Reference range (Conditional)

Reference range should be captured as described in 4.8.8.

8.4 Specified Substance Group 3 (Conditional)

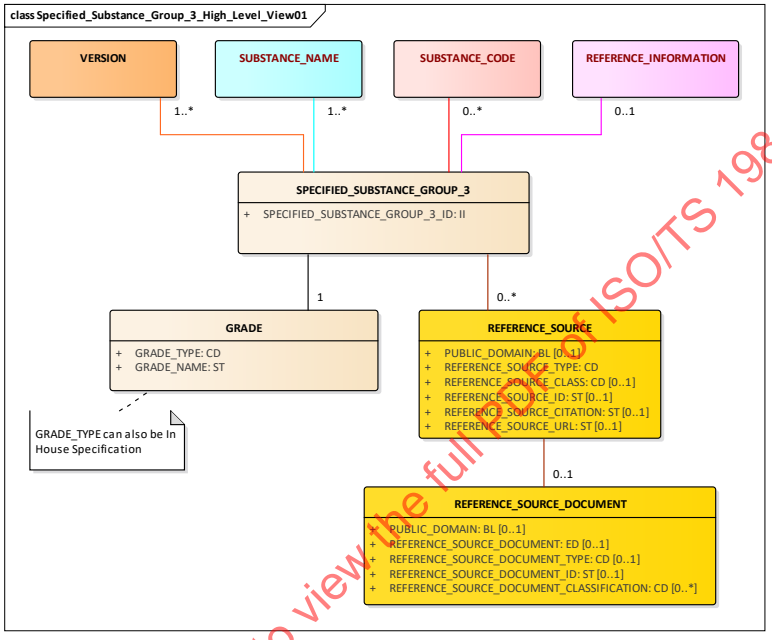


Figure 38 — Information model for the Specified Substance Group 3

Figure 38 provides the information to capture the grade of a substance. This group is meant to be for Pharmacopoeial Grades (Ph.Eur., USP). Each grade will lead for a separate Specified Substance Group 3 Identifier. However, there are applications in which regulatory approval has been achieved for more than one grade and sometimes the sponsor will add an extra specification, such as particle size which is not captured in the Pharmacopoeial monograph. In this case the model provides in the Reference documentation type "In-House" Grade in which a specification set can be laid down covering the Ph.Eur., USP as well as the intended particle size.

NOTE The general model 'Substance – Specified Substance' as presented in Figure 1 allows to connect a Specified Substance Group 2 to Specified Substance Group 3. There are many examples in which an In-house specification is provided for a given substance tied to a specific manufacturer. This In-house specification might be covering the Ph.Eur. but is tightened. So the grade (Ph. Eur. or USP) is provided and an In-house specification which makes it necessary to connect a Specified Substance Group 2 to a Specified Substance Group 3.

The information on the grade shall be specified by means of the following data elements.

8.4.1 Specified Substance Group 3 ID (Mandatory)

Table 238 — Specified Substance Group 3 ID

User Guidance	The unique identifier assigned to the Specified Substance Group 3 shall be specified. NOTE If a unique "Specified Substance ID" has been assigned, this "Specified Substance ID" is specified based on the Substance Name controlled vocabulary.

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	In the absence of a unique "Specified Substance ID" *e. g.* for the initial submission of the substance this data element is not required.
Conformance	MANDATORY
Data Type	II
Business Rule(s)	NOTE The Specified Substance ID is NOT SPECIFIED for Specified Substance ID Request

8.4.2 Substance Name (Mandatory)

The name of the Specified Substance Group 3 shall be provided in this field or it should be derived from the Specified Substance Group 1 Name (Preferred Term).

EXAMPLE Name in monograph appended to Grade Type (i.e. sterile water for injection USP).

Every reference to Pharmacopoeia generates a separate Secified Substance Group 3 identifier.

When reference is made to two or more Pharmacopoeias an In-House specification should be laid down covering both the Pharmacopoeial specifications.

The element shall be captured as shown in 5.3.

8.4.3 Grade (Mandatory)

The characteristics of the grade of the substance shall be specified.

8.4.3.1 Grade type (Mandatory)

Table 239 — Grade type

User Guidance	Pharmacopoeial specification type or other specification type including In-house specification. European Pharmacopoeia [Ph. Eur.], United States Pharmacopoeia [USP], British Pharmacopoeia [BP], and Japanese Pharmacopoeia [JP] are examples of Grade Type. In-house specification type is referring to the specification as laid down by the Applicant/Sponsor.
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	Each Pharmacopoeial Specification shall be given a separate record as described in the applicable Annexes.

8.4.3.2 Grade name (Mandatory)

Table 240 — Grade name

User Guidance	Typically, the Monograph Title that refers to a given Substance or Specified Substance; for herbal substances standardized or non-standardized will be appended to the name along with standardization.
Example(s)	quantified, standardized
Conformance	MANDATORY
Data Type	ST

8.4.4 Version (Mandatory)

Version information associated with a Specified Substance Group 3 shall be captured as described in 5.12.

8.4.5 Substance code (Conditional)

Codes associated with a Specified Substance Group 3 should be captured as described in 5.5.

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8.4.6 Reference information (Conditional)

Reference information should be captured as described in 5.6.

8.4.7 Reference source (Conditional)

The reference source information should be captured as described in 5.4.

8.4.7.1 Reference source document (Conditional)

The reference source document information should be captured as described in 5.4.7.

9 Description of the information modelling principles and practices

9.1 General considerations

The information modelling in this document follows the general principles described in other ISO IDMP Standards and Techncial Specifications (e.g. ISO 11615, ISO 11616, ISO/TS 20443, etc.) and uses the Unified Modeling Language (UML) which is maintained by the Object Management Group (OMG).

UML has different styles and patterns that may be followed. The use of UML in this document has been kept very simple, using classes, attributes, datatypes, and basic association relationships mostly. Some constructs, such as stereotypes and complex relationships have been avoided for this reason. In addition, colour coding has been used in the diagrams to help visualize groups of associated entities (for example, see Figure 39).

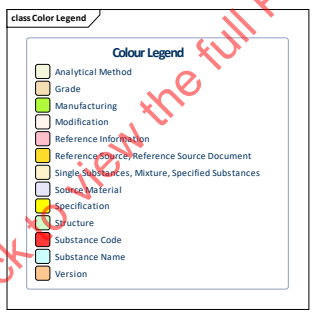


Figure 39 — Legend for Colour Coding of Model Classes

The following aims to explain the style that has been followed in this document.

9.2 Conceptual overview diagrams

The conceptual overview diagram provides a framework with which to view the more detailed descriptions of information

The conceptual overview diagram (see Figure 40) provides a framework with which to view the more detailed descriptions of information. The Substance and Specified Substance high level information models (see Figure 1 and Figure 3) show a single representative class from each information section, related to the core concept (Substance).

Basic cardinalities between the Substance or the Specified Substance and these core classes are shown, but not the detailed entities, relationships or attributes.

NOTE 1 The expressions 'Element Group' and 'Class' have the same meaning in the context of ISO 11238 and ISO/TS 19844.

NOTE 2 The terms cardinality and multiplicity (used by UML) are interchangeable in the context of ISO 11238 and ISO/TS 19844.

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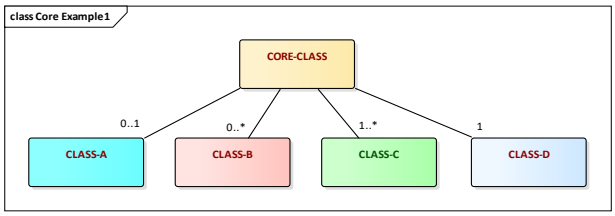


Figure 40 — Example Conceptual Overview Diagram

9.3 Section high-level diagrams

The high-level diagrams (see Figure 41, Figure B.1) show all the classes required to describe the information for that section and the conceptual relationships between those classes, with the starting point always as the section's core class.

No attributes or detailed cardinalities are shown in these conceptual diagrams, as their primary purpose is to provide a framework for viewing the detailed diagrams which follow.

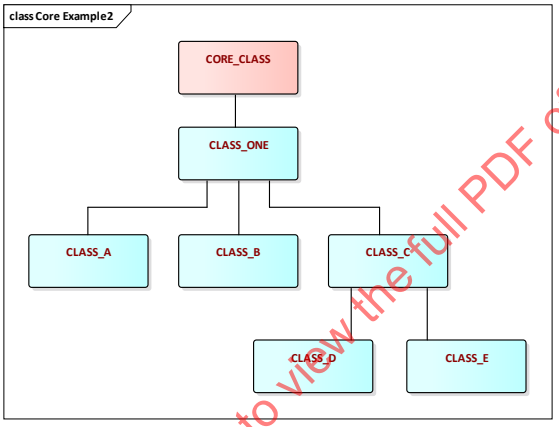


Figure 41 — Example High-level Diagram

9.4 Detailed diagrams

The detailed description diagrams (see Figure 42) for each section show all the classes and all the attributes required to describe the information for that section and the detail of the conceptual relationships between those classes.

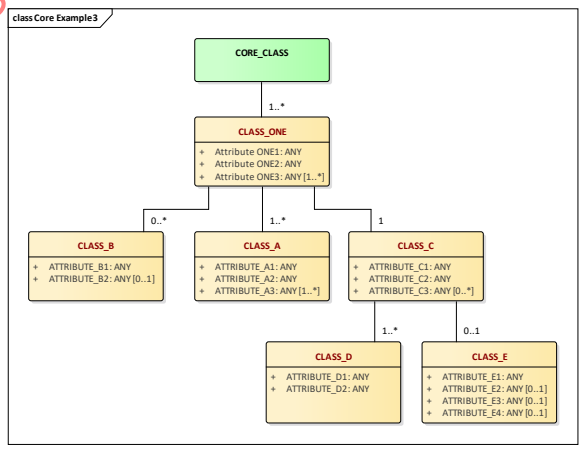


Figure 42 — Example Detailed Description Diagram

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9.4.1 Relationships between classes

Classes related to each other in specific ways. This document uses only a few of the connection features that are possible in UML: association, directed association, reflexive association, multiplicity, aggregation, composition, inheritance/generalization and realization. In the context of this document, the association (Figure 43), multiplicity (Figure 44) and inheritance/generalization (Figure 45).

An association is any logical connection or relationship between classes. For example, MOIETY and AMOUNT may be linked as shown in Figure 43.

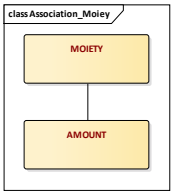


Figure 43 — Association

UML multiplicity is when the number of repetitions of a class in relation to another is shown. For example, one structure may contain zero to many structural representations. The notation 0..* in the diagram means 'zero to many' (see Figure 44).

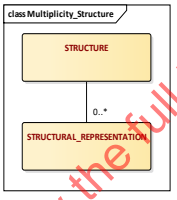


Figure 44 — Multiplicity

Inheritance/generalization (see Figure 45) refers to a type of relationship where one class is a child of another, and assumes the same functionalities of the parent class. For example, the child class Chemical is a specific type of the parent class Single Substance (which itself is a specific type of the parent class Substance). To show inheritance in a UML diagram, a solid line from the child class to the parent class is drawn using an unfilled arrowhead.

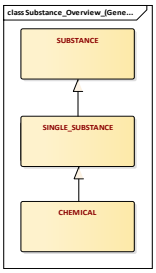


Figure 45 — Inheritance/Generalization

Note When displaying a Class with attributes, the inherited attributes from parents can be shown (see Figure 46), including parents of parents.

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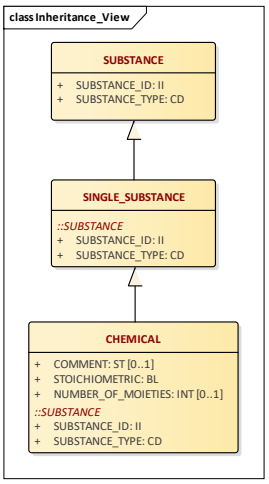


Figure 46 — Display of Inherited Attributes

To keep the model simple, relationships between classes/element groups are generally described as associations having multiplicities, with no further qualification as to the role or type of the association.

Cardinalities on relationships are given in a single direction only: the direction that is away from the Substance/Specified Substance. The rationale for this is that the scope of this document is to describe the Substance/Specified Substance and their associated information. Having these classes always as the source entity avoids describing complex many-to-many cardinalities that might occur in a reverse direction from an entity towards the Substance/Specified Substance.

A cardinality of "1" is synonymous with a cardinality of "1..1".

A cardinality of "1" between entities indicates that the information for that entity shall be specified and that only one set of the entity information shall be given.

A cardinality of "1..*" between entities indicates that the information for that entity shall be specified and that one or more sets of the entity information shall be given.

A cardinality of "0..1" between entities indicates that the information for that entity can be specified and that one set of the entity information can be given.

A cardinality of "0..*" between entities indicates that the information for that entity can be specified and that one or more sets of the entity information can be given.

Some optional entities can be elevated to mandatory if some conditions are met (see subclause).

See ISO 21090 [134] for more information on composition of attributes. An ISO 21090 datatype for the data in each attribute is shown directly in the model and, the text description for each attribute, indicates the form in which data should be specified.

9.4.2 Notes

Notes are comments in the diagrams and may stand on their own or be linked by a dashed line to the elements they are referring to (see Figure 47).

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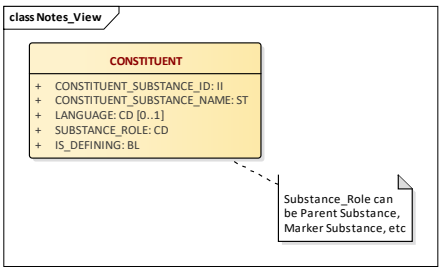


Figure 47 — Note used as a Comment on a Diagram

9.4.3 Attributes

Attributes of a class are described using an attribute name in the model. The definition, description and example values for the attribute are given in the text following the model diagram.

An attribute showing no explicit cardinality means that the attribute shall have one value (this is the equivalent to [1...1]).

An attribute showing a cardinality of [1...*] means that the attribute shall have one or more values.

An attribute showing a cardinality of [0...1] means that the attribute may have one value.

An attribute showing a cardinality of [0...*] means that the attribute may have one or more values.

All optional attributes can be conditionally elevated to mandatory if certain conditions are met (see 8.4.5).

See ISO 21090 for more information on composition of attributes.

9.4.4 Message exchange format

HL7 messaging standards are widely implemented globally. ISO[19] recognizes HL7[20] as an accredited partner organization for mutually issuing standards. The first mutually published standard was ISO/HL7 21731 [5][6].

HL7 V3 was developed to address the complex requirements of health information technology. The HL7 model-driven methodology is used to develop consensus-based standards for healthcare system interoperability and information exchange. The HL7 Reference Information Model (RIM) is the cornerstone of V3 and the essential model from which all HL7 V3 messages are derived. The RIM defines data content needed in a specific context and provides an explicit representation of the semantic and lexical connections that exist between the information items carried. HL7 V3 messages are based on an XML encoding syntax.

HL7/FHIR (Fast Healthcare Interoperability Resources)[21] is a new specification based on emerging industry approaches, but informed by years of lessons learned and experience gained of requirements, successes and challenges gained through implementing HL7 V2, HL7 V3 and CDA. FHIR was built using the modern technology of the Internet, particularly RESTful interfaces. It is organized around the concept of "resources" and defines many types of resources that describe the healthcare space. FHIR is rapidly becoming the worldwide standard for health and life sciences data exchange. It has an open license, a focus on implementation, and a formal maturity process linked to implementation outcomes [7].

The ISO IDMP standards were designed to specify the necessary data elements and associated standards to be used to support unique identifiers. These were developed as an integral part of the IDMP consensus requirements and they are consistent with the HL7 Common Product Model (CPM) V4 [8] and the HL7 Structured Product Labeling V8 (SPL) [9]. The IDMP data elements represent a subset of those in the CPM.

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19 http://www.iso.org

20 http://www.hl7.org

21 http://www.hl7.org/fhir

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In addition, the FHIR SubstanceSpecification[22] and MedicinalProduct[23] resources will ensure that FHIR is one of the messaging options for IDMP in the short and long term.

It is anticipated that implementation of ISO 11238 will use HL7 messaging standards. The normative use of HL7 standards will facilitate the integration of IDMP into the broader healthcare community.

9.4.5 Conformance terminology and context as it relates to the ISO 11238 and ISO/TS 19844 exchange format

— *Mandatory*: Defining elements ***necessary*** for the unique identification of Substances and Specified Substances per the ISO IDMP standards/technical specifications.

— *Conditional*: Conditional applies to the 'within category' data elements, as applicable, when there are alternative data sources for a given data element(s) to identify a Substance/Specified Substance. Regional implementation of the ISO 11238 and ISO/TS 19844 may elevate the conditional conformance categories to '***mandatory***' per regional requirements.

— *Optional*: When listed at the category level (e.g. Specified Substance), optional corresponds to ISO categories or data elements that are not absolutely necessary for the ***unique*** identification of Substances/Specified Substances as per ISO 11238 standard and ISO/TS Technical Specification. Regional implementation of the ISO 11238 and ISO/TS 19844 may elevate the optional conformance categories to ***'mandatory'*** or ***'conditional'*** per regional requirements.

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[22] http://wiki.hl7.org/index.php?title=SubstanceSpecification_FHIR_Resource_Proposal

[23] http://wiki.hl7.org/index.php?title=MedicinalProduct_FHIR_Resource_Proposal

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Annex A
(normative)

Choosing a Substance ID

A.1 General

Public access to substance identifiers should be provided. Identifiers should be mapped to a variety of names and also provide defining information to assist in proper choice of a substance identifier. Before requesting a Substance ID, the Substance ID list on the public website should be checked to determine if a Substance ID has already been generated for the relevant substance. Most of the substances in medicinal products will already have a substance identifier associated with the material.

When selecting a Substance ID, always choose the Substance ID that is the most specific to the material being used. For example, for bacterial derived products, if a single strain of bacteria is used in a given product, the identifier should map to the particular strain. For other products, the strain may not be known or important for the function of the product and in that instance an identifier for the bacterial species may be sufficient to describe the material. In general, for structurally diverse material derived from biological matrices an attempt should always be made to map the material at least to the species level.

For chemical substances, material that differs either in salt or solvate stoichiometry will be assigned separate identifiers. It is important to choose the identifier that maps to the actual material used in the product. It should be noted that the same USAN and INN will frequently map to different substances. INN typically do not refer to solvated substances while USAN names do. For example, the USAN term Amoxicillin is defined as a trihydrate while the INN term Amoxicillin refers to the anhydrous substance.

Care should always be taken to ensure that the correct substance identifier is used in describing the formulation of a product. In ISO 11615, substance identifiers are also needed for both the active moiety and the basis of strength. Links between substance and active moieties for all active substances that can be used in a product should be provided. Pharmacopoeias or the maintenance organization may also need to be consulted to determine the substance identifier to be used for the basis of strength for a given product. The concept of what constitutes an active moiety could vary between jurisdictions or even by type of product. The substance or concept related to basis of strength will often be indicated in regional pharmacopoeias and could vary between regions.

A.2 Requesting a Substance ID and providing information

If the appropriate Substance ID is not available on this list, a Substance ID request should be sent to the maintenance organization.

In submitting information for the assignment of a Substance ID, any information considered confidential should be so indicated. Any confidential information linked to the substance will only be released with the permission of the submitter or if it is unambiguously found in the public domain associated with the substance.

If a chemical structure or protein sequence is found in INN, USAN, or JAN, that information along with the Substance ID should be released to the public even if it was marked confidential when the Substance ID was generated. Substance identifiers will not be released to the public unless the defining information is in the public domain and unambiguously associated with the preferred term of a given substance. For substances identified with company codes or trade name, the association of the company code or trade name with Substance ID will not be released unless the defining information is found within a single reputable source associated with the company code or trade name. A company can always request to have its trade name or company code associated with a given substance. The company should ensure that

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any substance associated with a trade name or company is completely defined and the trade name unambiguously refers to that single substance or Specified Substance.

At least one name or company code should be associated with each request for a Substance ID. To facilitate mapping and to limit ambiguity, the submitter should include all codes and common names that are known to have been associated with a given substance. Once an ID is assigned it will be permanently associated with that substance. A submitter should explicitly indicate which information, whether defining or reference, is considered to be in the public domain and which is confidential.

The accompanying annex documents will provide information on the specific information that is necessary to assign a Substance ID that is compliant with the ISO standard.

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Annex B
(informative)

Chemical substance

B.1 Introduction

In Figure B.1 a high-level information is provided regarding chemical substances.

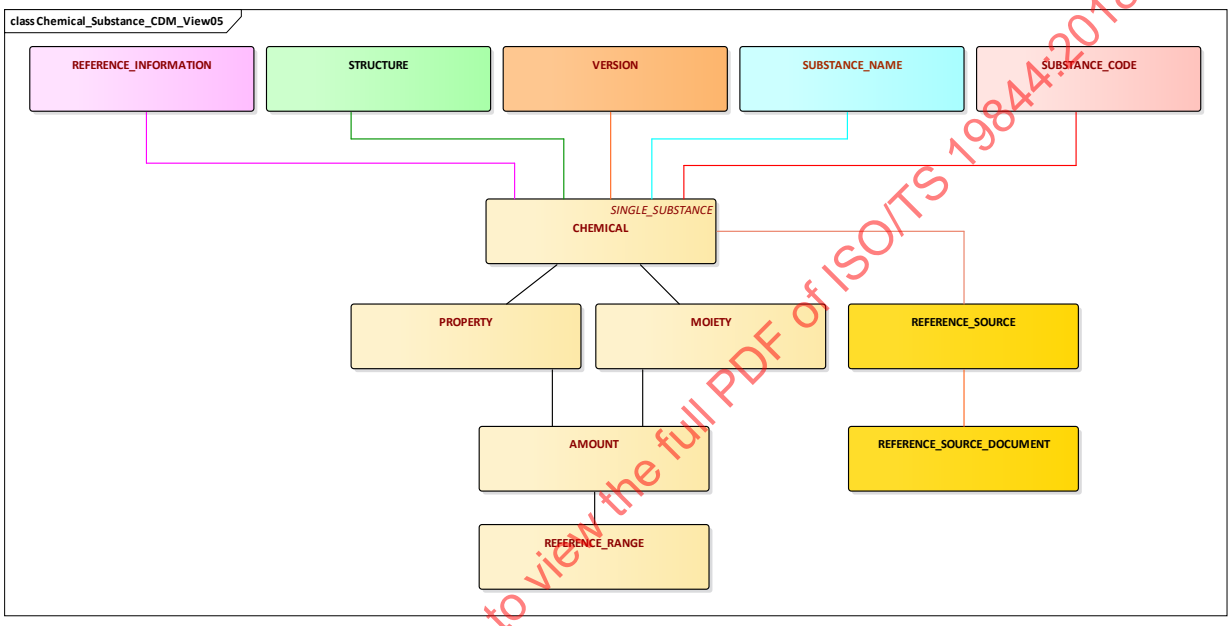


Figure B.1 — High-level overview of Chemical Substance information

NOTE All element names are defined within the Terms and Definitions in the main body of this document.

A substance is described as any matter that has a discrete existence, irrespective of origin, which may be biological or chemical. Characteristics are described by two logical levels: Substance level and Specified Substance level. The chemical substance class is one of the five single substance types (see Figure 3 and 5.2.1).

For both levels, at least one Substance Name or Specified Substance Name is a mandatory object. When in special cases no name has been provided, a (company—) code should be provided with a short description of the substance.

NOTE A company code is considered to be a Substance Name.

Chemical substances, whose primary defining element is the molecular structure, shall be defined on the basis of their complete covalent molecular structure; the presence of a salt (counter-ion) and/or solvates and co-crystals are also captured. The molecular structure, the molecular formula, the molecular weight and optical activity, together with the representation of the stereochemistry are mandatory elements to be provided.

Although the molecular weight can be derived from the structure, this element should be presented at the Substance level for chemical substances in order to substantiate the provided structural information.

The molecular formula should be described according to the moieties even for stoichiometric substances.

EXAMPLE Amlodipine besilate, Element Molecular Formula:

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Molecular Formula: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$

NOTE 1 The molecular formula (see 5.7.3 and 5.7.4) is specified in accordance with the Hill system. For a salt, the base or the acid and the salt moiety are separated by a dot; in this case $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$.

NOTE 2 The representation of the molecular formula is presented per moiety next to (in addition to) the representation of the total elements: $C_{26}H_{31}ClN_2O_8S$.

NOTE 3 For stoichiometric chemicals the molecular formula is directly derived from the molecular structure of the chemical.

Element Group: Molecular Weight

Molecular Weight Method: Calculated

Molecular Weight Type: Number Average

NOTE 4 The molecular weight type for small molecules is number average. There are basically four types of molecular weight available: number average Mn; viscosity average, Mv; weight average Mw; and Z-average, Mz. For further information, see subclause B.6.4 and 6.2.7.

Element Group: Amount

Amount Type: Exact

Average: 567,06 = (408,88 + 158,18) or rounded at 567,1 in accordance with the Ph.Eur. monograph

Unit**:** g/mol

NOTE 5 For stoichiometric chemicals the molecular weight is directly derived from the molecular structure of the chemical.

The Element Group 'Moiety' is attached also to the element class Chemical, Stoichiometric substances and Non-Stoichiometric substances in order to describe a salt and solvates relationship to the active moiety in an unambiguous way with respect to the description of the molecular formula and sometimes the official names.

B.1.1 Molecular Weight, Moiety and Amount for stoichiometric chemical substances

The element Molecular Weight shall be included in the Structure Class and connected to the Element Group Amount. The Element Groups Moiety and Amount should also be tied to the Element Group Stoichiometric substances.

This will help to describe salts, solvates, hydrated substances and co-crystals in a more unambiguous way with respect to the description of the molecular formula and sometimes official names (see Figure B.2).

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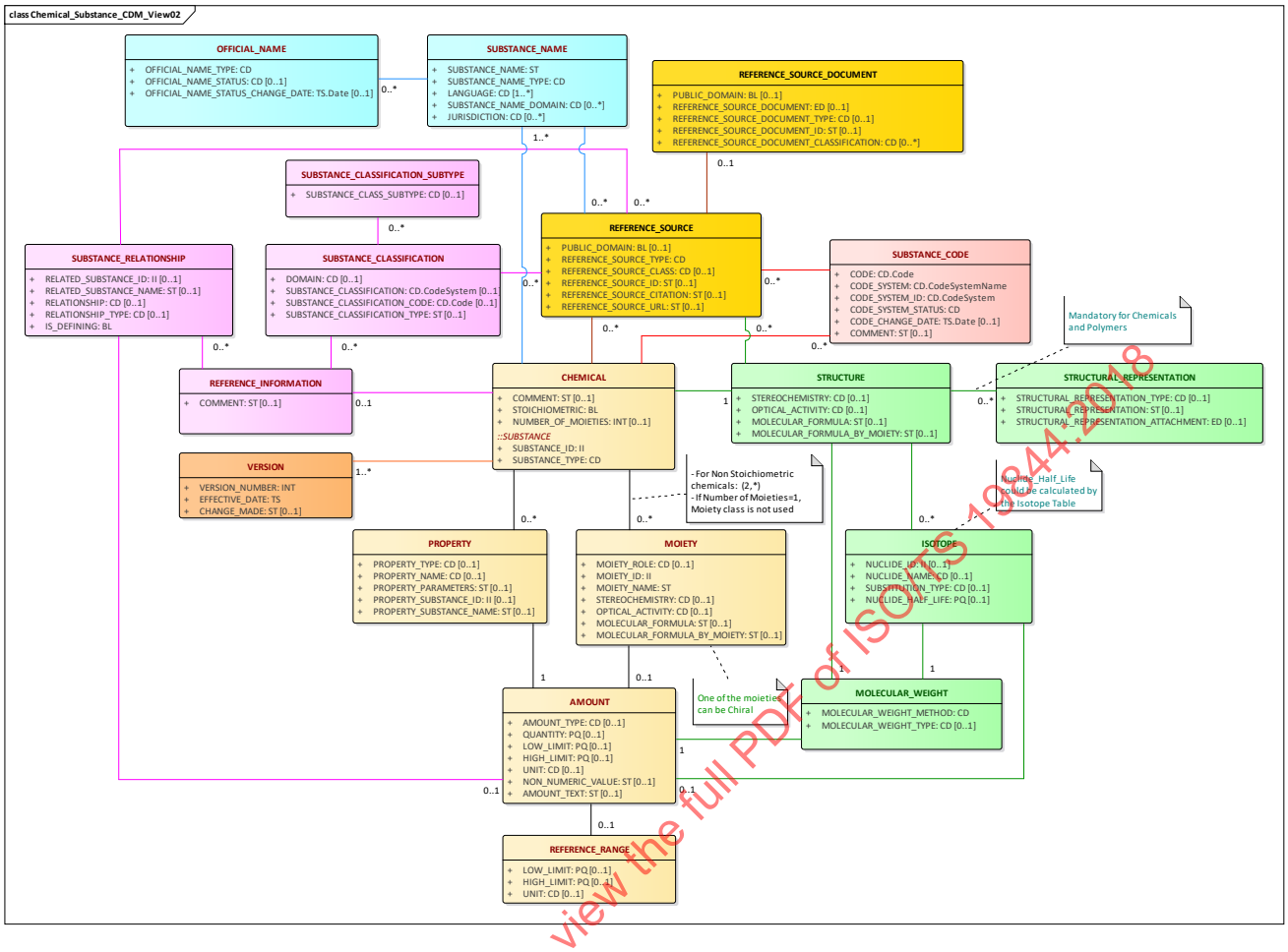


Figure B.2 — Detail overview of Chemical Substance information

According to (EU)-legislation[24] the qualitative and quantitative composition of a medicinal product should be described in terms of the active substances and constituents of the excipient.

This means that weight calculation from the active substance salt/solvate/salt hydrate form has to be calculated and expressed as the active substance base/acid. For this, the molecular formula is needed for the active substance salt/solvate/hydrate form and of the free base. In order to perform this calculation, the molecular weight shall be provided and not only calculated from the structure of the active substance. Therefore, the name of the active substance, including the crystal form, molecular formula and molecular weight are mandatory fields next to the structure to comply with this (EU)-legislation.

The Moiety Group is also tied to the Chemical Substance: e.g.:

Describing Amlodipine besilate hydrate (1:1:1) in equal mole ratios with the Molecular Formula:

$C_{20}H_{25}ClN_2O_5.C_6H_6O_3S.H_2O$ instead of $C_{26}H_{33}ClN_2O_9S$; rINN: = Amlodipine besilate

Molecular Weight: 585,06 = (408,88 + 158,18 + 18,00), rounded to 585,1 g/mol.

There will be two terms used to describe the Molecular Formula:

Molecular Formula: $C_{26}H_{33}ClN_2O_9S$, which is equal to the sum of the molecular formula of the moieties.

Molecular Formula by Moiety: $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S.H_2O$

NOTE ISO/TS 19844 describes moities with no respect to their activity of the substance or how it is used. In order to describe this, we use the element class 'Substance Relationship' to describe the type of the moiety.

[24] Directive 2001/83/EC on the Community code relating to medicinal products for human use.

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B.1.2 Relations with other Element Groups (see Figure B.2)

B.1.2.1 Element Group: Moiety

Element Group: Chemical
Element Group: Stoichiometric
Number of Moieties: 3

Element Group: Moiety
Moiety Role: Parent molecule
Moiety ID: PTYF75643O (Artificial ID); [1J444QC288 (UNII)]
Moiety Name: Amlodipine
Stereochemistry: Racemic
Optical Activity: (+/-)
Molecular Formula: $C_{20}H_{25}ClN_2O_5$

Element Group: Substance Code

Code: SUB05467MIG
Code System: EMA, EVCode
Code System ID: 0051
Code System Status: Migrated

Element Group: Substance Code (Repeat)
Code: 1J444QC288
Code System: FDA Substance Registration (UNII)
Code System ID: 0050
Code System Status: Migrated

Element Group: Moiety
Moiety Role: Salt molecule
Moiety ID: BENZ67891A (Artificial ID);
Moiety Name: Benzenesulfonic acid
Stereochemistry: Achiral
Molecular formula: $C_6H_6O_3S$

Element Group: Substance Code
Code: 685928Z18A
Code System: FDA Substance Registration (UNII)
Code System ID: 0050
Code System Status: Migrated

Element Group: Amount
Amount Type: Exact
Quantity: 1
Unit: {mol/mol}
Amount Text: Mole Ratio to Parent (Amlodipine)

Element Group: Moiety (Repeat)
Moiety Role: Hydrate molecule
Moiety ID: WATE12456H (artificial ID)
Moiety Name: Water
Stereochemistry: Achiral
Molecular Formula: H_2O

Element Group: Amount
Amount Type: Exact

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Quantity: 1
Unit: {mol/mol}
Amount Text: Mole Ratio to Parent (Amlodipine)

Element Group: Substance Code
Code: 059QF0KO0R
Code System: FDA Substance Registration (UNII)
Code System ID: 0050
Code System Status: Migrated

B.1.2.2 Element Group: Substance Relationship

— The Active Moiety relationship is a one-way relationship.

— Parent molecule to a salt/solvate molecule is a two-way relationship.

— Both one-and two-way relationships are possible.

Element Group: Reference Information
Element Group: Substance Relationship
Related Substance ID: PTYF75643O (Artificial ID); [1J444QC288 (UNII); SUB05467MIG (EVCode)][25]
Related Substance Name: Amlodipine
Relationship: Active Moiety (equivalent substance of a salt/solvate)
Relationship Type: Ionic
Is Defining: Yes

Element Group: Amount
Amount Type: Exact
Quantity: 69,8
Unit: %{w/w}
Amount Text: Equivalence Factor 0,698 (weight per cent to salt hydrate)

NOTE 1 The relationship from a parent molecule to a salt is an example of a two-way relationship.

NOTE 2 The active Moiety of a salt e.g. Amlodipine of the salt-hydrate Amlodipine besilate hydrate is also called equivalent substance. The Equivalence Factor is the ratio of the molecular weight of the base/salt (hydrate) e.g. 408.88 g/mol/ 585.1 g/mol = 0.698. The Equivalence Factor can be used to calculate automatically the reference strength, that is:

<Strength Amlodipine besilate hydrate e.g. 10 mg/ tablet> ×<Equivalence Factor (0,698)> = <Reference strength (ATIB) Amlodipine e.g. 7 mg/ tablet), see ISO/TS 20443.

In fact, in accordance to the SmPC Amlodipine is the basis of strength and equal to 10 mg in this case. In the formulation of Amlodipine besilate tablets the anhydrous salt is used. The Equivalence Factor Amlodipine besilate is 0,721 (Weight per cent to salt 72,1 w/w) which means that (1/0,721 × 10 mg =) 13,86 mg Amlodipine besilate is equivalent to 10 mg Amlodipine (ATIB).

Element Group: Substance Relationship (Repeat)
Related Substance ID: PTYF75643O (Artificial ID); 1J444QC288 (UNII)
Related Substance Name: Amlodipine
Relationship: Parent molecule to Salt/Solvate
Is Defining: Yes

[25] Since only one ID is allowed by the element 'Related Substance ID', the values mean a "repeat" of the element group.

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Element Group: Substance Relationship (Repeat)
Related Substance ID: JUTYR9087S (Artificial ID); 685928Z18A (UNII)
Related Substance Name: Benzenesulfonic acid
Relationship: Salt to parent
Is Defining: Yes

Element Group: Substance Relationship (Repeat)
Related Substance ID: WATE12456H (artificial ID); 059QF0KO0R (UNII)
Related Substance Name: Water
Relationship: Hydrate to parent
Is Defining: No

NOTE Since only one ID is allowed by the 'Related Substance ID' element, the values mean a "repeat" of the element group 'Substance Relationship'.

B.1.2.3 Requesting a Substance ID

When requesting a Substance ID for a substance in the development stage or substance under investigation, only a minimum set of information needs to be provided.

When the name is not available at least the Company code shall be provided and a short description of the chemical substance with a representation of the structure, molecular formula and molecular weight.

The reference source should be provided with the indication whether the name is in the public domain or not (e.g. public databases such as CAS, name and number).

B.2 Outline of Annex B

This document follows the main classification of the 'Substance Type': Chemical Substance in view of ISO 11238 and ISO/TS 19844 by describing:

- **Chemical Substances and Mixture**
  - **Captured at the Substance level:**
    - Stoichiometric chemical substances with respect to their solid state: Co-crystals, chemical salts, solvates and hydrates and (polymorphic form captured at the Specified Substance level);
    - Non-Stoichiometric chemical substance;
    - Mixture.
  - **Captured at the Specified Substance level:**
    - Multi substance material.
- **Key elements of a chemical substance are:**
  - Substance name and/or Company-code;
  - Substance structure;
  - Substance molecular formula;
  - Substance molecular weight;

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— Decisions for assigning a new Substance ID.

— **Discussing other elements and properties of importance regarding the characteristics of the substance.**

— **Providing examples of chemical substances and describing the elements captured at the Substance level and Specified Substance Group 1, 2 or 3 level when appropriate.**

— **Discussing Radionuclide Substance.**

B.3 Scope

This Annex provides guidance for Chemical Substance, Mixture and Radionuclide to define elements that describe mandatory and conditional requirements/fields in order to generate ISO IDMP Substance Identifiers in respect to the ISO 11238 standard (hereafter ISO 11238) and ISO/TS 19844 Implementation Guidelines (hereafter ISO/TS 19844) by providing examples of substances belonging to the classes described above.

B.4 Terms and definitions

For the purposes of this Annex B, both the terms and definitions given in ISO 11238 and the following apply.

B.4.1
ATC Code, Substance classification code
Anatomic Therapeutic Chemical Classification code

Note 1 to entry: The Anatomical Therapeutic Chemical (ATC) Classification System is used for the classification of drugs. It is controlled by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC).

Note 2 to entry: This pharmaceutical coding system divides drugs into different groups according to the organ or system on which they act and/or their therapeutic, pharmacological and chemical properties. Each bottom-level ATC code stands for a pharmaceutically used substance or a combination of substances in a single indication (or use). This means that one drug can have more than one code: Acetylsalicylic acid, for example, has A01AD05 as a drug for local oral treatment, B01AC06 as a platelet inhibitor, and N02BA01 as an analgesic and antipyretic. On the other hand, several different brands share the same code if they have the same active substance and indications.

B.4.2
boiling point
corrected temperature at which the vapour pressure of a liquid is equal to 101,3 kPa

B.4.3
co-crystals
homogenous (single phase) crystalline structures made up of two or more components in a definite stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds

B.4.4
CV
controlled vocabulary
finite set of values that represents the only allowed values for a data item

Note 1 to entry: The allowed values can be codes, text, or numeric.

Note 2 to entry: Adapted from CDISC Clinical Research Glossary[10].

Note 2 to entry: Adapted from CDISC Clinical Research Glossary

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B.4.5
CAS Index name
Chemical Abstracts Service Index Name, also referred to as CAS Registry name

B.4.6
CAS Registry Number/CAS number
unique numerical identifier of a substance in the CAS Registry system

Note 1 to entry: The numbers are sequential and are assigned as a substance enters the registry system. The numbers do not have a common length and lengths can be up to 10 digits. Each CAS number contains a single check digit. The CAS registry system is maintained by the Chemical Abstracts Service of the American Chemical Society. The CAS number for formaldehyde is 50-00-0.

B.4.7
Cahn-Ingold-Prelog priority rules, CIP system or CIP conventions
set of rules used in organic chemistry to name the stereoisomers of a molecule

Note 1 to entry: A molecule may contain any number of stereogenic carbon centres and any number of double bonds, and each gives rise to two possible configurations. The purpose of the CIP system is to assign an R or S descriptor to each stereogenic carbon centre and an E or Z descriptor to each double bond so that the configuration of the entire molecule can be specified uniquely by including the descriptors in its systematic name.

B.4.8
configuration
method for indicating the three-dimensional arrangement of atoms at a stereogenic carbon, phosphorous, sulfur centre or stereocenter

Note 1 to entry: Look at the four atoms directly attached to the stereogenic carbon centre and assign priorities in order of decreasing atomic number. The atom with the highest atomic number is ranked first; the atom with the lowest atomic number is ranked fourth.

Note 2 to entry: If a decision about priority cannot be reached by applying the rule in Note 1, compare atomic numbers of the second atoms in each substituent, continuing on as necessary through the third or fourth atoms until a point of difference is reached.

Note 3 to entry: Multiple-bonded atoms are considered equivalent to the same number of single-bonded atoms.

Two examples of stereogenic carbon centres: The lowest substituent is shown only by a wavy line, and is assumed to be behind the rest of the molecule. Both centres shown are S isomers (see Figure B.3).

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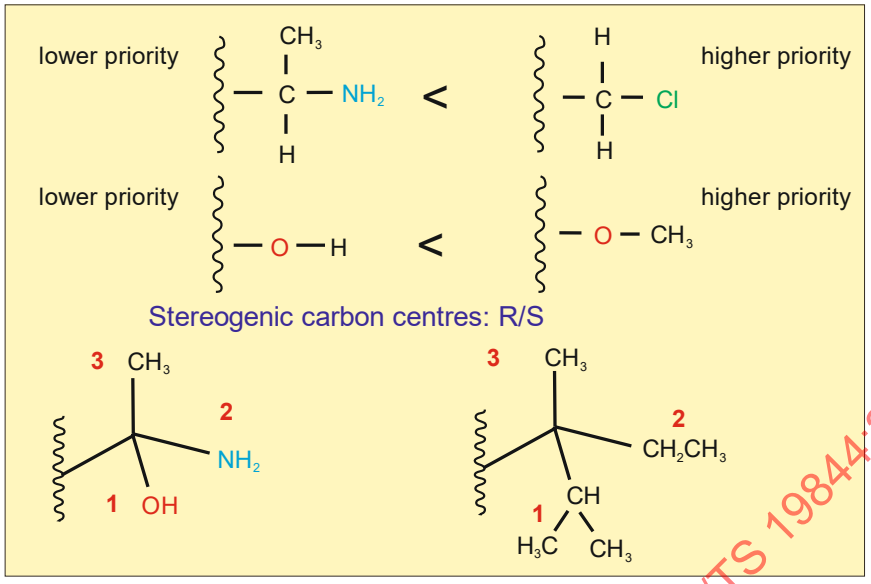


Figure B.3 — Examples of stereogenic carbon centres

After the substituents of a stereogenic carbon centre have been assigned their priorities, the molecule is oriented in space so that the group with the lowest priority is pointed away from the observer. If the substituents are numbered from 1 (highest priority) to 4 (lowest priority), then the sense of rotation of a curve passing through 1, 2 and 3 distinguishes the stereoisomers. A centre with a **clockwise** sense of rotation is an ***R*** or *rectus* centre and a centre with a **counter clockwise** sense of rotation is an ***S*** or *sinister* centre. The names are derived from the Latin for right and left, respectively.

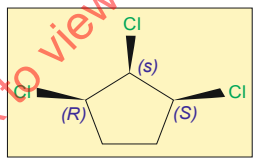


Figure B.4 — (1R,2s,3S)-1,2,3-trichlorocyclopentane

It is possible in rare cases that two substituents on an atom differ only in their absolute configuration (R or S). If the relative priorities of these substituents need to be established, R takes priority over S. When this happens, the descriptor of the stereogenic carbon centre is a lowercase letter (r or s) instead of the uppercase letter normally used.

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EXAMPLES

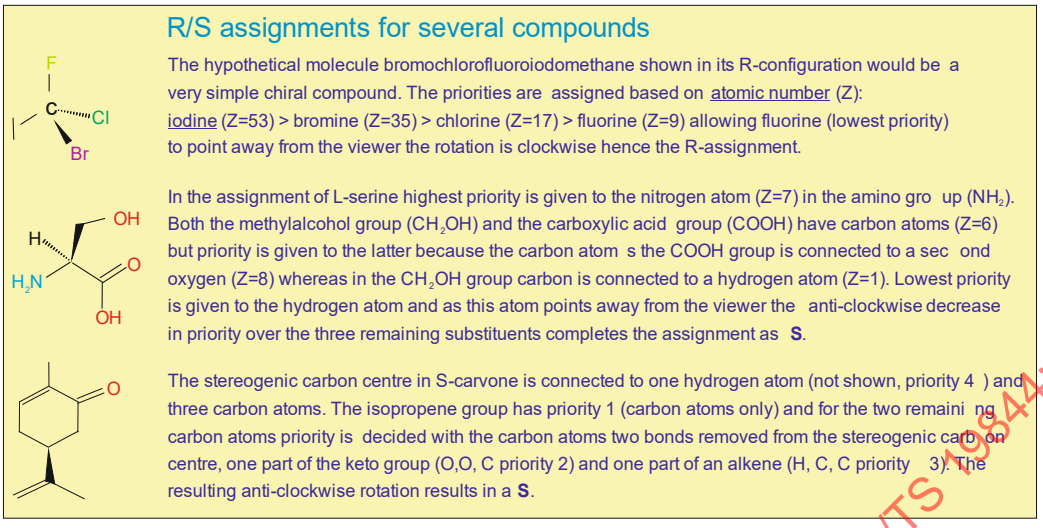


Figure B.5 — R/S assignments for several compounds

B.4.9
critical point, critical temperature, critical pressure
behaviour of a heated liquid

Note 1 to entry: The behaviour of a heated liquid in an open vessel differs from that of a liquid in a sealed vessel.

In an open vessel, the liquid vaporizes from its surface as it is heated. At the temperature at which its vapour pressure would be equal to the external pressure, vaporization can occur throughout the bulk of the liquid and the vapour can expand freely into the surroundings. The condition of free vaporization throughout the liquid is called **boiling**. The temperature at which the vapour pressure of a liquid is equal to the external pressure is called the **boiling temperature at that pressure**.

When a liquid is heated in a sealed vessel, boiling does not occur. Instead, the temperature, vapour pressure, and the density of the vapour rise continuously (see (A) in Figure B.7). At the same time the density of the liquid decreases as a result of its expansion (see (B) in Figure B.7) There comes a stage at which the density of the vapour is equal to that of the remaining liquid and the surface between the two phases disappears and this point is referred as the critical point (see (C) in Figure B.7). The temperature at which the surface disappears is the **critical temperature T_c**. The corresponding vapour pressure is the **critical pressure p_c**.

B.4.10
distillation range
the temperature interval, corrected for a pressure of 101.3 kPa, within a liquid, or specified fraction of a liquid, distils under specified conditions as described in a Pharmacopoeia

B.4.11
elemental composition
pure chemical substances consisting of a single type of atom distinguished by its atomic number, which is the number of protons in its atomic nucleus. Elements are divided into metals, metalloids, and non-metals

Note 1 to entry: When two or more distinct elements are chemically combined, with the atoms held together by chemical bonds, the result is termed a chemical compound. Chemical compounds may be composed of elements combined in exact whole-number ratios of atoms to form a molecular formula. The elemental composition of the molecule CH_4 is [C, H] since it consists of two chemical elements.

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B.4.12
EV-Code
EudraVigilance Code
code for a substance used in the Extended EudraVigilance Medicinal Product Dictionary (XEVMPD), developed by the European Medicines Agency (EMA)

Note 1 to entry: The XEVMPD is designed to support the collection, reporting, coding and evaluation of authorized and investigational medicinal product information in a standardized and structural way.

B.4.13
Hill system/Hill notation
system of writing chemical formulas such that the number of carbon atoms in a molecule is indicated first, the number of hydrogen atoms next, and then the number of all other chemical elements subsequently, in alphabetical order. When the formula contains no carbon, all the elements, including hydrogen, are listed alphabetically

B.4.14
InChI
IUPAC International Chemical Identifier
textual identifier for chemical substances, designed to provide a standard and human-readable way to encode molecular information and to facilitate the search for such information in databases and on the web

Note 1 to entry: InChI is a linear identifier that deals with chemical structural representation using a layered approach. The identifiers describe chemical substances in terms of layers of information.

Note 2 to entry: Every InChI starts with the string "InChI=" followed by the version number. This is followed by the letter S for standard InChIs. The remaining information is structured as a sequence of layers and sub-layers, with each layer providing one specific type of information. The layers and sub-layers are separated by the delimiter "/" and start with a characteristic prefix letter (except for the chemical formula sub-layer of the main layer).

Note 3 to entry: The delimiter-prefix format has the advantage that a user can easily use a wildcard search to find identifiers that match only in certain layers. The InChI for benzene is: $1/C_6H_6$ /c1-2-4-6-5-3-1/h1-6H.

B.4.15
InChIKey
fixed length (25 characters) condensed digital representation of the InChI designed to allow for easy web searches of chemical compounds

Note 1 to entry: The full InChI is too lengthy for easy searching, and therefore the InChIKey was developed.

Note 2 to entry: This is sometimes referred to as hashed InChI.

B.4.16
InChI resolvers
lookup service to make the links between the InChIKey and InChI

Note 1 to entry: The InChIKey always needs to be linked to the original InChI to get back to the original structure as the InChI cannot be reconstructed from the InChIKey.

B.4.17
isomers

B.4.17.1
stereoisomers
isomeric molecules that have the same molecular formula and sequence of bonded atoms (identical in atomic constitution) but differ in the three-dimensional arrangement of the atoms. Stereoisomers can either be enantiomers, diastereomers, geometric isomers or constitutional isomers

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B.4.17.1.1
enantiomers
two stereoisomers related to each other by a reflection. They are mirror images of each other which are non-superimposable

Note 1 to entry: Every stereogenic centre in one molecule has the opposite configuration in the other. Two compounds that are enantiomers of each other have the same physical properties except for the direction in which they rotate polarized light and how they interact with different optical isomers of other compounds. As a result, different enantiomers of a compound may have substantially different biological effects. Pure enantiomers also exhibit the phenomenon of optical activity and can be separated only with the use of a chiral agent.

B.4.17.1.2
diastereomers
stereoisomers not related through a reflection operation. Diastereomers are pairs of stereoisomers that are not mirror images of each other

Note 1 to entry: Diastereomers have opposite configurations at one (or more) stereogenic centres, but have the same configuration at others. Diastereomers include meso compounds, cis-trans (E/Z) isomers, and non-enantiomeric optical isomers. Meso compounds are achiral, but they contain stereogenic centres of a (C)-atom. Diastereomers will not have identical physical properties.

B.4.17.1.3
geometric isomers
sub-class of diastereomers which exist due to restricted rotation in a molecule and do not require stereogenic centres to exist

Note 1 to entry: Their relationship is commonly defined in terms of the relative stereochemical arrangement of groups rather than the absolute (*R*/*S*) configuration of stereogenic centres. The term cis and trans are also used to describe the relative position of two substituents on a ring: *cis* on the same side, otherwise *trans*.

Note 2 to entry: Z and E are not always interchangeable.

EXAMPLE 1 *cis-trans*; Z= Zusammen, together/E=Entgegen, opposite.

EXAMPLE 2 Stereochemistry of 1-Phenyl-1,3-pentadiene.

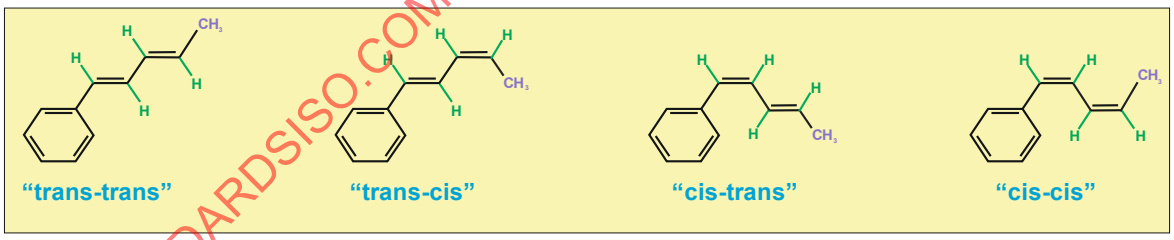


Figure B.6 — Stereochemistry of 1-Phenyl-1,3-pentadiene

B.4.17.2
conformers
form of isomerism that describes the phenomenon of molecules with the same structural formula having different shapes due to rotations around one or more bonds

Note 1 to entry: Different conformations can have different energies, but usually interconvert, and are very rarely isolatable. For this reason, most conformers will not be considered separate substances in this standard. Possible exceptions are substituted biphenyls where rotation is restricted and different conformers are isolatable.

B.4.17.3
constitutional isomers

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isomers that share the same molecular formula, but the bond connections (atomic constitution) and/or their order differ(s) between different atoms/groups

EXAMPLES *n*-Butane and *iso*-Butane; Ethyl alcohol and Dimethyl ether; Isopropylamine and *n*-Propylamine.

B.4.18
IUPAC nomenclature
chemical nomenclature with a set of rules to generate systematic names for chemical compounds. The nomenclature is created and developed by the International Union of Pure and Applied Chemistry (IUPAC)[26]

B.4.19
melting point
melting point determined by the capillary method is the temperature at which the last solid particle of a compact column of a substance in a tube passes into the liquid phase

B.4.20
mixture
type of polydisperse substance that is a combination of single substances isolated together or produced in the same synthetic process

Note 1 to entry: Single substances of diverse origin that are brought together and do not undergo a chemical transformation as a result of that combination are defined as multi-substance materials (Specified Substance Group 1) and not as mixture.

EXAMPLE Gentamicin is defined as a mixture substance of Gentamicin C1, Gentamicin C1A, Gentamicin C2, Gentamicin C2A and Gentamicin C2B. Glyceryl monoesters are defined as mixture substances of two single substances which differ in the position of esterification. Simethicone, which consists of dimethicone and silicon dioxide, is not defined as a mixture substance since these are diverse materials brought together to form a multi-substance material.

EXAMPLE Glyceryl monoesters could be defined as a mixture of two single substances which differ in the position of esterification.

Note 2 to entry: Mixture could be used for a homologous group of structurally diverse single substances used as starting materials in order to prepare an allergen extract. The extract is further described by using the class source material, element group fraction description (allergen preparation) obtained from the structurally diverse single substances (starting materials) as parent substances. This substance (allergen extract) is the result of the same (synthetic) process and hence the extract is considered as a mixture substance.

B.4.21
moiety
moiety is an entity within a substance that has a complete and continuous molecular structure

EXAMPLE The strength of a medicinal product is often based on what is referred to as the active moiety of the molecule responsible for the physiological or pharmacological action of the drug substance. To avoid ambiguity, the free acid and/or free base should be used as the moiety upon which strength is based.

Note 1 to entry: The active moiety of a stoichiometric or non-stoichiometrical substance molecule is considered that part of the molecule that is the base, free acid or ion molecular part of a salt, solvate, chelate, clathrate, molecular complex or ester.

B.4.22
molecular formula
chemical formula that shows the total number and kind of atoms in a molecule indicating atomic

[26] See http://www.chem.qmul.ac.uk/iupac/index.html#01 ; and http://www.chem.qmul.ac.uk/iupac/iupac.html

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proportional ratios (the numerical proportions of atoms of one type to those of other types) which is a way of expressing information about the proportions of atoms that constitute a particular chemical compound, using a single line of chemical element symbols, numbers, and sometimes other symbols

Note 1 to entry: the molecular formula could contain other symbols, such as parentheses, dashes, brackets, and plus (+) and minus (-) signs. These are limited to a single typographic line of symbols, which may include subscripts and superscripts. A chemical formula contains no words (e.g. Glucose is represented as $C_6H_{12}O_6$).

Note 2 to entry: Molecular formulas are written in accordance with the Hill system/Hill notation such that the number of carbon atoms in a molecule is indicated first, the number of hydrogen atoms next, and then the number of all other chemical elements subsequently, in alphabetic order. When the formula contains no carbon, all the elements, including hydrogen, are listed alphabetically.

Note 3 to entry: Inorganic acids and metal salts are shown without charges or bonds: $HClO_4$ and $KMnO_4$ respectively. If metal salts of inorganic acids include several metals, the symbols for the metals are shown in alphabetic order, e.g. K_2NaPO_4.

B.4.23
molecular formula by moiety
way of describing of the molecular formula of a stoichiometric or non-stoichiometric substance existing of two or more moieties, the molecular formula of each moiety shall be described separated by a dot

Note 1 to entry: The molecular formula of the chemical salt Amlodipine besilate is described as $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$.

Note 2 to entry: In non-cyclic linear structures like sodium nitroprusside: $Na_2[Fe(CN)_5(NO)].2H_2O$, a non-cyclic structure is constructed in the following order:

a) symbol of the central atom placed on the left;

b) ionic ligands with cations first then anions;

c) neutral ligands.

B.4.24
molecular structure
unambiguous representation of the arrangement of atoms

Note 1 to entry: For the purposes of defining substances, three dimensional conformations shall not be captured.

B.4.25
molecular weight
mass of one molecule of a homogenous substance or the average mass of molecules that comprise a heterogeneous substance and is derived from the molecular structure or the molecular formula

Note 1 to entry: It is calculated as the sum of the mass of each constituent atom multiplied by the number of atoms of that element in the molecular formula. The unified atomic mass unit is the unit of molecular weight and includes the type of molecular weight (g/mol).

Note 2 to entry: For stoichiometric chemicals, the molecular weight is calculated from the molecular formula using standard masses for each of the elements. The molecular mass refers to the complete structure or a moiety or a fragment.

Note 3 to entry: The unified atomic mass unit or Dalton is the unit of molecular weight. The type of molecular weight should always be captured.

Note 4 to entry: For polymers, there are several different types of molecular weight (weight average, number average, etc.).

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Note 5 to entry: For a substance not described in a Pharmacopoeia a mass spectrum may be provided to substantiate the calculated molecular weight.

B.4.26
multi-substance material
single substances or specified substances of diverse origin that are brought together and do not undergo a chemical transformation

EXAMPLE Materials such as human insulin isophane, simethicone, aluminium lakes, nicotine polacrilex, and phosphate buffered saline are all multi-substance ingredients.

Note 1 to entry: Each substance part of the multi-substance material is a parent substance of the multi-substance material and should be registered first. The multi-substance material is captured at the Specified Substance Group 1 information level.

B.4.27
official name
name given by an official registration authority/organization

EXAMPLES INN: International Nonproprietary Name, also known as rINN, recommended International Nonproprietary Name or pINN, proposed International Nonproprietary Name or INNM, Modified International Nonproprietary Name published by WHO: World Health Organization: in accordance with rules[27].

B.4.28
optical rotation
property displayed by chiral substances of rotating the plane of polarization of polarized light

Note 1 to entry: The amount of rotation observed in a polarimetry experiment depends on the number of optically actives molecules the light beam encounters. The more molecules the light encounters, the greater the observed rotation. Thus, the amount of rotation depends on sample concentration, sample path length and temperature.

Note 2 to entry: Optical rotation is considered to be positive (+) for dextrorotatory substances and negative (-) for laevorotatory substances.

B.4.28.1
specific optical rotation $[\alpha m]t\lambda$
rotation, expressed in radians, measured at the temperature *t* (20 °C) at a wavelength λ (usual D, light of 589,3 nanometre wavelength of the Sodium D-line, that is the yellow light emitted from common sodium lamps) and a path length of 1 decimetre (1 dm = 10 cm)

$$[\alpha]^{20}{}_{\mathrm{D}} = \frac{\text{Observation rotation}(\text{degrees})}{\text{Path length}(\text{dm}) \times \text{Concentration C}(\text{g/ml})}$$

B.4.29
phase transition
transition between solid, liquid and gaseous state of matter at a characteristic temperature for a given pressure[28]

Note 1 to entry: The precise locations of the phase boundaries can be found – the pressures and temperatures at which two phases can coexist - by making use of the fact that when two phases are in equilibrium their chemical potentials must be equal. Where liquid and solid phases of a substance is in equilibrium, the chemical potential of

[27] http://www.who.int/medicines/services/inn/INNMreview%20paperWkDoc167_Feb06_3_.pdf?ua=1

[28] P.W. Atkins, 'Physical Chemistry" Chapter 6: Physical transformations of pure substances, Oxford University Press, 1997 ISBN 0 19 855730 2

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the substance is the same throughout the liquid and throughout the solid, and is the same in the solid as in the liquid and phase transition can take place.

Note 2 to entry: Thus at 1 atm, ice is the stable phase of water below 0 °C but above 0 °C the liquid is liquid water, μ(s)<μ(l) (Figure B.3[1]). The Phase diagram of a substance shows the regions of pressure and temperature at which its various phases are thermodynamically stable. The boundaries between regions, the phase boundaries, show the values of p and T at which two phases coexist in equilibrium.

Note 3 to entry: There is a set of conditions under which three different phases (typically solid, liquid and vapour) all simultaneously coexist in equilibrium. It is represented by the triple point.

Take the line TC which gives the vapour pressure of liquid water up to the critical point C. Along this line, liquid and vapour coexist in equilibrium. At temperatures, higher than that of point C, condensation does not occur at any pressure. The line TB represents the vapour pressure of solid ice, which is a plot of the temperatures and pressures at which the solid and vapour are in equilibrium. Finally, line TA gives the melting point of ice and liquid water. The plot shows the temperatures and pressures at which ice and liquid water are in equilibrium.

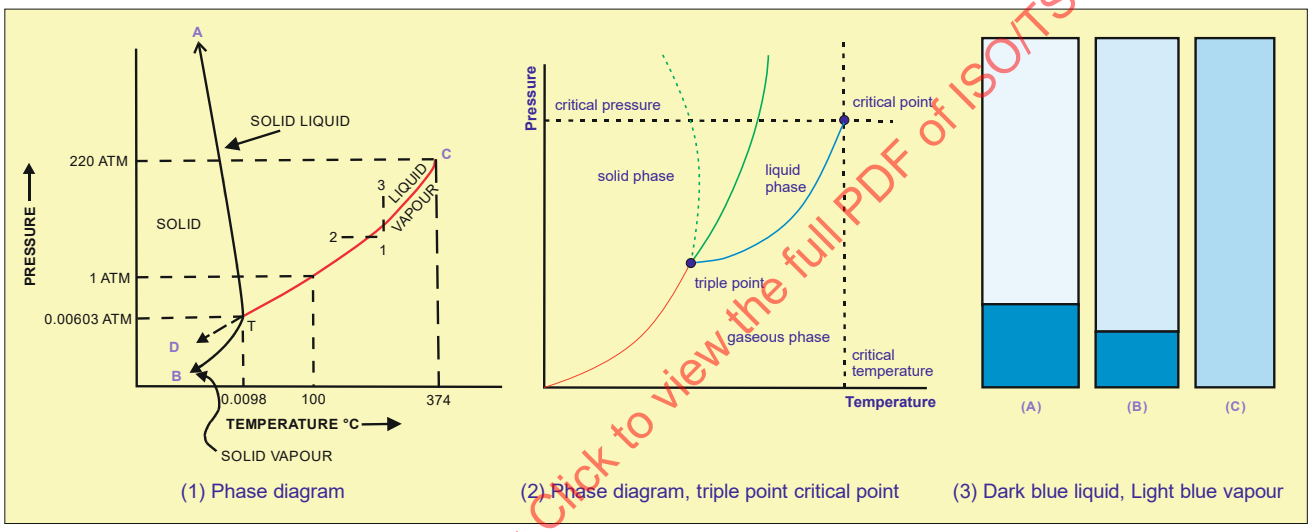


Figure B.7 — Phase diagrams

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B.4.30
physical form

physical state, either gas, liquid, or solid, and the type of organization for solid matter

Note 1 to entry: Solids can be either crystalline or amorphous and can show polymorphism. Amorphous material is characterized by the absence of distinct reflections in the X-ray powder diffraction (XRPD) pattern. Polymorphism which is ability of crystalline materials to exist in more than one form, can also be captured.

B.4.31
polymorphism

ability of a compound in the solid state to exist in different crystalline forms having the same chemical composition

Note 1 to entry: These different forms are formed by weak interactions between the components present in the solid state. These different forms may possess different physico-chemical properties. Different crystalline forms or solvates may be produced by varying the crystallization conditions (temperature, pressure, solvent, concentration rate of crystallization, seeding of the crystallization medium, presence and concentration of impurities etc.). Techniques to study polymorphism, X-ray diffraction of powders or crystals, thermal analysis (differential scanning calorimetry), infrared absorption spectrophotometry and near-infrared (NIR) spectrophotometry which is another

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technique used to measure the degree of crystallinity, and has been proven to be useful in studies of polymorphism and changes in the amorphous and crystalline state.

B.4.32
refractive index
index, n^{20}_D, of a medium with reference to air equal to the ratio of the sine of the angle of incidence of a beam of light to the sine of the angle of refraction of the refracted beam in the given medium

Note 1 to entry: Unless otherwise prescribed, the refractive index is measured at 20 °C ± 0,5 °C, with reference to the wavelength of the D-line of sodium (λ = 589,3 nm).

B.4.33
salt
ionic substances formed from the neutralization reaction of an acid and base

Note 1 to entry: Salts are ionic compounds composed of cations (positive ions) and anions (negative ions).

B.4.34
solvate
substance formed through association of a solvent molecule (e.g. water, alcohol) with another moiety

Note 1 to entry: Solvates can be either stoichiometric or non-stoichiometric and are predominately present in the solid form of substances.

Note 2 to entry: Solvates formed with water as solvent are referred as hydrates.

B.4.35
solubility
property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent

Note 1 to entry: The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of the solubility of a substance in a specific solvent is measured as the saturation concentration, where adding more solute does not increase the concentration of the solution.

B.4.36
stoichiometry

B.4.36.1
stoichiometric substance
substance that contains moieties in simple integral ratios

Note 1 to entry: Defined stoichiometry is represented in the structural representation of a given substances. Moieties are represented using the lowest common factors such that a fractional representation is avoided. Substances will either be defined as stoichiometric or non-stoichiometric.

Note 2 to entry: Chemicals have defined stoichiometry when the ratio of all moieties (ion, counter-ion and solvate), can be represented as simple integral ratios.

B.4.36.2
non-stoichiometric substances
substances that contain moieties in variable integral ratios

B.4.37
UNII
10 characters, randomly generated alpha-numeric string that is currently used to identify substances in medicinal products

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Note 1 to entry: The UNII is generated by the FDA/USP Substance Registry System, which is a robust system with detailed business rules for entry and the generation of UNIIs for both simple and complex substances. The first nine characters are randomly generated followed by a check character.

B.4.38
viscosity
measure of a fluid of its resistance to gradual deformation by shear stress or tensile stress. For liquids, it corresponds to the informal notion of "thickness"

B.4.38.1
dynamic viscosity or viscosity coefficient η
tangential force per unit surface, known as shearing stress T and expressed in pascals, necessary to move, parallel to the sliding plane, a layer of liquid of 1 m^2 at a rate (v) of 1 m/s relative to a parallel layer at a distance (x) of 1 metre

Note 1 to entry: The unit of dynamic viscosity is the pascal second (Pa.s). The most commonly used submultiple is the millipascal second (mPa.s).

B.4.38.2
inherent viscosity
ratio of the natural logarithm of the relative viscosity to the mass concentration of the polymer. Inherent viscosity is defined as

$$\eta_{\text{inh}} = \frac{\ln \eta_{\text{rel}}}{c}$$

where

c is the mass concentration of the polymer (g/dL);

η_{rel} is the relative viscosity, which is defined as:

$$\eta_{\text{rel}} = \frac{\eta}{\eta_{\text{o}}}$$

where

η is the viscosity of the solution;

η_{o} is the viscosity of the neat solvent.

The unit of inherent viscosity is dL/g.

B.4.38.3
kinematic viscosity
ratio of the dynamic viscosity $\boldsymbol{\eta}$ to the density of the fluid $\boldsymbol{\rho}$ expressed in kilograms per m^2, of the liquid measured at the same temperature (ν) = η/ρ. The kinematic viscosity is usually expressed in m^2/s

B.5 Chemical Substance subtypes and Mixture

B.5.1 Substance type, Chemical substance

B.5.1.1 Stoichiometric chemical substances

Stoichiometric chemical substances are substances that contain complete chemical structures and definite stoichiometric ratios among moieties. Stoichiometric ratios between moieties should be whole integers and not fractions. They can be defined by a single representation of the complete molecular structure and a stereochemistry descriptor.

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Chemical substances are defined on the basis of their covalent molecular structure; the presence of a salt (counter-ion) and/or solvates (e.g. water, alcohols, acetone) is captured. (Purity, grade, physical form or particle size are not taken into account in the definition of a chemical substance or in the assignment of a Substance ID).

EXAMPLE Purified Water, Water for Injection, Sterile Water for Injection USP, ice and steam all map to the substance Water.

In order to assign a Substance ID for a chemical substance, a complete covalent structure with all stereochemistry (Axial *R* or *S* and geometric stereochemistry E or Z) defined is needed. The stoichiometry (mole ratio) of counter-ions or solvates present in the material should also be provided.

For all chemical substances, a molecular representation of the substance should be provided with all stereochemistry assigned or sites of unknown stereochemistry identified. An actual image of the structure can be provided in an accompanying document or a structural representation type 'molfile', 'SMILES', 'InChI'.

The structural information typically provided to INN, USAN, BAN or JAN to assign a nonproprietary name is usually sufficient to define chemical substances. Active substances and excipients are typically defined in accordance with INN, JAN or USAN definitions or USP/NF and European Pharmacopoeia (Ph.Eur.) monographs. The labelling requirements provided by monographs should be taken into account when defining and distinguishing substances. Information beyond monograph requirements may occasionally be necessary to distinguish substances.

B.5.2 Solid state forms of the Substance

B.5.2.1 Co-crystals

Over the last decade, co-crystals have gained considerable attention as alternative solid-state forms in drug development. By making co-crystals of pharmaceutically interesting substances, their solid state properties such as solubility, hygroscopicity and stability may be improved as well as manufacturing behaviour (e.g. compaction, flowability, filterability, etc.). The salt formation is already widely used for this purpose, but with co-crystal formation this can now be achieved also for substances that lack the possibility of salt formation.

A principal tool is the hydrogen bond, which is responsible for the majority of directed intermolecular interactions in molecular solids. Co-crystals are multi-component crystals based on hydrogen bonding interactions without the transfer of hydrogen ions to form salts; this is an important feature, since Bronsted acid-base chemistry is not a requirement for the formation of a co-crystal. Co-crystallization is a manifestation of directed self-assembly of different components.

Salts are formed in an acid-base reaction between the active pharmaceutical ingredient (API) and an acidic or basic substance by proton (H+) transfer from acid (A) to base (B). The components are arranged in the crystal lattice dominantly based on ion pairing.

The components in co-crystals assemble via weaker interactions such as e.g. hydrogen bonding, n-n stacking or van der Waals interactions. From a scientific point, solvates and hydrates can be considered as a subgroup of co-crystals. The solvent or the water act as a conformer in the same way as other conformers.

Salt formation: A-H + B ↔ AB^+ -H (salt);

Co-crystal formation: A-H + B ↔ A-H…B (Co-crystal).

Both co-crystals and salts have defined stoichiometries, similar solution specification characteristics, as well as a solubility product K_{sp}.

B.5.2.2 Solvates and hydrates

Water or other solvents act as conformers. They may be the result of a design with the aim to achieve crystals with certain properties, but may also rather be the result of a selection of the final solvent based on other criteria. To be able to distinguish hydrates and solvates from (other) co-crystals it has been

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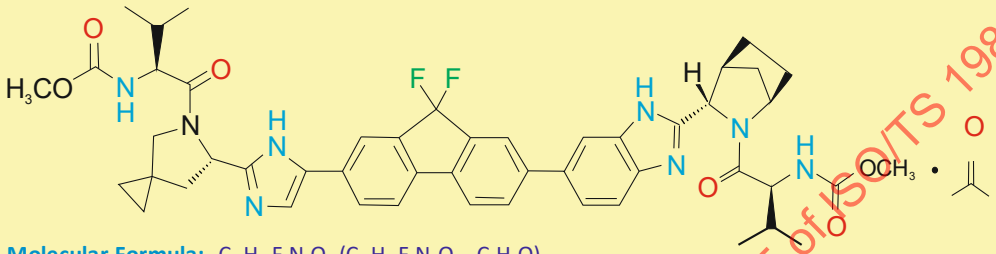
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stated that components of a co-crystal should exist as individual solids at ambient conditions. However, the terms “hydrates” and “solvates” are descriptive and widely used and should be therefore retained while keeping in mind that they are part of, rather than separate from, the general concept of co-crystals.

In ISO 11238 and ISO/TS 19844 these materials are considered as separate substances from the parent substance, describing the active moiety. Hydrates, solvates and co-crystals will have a separate Substance ID at the Substance level.

EXAMPLE 1 Disodium hydrogen phosphate (anhydrous) **[Na_2HPO_4]** will have a separate Substance ID from Disodium hydrogen phosphate dihydrate **[$Na_2HPO_4.2H_2O$]**.

EXAMPLE 2 Lepidasivir acetone solvate **[$C_{49}H_{54}F_2N_8O_6.C_3H_6O$]** will have a separate Substance ID from the parent substance Lepidasivir **[$C_{49}H_{54}F_2N_8O_6$]** see Figure B.8.



Molecular Formula: $C_{52}H_{60}F_2N_8O_7$ ($C_{49}H_{54}F_2N_8O_6$. C_3H_6O)

Molecular Weight: 946.46 g/mol

Systematic Name (INN): methyl [(1*S*)-1-{1*R*,3*S*,4*S*)-3-{5-(9,9-difluoro-7-{2-[(6*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-azaspiro[2.4]hept-6-yl]-1*H*-imidazol-4-yl}-9*H*fluoren-2-yl)-1*H*-benzimidazol-2-yl]-2-azabicyclo[2.2. 1]heptane-2-carbonyl-2-methylpropyl]carbamate

Figure B.8 — Illustrative representation of Lepidasvir acetone solvate

EXAMPLE 3 Edoxaban tosilate monohydrate **[$C_{24}H_{30}ClN_7O_4S.\ C_7H_8O_3S.\ H_2O$]** (see Figure B.9) will have a separate Substance ID from the parent substance Edoxaban **[$C_{24}H_{30}ClN_7O_4S$]** and from Edoxaban tosilate anhydrous **[$C_{24}H_{30}ClN_7O_4S.\ C_7H_8O_3S$]**.

NOTE Systematic name (INN) of the base: N-(5-chloropyridin-2-yl)-N'-[(1S,2R,4S)-4-(N,Ndimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridine-2-carboxamido)cyclohexyl]oxamide].

EXAMPLE 4 Trametinib [$C_{26}H_{23}FIN_5O_4$] is a novel active substance not described in any pharmacopoeia. Trametinib dimethyl sulfoxide [$C_{26}H_{23}FIN_5O_4$. C_2H_6OS] is a 1:1 stoichiometric DMSO solvate, where DMSO is fully incorporated into the crystal lattice. In solid state, one form has been identified (form 1).

In Figure B.10 the structure of the parent substance Trametinib is provided as well as the structural relationship with its dimethyl sulfoxide solvate.

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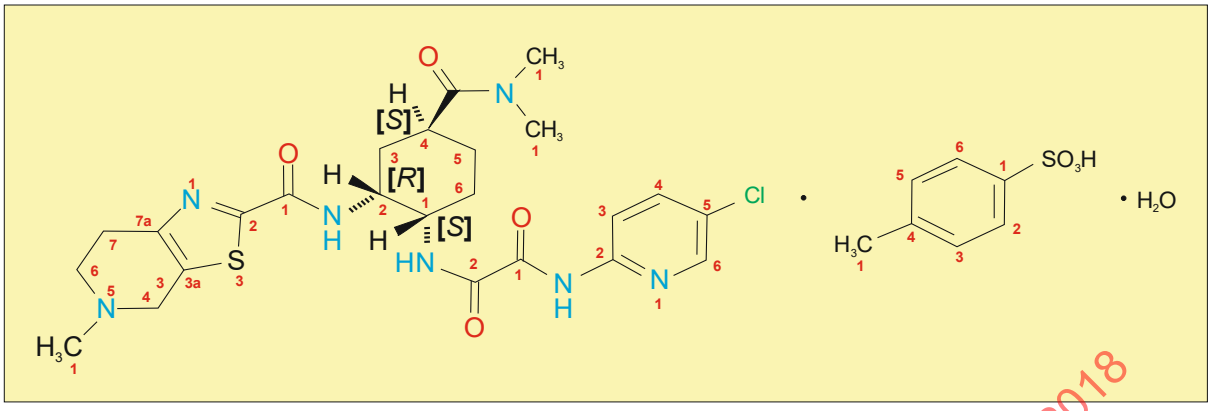


Figure B.9 — Full structural representation of Edoxaban tosilate monohydrate

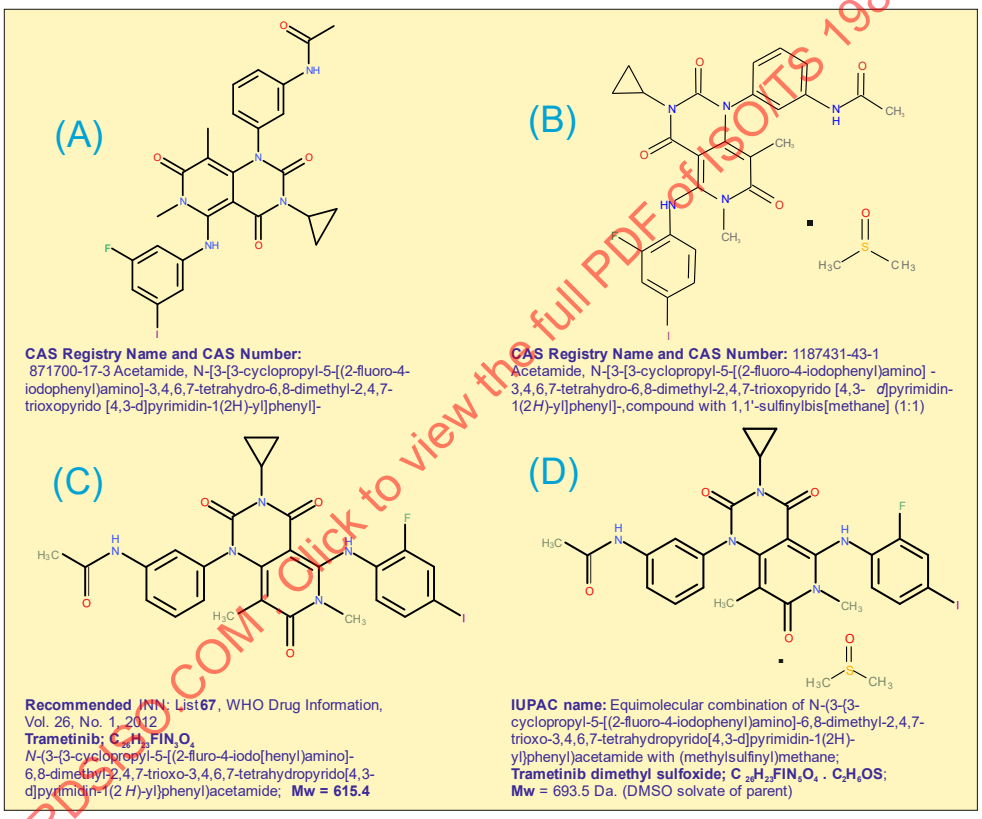


Figure B.10 — Structural representation of Trametinib and Trametinib dimethyl sulfoxide

NOTE Figure B.10/(B),(C),(D) are correct structural representations as the complete chemical structures and definite stoichiometric ratios among moieties are described in 5.7.

B.5.3 Need to substantiate the chemical structure, molecular formula and molecular weight

When an INN and/or the systematic name of the substance is not described in a Pharmacopoeia of the Ph.Eur., USP, or any other pharmacopoeia, the structural formula, molecular formula and molecular weight, as mandatory information, plus a Mass spectrum (and/or NMR-spectrum) should be supplemented as part of the Reference Source Document (see 5.4.7) in order to substantiate the structure and molecular weight. For example, the mass spectrum of trametinib dimethylsulfoxide was obtained by positive ion electrospray ionization with collisional induced dissociation (CID) of the protonated molecule of trametinib $(M+H)^+ = 616\ M/z$ to give the product ion spectrum. The fragment structure of the base peak $[C_{20}H_{17}FIN_4O_2]^+ = 491 M/z$ is shown in the Figure B.11.

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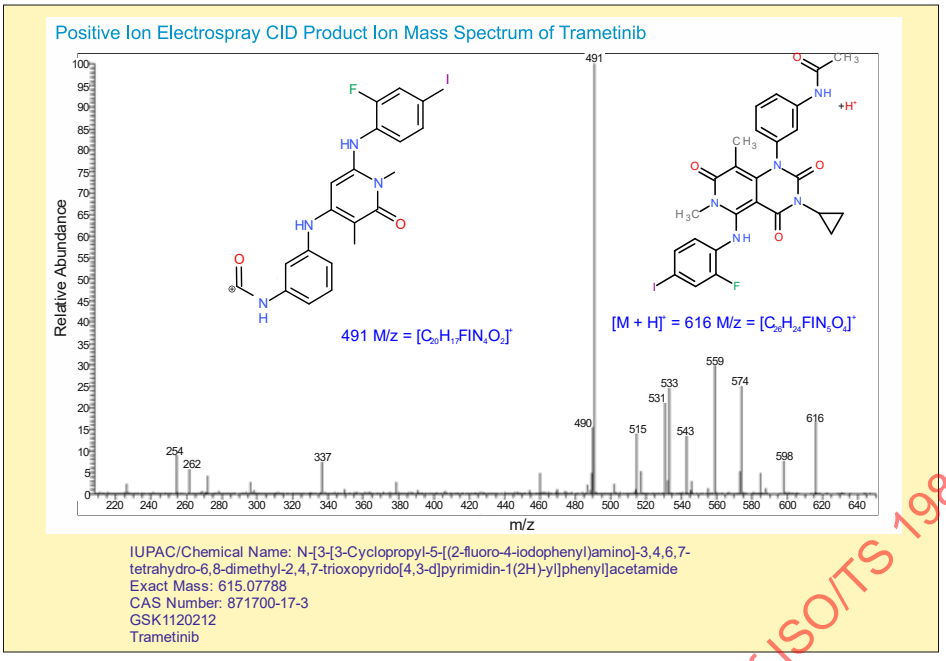


Figure B.11 — Mass Spectra and proposed structure of the molecular [M+1] ion and the [491] + fragment ion of Trametinib

B.5.4 Polymorphism

In the solid state, single as well as multiple entities, such as salt, hydrates, co-crystals etc., may exhibit polymorphism. Polymorphism is the ability of a compound in the solid state to exist in different crystalline forms having the same chemical composition. These different forms are formed by weak interactions between the components present in the solid state. These different forms may possess different physico-chemical properties.

In ISO 11238 and ISO/TS 19844 these polymorphic forms are considered as a Physical Form Type which is captured at the Specified Substance Group 1 level.

Separate polymorphic forms of the parent substance, describing the active moiety or the corresponding hydrates, solvates and co-crystals, will have a separate ID at the Specified Substance Group 1 level, see 7.1 and 7.1.6.

B.5.4.1 Example: Tibolone [$C_{21}H_{28}O_2$]

Tibolone is a marketed substance containing a very small amount of the unwanted polymorphic form.

It is known that different polymorphic forms could have different influence on the solubility of Tibolone and consequently on the dissolution rate of Tibolone from the drug product. According to the Note for guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substance (ICH Topic Q 6A)[29], the polymorphic forms of the active substance should be adequately specified.

Tibolone, form 1 has a monoclinic structure with four molecules in the unit cell, two molecules A and two molecules B linked one after another. Crystal form 1 has two types of hydrogen bond, between $O_{(17)}H$ of one type of molecule and the $O_{(3)}$ carbonyl of the other type of the molecule.

[29] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6A/Step4/Q6Astep4.pdf

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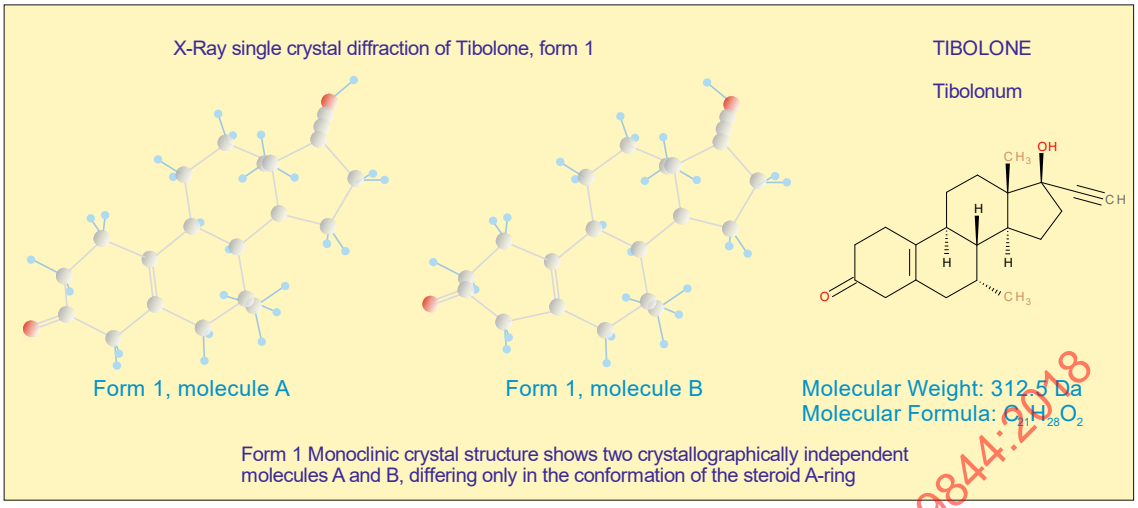


Figure B.12 — Representation of Tibolone monoclinic crystal structure and triclinic crystal structure

Tibolone, form 2 has a triclinic crystal structure with one molecule in the unit cell. This molecule resembles B in crystal form 1. Form 2 has only one type of hydrogen bond.

The company manufactures the API Tibolone only with the polymorphic form 1 because drug product batches with this form show much higher bioavailability than batches manufactured with polymorphic form 2 and form 1 shows more stability than form 2.

NOTE Source: Araujo, Gabriel Lima Barros de *et al.* [11] and Araujo, Gabriel Lima Barros de [12]; the results confirm that two pure polymorphic forms for Tibolone were crystallized: Form 1, monoclinic, obtained by recrystallization from acetone and water and Form 2, triclinic, recrystallized from toluene or hexane. Substantial differences were detected comparing the polymorphs with regard to their solid-state properties.

Conclusion: The property Polymorphic Form will be captured at the Specified Substance Group 1 information level. Tibolone, polymorph form 1 will have a different Specified Substance Group ID from Tibolone, polymorphic form 2.

B.5.5 Non-stoichiometric chemical substances

Non-stoichiometric chemical substances are substances having variable ratios among moieties; each moiety in itself has a discrete molecular structure. The monosulfides of the transition metals are often non-stoichiometric e.g. iron(II) sulfide (the mineral Pyrrhotide) with a composition Fe(1-x) S (x = 0 to 0,2), see 6.1.2.2).

B.5.5.1 Example: USP monograph: Aluminium Chlorohydrex Propylene Glycol

Aluminium Chlorohydrex Propylene Glycol is a complex of aluminium chlorohydrate and propylene glycol in which some of the waters of hydration of the aluminium chlorohydrate have been replaced by propylene glycol. It contains the equivalent of not less than 90.0 per cent and not more than 110,0 per cent of the labelled amount of anhydrous aluminium chlorohydrate.

Molecular formula: $Al_y(OH)_{3y-z}Cl_z{\cdot}nH_2O{\cdot}mC_3H_8O_2$ $Al_2(H_2O)_{y-z}(OH)_{6-n}(Cl)_n(C_3H_8O_2)_z$

B.5.5.2 Example: Octeotride Acetate

An example for non-stoichiometric organic chemical substance is Octreotide acetate. The acetate moiety can vary by 1-2 molecules. In Figure B.12, Octreotide base **[$C_{49}H_{66}N_{10}O_{10}S_2$],** Mol. weight 1019,25, Octreotide monoacetate **[$C_{49}H_{66}N_{10}O_{10}S_2 . C_2H_4O_2$],** and Octreotide diactetate **[$C_{49}H_{66}N_{10}O_{10}S_2 . 2C_2H_4O_2$]** are shown obtained from the FDA GSRS (base) and from ChemID*plus* for the mono and diacetate salts, see Figure B.13.

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In Figure B.13, the coloured structures are in agreement with 5.7.6, but do not show the *R,S*-denominators. These are described in the systematic name.

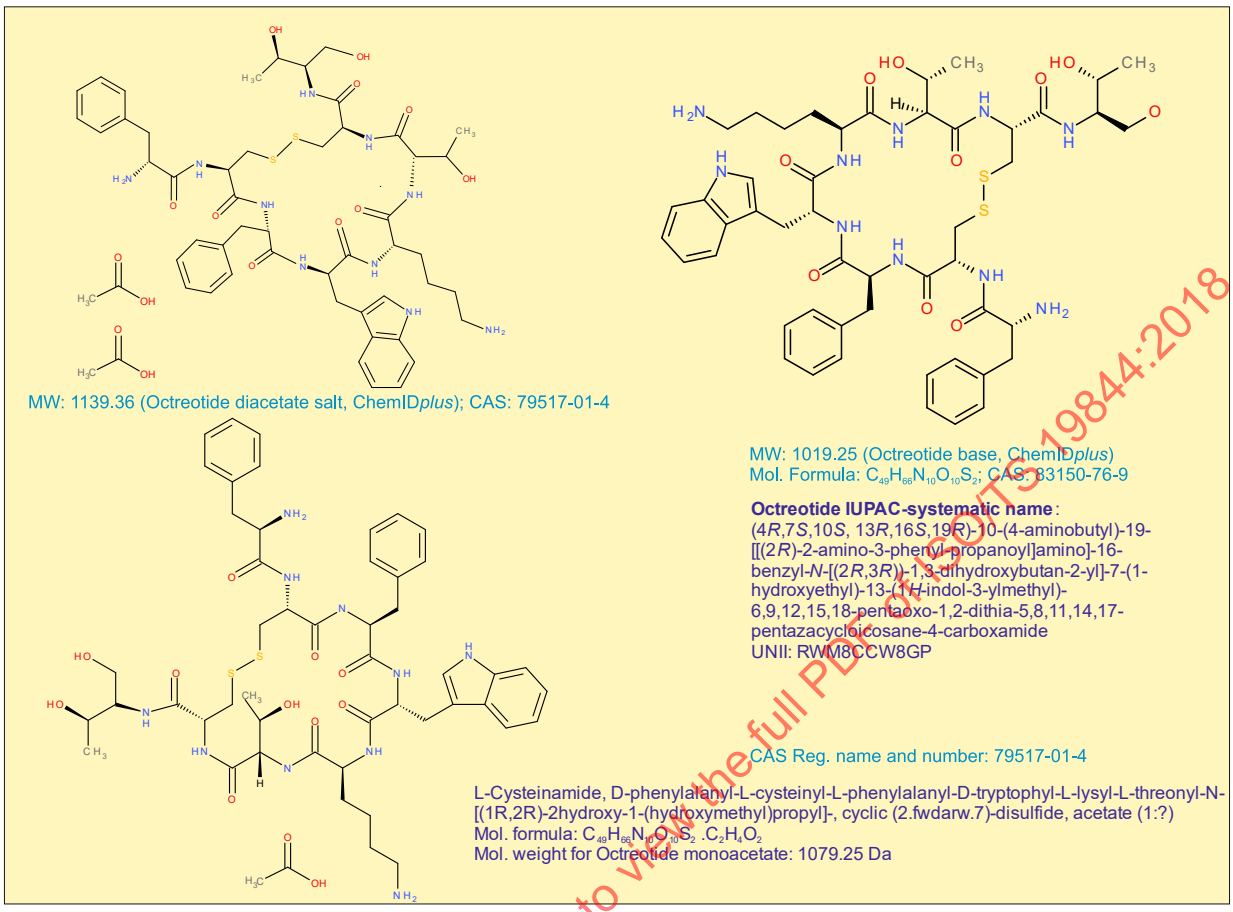


Figure B.13 — Structural representation of Octreotide Acetate

B.5.6 Mixture

A mixture is a type of polydisperse substance that is a combination of single substances isolated together or produced in the same synthetic process. An example is provided, Teicoplanin.

B.5.6.1 Teicoplanin (Ph.Eur.)

Definition: Teicoplanin is a mixture of glycopeptides produced by certain strains of *Actinoplanes teichomyceticus sp.*; the fermentation product contains 6 principal components of the mixture; teicoplanin $A_{2\text{-}1}$ to $A_{2\text{-}5}$ and teicoplanin $A_{3\text{-}1}$. The chemical structure consists of 6 components of glycopeptides, which are composed of a hepta peptide core of 7 amino acids connected with 3 sugars N-acetylglucosamine, α-mannitose and the glucose substituted by different N-acylamino moieties.

Chirality: The configuration of the 7 amino acids is: 1R, 2R, 3S, 4R, 6S and 7S. Five formations of the six amide linkages are trans, the 5-6 linkage is cis. The mixture contains as active multiple active components two pairs of constitutional isomers ($A_{2\text{-}4/5}$, Mw 1894 g/mol) and ($A_{2\text{-}2/3}$, Mw 1880 g/mol) as active multiple active components, see Figure B.14.

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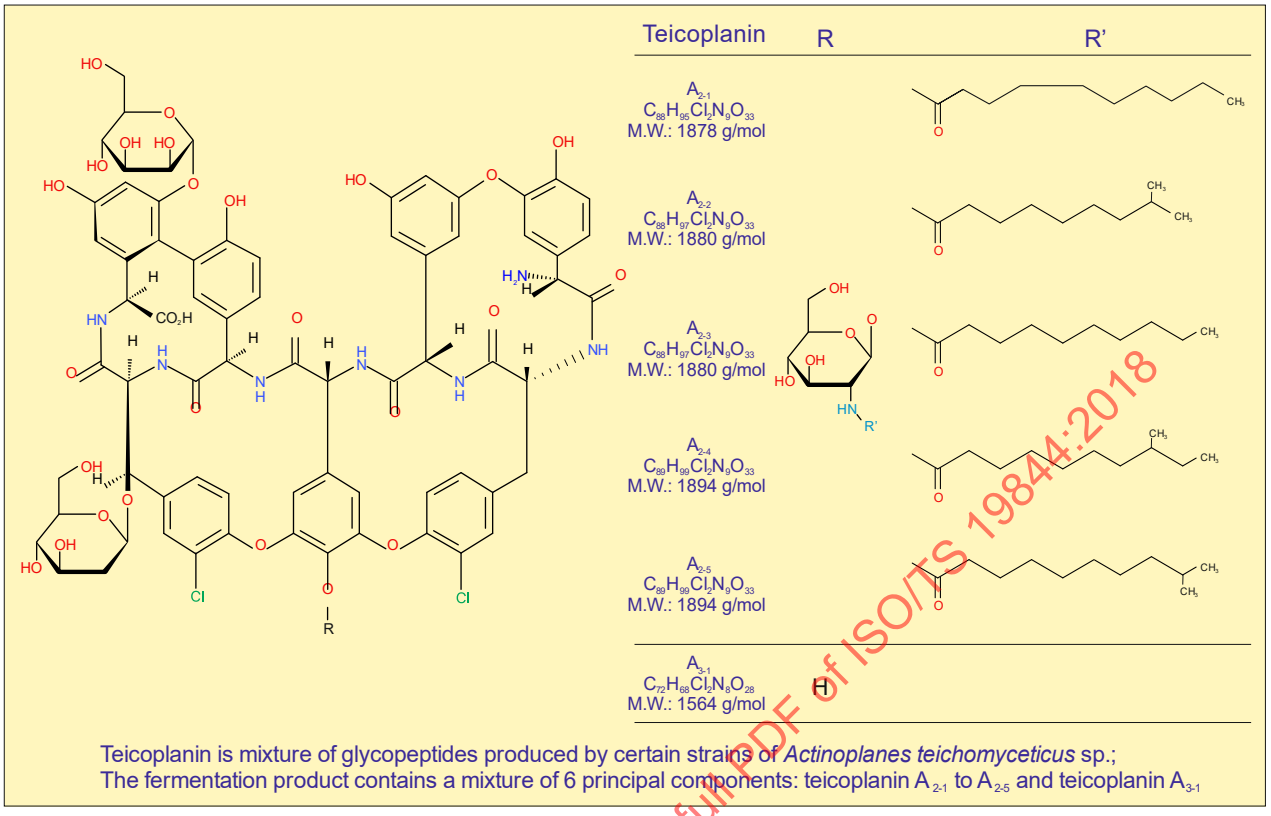


Figure B.14 — Structural representation of Teicoplanin (Ph.Eur.)

B.5.7 Multi-substance material

Multi-substance material is defined as single substances or specified substances of diverse origin that are brought together and do not undergo a chemical transformation. It is considered as multi-substance material (Specified Substance Group 1) and not a mixture substance (e.g. Simethicone consist of two substances: dimethicone and silicon dioxide). These substances are not typically isolated together or synthesized together, but physically mixed together. They would be defined as a Specified Substance Group 1 substance.

B.5.7.1 Example: Paclitaxel-Albumin complex

Abraxane ® is presented as a sterile lyophilisate for suspension for injection. Before use the product has to be reconstituted with 0,9 % sodium chloride solution to obtain a suspension containing 5 mg paclitaxel per ml. Paclitaxel is present in the form of non-covalently albumin-bound nanoparticles with a mean size of approximately 130 nm. Other ingredients include human albumin solution, water for injections and nitrogen. Only human albumin is left in the finished product.

Paclitaxel is a known active substance described in the Ph.Eur. and the USP. The chemical name of paclitaxel is: 5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-N-benzoyl-3-phenylisoserine, see Figure B.15. It is a white or almost white crystalline powder, practically insoluble in water, soluble in methanol and freely soluble in dichloromethane. Paclitaxel has 11 stereogenic centres and may exist in different crystalline forms. However, only one crystal form of paclitaxel is found in the active substance used in the manufacture of the finished product.

In Abraxane ® the solubility problem of paclitaxel is solved by reducing its size at nano-scale level, thereby greatly increasing the surface area of the particles and improving dissolution. Human albumin functions as a surface-active polymer providing charge and steric stabilization to the paclitaxel nanoparticles to prevent aggregation. Stabilization is achieved by the fact that albumin adsorbs onto the

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surface of the paclitaxel nanoparticles, thus creating a sheet that functions as a surface-active polymer preventing aggregation of paclitaxel particles. The interaction between paclitaxel and human albumin is weak and both substances freely dissociate after reconstitution.

Conclusion: Paclitaxel as nanoparticles is stabilized by human albumin in a ratio 1:8 (w/w), based on stability studies, by weak interaction between the nanoparticles and the human albumin, but the two substances are not typically isolated together in the same manufacturing process or form covalent bonds or are packed in a lattice or form a salt.

In terms of the ISO standard Paclitaxel, nanoparticles — Albumin "complex" is considered as a multi-substance material consisting of two separate substances Paclitaxel and Albumin, having a weak interaction. The Paclitaxel-Albumin 1:8 ratio complex is captured at the Specified Substance Group 1 level. The structure of Paclitaxel and names are shown in Figure B.15.

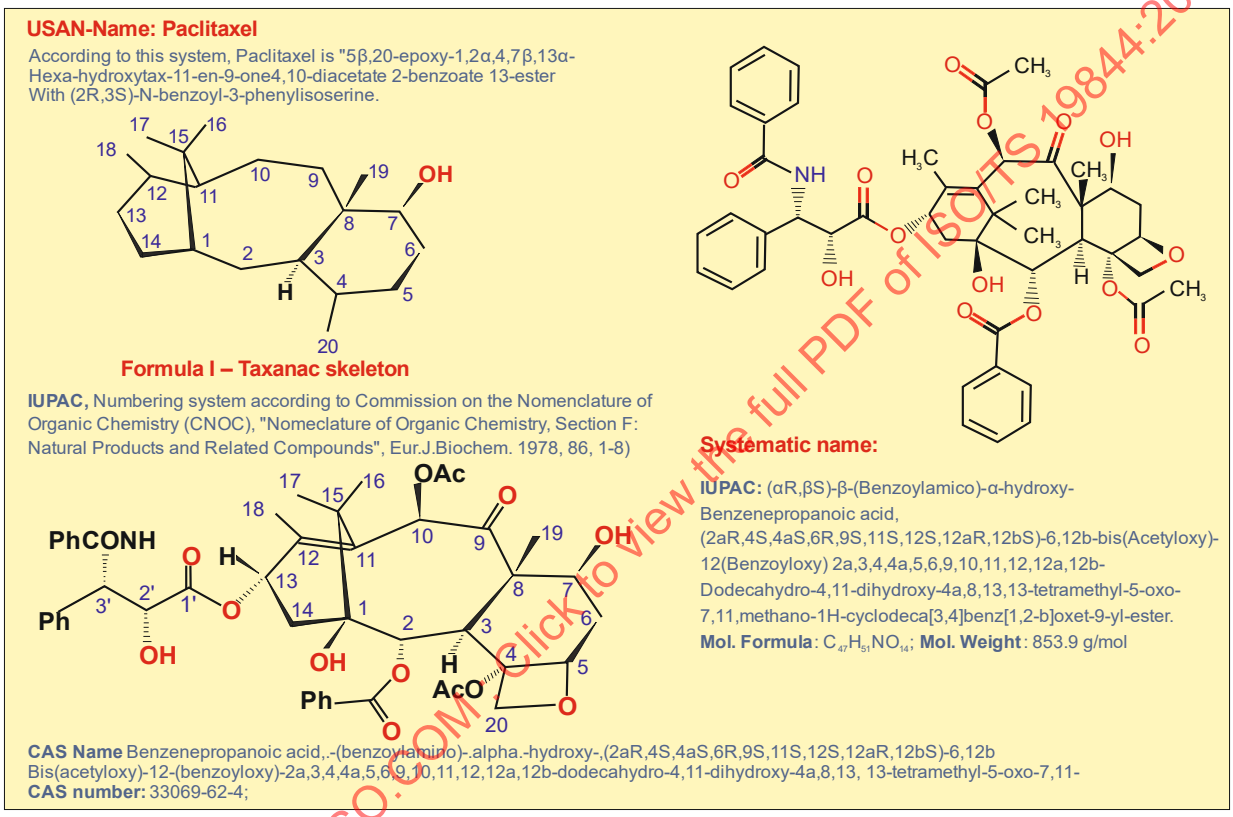
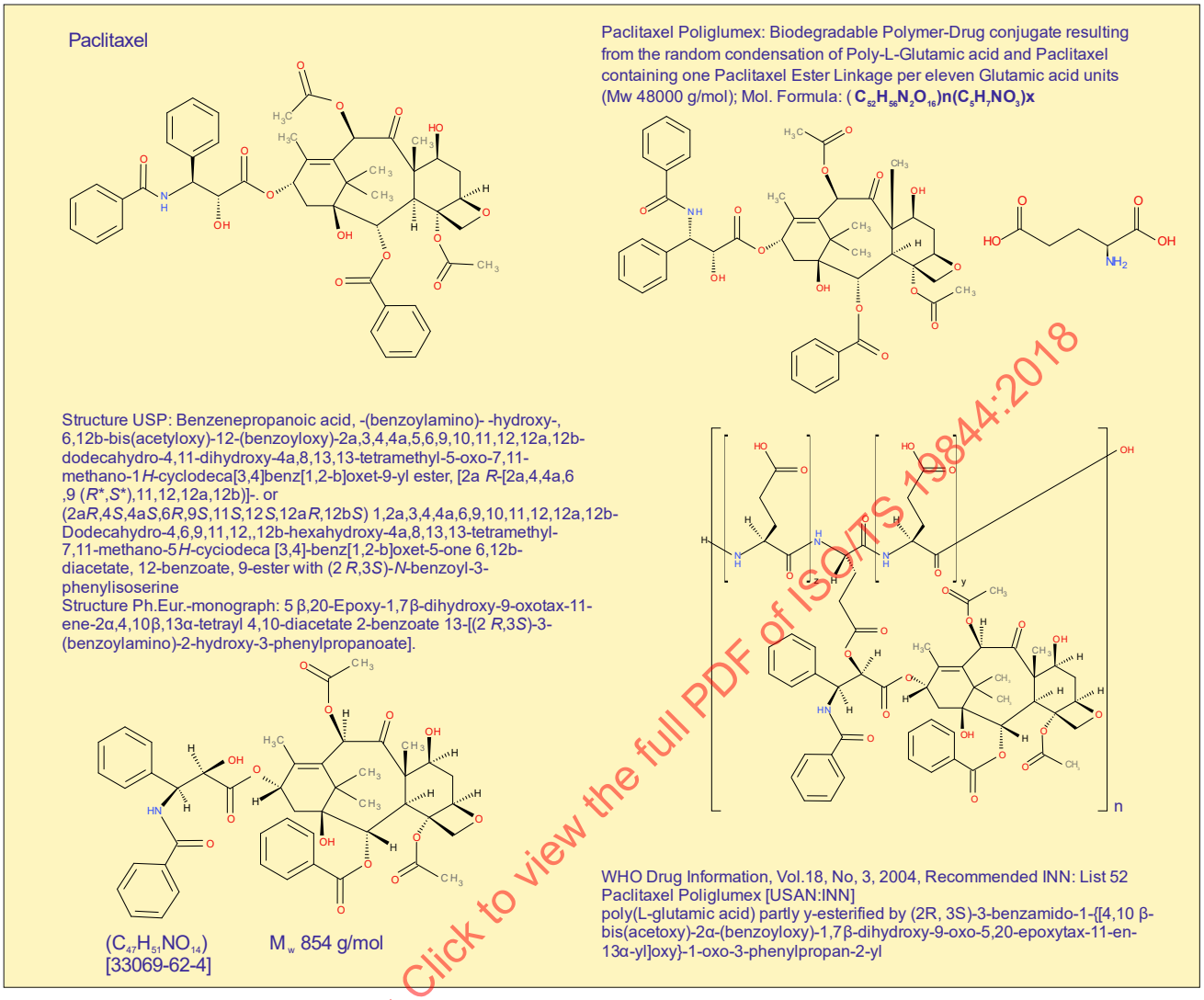


Figure B.15 — Structural representation of the Paclitaxel skeleton and Paclitaxel

In Figure B.16, the structure, names and molecular formula and molecular weight of Paclitaxel and Paclitaxel Poliglumex substances are presented.

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Figure B.16 — Structural representation of Paclitaxel and Paclitaxel Poliglumex

Paclitaxel Poliglumex is a covalent modification of the Paclitaxel molecule. Paclitaxel Poliglumex is captured at the substance level.

Paclitaxel Poliglumex is described according to the WHO Drug Information, Vol. 18, No. 3, 2004 Recommended INN: List 52 as: poly(L-glutamic acid) partly γ-esterified by (2R,3S)-3-benzamido-1-{[4,10β-bis(acetoxy)-2α-(benzoyloxy)-1,7β-dihydroxy-9-oxo-5,20-epoxytax-11-en-13α-yl]oxy}-1-oxo-3-phenylpropan-2-yl.

Paclitaxel Poliglumex is described in the FDA GSRS system by:

"BIODEGRADABLE POLYMER-DRUG CONJUGATE RESULTING FROM THE RANDOM CONDENSATION OF POLY-L-GLUTAMIC ACID AND PACLITAXEL CONTAINING ONE PACLITAXEL ESTER LINKAGE PER ELEVEN GLUTAMIC ACID UNITS (MW 48000)"; UNII: TQ64FZ98ZN.

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B.6 Discussion of the key elements of a chemical substance

B.6.1 Identity of material

The identity, nomenclature and chemical structure of the substance type chemical substance which is the subject of an application for marketing authorization, or is under clinical investigation, or is already marketed, is characterized by five key elements mentioned below of which in B.5.2 the solid state form already has been discussed:

— Substance name and/or Company-code;

— Substance structure;

— Substance molecular formula;

— Substance molecular weight;

— Physical form.

The first two elements have been extensively discussed in clauses 5.3, 5.4, 5.5, 5.7, whereas abbreviations and molecular formula and molecular weight are described below.

The structural representation of the chemical substances shown in the figures inside Figure B.15, is discussed for each figure with respect to clause 5.7. Additional information will be discussed in the next clauses.

B.6.2 Nomenclature

Regarding the nomenclature for chemical substances, a hierarchy for naming substances is used;

Hierarchy of Official Name Types.

a) **INN:** (Official Name Type, Official Name Status (see subclases 5.3.6.1, 5.3.6.2) following the WHO-application International Nonproprietary Name rules.

NOTE An INN for a new chemical entity does not routinely specify the stereoisomeric state of the molecule in the nonproprietary name. If stereochemistry has been determined, then this information is presented in the chemical name(s) to identify the substance.

An INN can, therefore, represent the racemic mixture (e.g. ibuprofen), the *levo*-isomer (e.g. amifostine), or the *dextro*-isomer (e.g. butopamine).

b) **Other Official names and Pharmacopoeial names:** Typical nonproprietary names used in a given jurisdiction: USAN, BAN, Martindale, JAN, Ph.Eur., USP, JP, DAB.

c) **Systematic names:** IUPAC name, CAS Registry Name and definitions of a Pharmacopoeial Monograph.

d) **Codes**: In some cases, a **Company code** can replace a name for a substance under development when name is not available.

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B.6.3 Molecular formula

The molecular formula is directly derived from the molecular structure and is represented following the **Hill system**. The Hill system (or Hill notation) is a system of writing chemical formulas such that the number of carbon atoms in a molecule is indicated first, the number of hydrogen atoms next, and then the number of all other chemical elements subsequently, in alphabetic order. When the formula contains no carbon, all the elements, including hydrogen, are listed alphabetically. In ISO/TS 19844 the molecular formula for an organic salt, solvate or hydrate will notate first the molecular formula of the Parent substance followed by the molecular formula of the salt, solvate or hydrate.

The molecular formula of Amlodipine besilate will be presented by both **$C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$** and **$C_{26}H_{31}ClN_2O_8S$.** The dot between the two moieties is following the IUPAC recommendation. By the terms: **Molecular Formula by Moiety: $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$** and **Molecular Formula** following the Hill system: **$C_{26}H_{31}ClN_2O_8S$.**

Inorganic acids and salts and metal salts are shown without charges or bonds: **$HClO_4$** and **$KMnO_4$** respectively.

If metal salts of inorganic acids include several metals, the symbols for the metals are shown in alphabetic order (e.g. **K_2NaPO_4**).

In salts of **inorganic acids**, the metal precedes the hydrogen (e.g. NaH_2PO_4). Molecules of water of crystallization or of substances of solvation follow the formula of the salt. (e.g. **$H_3PO_4.5H_2O$**).

Hydrates and solvates of **organic acids**: Sodium acetate trihydrate will be represented as **$C_2H_3NaO_2.3H_2O$.** In metal salts of organic acids and in metal compounds of alcohols, phenols (and their sulfur, selenium and tellurium analogues), amines and amides, the metal symbol usually replaces the acid hydrogen.

In non-cyclic linear structures such as Sodium nitroprusside: **$Na_2[Fe(CN)_5(NO)].2H_2O$,** a non-cyclic structure is constructed in the following order:

a) symbol of the central atom placed on the left;

b) ionic ligands with cations first then anions;

c) neutral ligands.

B.6.4 Molecular weight

Molecular mass or **molecular weight** refers to the mass of a molecule and is also directly derived from the molecular structure or molecular formula. It is calculated as the sum of the mass of each constituent atom multiplied by the number of atoms of that element in the molecular formula. For stoichiometric chemicals, the molecular weight is calculated from the molecular formula using standard masses for each of the elements. In ISO/TS 19844 the molecular mass refers to the complete structure or a moiety or a fragment.

For Amlodipine besilate it is the sum of the molecular mass of the free base + the organic salt = 567,06 Da or 567,06 g/mol.

NOTE 1 408,88 g/mol. (Parent Amlodipine), 158,18 g/mol. (Besilate).

NOTE 2 For a substance not described in a Pharmacopoeia (e.g. Ph.Eur., USP, JP) a mass spectrum is provided to substantiate the calculated molecular weight.

B.6.5 Substance structure

Subclause 5.7 describes that structural information is an essential element for chemical substances and for other types of substances that have structurally definable modifications. The representation should contain structural information in one or more of the standardized formats (see 5.7.6).

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A FULL structure is a structure in which the complete connectivity of the substance is known and the substance is monodisperse.

A PARTIAL structure is a structure in which either complete connectivity or stereochemistry is not defined.

A REPRESENTATIVE structure is used when the connectivity of the underlying material is diverse and a single structure is needed to represent that material.

Sometimes the term "illustrative" or "incorrect" in this Annex B is used to indicate that some elements of a structure are not presented in accordance with the ISO/TS 19844.

The structure is "incomplete" to the definition of FULL structure and therefore called "illustrative" in the examples of this document.

B.6.5.1 Stereochemistry

The stereochemistry of the substance shall be indicated in the structure if it can be, as is stated in 5.7.1. Special cases of stereochemistry that cannot be indicated in the structure shall be described based on a controlled vocabulary. Figure B.17 shows a graphical representation (image) of a full structural representation type and the descriptors assigned in the structure: Racemic, Axial S and Axial R respectively.

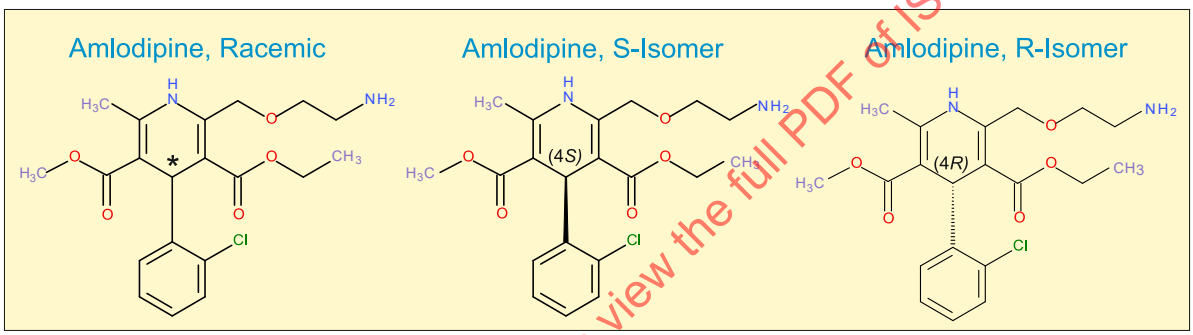


Figure B.17 — Full structural representation of Amlodipine

This means that the stereochemistry of mononuclear complexes is expressed by means of special descriptors formed from an abbreviated for the central atom geometry and the coordination number (Figure B.17).

NOTE In a **tetrahedral molecular geometry**, a central atom is located at the centre with four substituents that are located at the corners of a tetrahedron. The bond angles are $\cos^{-1}(-1/3) \approx 109{,}5°$ when all four substituents are the same, as in CH_4. The perfectly symmetrical tetrahedron belongs to point group T_d, but most tetrahedral molecules are not of such high symmetry. Tetrahedral molecules can be chiral (Figure B.18).

ISO/TS 19844 provides the following information in subclase 5.7.1.

NOTE Clarification of the Value Allowed in the conformance table is provided below. Source: NCI thesaurus: https://ncit.nci.nih.gov/ncitbrowser/

The overall stereochemistry of the substance should be indicated in this field.

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ABSOLUTE **Definition:**	**Chiral** An object or molecule that is not superimposable on its mirror image. The classic description of chirality is the comparison of the hand in a mirror, because the mirror image is the opposite. A chiral molecule has one or more chiral centres
TETRAHEDRAL **Definition:**	**Tetrahedral Molecular Geometry** A molecule in which the central atom is bound to four atoms that form the vertices of a tetrahedron and are described by the chirality symbols (R) and (S)
AXIAL R **Definition:**	Chirality axis based stereochemistry where, using the Cahn-Ingold-Prelog (CIP) priority rules, the priorities (from highest to lowest) of the substituent atoms exist in a clockwise direction.
AXIAL S **Definition:**	Chirality axis based stereochemistry where, using the Cahn-Ingold-Prelog (CIP) priority rules, the priorities (from highest to lowest) of the substituent atoms exist in a anti-clockwise direction
RACEMIC **Definition:**	**Racemate** An equimolar mixture of two enantiomers. A racemate is optically inactive.
EPIMERIC **Definition:**	**Epimeric Centres** A particular kind of diastereomers that differ in their stereochemistry at only one chiral centre; the stereochemistry at all other chiral centres is identical.
Cis-Trans Geometry	
SQUARE PLANAR 1 **Definition:**	**Square Planar 1 Molecular Geometry** Square planar molecular geometry where the Cahn-Ingold-Prelog (CIP) priority of the donor atom directly across from the priority 1 donor atom is also 1.
SQUARE PLANAR 2 **Definition:**	**Square Planar 2 Molecular Geometry** Square planar molecular geometry where the Cahn-Ingold-Prelog (CIP) priority of the donor atom directly across from the priority 1 donor atom is 2.
SQUARE PLANAR 3 **Definition:**	**Square Planar 3 Molecular Geometry** Square planar molecular geometry where the Cahn-Ingold-Prelog (CIP) priority of the donor atom directly across from the priority 1 donor atom is 3.
SQUARE PLANAR 4 **Definition:**	**Square Planar 4 Molecular Geometry** Square planar molecular geometry where the Cahn-Ingold-Prelog (CIP) priority of the donor atom directly across from the priority 1 donor atom is 4.
OCTAHEDRAL 12 **Definition:**	**Octahedral 12 Molecular Geometry (trans Octahedral)** Octahedral molecular geometry where the Cahn-Ingold-Prelog (CIP) priority of the lowest priority donor atom directly across from (trans to) a priority 1 donor atom is also 1 and the priority of the donor atom across from (trans to) the highest priority atom in the plane perpendicular to this reference axis is 2.
OCTAHEDRAL 21 **Definition:**	**Octahedral 21 Molecular Geometry (trans Octahedral 21)** Octahedral molecular geometry where the Cahn-Ingold-Prelog (CIP) priority of the lowest priority donor atom directly across from (trans to) a priority 1 donor atom is 2 and the priority of the donor atom across from (trans to) the highest priority atom in the plane perpendicular to this reference axis is 1.
OCTAHEDRAL 22 **Definition:**	**Octahedral 22 Molecular Geometry (trans Octahedral 22)** Octahedral molecular geometry where the Cahn-Ingold-Prelog (CIP) priority of the lowest priority donor atom directly across from (trans to) a priority 1 donor atom is 2 and the priority of the donor atom across from (trans to) the highest priority atom in the plane perpendicular to this reference axis is 2.

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B.6.5.2 General aspects of stereochemistry

Stereochemistry is concerned with the 3-dimensional arrangement of atoms in molecules, and stereoisomers are isomers with no difference in connectivity or bond multiplicity, but whose atomic

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spatial arrangements differ. A broken line denotes a bond projecting behind the plane of the paper and a filled wedge denotes one projecting in front of that plane. A line of normal thickness denotes a bond lying in the plane of the paper, see Figure B.18. Isomers can be classified in Stereoisomers (Enantiomers and Diastereomers), Geometric isomers, Conformers and Constitutional isomers. The definitions are described in B.4. In the following subclauses Stereoisomers and Geometric isomers are discussed.

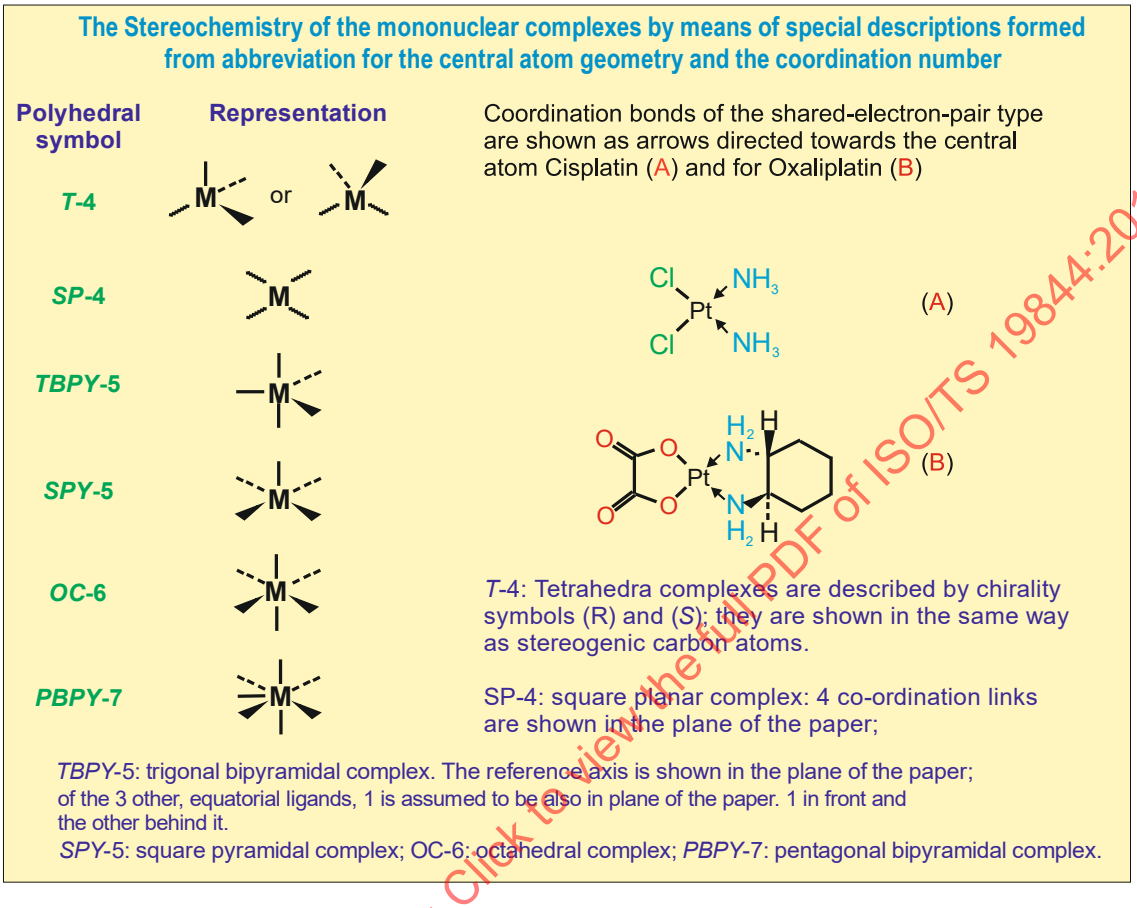


Figure B.18 — Stereochemistry of mononuclear complexes

B.6.6 Geometric isomerism

B.6.6.1 (*E*/*Z*) isomerism

Compounds containing carbon-carbon double bonds are represented as lines at an angle to each other. The representation of (*E*/*Z*) isomers shows that the (*Z*) configuration produces a bend in the chain whereas the (*E*) configuration does not. Figure B.19 presents example 1-Phenyl-1,3-pentadiene.

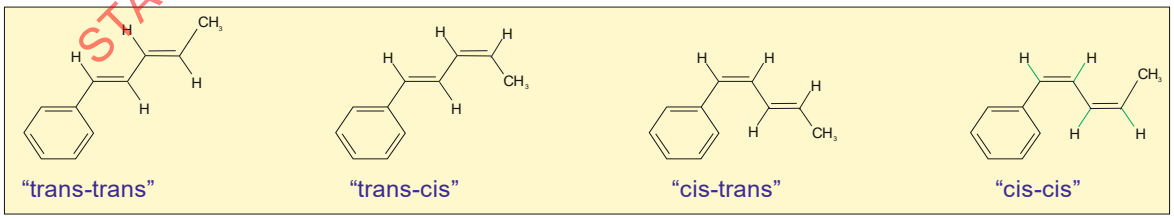


Figure B.19 — Stereochemistry of 1-Phenyl-1,3-pentadiene

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It should be noted that the hydrogen atoms attached to the two carbon atoms forming the double bond are omitted in the case of (*E*/*Z*)-isomerism. The same convention is used for the isomers of imines/oximes and compounds containing several bonds, as in Figure B.20.

B.6.6.2 *Cis-Trans* Ring-isomerism

Cis-Trans Ring-isomerism (chirality) is defined for a molecule with a plane of symmetry as the existence of cis and trans isomerism according to the arrangement of the substituents on a ring with respect to the plane of this ring, as in Figure B.20.

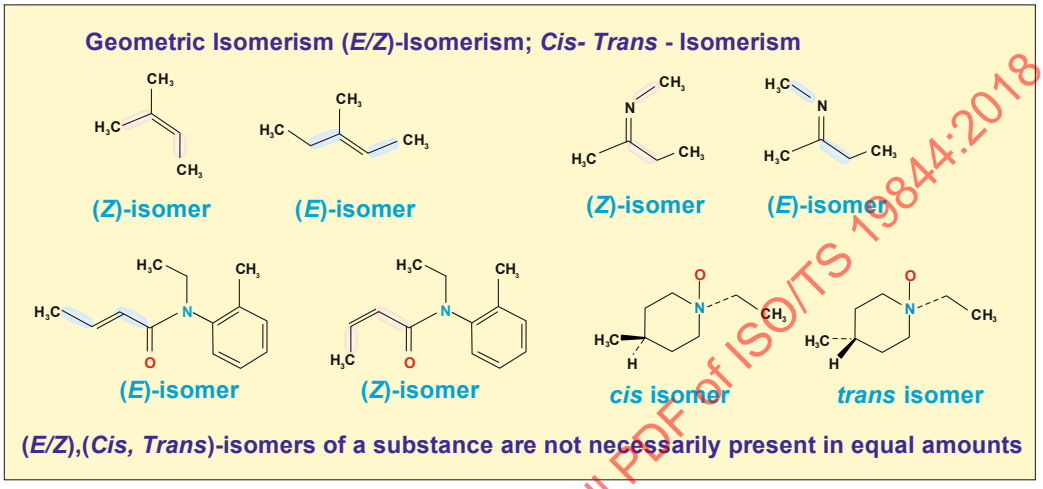


Figure B.20 — Geometric isomerism Stereo-descriptors in systematic nomenclature: Substance with one centre of asymmetry

An enantiomer is one of a pair of molecular entities that are mirror images of each other and are non-superimposable. The descriptors (*R*) and (*S*) are symbols proposed by Cahn, Ingold and Prelog (CIP) and indicate the chiral absolute configuration around 4-coordinate (quadriligant) and 6-coordinate (sexiligant) stereogenic centres.

NOTE The CIP sequence rules are explained in B.1.1. **When the enantiomeric pair is of equal amounts the pair is called a racemic mixture or the substance is a 'racemate"** (e.g. Amlodipine, Figure B.16). The Element Groups capturing Amlodipine besilate are described in B.8.1, tabular example 1.

B.6.7 Substance with two centres of Asymmetry, Epimers, Diastereomers

Epimers are diastereomers that have the opposite configuration at only 1 of 2 or more tetrahedral stereogenic centres present in the respective molecular entities. If a substance has two centres of asymmetry, there are four different stereoisomers. Two epimers of this substance have the same configuration at one centre of asymmetry and a different configuration of the other. Figure B.21 presents an example of the enantiomer and diastereomers of CAS number 191226-98-9 with the CAS Registry name:

Carbamic acid, N-[(1S,2R)-2-hydroxy-3-[(2-methylpropyl)[(4-nitrophenyl)sulfonyl]amino]-1-(phenylmethyl)propyl]-, 1,1-dimethylethyl ester.

NOTE At the right-top of the figure a section of the chromatogram is presented obtained by an HPLC-Chiral column experiment, showing that the properties of the diastereomers differ from the enatiomers so that both groups of stereoisomers could be separated.

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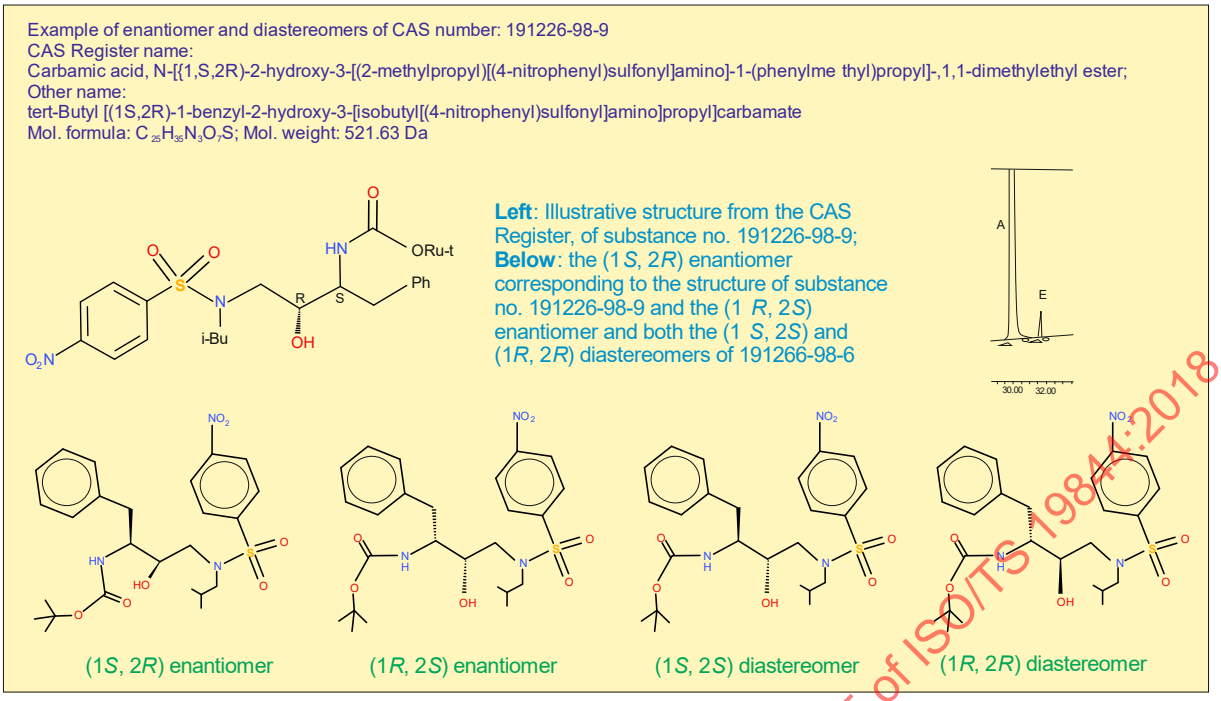


Figure B.21 — Structural representation of substances with two asymmetric centres

B.6.8 Anomers

A special case of epimerism is that of anomerism of sugars. Anomers are defined as diastereomers of glycosides, hemiacetals or related cyclic forms of sugars, or related molecules differing in configuration only at C-1 of an aldose, C-2 of a 2-ketose, etc.

In subclause 5.7.6, the structural representation of glucose in the crystalline state is provided as well as the introduction of an anomeric C1-atom after cyclization of D-glucose and representation of D-glucose in the Haworth projection in Figure B.22. In Figure B.23, the structure of the disaccharide lactose is shown. The O-Glycosidic bond is a type of covalent bond that joins a carbohydrate (sugar) molecule to another group, which may be another carbohydrate. In the Haworth-projection C^*_1-OH group is *cis* to the C_5-CH_2OH group resulting in the β-anomeric form.

In Figure B.24, the examples of anhydrous α-lactose (β-D-Galactose, α-D-Glucose connected by a β-glycosidic bond) and anhydrous β-lactose (β-D-Galactose, β-D-Glucose) will be presented in accordance with the ISO/TS 19844 Implementation Guide, subclause 5.7 Example α-, and β-Glucose anhydrous. The examples provided in Figure B.24 are for the comparison of the Haworth presentation of structures to the "correct" presentations of the same substances. The structural representation as presented in Figure B.24 should be provided. Note that none of the electronic structural representation understands Haworth projections.

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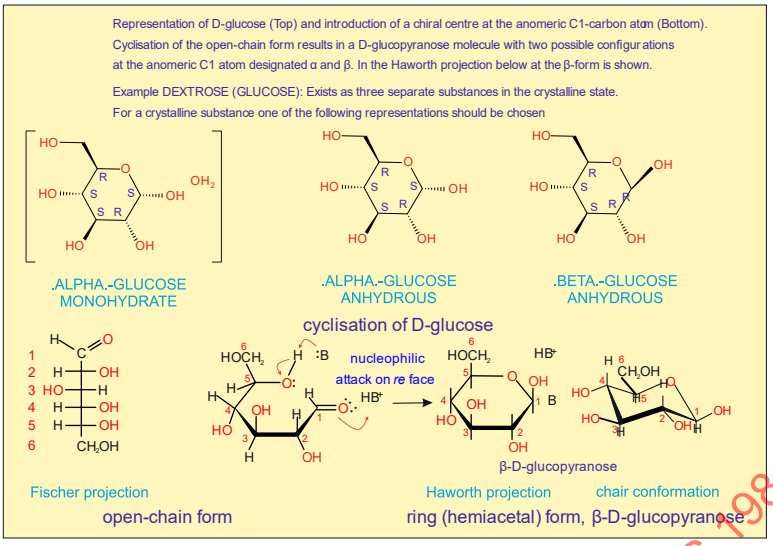


Figure B.22 — Structural representation of α- and β- Glucose and α-Glucose monohydrate and in Haworth projection

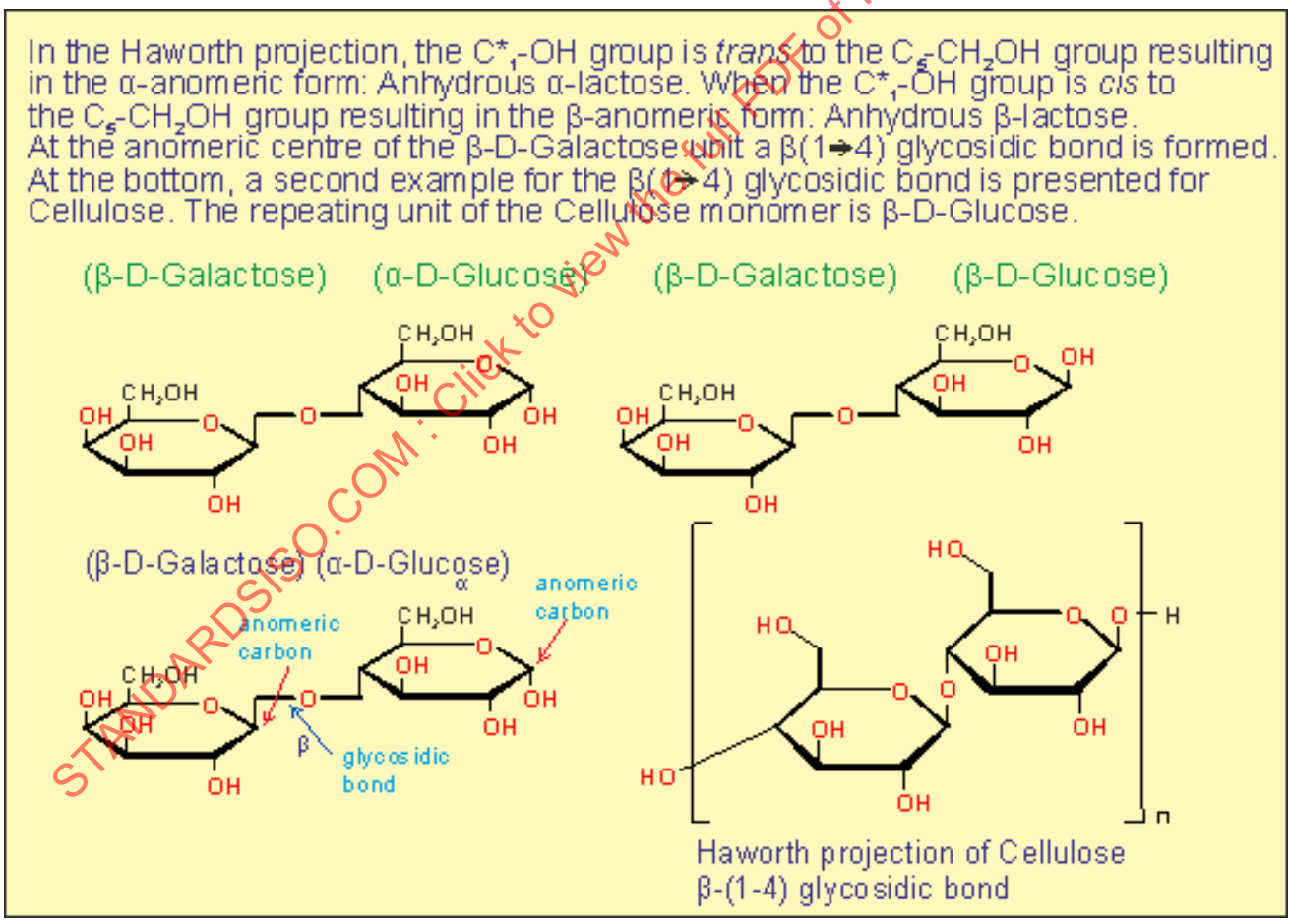


Figure B.23 — Haworth projection of α- and β- Lactose anhydrous

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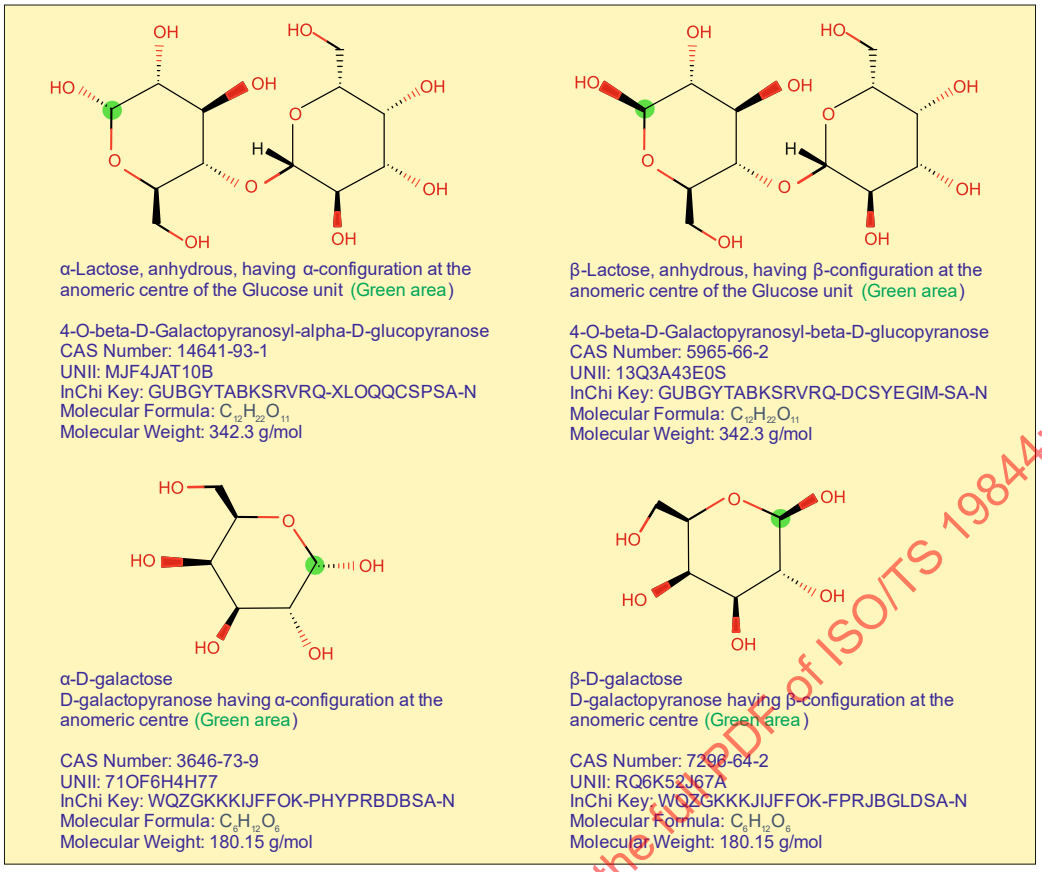


Figure B.24 — α- and β-Lactose, α-D- and β-D-Galactose in absolute Structural Representation in accordance with ISO/TS 19844

B.6.9 Substance with more than two centres of Asymmetry (Mixture of stereoisomers)

In 5.7.1, the user guidance reads that mixture of stereoisomers shall be represented explicitly as a mixture of substances with absolute stereochemistry. In the case the absolute stereochemistry is unknown the substance definition should be marked as "Incomplete".

The next **example, Misoprostol,** provides the information needed to comply as a "complete" representation.

The Ph.Eur., current edition, defines Misoprostol as:

Chemical Name	Mixture of methyl 7-[(1RS, 2RS, 3RS)-3-hydroxy-2-[(1E,**4RS**)-4-hydroxy-4-methoxloct-1-enyl]-5-oxocyclopentyl] heptanoate and methyl 7-[1RS, 2RS, 3RS)-3-hydroxy-2-[(1E, **4SR**)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl] heptanoate
The FDA GSRS refers to	(+/-)-METHYL (1R, 2R, 3R)-3-HYDROXY-2-((E)-(4RS)-4-HYDROXY-4-METHYL-1-OCTENYL)-5 OXOCYCLOPENTANEHEPTANOATE
Other Name	PROST-13-EN-1-OIC ACID, 11, 16-DIHYDROXY-16-METHYL-9-OXO-, METHYLESTER, (11.ALPHA. 13E)-(+/-)-
IUPAC Name	methyl 7-[(1R, 2R, 3R)-3-hydroxy-2-[(E)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl] heptanoate+
Molecular Formula	$C_{22}H_{38}O_5$
Molecular Weight	382,5
Unit	g/mol

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CAS Registry Number	59122-46-2
Substance Code	**UNII**: 0E43V0BB57
Chirality	Misoprostol has four chiral centres. The presence of 2^4 = 16 stereoisomers is thus possible. Four of the 16 enantiomers compose Misoprostol [methyl (13E)-(±)-11, 16-dihydroxy-16-methyl-9-oxoprost- 13-en-1-oate]

The centre at **C_{16} is epimeric** and the centres at C_8, C_{11} and C_{12} are controlled relative to each other with *cis* substitution on the cyclopentanone ring. Misoprostol is therefore a mixture of four stereoisomers, Figure B.25.

When possible, the structure should contain the numbering of the Carbon atoms in case of complex structures. (e.g. difference in the conventional prostaglandin numbering of the carbons and the numbering used by IUPAC and Ph.Eur., starting with the oxocyclopentyl ring (1 to 5), and counting the side chains separately).

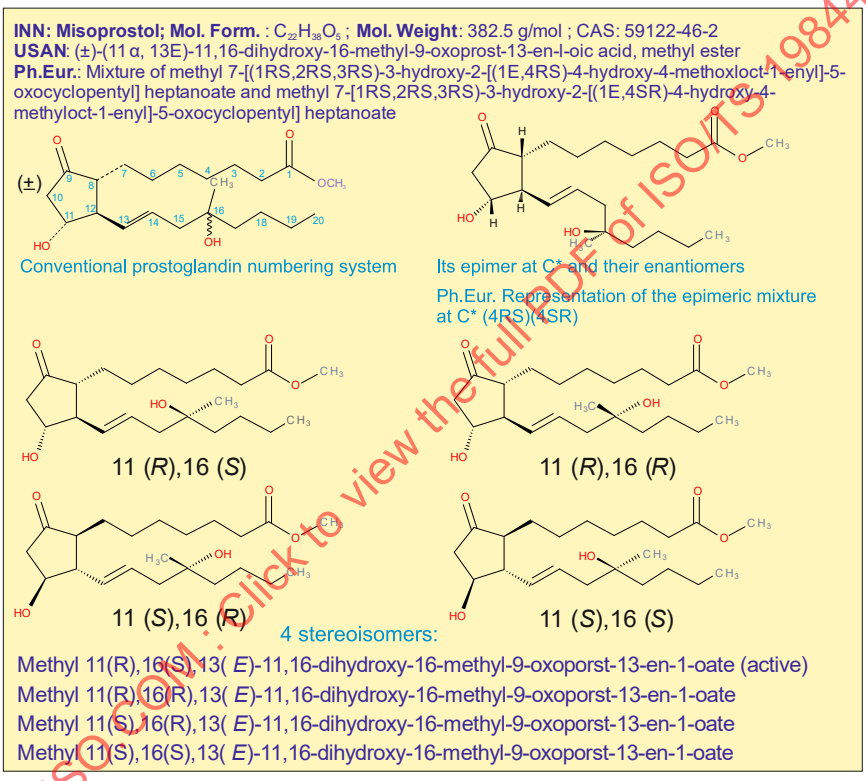


Figure B.25 — Structural representation of Misoprostol

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B.6.10 Conclusion for the Key elements

In order to assign a Substance ID for a chemical substance, a complete covalent structure with all stereochemistry (*R* or *S* and *E* or *Z* and *sn*) defined is needed. The stoichiometry (mole ratio) of counter-ions or solvates present in the material should also be provided.

For all chemical substances, a molecular representation (molfile, SMILES, InChI, CDX (ChemDraw)) of the substance should be provided with all stereochemistry assigned or sites of unknown stereochemistry identified. An actual image of the structure can be provided in an accompanying document (see 5.7). In addition to the structure the molecular formula, molecular weight, and systematic name should be provided at the structural representation.

B.6.11 Decision tree for a new Substance ID

Figure B.26 provides a decision tree for the conditions of elements needed which might help in the choice whether a new Identifier is needed or not.

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DECISIONS FOR ASSIGNING A NEW IDENTIFIER			
Example: Substance Elemental Composition: [C, H]			**Substance ID**
		When a new ID is Needed?	
➢	1)	Change in elemental composition (e.g. C, H, O)	YES
➢	2)	Same elemental composition but different molecular weight C, H, O mass 400 g/mol →418 g/mol. C, H, O Hydrate Isotopes F → ^{18}F (^{18}Fludeoxyglucose)	YES
➢	3)	Same elemental composition, same molecular weight, different stereochemistry (e.g. Isomers)	YES
			Specified Substance Group 1 ID
➢	4)	Same elemental composition, same molecular weight, same stereochemistry, different physical form (e.g. polymorphic form)	YES
			Specified Substance Group 3 ID
➢	5)	Same elemental composition, same molecular weight, same stereochemistry, same physical form, different technical grade	YES
➢	6)	Same elemental composition, same molecular weight, same stereochemistry, same physical form, technical grade, Ph.Eur. or USP	YES

Figure B.26 — Decision tree for a new Substance ID

B.7 Discussing other elements of importance regarding the characteristics of a substance

B.7.1 Introduction

At ISO 11238 Specified Substance Group 3 Information level **vegetable oils** are captured as described in several Pharmacopoeial monographs e.g. Olive Oil, Virgin Ph.Eur. and Olive Oil, Refined Ph.Eur. Definition Olive Oil, Virgin: Fatty oil obtained by cold expression or other suitable mechanical means from the ripe drupes of *Olea europaea* L.

These types of substances are discussed in detail in Annex E (**Structurally Diverse Substance, herbals**).

B.7.2 Naming Vegetable Oils

The **business rules** for naming of vegetable oils are described in 6.5.13.1 and in the subclause Source Material 5.9.

As outlined in Annex E, the information for the Herbal Drug (a term used here in preference to herbal substance) and the Herbal preparation is captured at the substance information level, see Figure E.3. Additional Herbal Drug and Herbal preparation information can be included in the Substance Type Structurally Diverse, Specified Substance Group 1 information level. This is needed to capture the marker and signature substances at this level in order to comply with the Regulatory requirements.

Within this Annex, the terms Substance and Specified Substance are used as defined by ISO 11238. The terms Herbal Drug (herbal substance) and Herbal preparation are used as defined by pharmacopoeias, and will both be captured at the Substance level. In addition, a more basic unit, comprising unprocessed, fresh material of a single species or intraspecies (occasionally a genus) and part, with no affiliation to any particular pharmacopoeia, will also be captured at the Substance level; for clarity, these will be referred to as Substance (fresh) in this document. The information model also accommodates fraction information at the substance level. The **element <Fraction>** corresponds to **two** types of **Herbal preparations**: <Oil, Exudate, Juice> or <Extract>, each requiring different information.

Specified Substance Group 1 includes additional information for substances and multi-substance material. Additional information for Herbal Drugs and for Herbal preparations e.g. additional information

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for an extract such as extraction solvent composition, Herbal Drug/Herbal extract ratio (DER) will be captured at this level along with the constituents and marker or signature substances.

Specified Substance Group 2 captures manufacturer information along with limited manufacturing information.

Specified Substance Group 3 captures the grade of a given Substance or Specified Substance Group 1 as outlined in a Pharmacopoeia or approved by a given regulatory agency.

In Figure B.27 the Substances subclasses are shown belonging to the Substance Type: Structurally Diverse.

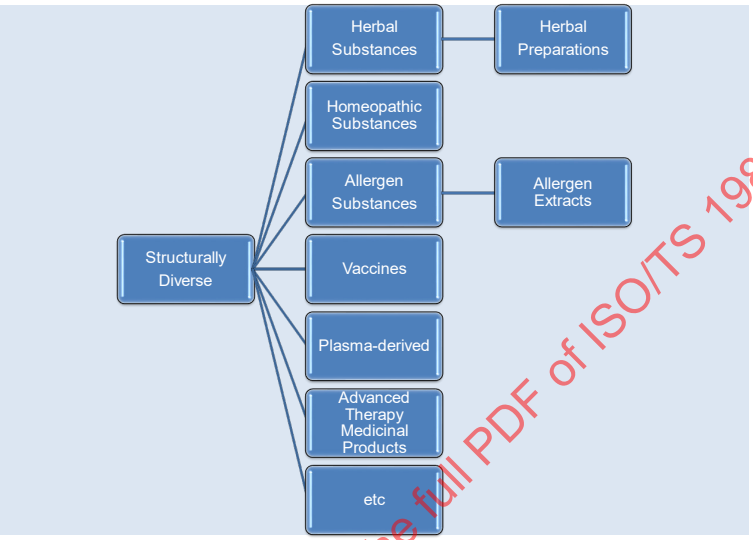


Figure B.27 — Examples of Substance classes belonging to Substance Type: Structurally Diverse

B.7.3 Example Olive Oil, Virgin

Olive Oil, Virgin Ph.Eur. is defined as a Herbal preparation (because it has been obtained by expression). There is no defined Herbal Drug for this Herbal preparation, but instead its source material is the ripe drupes (fruit) of *Olea europaea* L.

For the purposes of the ISO 11238, the Herbal preparation is defined as a Substance as [<Scientific genus/binomial/trinomial **without Author**>,<Part(s)>,<Fraction>], i.e. *Olea europaea*, Fruit, Oil.; Common name: Olive Oil, Virgin. The source material for the Herbal preparation, with the **relationship** of **Parent substance**, is a separate Substance (fresh) defined as [<Scientific genus/binomial/trinomial **with Author**>,<Part(s)>], i.e. *Olea europaea* L., Fruit.

The **name** [<Scientific genus/binomial/trinomial **with Author**>,<Part(s)>] refers to a **Substance Name** in terms of the ISO 11238 that is not an official name in any pharmacopoeia or other legislation. The inclusion of the author is to ensure that it is not confused with the official names for Herbal Drugs and Herbal preparations which are also defined as Substances by the ISO 11238. The scientific element of the name is usually a binomial (species), but may be a trinomial (intraspecies such as a variety or subspecies) or a genus, as appropriate, together with the author of the name. The Part element of the name should be chosen from a CV consisting of a restricted number of terms.

Taxonomic information, particularly the scientific name of a medicinal plant, is essential for defining herbal substances in medicinal products. The Kew Gardens Medicinal Plant Names Services (MPNS) should be the authoritative source for all scientific names and should also maintain a list of plant parts and fractions. A controlled vocabulary for medicinal plant taxonomy has been developed and will be maintained by the Kew Gardens Medicinal Plant Names Services. A submitter should choose the current accepted scientific name provided by MPNS. The MPNS Portal should be accessed via www.kew.org/mpns. The service should be contacted if the herbal substance material cannot be mapped to records in MPNS. It should be noted that many common and even pharmacopoeial names of plants

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often map to more than one plant species, but it is important that the actual herbal substance (defined as a particular species) is used in defining a substance.

The **name** [<Scientific genus/binomial/trinomial **without Author**>,<Part(s)>] refers to a **Substance Name** in terms of the ISO 11238 and is the equivalent to a Herbal Drug Name. There is no such Substance Name for Olive Oil in this example from the Ph.Eur., although other pharmacopoeias might define a Herbal Drug for *Olea europaea*, Fruit.

The **name** [<Scientific genus/binomial/trinomial **without Author**>,<Part(s)>], [Fraction] refers to a **Substance Name** in terms of the ISO 11238 and is **equivalent** to a **Herbal preparation Name.** The Herbal preparation Name corresponds to two types of Herbal preparation; one for the Substance fraction: Oil, Exudate, Juice and one for the Substance fraction: Extract. This is done to differentiate between the cardinalities of the two types of Herbal preparation.

The Herbal preparation relationship to the Substance (fresh) is a two-way relationship. The fraction <Oil, Exudate, Juice> is prepared from **one** Substance (fresh).

Note that several Herbal preparations, e.g. Juices, can be a mixture of separately obtained juices obtained from the Herbal substances and mixed after expression. The final preparation is then a multi-substance material which is captured at the Specified Substance Group 1 level.

The fraction <Extract> can be prepared from **one or more** Herbal Drugs and by **one or more** extraction steps and by **one or different** extraction solvent compositions. Only the first extraction solvent composition is used in the element solvent. Further details of the Herbal preparation and Herbal Drug are described in the Annex E.

For the Herbal preparation Olive Oil, Virgin the result of the information model reads:

Table B.1

Substance ID	HJFTE78543 (Artificial ID); (UNII: 6UYK2W1W1E)
Substance Name (Herbal preparation Name)	*Olea europaea*, Fruit, Oil
Substance Name Type:	Other
Fraction (Herbal preparation)	Oil [1)]
Substance Name	Olive Oil, Virgin
Substance Name Type:	Official (for further elements see tabular format)
Parent Substance ID	OLIJF5643S
Parent Substance Name	*Olea europaea* L., Fruit
[1] The value Oil is appropriate here. The Herbal preparation is valid for: Oil, Exudate, Juice.	

The relationships between the description of the parent of Olive Oil [Substance (fresh)] and the Substance Olive Oil, Virgin (Herbal preparation) are represented in the Figure B.28.

For comparison, the relationships between the description of the Substance (fresh), the Substance (Herbal Drug) and the Substance (Herbal preparation) for Ginkgo biloba, Dry Extract are presented in Figure B.29.

Further details and discussion is described in the Annex E.

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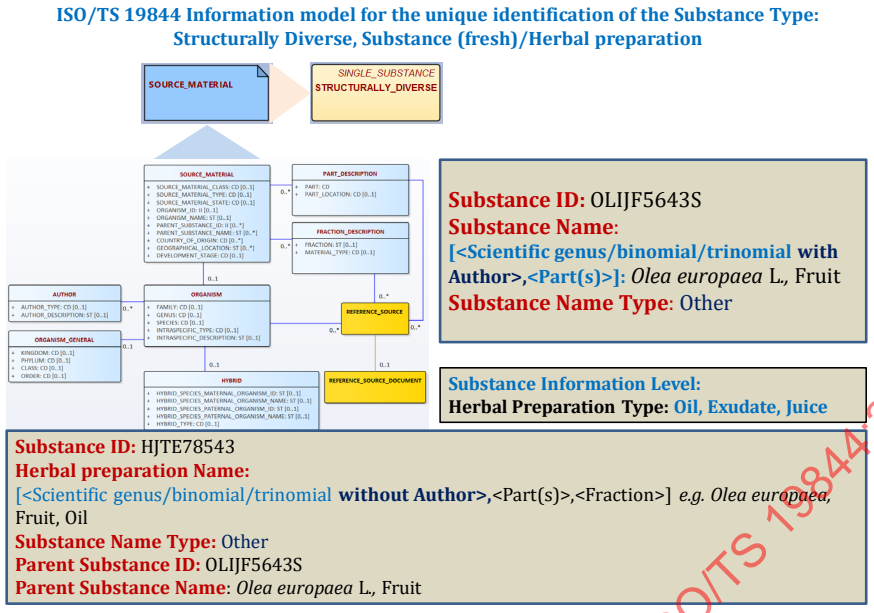


Figure B.28 — Information model for Structurally Diverse, Substance (fresh)/Herbal preparation

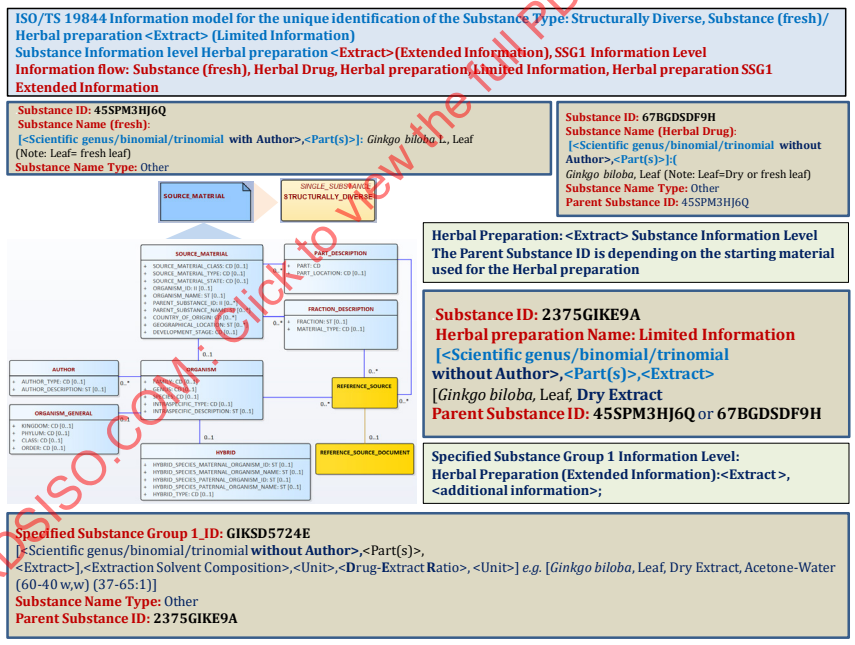


Figure B.29 — Information model for Structurally Diverse, Substance (fresh)/Herbal preparation and Herbal preparation at the Specified Substance Group 1 level

NOTE At the Substance level, the *Ginkgo biloba* L., Leaf is per definition always the fresh material. Consequently, *Ginkgo biloba*, dry leaf is a Herbal Drug and is considered to be captured at the Substance level and will therefore have a distinct Substance ID from the fresh leaf.

Captured at the Substance Level:

Ginkgo biloba L.: = Substance (fresh material)

Ginkgo biloba, Leaf: = Herbal Drug (dry material as defined by the Pharmacopoeia)

Ginkgo biloba, Leaf, Dry Extract: = Herbal preparation (as defined by the Pharmacopoeia)

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Captured at the Specified Substance Group 1 Level:

Ginkgo biloba, Leaf, Dry Extract, Acetone-Water (60-40, w/w) (37-65=1) (as defined in the application dossier for registration).

Additional information for more elements at the Substance level for the Substance *Olea europaea* L., Fruit and the Herbal preparation Olive Oil, Virgin is provided in Figure B.30.

Substance (fresh)/Herbal preparation

Substance (fresh)

Substance ID: OLIJF5643S
Substance Type: Structurally Diverse Substance, (Substance (fresh))
Element Group: Substance Name
Substance Name: *Olea europaea* L., Fruit
Substance Name Type: Other
Element Group: Source Material
Source Material Type: Plant
Element Group Organism
Full Taxonomical description:

Element Group: Organism	
Family	Oleceae
Species	Europaeae
Element Group: Organism General	
Kingdom	Plantae
Phylum	Tracheophyta
Class	Magnoliopsida
Order	Lamiales
Element Group: Authors	
Author Description	L.

Element Group: Part Description
Part: Fruit

Herbal preparation

Substance ID: HJTE78543
Substance Type: Structurally Diverse Substance, (Herbal preparation)
Element Group: Substance Name
Substance Name: *Olea europaea*, Fruit, Oil
Substance Name Type: Other
Element Group: Source Material
Parent Substance ID: OLIJF56435
Parent Substance Name: *Olea europaea* L., Fruit
Element Group: Part Description: Fruit
Element Group: Fraction Description: Oil

Element Group: Property	
Property Type	Physical
Property Name	Acid Value
Property Substance Name	Olive Oil, Virgin
Element Group: Amount	
Amount Type	Average
Quantity	1.0
Unit	mg/g
Amount Text	mg KOH/5 g
Element Group: Reference Range	
Low Limit	0.10
High Limit	2.0
Unit	mg/g
Element Group: Amount (Olive Oil, Refined)	
Amount Type	Average
Quantity	0.21
Unit	mg/g
Amount Text	mg KOH/10 g
Element Group: Reference Range	
Low Limit	0.10
High Limit	0.3
Unit	mg/g

Figure B.30 — Substance (fresh)/Herbal preparation of Olive Oil, Virgin (Ph.Eur.)

B.7.4 Description of Elements at the Specified Substance Group 1 Information level

The Element Group Property is envisioned to be allocated at the Substance or at the Specified Substance Group 1 information level for the description of the characteristics of the Substance (fresh), Herbal Drug and/or Herbal preparation.

Captured properties related to liquids (oils) and the description can be found in B.7.8.

NOTE 1 It is necessary to describe the Herbal preparation "Extract" in more detail compared to the Herbal preparation "Oil" in order to comply to jurisdictional legislations (e.g. European legislation), since marker substances are described and referred to standardized and quantified Herbal preparations. Marker substances are described in the Constituent Group by the attribute 'constituent susbtance'. Also captured by the element group 'Constituent' are the parent substance and the extraction solvents. The element group 'Chateristic Attribute' is used to describe the Drug Extract Ratio (DER) as well as other characteristics like the 'Country of Origin' and properties related to the substance. The element group 'Attribute Parameter' is used to describe additional conditions for a certain Characteristic Attribute (parameter) e.g. the temperature measured at a pH value.

NOTE 2 Further information and examples are provided in Annex E.

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B.7.5 Description of Elements at the Specified Substance Group 2 Information level

At Specified Substance Group 2 Information level, the Manufacturing information is captured. For the **Herbal Drug** this information will tie the manufacturer which collects, processes (comminuted, cutting of the material) and stores the Herbal Drug.

For the **Herbal preparation** the manufacturer of the processed Herbal Drug is captured.

The Element Group 'Reference Source Document' is included and provides the manufacturer to submit the Release Specification of the manufactured preparation. For more details, see 7.2, Annex E and Figure 36.

B.7.6 Description of Elements at the Specified Substance Group 3 Information level

At Specified Substance Group 3 information level the Pharmacopoeial Grade of a (Specified) Substance refers to a specification for Olive Oil, Virgin with the (Specified) Substance (Group 3) name of Olive Oil, Virgin Ph.Eur. The information model is provided in Figure 38.

EXAMPLE

Specified Substance Group 3 ID: JFGDRW4526 (Artificial ID)

Substance Name: Olive Oil, Virgin-Ph.Eur.

Substance Name Type: Specified Substance Group 3

Language: en

(Parent) Substance ID: HJFTE78543

Grade Type: Ph.Eur.

Grade Name: Olive Oil, Virgin

NOTE The (Parent) Substance ID corresponds to the:

(Parent) Substance: *Olea europaea*, Fruit, Oil (= Herbal preparation) which is related in turn to the:

(Parent) Substance: *Olea europaea* L., Fruit (= Substance (fresh)) and corresponding (Parent) Substance ID

(HJFTE78543).

As shown in the model in Figure 38, the information is provided to capture the grade of a substance. This group is meant to be for Pharmacopoeial Grades (Ph.Eur., USP). Each grade will have a separate Specified Substance Group 3 identifier. However, there are applications in which regulatory approval has been achieved for more than one grade and sometimes the sponsor will add an extra specification, such as particle size which is not captured in the Pharmacopoeial monograph. In this case the model provides in the Reference documentation type "In-house" Grade in which a specification set can be laid down covering the Ph.Eur. and USP as well as the intended particle size.

B.7.7 Olive Oil, Refined

In the Ph.Eur. monograph Olive Oil, Refined the definition reads: Fatty oil obtained by refining of crude olive oil, obtained by cold expression or other suitable mechanical means from the ripe drupes of *Olea europaea* L.

This means that at the Substance level the source of Olive Oil, Refined (Ph.Eur.) is captured by the Substance (fresh) *Olea europaea* L., Fruit, which is thus the same as for Olive Oil, Virgin (Ph.Eur.). For the Substance, Herbal preparation, the fraction (Oil) will be captured as:

Substance ID: KHJGHR4523 (Artificial ID)

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Substance Name: *Olea europaea*, Fruit, Oil Refined

Substance Name Type: Other

Substance Name (Repeat): Refined Olive Oil

Substance Name Type: Official

Parent Substance ID: OLIJFF5643S[30]

The difference between the Virgin Olive Oil (Ph.Eur.) and the Refined Olive Oil (Ph.Eur.) is a reduction of the amount of free acids which will be captured as a modification. The result will be the difference in Grade, captured at Specified Substance Group 3 and probably a difference in manufacturing method captured in Specified Substance Group 2. There isn't any structural chemical modification process, such as (substitution, breaking covalent bonds, hydrogenation, etc.), but only a quantitative change in amount of constituents being expressed in the properties. These properties are captured in the Element Group 'Property'.

At the Specified Substance Group 3 level the Pharmacopoeial Grade of the substance is captured as a specification for Olive Oil, Refined with reference to the Ph.Eur.:

EXAMPLE

Specified Substance Group 3 ID: SDAUT12543 (Artificial ID)

Substance Name: Olive Oil, Refined-Ph.Eur.

Substance Name Type: Specified Substance Group 3

Language: en

(Parent) Substance ID: KHJGHR4523 [31]

Grade Type: Ph.Eur.

Grade Name: Olive Oil, Refined

B.7.8 Properties to be captured, related to liquids (vegetable oils)

As described in B.2, the key elements for defining the substance are: Structure, Molecular formula, Molecular weight and Solid state characterization.

For this group of liquid substances, properties such as refractive index, solubility, viscosity, UV-absorption, specific gravity, saponification value, acid value, peroxide value and the composition of the mixture material, such as the mixture and relative quantity of the fatty-oil fraction and sterol-fraction of the oil, are essential in defining the Substance, whether it is Virgin Olive Oil (Ph.Eur.), or Refined Olive Oil (Ph.Eur.), which is essential for use in parenteral preparations.

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30 This corresponds to:

Related Substance: *Olea europaea*, Fruit, Oil (= Herbal preparation), which in turn is related to the parent organism *Olea europaea* L., Fruit with the Parent Substance ID: OLIJF5643S [= Substance (fresh)].

(The manufacturing is described in one step for this example so the Parent Substance is the organism. In fact, the manufacture of Olive Oil, Refined is a two-step process. The first step is the preparation of Olive Oil, Virgin out of the source material and thereafter the refinement of the Oil to get the final resultant substance).

31 Corresponding to the:

Parent Substance: *Olea europaea*, Fruit, Oil Refined (= Herbal preparation), which in turn is related to the parent organism *Olea europaea* L., Fruit with the

Parent Substance ID: OLIJF5643S [= Substance (fresh)].

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In Figure B.31 and Figure B.32 these elements are discussed regarding the definition of a vegetable oil. In Figure B.30, the two Ph.Eur. grades are compared. The elements described in **red** are different for the grades, but important for whether the material can be used in a parenteral preparation.

In fact, the two grades are different Substances with respect to ISO 11238, since the Olive Oil, Refined (Ph.Eur.) is sourced from the Olive Oil, Virgin (Ph.Eur.), but has been refined by a (physical) modification process in order to remove or reduce free acids and peroxides.

In both the Virgin Olive Oil (Ph.Eur.) and the Refined Olive Oil (Ph.Eur.) the specifications for the fractions for fatty-acids and sterol-fraction are the same. Indeed, not only the qualitative composition is important but also the quantitative composition in order to decide whether the substance is Crude Olive Oil or Refined Olive Oil. The difference between the two grades is managed by testing **quantitatively** the other properties of the constituents of the Olive Oil types by measuring the solubility, UV-absorbance, acid value, peroxide value and water content.

Conclusion: To distinguish between Olive Oil (Ph.Eur.), Virgin and Olive Oil, Refined (Ph.Eur.), a Certificate of Analysis and a batch result should be provided to substantiate the submission for a Specified Substance Group 3 ID and as a consequence information should be provided up to the substance level (Source Material), since quantitative results of the properties make the difference between the two types of Olive Oil.

In Figure B.32 a batch result is shown. In the **red box** the elements and values are captured demonstrating that the batch complies with the **quantitative** values of the properties requirements. The fatty-acid qualitative and quantitative composition as well as for the sterols composition show that the batch results comply with both the Olive Oil types. The results in the red box are making the difference. They show by **quantitative values** that the sample complies with Olive Oil, Refined (Ph.Eur.).

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Specifications Refined Olive Oil as specified by the applicant sponsor compared to the requirements of Olive Oil, Virgin (Ph.Eur.) and Olive Oil, Refined (Ph.Eur.) Key properties red box

Specifications Olive Oil, Virgin & Olive Oil, Refined (Ph.Eur.)

Specifications Olive Oil, Virgin (Ph.Eur.)	**Specifications Olive Oil, Refined (Ph.Eur.)**
General properties:	**General properties:**
Appearance: Clear, colourless or greenish-yellow transparent liquid. ***Solubility***: Practically insoluble in ethanol (96%), miscible with light petroleum (bp: 50-70°C). When cooled, it begins to become cloudy at 10°C and becomes a butter-like mass at about 0°C. **Absorbance: MAX 0.20 at 270 nm; Ratio absorbance 232/270 nm>8.** **Acid value: Limit test: NMT 2.0, determined on 5 g** **Peroxide value: Limit test: MAX 20.0 (Method A)** **Alkaline** ***Unsaponifiable matter***: 1.5 % on 5.0 g	***Appearance***: Clear, colourless or greenish-yellow transparent liquid. ***Solubility***: Practically insoluble in ethanol (96%), miscible with light petroleum (bp: 50-70°C). When cooled, it begins to become cloudy at 10°C and becomes a butter-like mass at about 0°C. **Specific Absorbance: MAX 1.20 at 270 nm;** **Acid value: Limit test: NMT 0.3, determined on 10 g** **Peroxide value: Limit test: MAX 10.0 (Method A)** **Parenteral preparations: MAX 5.0 (Method A)** ***Unsaponifiable matter***: 1.5 % on 5.0 g **Alkaline impurities: Complies with the test (1.14.19)**

Fatty acid composition		
Lauric acid	(C 12:0)	< 0.05 %
Myristic acid	(C 14:0)	< 0.05 %
Myristoteic acid	(C 14:1)	< 0.05 %
	(<C 16:0)	< 0.05 %
Palmitic acid	(C 16:0)	10.75 %
Palmitoleic acid	(C 16:1)	0.82 %
Marganic acid	(C 17:0)	0.08 %
Heptedecic acid	(C 17:1)	0.11 %
Stearic acid	(C 18:0)	3.66 %
Oleic acid	(C 18:1)	76.00 %
Linoleic acid	(C 18:2)	6.89 %
Linolenic acid	(C 18:3)	0.66 %
Octadecafetraen acid	(C 18:4)	< 0.05 %
Arachidic acid	(C 20:0)	0.43 %
Eicosenoic acid	(C 20:1)	0.27 %
Eicosanedienoic acid	(C 20:2)	< 0.05 %
Eicosanetetraenoic acid	(C 20:4)	< 0.05 %
Behenic acid	(C 22:0)	0.12 %
Erucic acid	(C 22:1)	< 0.05 %
Lignoceric acid	(C 24:0)	0.06 %
...	...	...

Specifications of the Applicant/sponsor

OLIVE OIL, REFINED
Ph.Eur.7, 2011, USP 33 – NF28
lot:503500

Analysis results:	
Specific gravity (20-degree C)	0.913
Refractive index (20-degree C)	1.469
Absorption at 270 nm	0.47
Lodine value	80
Saponification value	191
Acid value	0.21
Peroxide value	Complies
Unsaponifiable Matter	1.18 %
...	...

Figure B.31 — Specifications for Olive Oil (Ph.Eur.), Virgin and Olive Oil, Refined (Ph.Eur.)

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Specifications Olive Oil, Refined as specified by the Applicant (Sponsor) used as an Excipient in Cholecalciferol/1.0 ml Refined Olive Oil, oral solution Key properties (shown in red box)

Fatty acid composition

Lauric acid	(C 12:0)	< 0.05 %
Myristic acid	(C 14:0)	< 0.05 %
Myristoteic acid	(C 14:1)	< 0.05 %
	(<C 16:0)	< 0.05 %
Palmitic acid	(C 16:0)	10.75 %
Palmitoleic acid	(C 16:1)	0.82 %
Marganic acid	(C 17:0)	0.08 %
Heptedecic acid	(C 17:1)	0.11 %
Stearic acid	(C 18:0)	3.66 %
Oleic acid	(C 18:1)	76.00 %
Linoleic acid	(C 18:2)	6.89 %
Linolenic acid	(C 18:3)	0.66 %
Octadecafetraen acid	(C 18:4)	< 0.05 %
Arachidic acid	(C 20:0)	0.43 %
Eicosenoic acid	(C 20:1)	0.27 %
Eicosanedienoic acid	(C 20:2)	< 0.05 %
Eicosanetetraenoic acid	(C 20:4)	< 0.05 %
Behenic acid	(C 22:0)	0.12 %
Erucic acid	(C 22:1)	< 0.05 %
Lignoceric acid	(C 24:0)	0.06 %
Nervonic acid	(C 24:1)	< 0.05 %
Other		0.20 %

OLIVE OIL, REFINED
Ph.Eur.7, 2011, USP 33 – NF28
lot:503500

Analysis results:

Specific gravity (20-degree C)	0.913
Refractive index (20-degree C)	1.469
Absorption at 270 nm	0.47
Lodine value	80
Saponification value	191
Acid value	0.21
Peroxide value	complies
Unsaponifiable Matter	1.18 %
Color gardner	1.9
Color lovibond 5 ¼* yellow	10.0
Color lovibond 5 ¼* red	1.0
Sesameoil	complies
Alkaline impurities	complies
Water	0.02 %

Sterols in %

Bets-eitosterol*	94.0 %
Delta-7-stigmastenol	0.3 %
Campesterol	3.4 %
Sigmasterol	1.5 %
Cholesterol	0.1 %
Sigmasterol	<campesterol

* Sum of contents of beta-Sitosterol, delta 5.23-stigmastadienol, derosterol, sitostanol, delta 5-avenasterol and delta 5.24-stigmastadienol

Identity	complies
Purity	Complies

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Figure B.32 — Specifications for Olive Oil, Refined by the applicant (sponsor) documentation

B.7.8.1 Example: Identity of material, combining the elements for Olive Oil, Virgin (Ph.Eur.) and Olive Oil, Refined (Ph.Eur.)

Table B.2 — Olive Oil, Virgin (Ph.Eur.) (Pre-registration of the Species)

Element Name	Value	Data Format	Note #
Element Group: Substance (fresh)			
Substance ID	OLIJF5643S (Artificial ID)	II	
Substance Type	Structurally Diverse	CD	
Element Group: Substance Name			
Substance Name	*Olea europaea* L., Fruit	ST	1)
Substance Name Type	Other	CD	
Language	En	CD	

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Element Name	Value	Data Format	Note #
Substance Name Domain	Drug, Botanical	CD	
Jurisdiction	EU, US	CD	
Element Group: Source Material			
Source Material Class	Botanical	CD	
Source Material Type	Plant	CD	
Source Material State	Live	CD	
Organism ID	LHJFG63421 (Artificial ID)	II	2)
Organism Name	*Olea europaea* L.	CD	2)
Parent Substance ID	N/A		
Development Stage	Fruiting	CD	
Element Group: Organism			
Family	*Oleaceae*	CD	
Genus	Olea	CD	
Species	Europaea	CD	
Element Group: Author			
Author Type	Species Primary Author	CD	
Author Description	L.	ST	
Element Group: Organism General			
Kingdom	Plantae	CD	
Phylum	Tracheophyta	CD	
Class	Magnoliopsida	CD	
Order	Lamiales	CD	

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Element Name	Value	Data Format	Note #
Element Group: Part Description			
Part	Fruit	CD	
Part location	N/A		
Element Group: Substance Structurally Diverse, Herbal preparation, Substance (Olive Oil, Virgin Ph.Eur.)			
Substance ID	HJFTE78543 (Artificial ID)	II	
Substance Type	Structurally Diverse	CD	
Element Group: Substance Name (Herbal preparation)			
Substance Name	*Olea europaea*, Fruit, Oil	ST	
Substance Name Type	Other	CD	
Language	En	CD	
Substance Name Domain	Drug, Vegetable Oil	CD	
Jurisdiction	EU, US	CD	
Element Group: Substance Name (Repeat)			
Substance Name	Olive Oil, Virgin	ST	
Substance Name Type	Official	CD	
Language	En	CD	
Substance Name Domain	Drug, Botanical	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur. monograph **07/2011:0518**	ST	
Element Group: Source Material			
Source Material Class	Botanical	CD	
Source Material Type	Plant	CD	
Source Material State	Live	CD	
Organism ID	LHJFG63421 (Artificial ID)	II	2)
Organism Name	*Olea europaea* L.	ST	2)
Parent Substance ID	OLIJF5643S (Artificial ID)	II	
Parent Substance Name	*Olea europaea* L., Fruit	ST	
Development Stage	Fruiting	CD	

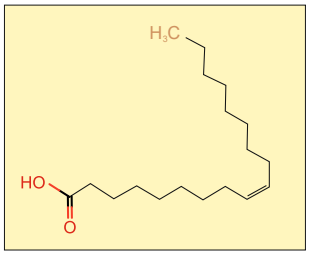
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Element Name	Value	Data Format	Note #
Element Group: Organism			
Family	*Oleaceae*	CD	
Genus	*Olea*	CD	
Species	*Europaea*	CD	
Element Group: Author			
Author Type	Species Primary Author	CD	
Author Description	L.	ST	
Element Group: Organism General			
Kingdom	Plantae	CD	
Phylum	Tracheophyta	CD	
Class	Magnoliopsida	CD	
Order	Lamiales	CD	
Element Group: Part Description			
Part	Fruit	CD	
Part Location	N/A		
Element Group: Fraction Description			
Fraction	Oil	ST	
Material Type	Vegetable Oil	CD	
Element Group: Structure			
Stereochemistry	Achiral	CD	
Molecular Formula	$C_{18}H_{34}O_2$	ST	
Molecular Formula by Moiety	N/A		
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	282,5	PQ	
Unit	g/mol	CD	

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Element Name	Value	Data Format	Note #
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure B.1 — Sructural representation Oleic acid**	ED	
Element Group: Property			
Property Type	Physical	CD	
Property Name	Relative density	CD	
Property Parameters	Measured at 20 °C	ST	
Property Substance ID	HJFTE78543	II	3)
Property Substance Name	Olive Oil, Virgin	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	0,913	PQ	
Unit	N/A (dimensionless quantity)		
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Acid value	CD	
Property Parameters	N/A		
Property Substance ID	HJFTE78543	II	3)
Property Substance Name	Olive Oil, Virgin	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	0,2	PQ	
Unit	mg/g	CD	
Amount Text	1 mg Potassium hydroxide (KOH) used per 5 g Olive Oil	ST	
Element Group: Reference Range			
Low Limit	0,02	PQ	
High Limit	0,4	PQ	
Unit	mg/g	CD	

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Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 3 (Olive Oil, Virgin-Ph.Eur.)			
Specified Substance Group 3 ID	JFGDRW4526 (Artificial ID)	II	
Substance Name			
Substance Name	*Olea europaea*, Fruit, Oil-Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	HJFTE78543 (Artificial ID)	II	3)
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name (= Name of the Ph.Eur. monograph)	Olive Oil, Virgin	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur. monograph **07/2011:0518**	ST	

NOTE 1 The substance Name *Olea europaea* L., Fruit is the herbal Substance (fresh) Name. There is no Herbal Drug equivalent defined in the European Pharmacopoeia.

NOTE 2 The Organism ID and Name are provided by The Kew Gardens Medicinal Plant Names Services (MPNS).

NOTE 3 The (Parent) Substance ID refers to the Substance Name: *Olea europaea*, Fruit Oil.

Table B.3 — Olive Oil, Refined (Ph.Eur.)

Element Name	Value	Data Format	Note #
Element Group: Substance Structurally Diverse, Herbal preparation, Substance (Olive Oil, Refined)			
Substance ID	KHJGHR4523 (Artificial ID)	II	
Substance Type	Structurally Diverse	CD	
Element Group: Substance Name (Herbal preparation)			
Substance Name	*Olea europaea*, Fruit, Oil Refined	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Substance Name Domain	Drug, Botanical	CD	
Jurisdiction	EU, US	CD	

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Element Name	Value	Data Format	Note #
Element Group: Substance Name (Repeat)			
Substance Name	Refined Olive Oil	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Substance Name (Repeat)			
Substance Name	Olive Oil, Refined	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia, monograph **07/2011:1456**	ST	
Element Group: Source Material			
Parent Substance ID	OLIJF5643S (Artificial ID)	II	
Parent Substance Name	*Olea europaea* L., Fruit	ST	
Element Group: Part Description			
Part	Fruit	CD	
Part Location	N/A		
Element Group: Fraction Description			
Fraction	Oil Refined	ST	
Material Type	Vegetable oil	CD	
Element Group: Property			
Property Type	Physical	CD	
Property Name	Relative density	CD	
Property Parameters	Measured at 20 °C	ST	
Property Substance ID	KHJGHR4523	II	
Property Substance Name	Olive Oil, Refined	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	0,913	PQ	
Unit	N/A (dimensionless quantity)	ST	

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Element Name	Value	Data Format	Note #
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Acid value	CD	
Property Parameters	N/A		
Property Substance ID	KHJGHR4523	II	
Property Substance Name	Olive Oil, Refined	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	0,021	PQ	
Unit	mg/g	CD	
Amount Text	0,21 mg Potassium hydroxide (KOH) used per 10 g Olive Oil	ST	
Element Group: Reference Range			
Low Limit	0,01	PQ	
High Limit	0,03	PQ	
Unit	mg/g	CD	
Element Group: Specified Substance Group 3 (Olive Oil, Refined-Ph.Eur.)			
Specified Substance Group 3 ID	SDAUT12543 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Olea europaea*, Fruit, Oil, Refined, Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	KHJGHR4523 (Artificial ID)	II	1)
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name	Olive Oil, Refined	ST	
Element Group: Reference source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	ST	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur. monograph **07/2011:1456**	ST	
NOTE This (Parent) Substance ID referes to the Substance Name: *Olea europaea* L., Fruit, Oil Refined.			

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B.7.9 Castor Oil and related products

In the range from substances of vegetable origin somewhere the line has to be drawn whether these materials can be related to the Plant, Plant part or fraction and whether the substance is considered to be a mixture or another substance type e.g.:

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— Castor Oil, Virgin;

— Castor Oil, Hydrogenated;

— Castor Oil, ethoxylated;

— 12-Hydroxystearic acid;

— Derivatives produced first by transesterification of the castor oil to methyl ricinoleate, followed by steam cracking to methyl undecylenate and n-heptaldehyde.

The two last examples are obvious: The Castor Oil is used as a starting material followed by a chain of chemical reactions and processes so that the relationship and the character of the Castor Oil material is no longer present in the processed material. These materials are then considered as single substances or as a mixture depending on the manufacturing process.

B.7.9.1 Castor Oil, Virgin (Ph.Eur.)

Castor Oil, Virgin is described in the Ph.Eur. as: Fatty oil obtained by cold expression from the seeds of *Ricinus communis* L. with the production specification that during the expression step, the temperature of the oil shall not exceed 50 °C.

At the Substance level the source of Castor Oil, Virgin (Ph.Eur.) is captured by the Substance (fresh) name *Ricinus communis* L., Seed.

The Herbal preparation name for Castor Oil, Virgin (Ph.Eur.) is:

Substance Name	*Ricinus communis,* Seed, Oil
Substance ID	JKGSDE6452 (Artificial ID); D5340Y2I9G (UNII);
Substance Name Type	Other
Substance Name	Castor Oil, Virgin
Substance Name Type	Official

B.7.9.2 Castor Oil, Hydrogenated (Ph.Eur.)

Castor Oil, Hydrogenated is described in the Ph.Eur. as: Fatty oil obtained by hydrogenation of Virgin Castor Oil. It consists mainly of the triglyceride of 12-hydroxystearic acid.

The Pharmacopoeia refers to Virgin Castor Oil which connects the Plant and Part of the Plant name.

At the substance level the source of Castor Oil, Hydrogenated (Ph.Eur.) is captured by the Substance (fresh) *Ricinus communis* L., Seed.

The Herbal preparation name for Castor Oil, Hydrogenated (Ph.Eur.) is:

Substance Name	*Ricinus communis*, Seed, Oil Hydrogenated
Substance ID	CFDSW67453 (Artificial ID); ZF94AP8MEY(UNII)
Substance Name Type	Other
Substance Name	Castor Oil, Hydrogenated
Substance Name Type	Official

B.7.9.3 Explanation of the differences between Castor Oil, Virgin and Castor Oil, Hydrogenated

Castor Oil and Castor Oil, Hydrogenated are separate substances. Castor Oil has been modified (e.g. hydrogenated) by a chemical process which has changed chemically the major component, **Recinoleic acid** [(9*Z*,12*R*)-12-Hydroxyoctadec-9-enoic acid, (12-Hydroxyoleic acid), $C_{18}H_{34}O_3$. (M_r 298.5)] side

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chains of the triglyceride ester into **12-hydroxystearic acid**, [$C_{18}H_{36}O_3$,(M_w 300.4 g/mol)] side chains, as shown in Figure B.34.

This process is to be considered as a chemical modification of the Castor Oil, Virgin into Castor Oil, Hydrogenated. This process is a one-step manufacturing process with Nickel as catalyst and will be captured in the element modification group at the substance level.

Based on the properties and chemically different main constituents Castor Oil, Virgin and Castor Oil, Hydrogenated are easily distinguished, as in Figure B.35.

NOTE Castor Oil shows optical activity and absorbance at 269 nm and the main constituent of the fatty acid composition is Ricinoleic acid.

Castor Oil, Hydrogenated does not have optical activity and absorbance and the main constituent of the fatty acid is the hydrogenated ricinoleic acid: 12-hydroxystearic acid. The other differences of the properties have more quantitative aspects, except for some of the minor qualitative different fatty acids constituents. This is another argument for the addition of the constituent group in the Structurally Diverse Information model.

B.7.9.4 Castor Oil, Ethoxylated

Castor Oil, Ethoxylated is the synonym for Macrogolglycerol Ricinoleate (Ph.Eur.). It is defined in the Ph.Eur. as being mainly ricinoleyl glycerol ethoxylated with 30-50 molecules of ethylene oxide (nominal value), with small amounts of macrogol ricinoleate and of the corresponding free glycols. It results from the reaction of castor oil with ethylene oxide.

NOTE The Ph.Eur. definition does not speak of Virgin Castor oil, but of castor oil reaction with ethylene oxide:

Characteristics:

— *Appearance*: clear, yellow viscous liquid or semi-solid;

— *Solubility*: freely soluble in water, very soluble in methylene chloride, freely soluble in ethanol (96 %);

— *Relative density*: about 1,05;

— *Viscosity*: 500 mPa·s to 800 mPa·s at 25 °C.

One of the major properties for the identification of this substance material is the viscosity. This property is a predominant property for the chemical Substance Type: “Polymer”. In Figure B.34, an illustrative representation is presented for Macrogolglycerol Ricinoleate. In Figure B.34 an illustrative representation is presented for the polymer when the polymeric reaction between Castor Oil and ethylene oxide chain is longer and of a different kind. The processed substance is a “Polymer”.

Conclusion: Macrogolglycerol Ricinoleate (synonym Castor Oil, Ethoxylated) is not a modification of Castor Oil, Virgin but is a Substance, with the 'Substance Type' Polymer, in view of the ISO 11238 and is captured at the Substance level having a Substance ID. Castor Oil and Ethylene oxide are both used as starting materials in a polymerising process.

Figure B.34 shows the specifications for Castor Oil, Virgin and Castor Oil, Hydrogenated.

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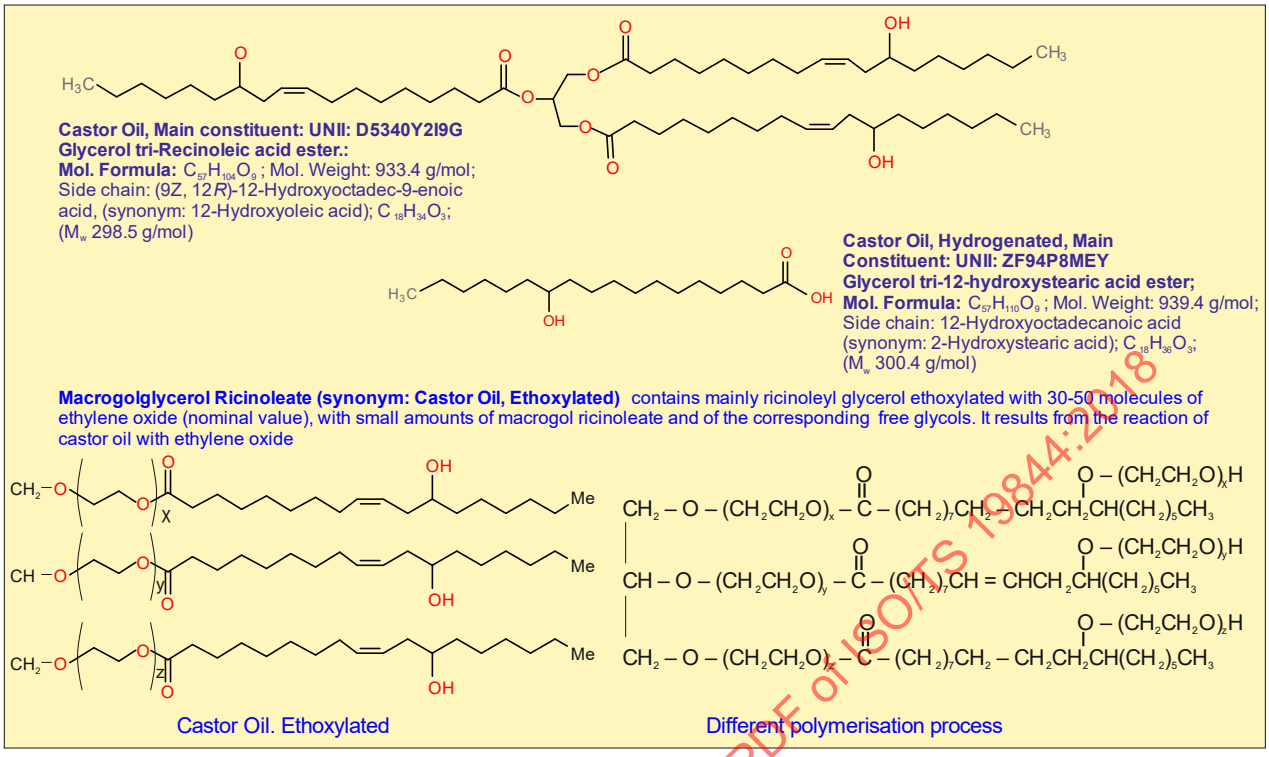


Figure B.34 — Structures of the major components of Castor Oil, Virgin, Castor Oil, Hydrogenated and Macrogolglycerol Ricinoleate (synonym Castor Oil, Ethoxylated)

Specifications Castor Oil, Virgin & Castor Oil, Hydrogenated (Ph.Eur.)	
Castor Oil, Virgin	Castor Oil, Hydrogenated
Definition: Fatty oil obtained by cold expression from the seeds of *Ricinus communis* L. Note: During the expression step, the temperature of the oil must not exceed 50°C.	**Definition**: Fatty oil obtained by hydrogenation of Virgin Castor oil. It consists mainly of the triglyceride of 12-hydroxystearic (12-hydroxyoctadecanoic) acid.
Properties tested:	Properties tested:
- Optical rotation: + 3.5° to + 6.0°	- Acid value: NMT 4.0
- Absorbance: at 269nm, NMT 1.5	- Hydroxyl value: 145 - 165
- Acid value: maximum 1.5	- Lodine value: NMT 5.0
- Hydroxyl value: minimum 160	- Alkaline impurities: Limit test
- Peroxide value: maximum 10	Composition of Fatty acid:
- Unsaponifiable matter: maximum 0.8 (5.0g)	- *Palmitic acid*: not more than 2.0%
Composition of Fatty acid:	- *Stearic acid*: 7.0% to 14.0%
- *Palmitic acid*: maximum 2.0%	- *Arachidic acid*: not more that 1.0%
- *Stearic acid*: maximum 2.5%	- *12-oxostearic acid*: not more than 5.0%
- *Oleic acid and isomers*: 2.5% to 6.0%	- *12-hydroxystearic acid*: 78.0% to 91.0%
- *Linoleic acid*: 2.5% to 7.0%	- *Any other fatty oil*: not more than 3.0%
- *Linolenic acid*: maximum 1.0%	- *Nickel (2.4.31)*: maximum 1 ppm
- *Eicosenoic acid*: maximum 1.0%	
- *Ricinoleic acid*: 85.0 % to 92.0%	
- *Any other fatty acid*: maximum 1.0%	

Figure B.35 — Specifications for Castor Oil, Virgin and Castor Oil, Hydrogenated (Ph.Eur.)

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B.7.10 Properties related to liquids (Gas), Nitrous oxide

Nitrous oxide (Ph.Eur.) is described in the Ph.Eur. monograph as a substance having a content of minimum 98,0 % (v/v) of N_2O in the gaseous phase sampled at 15 °C. The substance can occur as a liquid or as a gas. Although the substance is stored liquefied under pressure in suitable containers complying with the legal regulations the physical form is to be considered as a gas and captured as such at the Specified Substance Group 1 level. Nevertheless, the substance should comply with the specifications in the gaseous phase form as well as in the liquid phase form, as in 7.1.11 Physical Form and in 7.1.11.1 Physical State.

Table B.4 — Tabular format of the Elements captured at the Substance and Specified Substance Levels

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	NGHD56234L (Artificial ID)	II	
Substance Type	Chemical	CD	
Element Group: Substance Name			
Substance Name	Nitrous oxide	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia monograph 01/2008:0416	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Dinitrogen Oxide	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Martindale	CD	
Reference Source Class	Official Name Source	CD	

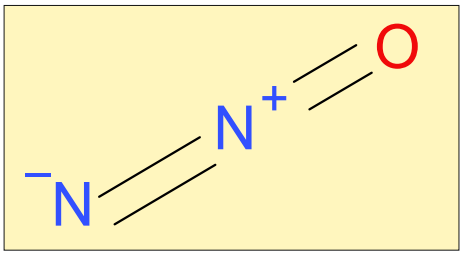
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Element Name	Value	Data Format	Note #
Reference Source Citation	Monograph Nitrous Oxide, latest modification 27 Oct 2016	ST	
Element Group: Substance Code			
Code	10024-97-2	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	K50XQU1029	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystem Name	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Reference Information			
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	N01AX13	CD.Code	
Substance Classification Type	Nitrous oxide	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHO Collaborating Centre for Drug Statistics methodology (WHOCC)	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=N01AX13	ST	
Element Group: Chemical			
Element Group: Stoichiometric			
Number of Moieties	1	INT	2)
Element Group: Structure			
Stereochemistry	Achiral	CD	
Molecular Formula	N_2O	ST	
Molecular Formula by Moiety	N/A		

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Element Name	Value	Data Format	Note #
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure B.2 — Structural representation of Nitrous oxide**	ED	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation	InChI=1S/N2O/c1-2-3	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	molfile	CD	
Structural Representation	See below:	ST	
-FDA-SRS-04301410562D 3 2 0 0 0 0 0 0 0 0999 V2000 -1.5958 -2.6833 0.0000 N 0 0 0 0 0 0 0 0 0 0 0 0 -0.8814 -2.2708 0.0000 N 0 0 0 0 0 0 0 0 0 0 0 0 -0.0625 -1.7167 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0 1 2 3 0 0 0 0 2 3 1 0 0 0 0 M CHG 2 2 1 3 -1 M END			
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Web	CD	
Reference Source URL	http://webbook.nist.gov/cgi/cbook.cgi?ID=C10024972&Mask=1	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	

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Element Name	Value	Data Format	Note #
Quantity	44,01	PQ	
Unit	g/mol	CD	
Element Group: Specified Substance Group 1			
Specified Substance Group 1 ID	PHJSGT785G (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Nitrous oxide, gas	ST	
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Constituent			
Constituent Substance ID	NGHD56234L (Artificial ID)	II	
Constituent Substance Name	Nitrous oxide	ST	
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	NLT	CD	
Quantity	98,0	PQ	2)
Unit	%{v/v}	CD	
Amount Text	NLT 98,0 % of Nitrous Oxide [Volume % (v/v) of substance]	ST	
Element Group: Physical Form			
Physical State	Gas	CD	

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Element Name	Value	Data Format	Note #
Element Group: Characteristic Attribute (see Figure below as additional information)			

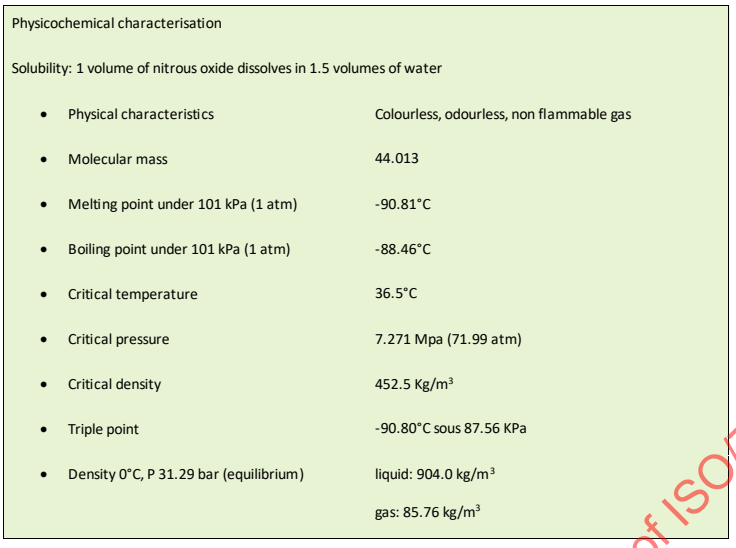


Figure B.3 — Examples of Characteristic attributes of Nitrous oxide

Attribute Type	Physical	CD	
Attribute Name	Melting point	ST	
Attribute Substance ID	PHJSGT785G (Artificial ID)	II	
Attribute Substance Name	Nitrous oxide, gas	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	–90,81	PQ	
Unit	Degree Celsius	CD	
Element Group: Attribute Parameter			
Attribute Parameter Name	Melting point condition	ST	
Attribute Parameter Value	Measured under 101 kPa	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Physical	CD	
Attribute Name	Boiling point	ST	
Attribute Substance ID	PHJSGT785G (Artificial ID)	II	
Attribute Substance Name	Nitrous oxide, gas	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	–88,46	PQ	
Unit	Degree Celsius	CD	

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Element Name	Value	Data Format	Note #
Element Group: Attribute Parameter			
Attribute Parameter Name	Boiling point condition	ST	
Attribute Parameter Value	Measured under 101 kPa	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Physical	CD	
Attribute Name	Critical temperature	ST	
Attribute Substance ID	PHJSGT785G (Artificial ID)	II	
Attribute Substance Name	Nitrous oxide, gas	ST	
Is Defining	No	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	36,5	PQ	
Unit	Degree Celsius	CD	
Element Group: Attribute Parameter			
Attribute Parameter Name	Critical temperature condition	ST	
Attribute Parameter Value	Measured under 101 kPa	ST	
Element: Characteristic Attribute (Repeat)			
Attribute Type	Physical	CD	
Attribute Name	Critical pressure	ST	
Attribute Substance ID	PHJSGT785G (Artificial ID)	II	
Attribute Substance Name	Nitrous oxide, gas	ST	
Is Defining	No	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	71,99	PQ	
Unit	Atm	CD	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Physical	CD	
Attribute Name	Critical density	ST	
Attribute Substance ID	PHJSGT785G (Artificial ID)	II	
Attribute Substance Name	Nitrous oxide, gas	ST	
Is Defining	No	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	452,5	PQ	
Unit	kg/m^3	CD	

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Element Name	Value	Data Format	Note #
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Physical	CD	
Attribute Name	Triple point	ST	
Attribute Substance ID	PHJSGT785G (Artificial ID)	II	
Attribute Substance Name	Nitrous oxide, gas	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	–90,80	PQ	
Unit	Degree Celsius	CD	
Element Group: Attribute Parameter			
Attribute Parameter Name	Triple point condition	ST	
Attribute Parameter Value	Measured under 87,56 kPa	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Physical	CD	
Attribute Name	Density	ST	
Attribute Substance ID	PHJSGT785G (Artificial ID)	II	
Attribute Substance Name	Nitrous oxide, gas	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	904,0	PQ	
Unit	Kg/m^3	CD	
Element Group: Attribute Parameter			
Attribute Parameter Name	Density condition	ST	
Attribute Parameter Value	Physical state: Liquid, at 0 °C, 31,29 atm at equilibrium	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Physical	CD	
Attribute Name	Density	ST	
Attribute Substance ID	PHJSGT785G (Artificial ID)	II	
Attribute Substance Name	Nitrous oxide, gas	ST	
Is Defining	Yes	BL	

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Element Name	Value	Data Format	Note #
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	85,76	PQ	
Unit	Kg/m^3	CD	
Element Group: Attribute Parameter			
Attribute Parameter Name	Density condition	ST	
Attribute Parameter Value	Physical state: Gas, at 0 °C, 31,29 atm at equilibrium	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Physical	CD	
Attribute Name	Solubility	ST	
Attribute Substance ID	WATE12456H (artificial ID)	II	
Attribute Substance Name	Water	ST	
Is Defining	No	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	1,5	PQ	
Unit	Volume Part	CD	
Element Group: Attribute Parameter			
Attribute Parameter Name	Solubility condition	ST	
Attribute Parameter Value	1 Volume part 20 °C and at a pressure of 101 kPa	ST	
Element Group: Specified Substance Group 2 (Nitrous oxide**)**			
Specified Substance Group 2 ID	KHJTYD674R (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Nitrous oxide-Manufacturer XX	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	NGHD56234L (Artificial ID)	II	3)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Synthetic	CD	
Production Method Description	Chemical decomposition reaction decomposition of the ammonium nitrate: $NH_4N0_3 = N_20 + 2H_20 +$ heat.	ST	
Production System Type	Continuous thermal decomposition	CD	

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Element Name	Value	Data Format	Note #
Critical Process Version Number	1	INT	4)
Version	NITROUS-001	ST	
Version Date	20170127	TS.Date	
Element Group: Organization			
Manufacturer ID	DUNS86745HF (Artificial ID)	II	
Manufacturer Name	Company XX	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	
Element Group: Specified Substance Group 3 (Nitrous oxide)			
Specified Substance Group 3 ID	GHDRW765T (Artificial ID)	II	
Element Group: Specified Substance Group 3			
Substance Name	Nitrous oxide-Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	NGHD56234L (Artificial ID)	II	3)
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name	Nitrous oxide	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia, (Ph.Eur. monograph 01/2008 :0416	ST	

NOTE 1 Access to Martindale is based on annual subscription fees.

NOTE 2 List of properties valid for Nitrous oxide, Gaseous phase sampled at –15 °C.

NOTE 3 This (Parent) Substance ID refers to the Substance Name: Nitrous oxide.

NOTE 4 The Critical Process Number Version Number would change if a substantial change in the (synthetic) manufacturing process occurred. These would include a change in the chemistry, addition of elimination of a purification step. The change in a version number is tied to the production system type.

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B.8 Examples

This part of the document is meant to walk through the separate information levels and to discuss minimal information required in order to obtain an ISO Substance identifier.

This information shall be seen in view of the substance characteristics as discussed in B.2, B.3, and, B.4.

For the Substance Type Chemical Substances all physico-chemical properties described of the Substance are placed at the Specified Substance Group 1 level, unless this property is essential for the defining of

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the substance and structural information is not enough in order to distinguish the substance from another substance.

For the Substance Type Chemical Substances, in almost all situations the physico-chemical properties prove to be non-defining elements at the Substance level, but are necessary to describe the character of the substance at the Specified Substance level and are in most cases mandatory information.

B.8.1 Example 1: Amlodipine besilate

Table B.5 — Identity of material combining the elements for Amlodipine Besilate

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	GHTD1234A (Artificial ID)	II	
Substance Type	Chemical	CD	
Element Group: Substance Name			
Substance Name	Amlodipine besilate	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia, monograph 01/2016:1491	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Amlodipine besylate	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name (Repeat)			
Official Name Type	USP	CD	
Official Name Status	Current	CD	

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Element Name	Value	Data Format	Note #
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	United States Pharmacopoeia, Monograph USP38-NF33 Page 2207	ST	
Element Group: Substance Name (Repeat)			
Substance Name	3-Ethyl 5-methyl (+-)-2-[(2-aminoethoxy)methyl]-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate	ST	
Substance Name Type	Systematic	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChemID*plus*	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://chem.sis.nlm.nih.gov/chemidplus/unii/864V2Q084H	ST	
Element Group: Substance Name (Repeat)			
Substance Name	3-Ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate	ST	
Substance Name Type	Systematic	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur. monograph 01/2016:1491	ST	
Element Group: Substance Name (Repeat)			
Substance Name	3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (±)-, monobenzenesulfonate	ST	
Substance Name Type	Systematic	CD	
Language	en		
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	

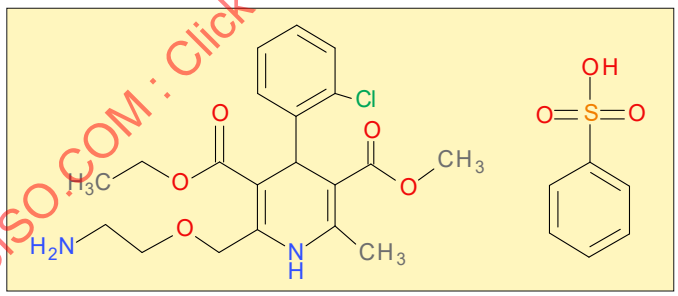
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Element Name	Value	Data Format	Note #
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP monograph USP38-NF33 Page 2207	ST	
Element Group: Substance Name (Repeat)			
Substance Name	A 1095	ST	
Substance Name Type	Company Code	CD	
Language	en		
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	111111 (Artificial ID)	ST	
Element Group: Substance Code			
Code	111470-99-6	CD.Code	
Code System	CAS Registry	CD.Code SystemName	
Code System ID	0049	CD.Code System	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	864V2Q084H	CD.Code	
Code System	FDA GSRS (UNII)	CD.Code SystemName	
Code System ID	0050	CD.Code System	
Code System Status	Active	CD	
Element Group: Reference Information			
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.Code System	
Substance Classification Code	C08CA01	CD.Code	
Substance Classification Type	Amlodipine	ST	

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Element Name	Value	Data Format	Note #
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Web	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=C08CA01	ST	
Element Group: Structure			
Stereochemistry	Racemic	CD	
Optical Activity	(+/-)	CD	
Molecular Formula	$C_{26}H_{31}ClN_2O_8S$	ST	1)
Molecular Formula by Moiety	$C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP, Current Edition	ST	
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure B.4 — Structural representation of Amlodipine besilate**	ED	1)
Element Group: Structural Representation (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation	InChI=1S/C20H25ClN2O5.C6H6O3S/c1-4-28-20(25)18-15(11-27-10-9-22)23-12(2)16(19(24)26-3)17(18)13-7-5-6-8-14(13)21;7-10(8,9)6-4-2-1-3-5-6/h5-8,17,23H,4,9-11,22H2,1-3H3;1-5H,(H,7,8,9)	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChemID*plus*	CD	

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Element Name	Value	Data Format	Note #
Reference Source Class	Public Database	CD	
Reference Source URL	http://chem.sis.nlm.nih.gov/chemidplus/unii/864V2Q084H	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	SMILES	CD	
Structural Representation	CCOC(=O)C1=C(NC(=C(C1c2ccccc2Cl)C(=O)OC)C)COCCN.c1ccc(cc1)S(=O)(=O)O	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChemID*plus*	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://chem.sis.nlm.nih.gov/chemidplus/unii/864V2Q084H	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	molfile	CD	
Structural Representation Attachment	Document TEXT	ED	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	222222 (Artificial ID)	ST	
Element Group: Reference Source Document			
Reference Source Document	TEXT, in attachment	ED	
Reference Source Document Type	Text file	CD	

Symyx 06091422262D 1 1.00000 0.00000 0
38 39 0 0 0 0 0 0 0999 V2000
13.1372 -9.5449 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
11.8497 -9.5449 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
12.5081 -9.1824 0.0000 C 0 0 3 0 0 0 0 0 0 0 0 0
11.8497 -10.2824 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
13.1372 -10.2241 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
12.4997 -10.6616 0.0000 N 0 0 3 0 0 0 0 0 0 0 0 0
13.7580 -9.2074 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
11.2163 -9.1658 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
12.5081 -7.9449 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0

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Element Name	Value	Data Format	Note #
13.1705 -7.5741 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 11.2163 -8.4199 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0 13.7580 -8.6741 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0 11.2122 -10.6616 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 14.3622 -9.6033 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0 10.5705 -9.5366 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0 13.7956 -10.6533 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 13.8080 -7.9324 0.0000 Cl 0 0 0 0 0 0 0 0 0 0 0 0 8.6580 -10.5908 0.0000 N 0 0 0 0 0 0 0 0 0 0 0 0 11.8747 -7.5741 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 10.6330 -10.2699 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0 13.1705 -6.8283 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 9.3038 -10.1949 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 9.9205 -9.1616 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 9.9205 -10.6616 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 14.9956 -9.1574 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 11.8747 -6.8283 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 9.2705 -9.5366 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 12.5330 -6.4449 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 16.6331 -8.2199 0.0000 S 0 0 3 0 0 0 0 0 0 0 0 0 17.3247 -8.2199 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0 15.9289 -8.2199 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0 16.6331 -8.9241 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 16.6331 -7.5199 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0 17.2455 -9.2741 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 16.0288 -9.2782 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 16.0288 -9.9824 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 17.2455 -9.9824 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 16.6372 -10.3324 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 24 20 1 0 0 0 0 25 14 1 0 0 0 0 26 19 2 0 0 0 0 27 23 1 0 0 0 0 28 26 1 0 0 0 0 4 2 2 0 0 0 0 28 21 2 0 0 0 0 2 3 1 0 0 0 0 3 1 1 0 0 0 0 4 6 1 0 0 0 0 5 1 2 0 0 0 0 6 5 1 0 0 0 0 M END			

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Element Name	Value	Data Format	Note #
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	567,1	PQ	2)
Unit	g/mol	CD	
Amount Text	[567,06 = (408,88 + 158,18); rounded at 567,1]		
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Class	Literature	CD	
Reference Source URL	https://www.researchgate.net/publication/23227282	ST	
Element Group: Reference Source Document			
Reference Source Document	PDF Document, see Figure below.	ED	

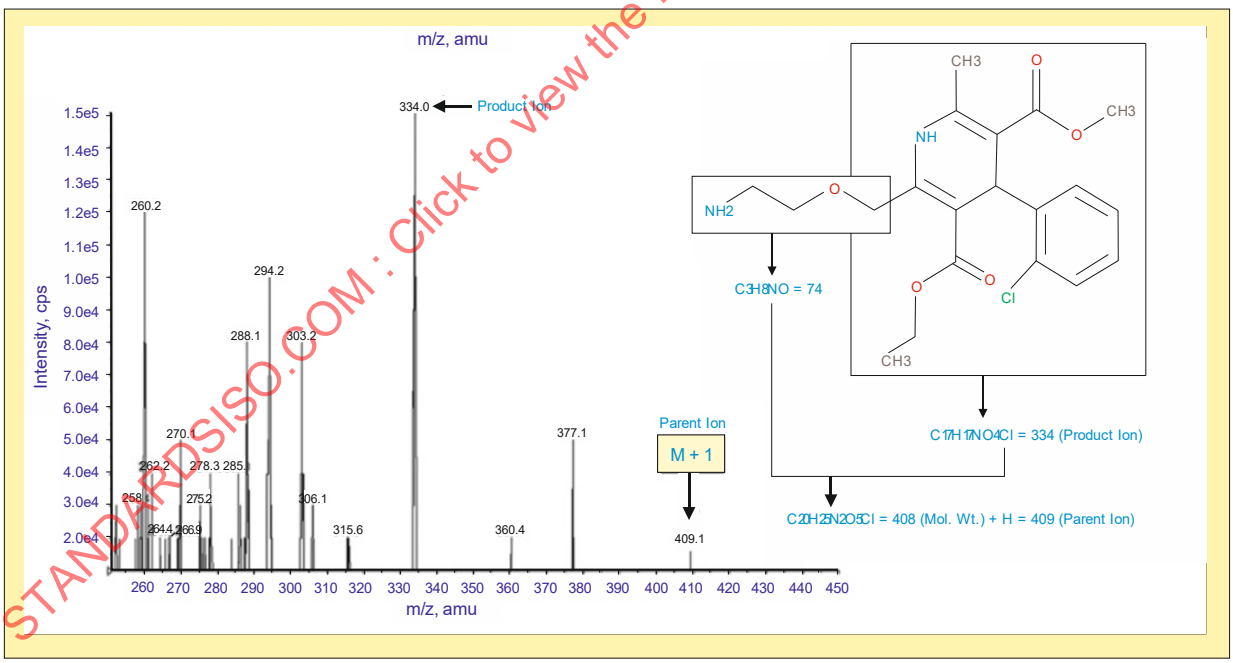


Figure B.5 — E.I. Mass spectrum of Amlodipine

Reference Source Document Type	Journal article	CD	
Reference Source Document Classification	Mass spectra	CD	

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Element Name	Value	Data Format	Note #
Element Group: Stoichiometric			
Number of Moieties	2	INT	
Element Group: Moiety			
Moiety Role	Parent Molecule	CD	
Moiety ID	PTYF756430 (Artificial ID); [1J444QC288 (UNII)]	II	
Moiety Name	Amlodipine	ST	
Stereochemistry	Racemic	CD	
Optical activity	(+/-)	CD	
Molecular formula	$C_{20}H_{25}ClN_2O_5$	ST	
Element group: Amount			
Amount Type	Exact	CD	
Quantity	1	PQ	
Unit	{mol/mol}	CD	
Amount Text	Mole Ratio to salt: Mol Ratio Amlodipine/Benzenesulfonic acid (1:1)	ST	
Element Group: Moiety			
Moiety Role	Salt molecule	CD	
Moiety ID	BENZ67891A (Artificial ID ; [685928Z18A (UNII)]	II	
Moiety Name	Benzenesulfonic acid	ST	
Stereochemistry	Achiral	CD	
Molecular Formula	$C_6H_6O_3S$	ST	
Element group: Amount			
Amount type	Exact	CD	
Quantity	1	PQ	
Unit	{mol/mol}	CD	
Amount Text	Mole Ratio to Parent: Mole Ratio to Amlodipine	ST	
Element group: Reference Information			
Element Group: Substance Relationship			**3)**
Related Substance ID	PTYF75643O (Artificial ID), [1J444QC288 (UNII)]	II	4)
Related Substance Name	Amlodipine	ST	
Relationship	Active Moiety	CD	3)
Relationship Type	Ionic	CD	
Is Defining	Yes	BL	

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Element Name	Value	Data Format	Note #
Element Group: Amount			
Amount Type		CD	
Quantity	71,9	PQ	
Unit	% {w/w}	CD	
Amount Text	Equivalence Factor: 0,72 (Weight per cent to salt)	ST	

NOTE 1 Structure and Molecular formulae are mandatory elements for a chemical substance.

NOTE 2 Comments made to the Business Rules in 5.7.3 and 5.7.4: The molecular formula is specified in accordance with the Hill system. For a salt/hydrate the molecular formula of the base or the acid and the salt/hydrate part are separated by a dot per moiety, e.g. Desmopressin Monoacetate Trihydrate: Molecular Formula by Moiety: $C_{46}H_{64}N_{14}O_{12}S_2.C_2H_4O_2.3H_2O$.

NOTE 3 The Parent molecule (Active Moiety) to salt is a one-way relationship. The amount as weight per cent of the Parent molecule/Equivalent Substance (in this case the Amlodipine base) to the Amlodipine besilate salt shall be provided.

NOTE 4 Since only one ID is allowed, these IDs mean a repeat of the element group.

B.8.2 Example 2: Ponatinib hydrochloride

Ponatinib hydrochloride is not described in a Pharmacopoeia.

Table B.6 — Tabular format of the captured elements at the Substance and Specified Susbtance levels for Ponatinib hydrochloride

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	POYFG4531Y (Artificial ID)	II	
Substance Type	Chemical	CD	
Element Group: Substance Name			
Substance Name	Ponatinib hydrochloride	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	USAN	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Martindale	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Martindale	ST	
Reference Source URL	https://www.medicinescomplete.com/mc/martindale/current/ms-28485-	ST	1)

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Element Name	Value	Data Format	Note #
	s.htm?q=Ponatinib%20hydrochloride&t=search&ss=text&tot=12&p=1#_hit		
Element Group: Substance Name (Repeat)			
Substance Name	3-(2-(Imidazo(1,2-b)pyridazin-3-yl)ethynyl)-4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide monohydrochloride	ST	
Substance Name Type	Systematic	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChemID*plus*	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://chem.sis.nlm.nih.gov/chemidplus/unii/96R6PU3D8J	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Benzamide, 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl]-,hydrochloride (1:1)	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	
Reference Source Citation	CAS Registry Name	ST	
Element Group: Substance Name (Repeat)			
Substance Name	XYWZ123	ST	
Substance Name Type	Company Code	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	CBG345267C (Artificial ID)	ST	

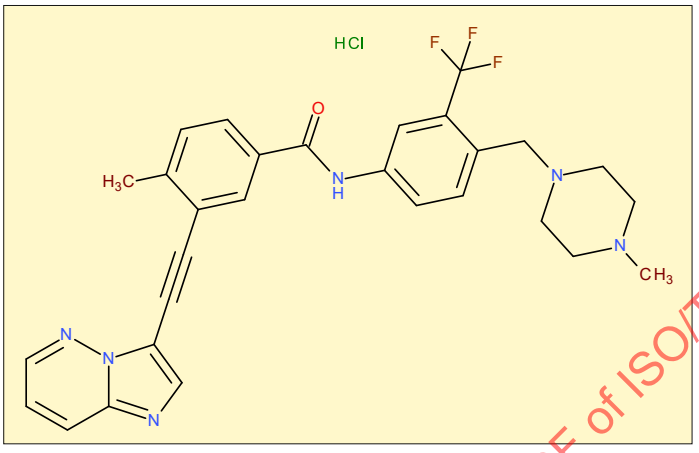
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Element Name	Value	Data Format	Note #
Element Group: Substance Code			
Code	1114544-31-8	CD.Code	
Code System	CAS Registry	CD.Code SystemName	
Code System ID	0049	CD.Code System	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	96R6PU3D8J	CD.Code	
Code System	FDA GSRS (UNII)	CD.Code SystemName	
Code System ID	0050	CD.Code System	
Code System Status	Active	CD	
Element Group: Reference Information			
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.Code System	
Substance Classification Code	L01XE24	CD.Code	
Substance Classification Type	Ponatinib	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Piblic Database	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=L01XE24	ST	
Element Group: Structure			
Stereochemistry	Achiral	CD	
Molecular Formula	$C_{29}H_{28}F_3ClN_6O$	ST	
Molecular Formula by Moiety	$C_{29}H_{27}F_3N_6O.HCl$	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChemID*plus*	CD	
Reference Source Class	Public Database	CD	

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Element Name	Value	Data Format	Note #
Reference Source URL	http://chem.sis.nlm.nih.gov/chemidplus/unii/96R6PU3D8J	ST	
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure B.6 — Structural representation of Ponatinib hydrochloride**	ED	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation	InChI=1S/C29H27F3N6O.ClH/c1-20-5-6-22(16-21(20)8-10-25-18-33-27-4-3-11-34-38(25)27)28(39)35-24-9-7-23(26(17-24)29(30,31)32)19-37-14-12-36(2)13-15-37;/h3-7,9,11,16-18H,12-15,19H2,1-2H3,(H,35,39);1H	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChemID*plus*	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://chem.sis.nlm.nih.gov/chemidplus/unii/96R6PU3D8J	ST	
Element Group: Structural Representation(Repeat)			
Structural Representation Type	SMILES	CD	
Structural Representation	Cc1ccc(cc1C#Cc2cnc3n2nccc3)C(=O)Nc4ccc(c(c4)C(F)(F)F)CN5CCN(CC5)C.Cl	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChemID*plus*	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://chem.sis.nlm.nih.gov/chemidplus/unii/96R6PU3D8J	ST	

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Element Name	Value	Data Format	Note #
Element Group: Structural Representation (Repeat)			
Structural Representation Type	molfile	CD	
Structural Representation Attachment	document TEXT, in attachment below	ED	

Symyx 06091422112D 1 1.00000 0.00000 0
40 43 0 0 0 999 V2000
-2.2340 -0.1661 0.0000 N 0 0 0 0 0 0 0 0 0 0
-1.5965 0.2006 0.0000 N 0 0 3 0 0 0 0 0 0 0
-1.5965 0.9381 0.0000 C 0 0 0 0 0 0 0 0 0 0
-2.2340 1.3048 0.0000 C 0 0 0 0 0 0 0 0 0 0
-2.8716 0.9381 0.0000 C 0 0 0 0 0 0 0 0 0 0
-2.8716 0.2006 0.0000 C 0 0 0 0 0 0 0 0 0 0
-0.9048 1.1589 0.0000 N 0 0 0 0 0 0 0 0 0 0
-0.4632 0.5714 0.0000 C 0 0 0 0 0 0 0 0 0 0
-0.9048 -0.0453 0.0000 C 0 0 0 0 0 0 0 0 0 0
-0.6840 -0.7327 0.0000 C 0 0 0 0 0 0 0 0 0 0
-0.4382 -1.4453 0.0000 C 0 0 0 0 0 0 0 0 0 0
-0.2174 -2.1327 0.0000 C 0 0 0 0 0 0 0 0 0 0
0.4952 -2.2827 0.0000 C 0 0 0 0 0 0 0 0 0 0
0.7160 -2.9953 0.0000 C 0 0 0 0 0 0 0 0 0 0
1.4535 -3.1411 0.0000 C 0 0 0 0 0 0 0 0 0 0
1.6743 -3.8536 0.0000 O 0 0 0 0 0 0 0 0 0 0
1.9451 -2.5994 0.0000 N 0 0 0 0 0 0 0 0 0 0
2.6576 -2.7494 0.0000 C 0 0 0 0 0 0 0 0 0 0
2.9035 -3.4619 0.0000 C 0 0 0 0 0 0 0 0 0 0
3.6159 -3.6077 0.0000 C 0 0 0 0 0 0 0 0 0 0
3.8368 -4.2953 0.0000 C 0 0 3 0 0 0 0 0 0 0
3.3451 -4.8619 0.0000 F 0 0 0 0 0 0 0 0 0 0
4.0618 -5.0119 0.0000 F 0 0 0 0 0 0 0 0 0 0
4.5535 -4.4703 0.0000 F 0 0 0 0 0 0 0 0 0 0
4.1077 -3.0661 0.0000 C 0 0 0 0 0 0 0 0 0 0
4.8201 -3.2161 0.0000 C 0 0 0 0 0 0 0 0 0 0
5.3118 -2.6494 0.0000 N 0 0 3 0 0 0 0 0 0 0
6.0493 -2.8203 0.0000 C 0 0 0 0 0 0 0 0 0 0
6.5410 -2.2578 0.0000 C 0 0 0 0 0 0 0 0 0 0
6.2951 -1.5703 0.0000 N 0 0 3 0 0 0 0 0 0 0
6.8118 -1.0286 0.0000 C 0 0 0 0 0 0 0 0 0 0
5.5827 -1.4203 0.0000 C 0 0 0 0 0 0 0 0 0 0
5.0909 -1.9620 0.0000 C 0 0 0 0 0 0 0 0 0 0
3.8868 -2.3536 0.0000 C 0 0 0 0 0 0 0 0 0 0
3.1493 -2.2077 0.0000 C 0 0 0 0 0 0 0 0 0 0

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Element Name	Value	Data Format	Note #
0.2243 -3.5369 0.0000 C 0 0 0 0 0 0 0 0 0 0 -0.4882 -3.3869 0.0000 C 0 0 0 0 0 0 0 0 0 0 -0.7090 -2.6744 0.0000 C 0 0 0 0 0 0 0 0 0 0 -1.4465 -2.5286 0.0000 C 0 0 0 0 0 0 0 0 0 0 3.5313 0.2188 0.0000 Cl 0 0 0 0 0 0 0 0 0 0 1 2 1 0 0 0 3 2 1 0 0 0 3 4 1 0 0 0 4 5 2 0 0 0 5 6 1 0 0 0 6 1 2 0 0 0 3 7 2 0 0 0 7 8 1 0 0 0 8 9 2 0 0 0 2 9 1 0 0 0 10 9 1 0 0 0 11 10 3 0 0 0 12 11 1 0 0 0 13 12 2 0 0 0 14 13 1 0 0 0 15 14 1 0 0 0 15 16 2 0 0 0 15 17 1 0 0 0 17 18 1 0 0 0 18 19 1 0 0 0 19 20 2 0 0 0 20 21 1 0 0 0 21 22 1 0 0 0 21 23 1 0 0 0 21 24 1 0 0 0 20 25 1 0 0 0 25 26 1 0 0 0 26 27 1 0 0 0 27 28 1 0 0 0 28 29 1 0 0 0 29 30 1 0 0 0 30 31 1 0 0 0 30 32 1 0 0 0			

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Element Name	Value	Data Format	Note #
32 33 1 0 0 0 27 33 1 0 0 0 25 34 2 0 0 0 34 35 1 0 0 0 18 35 2 0 0 0 14 36 2 0 0 0 37 36 1 0 0 0 38 37 2 0 0 0 38 39 1 0 0 0 12 38 1 0 0 0 M END			
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	569,02	PQ	2)
Unit	g/mol	CD	
Element Group: Stoichiometric			
Number of Moieties	2	INT	
Element Group: Moiety			
Moiety Role	Salt Molecule	CD	
Moiety ID	HJFGTE8954 (Artificial ID); [QTT17582CB (UNII)]	II	
Moiety Name	Hydrochloric acid	ST	
Stereochemistry	Achiral	CD	
Molecular Formula	HCl	ST	
Element group: Amount			
Amount Type	Exact	CD	
Quantity	1	PQ	
Unit	{mol/mol}	CD	
Amount Text	Mole Ratio to Parent: Mole Ratio to Ponatinib		
Element Group: Moiety			
Moiety Role	Parent substance	CD	
Moiety ID	PONG785632B (Artificial ID); [QTT17582CB (UNII)]	II	
Moiety Name	Ponatinib	ST	
Stereochemistry	Achiral	CD	
Molecular Formula	$C_{29}H_{27}F_3N_6O$	ST	

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Element Name	Value	Data Format	Note #
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	1	PQ	
Unit	{mol/mol}	CD	
Amount Text	Mole Ratio to Acid: Mol Ratio Ponatinib/Ponatinib hydrochloride (1:1)	ST	
Element Group: Reference Information			
Element Group: Substance Relationship			
Related Substance ID	GHF26754YQ (Artificial ID), [4340891KFS (UNII)]	II	3)
Related Substance Name	Ponatinib	ST	
Relationship	Parent substance to salt	CD	
Relationship Type	Ionic	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	93,6	PQ	
Unit	% {w/w}	CD	
Amount Text	Equivalence Factor: 0.936 (weight per cent to salt)	ST	
For the Specified Substance Group 1 and 2 see and .			

NOTE 1 This is a subscription database.

NOTE 2 Since the Substance is not described in any Pharmacopoeia evidence of the structure is substantiated by means of Mass spectrometry in order to substantiate the structure and molecular weight. The following information has been provided at the application, the supporting information for which will not be disclosed: Accurate Mass Determination and Mass Spectrometry (MS-MS Fragmentation). The Ponatinib fragments observed are consistent with both known fragmentation routes and the chemical structure of Ponatinib HCl.

NOTE 3 Since only one ID is allowed these IDs mean a repeat of the element group.

Table B.7 — Captured elements at the Substance level for Ponatinib (base)

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	GHF26754YQ (Artificial ID)	II	
Substance Type	Chemical	CD	
Element Group: Substance Name			
Substance Name	Ponatinib	ST	
Substance Name Type	Official	CD	
Language	en	CD	

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Element Name	Value	Data Format	Note #
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Recommended INN List	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	WHO Drug Information Vol. 25, no 3, 2011 Recommended INN: list 66	ST	
Reference Source URL	http://www.who.int/medicines/publications/druginformation/issues/RL_66.pdf	ST	
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Journal article	CD	
Element Group: Substance Name (Repeat)			
Substance Name	3-[2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl]-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl} benzamide	ST	
Substance Name Type	Systematic	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChemID*plus*	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://chem.sis.nlm.nih.gov/chemidplus/unii/4340891KFS	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Benzamide, 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl]-,	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS	CD	
Reference Source Class	Public Database	CD	

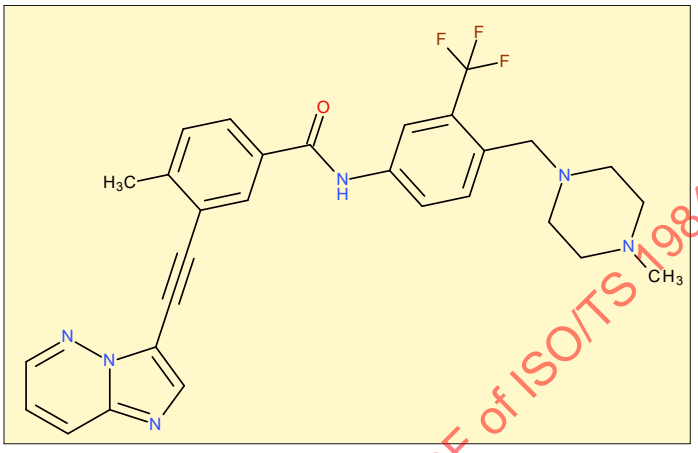
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Element Name	Value	Data Format	Note #
Reference Source Citation	CAS Registry Name	ST	
Element Group: Substance Code (Repeat)			
Code	943319-70-8	CD.Code	
Code System	CAS Registry	CD.Code SystemName	
Code System ID	0049	CD.Code System	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	4340891KFS	CD.Code	
Code System	FDA GSRS (UNII)	CD.Code SystemName	
Code System ID	0050	CD.Code System	
Code System Status	Active	CD	
Element Group: Reference Information			
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.Code System	
Substance Classification Code	L01XE24	CD.Code	
Substance Classification Type	ponatinib	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Web	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=L01XE24	ST	
Element Group: Structure			
Stereochemistry	Achiral	CD	
Molecular Formula	$C_{29}H_{27}F_3N_6O$	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChemID*plus*	CD	
Reference Source Class	Public Database	CD	

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Element Name	Value	Data Format	Note #
Reference Source URL	http://chem.sis.nlm.nih.gov/chemidplus/unii/4340891KFS	ST	
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure B.7 — Structural representation of Ponatinib**	ED	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation	InChI=1S/C29H27F3N6O/c1-20-5-6-22(16-21(20)8-10-25-18-33-27-4-3-11-34-38(25)27)28(39)35-24-9-7-23(26(17-24)29(30,31)32)19-37-14-12-36(2)13-15-37/h3-7,9,11,16-18H,12-15,19H2,1-2H3,(H,35,39)	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChemID*plus*	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://chem.sis.nlm.nih.gov/chemidplus/unii/4340891KFS	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	SMILES	CD	
Structural Representation	Cc1ccc(cc1C#Cc2cnc3n2nccc3)C(=O)Nc4ccc(c(c4)C(F)(F)F)CN5CCN(CC5)C	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChemID*plus*	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://chem.sis.nlm.nih.gov/chemidplus/unii/4340891KFS	ST	
Element Group: Structural Representation (Repeat)			

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Element Name	Value	Data Format	Note #
Structural Representation Type	molfile	CD	
Structural Representation Attachment	document TEXT	ED	

Marvin 06101411322D
39 43 0 0 0 0 999 V2000
7.6413 -1.1539 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
7.0617 -1.7615 0.0000 N 0 0 0 0 0 0 0 0 0 0 0 0
7.3375 -2.5327 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
6.7859 -3.1637 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
5.9586 -2.9720 0.0000 N 0 0 0 0 0 0 0 0 0 0 0 0
5.4071 -3.6077 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
4.6079 -3.4395 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
4.3601 -2.6402 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
3.5328 -2.4765 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
2.9812 -3.0842 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
2.1820 -2.9159 0.0000 N 0 0 0 0 0 0 0 0 0 0 0 0
1.6305 -3.5236 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
1.8782 -4.3229 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0
0.8032 -3.3601 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
0.2516 -3.9676 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
-0.5477 -3.7993 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
-0.7953 -3.0001 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
-1.6226 -2.8365 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
-0.2439 -2.3924 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
0.5555 -2.5607 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
-0.4916 -1.6213 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
-0.7673 -0.8219 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
-1.0150 -0.0508 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
-0.5196 0.6410 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
-1.0150 1.3000 0.0000 N 0 0 0 0 0 0 0 0 0 0 0 0
-1.7909 1.0523 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
-2.5060 1.4637 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
-3.2213 1.0523 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
-3.2213 0.2250 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
-2.5060 -0.1863 0.0000 N 0 0 0 0 0 0 0 0 0 0 0 0
-1.7909 0.2250 0.0000 N 0 0 0 0 0 0 0 0 0 3 0 0
3.2571 -3.8835 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
4.0562 -4.0470 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
4.3040 -4.8184 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
3.7524 -5.4540 0.0000 F 0 0 0 0 0 0 0 0 0 0 0 0
4.5564 -5.6222 0.0000 F 0 0 0 0 0 0 0 0 0 0 0 0

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Element Name	Value	Data Format	Note #
5.1080 -5.0147 0.0000 F 0 0 0 0 0 0 0 0 0 0 0 0 5.7108 -2.2009 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 6.2625 -1.5933 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 1 2 1 0 0 0 0 2 3 1 0 0 0 0 2 39 1 0 0 0 0 3 4 1 0 0 0 0 4 5 1 0 0 0 0 5 6 1 0 0 0 0 5 38 1 0 0 0 0 6 7 1 0 0 0 0 7 8 1 0 0 0 0 7 33 2 0 0 0 0 8 9 2 0 0 0 0 9 10 1 0 0 0 0 10 11 1 0 0 0 0 10 32 2 0 0 0 0 11 12 1 0 0 0 0 12 13 2 0 0 0 0 12 14 1 0 0 0 0 14 15 1 0 0 0 0 14 20 2 0 0 0 0 15 16 2 0 0 0 0 16 17 1 0 0 0 0 17 18 1 0 0 0 0 17 19 2 0 0 0 0 19 20 1 0 0 0 0 19 21 1 0 0 0 0 21 22 3 0 0 0 0 22 23 1 0 0 0 0 23 24 2 0 0 0 0 23 31 1 0 0 0 0 24 25 1 0 0 0 0 25 26 2 0 0 0 0 26 27 1 0 0 0 0 26 31 1 0 0 0 0 27 28 2 0 0 0 0 28 29 1 0 0 0 0 29 30 2 0 0 0 0 30 31 1 0 0 0 0 32 33 1 0 0 0 0			

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Element Name	Value	Data Format	Note #
33 34 1 0 0 0 0 34 35 1 0 0 0 0 34 36 1 0 0 0 0 34 37 1 0 0 0 0 38 39 1 0 0 0 0 M END			
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	532,56	PQ	
Unit	g/mol	CD	
Element Group: Chemical			
Element Group: Stoichiometric			
Number of Moieties	1	INT	
Element Group: Reference Information			
Element Group: Substance Relationship			
Related Substance ID	POYFG4531Y (Artificial ID), 96R6PU3D8J (UNII)	II	
Related Substance Name	Ponatinib hydrochloride	ST	
Relationship	Parent substance to salt	CD	
Relationship Type	Ionic	CD	

Discussion on the Specified Substance Information level

Table B.8 — Captured elements at the Specified Substance Group 1 level for Ponatinib hydrochloride

Element Type	Value	Data Format	Note #
Element Group: Specified Substance Group 1 (Characteristic attributes to be described Ponatinib hydrochloride)			
Element Group: Specified Substance Group 1			
Specified Substance Group 1 ID	PHIT2345RA (Artificial ID)	II	
Element Group: Substance Name			
Specified Substance Group 1 Name	Ponatinib hydrochloride, crystalline form 1	ST	
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	

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Element Type	Value	Data Format	Note #
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Constituent			
Constituent Substance ID	POYFG4531Y (Artificial ID)	II	
Constituent Substance Name	Ponatinib hydrochloride	ST	
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Physical Form			
Physical State	Solid	CD	
Physical Form Type	Anhydrous crystalline form 1	CD	1)
Element Group: Characteristic Attribute			
Attribute Type	Physical	ST	
Attribute Name	Solubility	ST	
Attribute Substance ID	DIMTH8976S (Artificial ID); [YOW8V9698H (UNII)]	II	
Attribute Substance Name	Dimethyl Sulfoxide	ST	
Is Defining	No	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	80	PQ	
Unit	mg/ml	CD	
Element Group: Attribute Parameter			
Attribute Parameter Name	Solubility Condition	ST	
Attribute Parameter Value	Measured at 20 °C	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Physical	CD	
Attribute Name	Solubility	ST	
Attribute Substance ID	METHA1234S (Artificial ID); [Y4S76JWI15 (UNII)]	II	
Substance Name	Methanol	ST	
Is Defining	No	BL	
Element Group: Attribute Parameter			
Attribute Parameter Name	Solubility Condition	ST	
Attribute Parameter Value	Measured at 20 °C	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	30	PQ	

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Element Type	Value	Data Format	Note #
Unit	mg/ml	CD	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Physical	CD	
Attribute Name	Melting point	ST	
Attribute Substance ID	PHIT2345RA (Artificial ID)	II	
Attribute Substance Name	Ponatinib hydrochloride, crystalline form 1	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	263	PQ	
High Limit	264	PQ	
Low Limit	262	PQ	
Unit	Degree Celsius	CD	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Physical	CD	
Attribute Name	pKa	ST	2)
Attribute Substance ID	PHIT2345RA (Artificial ID)	II	
Attribute Substance Name	Ponatinib hydrochloride, crystalline form 1	ST	
Is Defining	No	BL	
Element Group: Attribute Parameter			
Attribute Parameter Name	pH range	ST	
Attribute Parameter Value	Measured at pH range of 2,5 to 10,5	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	7,80	PQ	2)
Unit	N/A		
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Physical	CD	
Attribute Name	pKa	ST	2)
Attribute Substance ID	PHIT2345RA (Artificial ID)	II	
Attribute Substance Name	Ponatinib hydrochloride, crystalline form 1	ST	
Is Defining	No	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	2,77	PQ	2)

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Element Type	Value	Data Format	Note #
Unit	N/A		
Element Group: Attribute Parameter			
Attribute Parameter Name	pH range	ST	
Attribute Parameter Value	Measured at pH range of 2,5 to 10,5	ST	
Element: Characteristic Attribute (Repeat)			
Attribute Type	Physical	CD	
Attribute Name	UV absorption maxima	ST	
Attribute Substance ID	PHIT2345RA (Artificial ID)	II	
Attribute Substance Name	Ponatinib hydrochloride, crystalline form 1	ST	
Is Defining	No	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	258	PQ	
Unit	Nanometre	CD	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Physical	CD	
Attribute Name	UV absorption maxima	ST	
Attribute Substance ID	PHIT2345RA (Artificial ID)	II	
Attribute Substance Name	Ponatinib hydrochloride, crystalline form 1	ST	
Is Defining	No	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	301	PQ	
Unit	Nanometre	CD	

NOTE 1 When the same manufacture/or another manufacturer markets the Ponatinib hydrochloride, crystalline as a different polymorph (e.g. crystalline form 2) the (Specified) Substance (Group 1) Name will change into Ponatinib hydrochloride, crystalline, form 2 with a different Specified Substance Group 1 ID: [FFFFGGG89].

NOTE 2 There are instances where the pKa has two values depending on the electrochemical potential difference within a pH range of 2,5 to 10,5.

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Table B.9 — Tabular format of the captured elements at the Specified Substance Group 2 level for Ponatinib hydrochloride, crystalline form 1

Element Group: Specified Substance Group 2 (Ponatinib hydrochloride)			
Specified Substance Group 2 ID	KHJTYD674R (Artificial ID)	II	
Element Group: Substance Name			
(Specified) Substance (Group 2) Name	Ponatinib hydrochloride, crystalline form 1-Manufacturer YY	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	PHIT2345RA (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Synthetic	CD	
Production Method Description	Chemical synthesis from starting materials, purification steps and recrystallization to obtain crystalline form 1	ST	
Production System Type	Chemical synthesis	CD	
Critical Process Version Number	1	INT	2)
Version	POTO-001	ST	
Version Date	20170127	TS.Date	
Element Group: Organization			
Manufacturer ID	DUNS543210 (Artificial ID)	II	
Manufacturer Name	Company YY	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	

NOTE 1 This Parent Substance ID refers to the Specified Substance Group 1 Name: Ponatinib hydrochloride, crystalline form 1.

NOTE 2 The Critical Process Number Version Number would change if a substantial change in the (synthetic) manufacturing process occurred. These would include a change in the chemistry, addition of elimination of a purification step.

NOTE Since Ponatinib hydrochloride is not described in any pharmacopoeia the Specified Substance Group 3 information for the Pharmacopoeial Grade is not applicable. However, a Specified Substance Group 3 could be applicable if the applicant wishes to lay down an In-house specification by means of a reference document.

B.8.3 Example 3: Benzathine Benzylpenicillin tetrahydrate, sterilized.

Introduction

This example discusses the preparation of the sterile substance according to the requirements of the USP with the starting materials Potassium Benzylpenicillin according to the requirements of the Ph.Eur. and Benzathine diacetate with *In-house* specifications.

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Table B.10 — Tabular format of the captured elements at the Substance level for Benzathine, Benzylpenicillin tetrahydrate sterilized USP

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	GHFTE5643B (Artificial ID)	II	
Substance Type	Chemical	CD	
Element Group: Substance Name			
Substance Name	Penicillin G Benzathine	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP Pharmacopoeia	ST	
Element Group: Substance Name (Repeat)			
Substance Name	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino-], 2[S-(2,5,6)]-, compd. With N,N¢-bis(phenylmethyl)-1,2-ethanediamine (2:1), tetrahydrate.	ST	
Substance Name Type	Systematic	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP, Current Edition	ST	
Element Group: Substance Name (Repeat)			
Substance Name	4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-[2S-(2.alpha.,5.alpha.,6.beta.)]-, compd. With N,N'-bis(phenylmethyl)-1,2-ethanediamine (2:1), tetrahydrate	ST	
Substance Name Type	Other Name	CD	

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Element Name	Value	Data Format	Note #
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	
Reference Source Citation	CAS Registry Name	ST	
Element Group: Substance Name (Repeat)			
Substance Name	XYWZ123 (Artificial Company Code)	ST	
Substance Name Type	Company Code	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	CBG564357C (Artificial ID)	ST	
Element Group: Substance Code			
Code	41372-02-5	CD.Code	
Code System	CAS Registry	CD.Code SystemName	
Code System ID	0049	CD.Code System	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	RIT82F58GK	CD.Code	
Code System	FDA GSRS (UNII)	CD.Code SystemName	
Code System ID	0050	CD.Code System	
Code System Status	Active	CD	
Element Group: Reference Information			
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.Code System	

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Element Name	Value	Data Format	Note #
Substance Classification Code	J01CE08	CD.Code	
Substance Classification Type	Benzathine benzylpenicillin	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Web	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=J01CE08	ST	
Element Group: Structure			
Stereochemistry	Chiral	CD	
Optical Activity	(-)	CD	
Molecular Formula	$C_{48}H_{64}N_6O_{12}S_2$	ST	
Molecular Formula by Moiety	$[C_{16}H_{20}N_2].[C_{16}H_{18}N_2O_4S]2.4H_2O$	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	FDA GSRS	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://fdasis.nlm.nih.gov/srs/auto/rit82f58gk	ST	
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment	In below	ED	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	SMILES	CD	
Structural Representation	CC1([C@@H](N2[C@H](S1)[C@@H](C2=O)NC(=O)Cc3ccccc3)C(=O)O)C.CC1([C@@H](N2[C@H](S1)[C@@H](C2=O)NC(=O)Cc3ccccc3)C(=O)O)C.c1ccc(cc1)CNCCNCc2ccccc2.O.O.O.O	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChemID*plus*	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://chem.sis.nlm.nih.gov/chemidplus/rn/41372-02-5	ST	

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Element Name	Value	Data Format	Note #

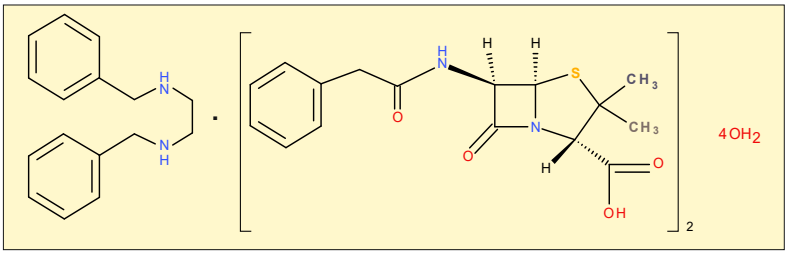


Figure B.8 — Structural representation of Benzathine Benzylpenicillin tetrahydrate

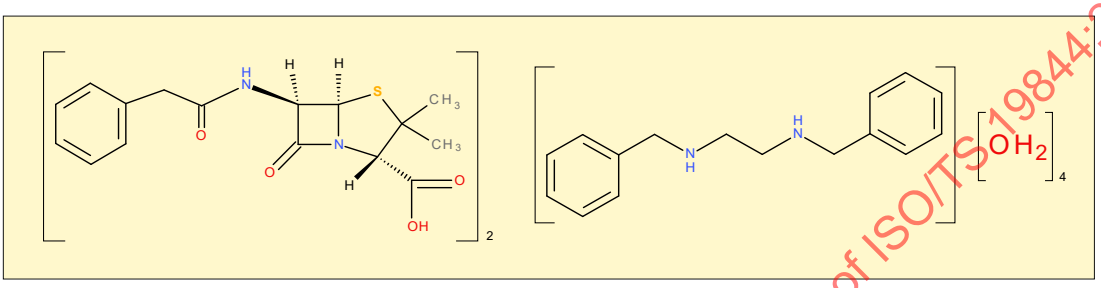


Figure B.43 — Structural representation of Benzathine Benzylpenicillin tetrahydrate in accordance with subclause 5.7.6

Element Group: Structural Representation (Repeat)			
Structural Representation Type	molfile	CD	
Structural Representation Attachment	document TEXT below:	ED	

-ISIS- 10311402042D
43 45 0 0 1 0 0 0 0 0999 V2000
3.4083 -6.7959 0.0000 N 0 0 3 0 0 0 0 0 0 0 0 0
3.4000 -5.9709 0.0000 C 0 0 1 0 0 0 0 0 0 0 0 0
2.5750 -6.7959 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
2.5750 -5.9709 0.0000 C 0 0 1 0 0 0 0 0 0 0 0 0
4.1917 -7.0500 0.0000 C 0 0 2 0 0 0 0 0 0 0 0 0
4.1833 -5.7125 0.0000 S 0 0 0 0 0 0 0 0 0 0 0 0
4.6750 -6.3792 0.0000 C 0 0 3 0 0 0 0 0 0 0 0 0
1.7500 -5.9709 0.0000 N 0 0 0 0 0 0 0 0 0 0 0 0
4.1875 -7.8709 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
1.0292 -5.5584 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
1.9917 -7.3834 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0
3.4667 -8.2834 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0
1.0333 -4.7334 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0
0.3167 -5.9667 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0
4.9000 -8.2834 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0
5.3875 -5.9584 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0

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Element Name	Value	Data Format	Note #
5.3875 -6.7917 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 -0.4000 -5.5542 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 -0.4000 -4.7250 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 -1.1125 -5.9667 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 -1.8292 -5.5584 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 -1.1167 -4.3125 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 -1.8333 -4.7250 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 3.3917 -5.1459 0.0000 H 0 0 0 0 0 0 0 0 0 0 0 0 9.6917 -5.9918 0.0000 N 0 0 0 0 0 0 0 0 0 0 0 0 11.8292 -5.5793 0.0000 N 0 0 0 0 0 0 0 0 0 0 0 0 8.2667 -6.0001 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 13.2542 -5.5751 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 12.5417 -5.9876 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 8.9792 -5.5876 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 11.1167 -5.9918 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 10.4042 -5.5793 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 7.5500 -5.5876 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 8.2667 -6.8293 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 13.9667 -5.9876 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 13.2500 -4.7543 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 6.8375 -6.0001 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 14.6792 -5.5751 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 13.9583 -4.3418 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 7.5500 -7.2418 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 14.6750 -4.7501 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 6.8375 -6.8293 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 9.2375 -8.3751 0.0000 O 0 0 0 0 0 0 0 0 0 0 0 0 5 1 1 0 0 0 0 6 2 1 0 0 0 0 7 5 1 0 0 0 0 4 8 1 1 0 0 0 5 9 1 6 0 0 0 10 8 1 0 0 0 0 11 3 2 0 0 0 0 12 9 2 0 0 0 0 13 10 2 0 0 0 0 14 10 1 0 0 0 0 15 9 1 0 0 0 0 16 7 1 0 0 0 0 17 7 1 0 0 0 0 18 14 1 0 0 0 0 19 18 2 0 0 0 0 20 18 1 0 0 0 0			

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Element Name	Value	Data Format	Note #
21 20 2 0 0 0 0 22 19 1 0 0 0 0 23 22 2 0 0 0 0 2 24 1 6 0 0 0 3 4 1 0 0 0 0 6 7 1 0 0 0 0 21 23 1 0 0 0 0 2 1 1 0 0 0 0 3 1 1 0 0 0 0 26 31 1 0 0 0 0 27 30 1 0 0 0 0 28 29 1 0 0 0 0 29 26 1 0 0 0 0 30 25 1 0 0 0 0 31 32 1 0 0 0 0 32 25 1 0 0 0 0 33 27 2 0 0 0 0 34 27 1 0 0 0 0 35 28 2 0 0 0 0 36 28 1 0 0 0 0 37 33 1 0 0 0 0 38 35 1 0 0 0 0 39 36 2 0 0 0 0 40 34 2 0 0 0 0 41 39 1 0 0 0 0 42 37 2 0 0 0 0 40 42 1 0 0 0 0 41 38 2 0 0 0 0 4 2 1 0 0 0 0 M STY 2 1 MUL 2 MUL M SLB 2 1 1 2 2 M SAL 1 15 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 M SAL 1 9 16 17 18 19 20 21 22 23 24 M SPA 1 15 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 M SPA 1 9 16 17 18 19 20 21 22 23 24 M SDI 1 4 -2.3000 -8.8000 -2.3000 -3.8500 M SDI 1 4 6.3500 -3.8500 6.3500 -8.8000 M SMT 1 2 M SAL 2 1 43 M SPA 2 1 43 M SDI 2 4 8.7500 -9.0500 8.7500 -7.9000 M SDI 2 4 10.1500 -7.9000 10.1500 -9.0500 M SMT 2 4			

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Element Name	Value	Data Format	Note #
M END			
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	981,20	PQ	
Unit	g/mol	CD	
Element Group: Stoichiometric			
Number of Moieties	3	INT	
Element Group: Moiety			
Moiety Role	Salt molecule	CD	
Moiety ID	BENZA98765; [C659VZ7P7T (UNII)]	II	
Moiety Name	Benzanthine	ST	
Stereochemistry	Achiral	CD	
Molecular Formula	$C_{16}H_{20}N_2$	ST	
Element Group: Amount			

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Element Name	Value	Data Format	Note #
Amount Type	Exact	CD	
Quantity	1	PQ	
Unit	{mol/mol}	CD	
Amount Text	Mole Ratio to salt: Mole Ratio to 2 molecules Penicillin G	ST	
Element Group: Moiety (Repeat)			
Moiety Role	Hydrate molecule	CD	
Moiety ID	WATE123456 (Artificial ID); [059QF0KO0R (UNII)]	II	
Moiety Name	Water	ST	
Stereochemistry	Achiral	CD	
Molecular Formula	H_2O	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	2	PQ	
Unit	{mol/mol}	CD	
Amount Text	mole ratio to hydrate: Mole Ratio to 2 molecules Penicillin G	ST	
Element Group: Moiety (Repeat)			
Moiety Role	Parent molecule	CD	
Moiety ID	PENC56432TY (Artificial ID) [Q42T66VG0C (UNII)]	II	
Moiety Name	Penicillin G	ST	
Stereochemistry	Achiral	CD	
Molecular Formula	$C_{16}H_{18}N_2O_4S$	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	0,5	PQ	
Unit	{mol/mol}	CD	
Amount Text	Mol Ratio to salt: Mol Ratio to Benzanthine	ST	
Element Group: Substance Relationship			
Related Substance ID	PENC56432TY (Artificial ID) [Q42T66VG0C (UNII)]	II	
Related Substance Name	Penicillin G	ST	
Relationship	Parent substance to salt-hydrate	CD	
Relationship Type	Ionic	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	68,2	PQ	

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Element Name	Value	Data Format	Note #
Unit	% {w/w}	CD	
Amount Text	Equivalence Factor: 0,682	ST	

Specified Substance Group 2 information level

The following table shows the elements captured at the Specified Substance Group 2 level for Benzathine, Benzylpenicillin tetrahydrate, sterilized (USP).

Table B.11 — Tabular format of the captured elements at the Specified Substance Group 2 level for Benzathine, Benzylpenicillin tetrahydrate, sterilized (USP)

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2 (Benzathine Benzylpenicillin tetrahydrate)			
Specified Substance Group 2 ID	BENZ97653M (Artificial ID)	II	
Element Group: Substance Name			
Specified Substance Group 2 Name	Benzathine Benzylpenicillin tetrahydrate – Manufacturer ZZ	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	GHFTE5643B (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Fermentation and Chemical synthesis	CD	
Production Method Description	Fermentation, Chemical synthesis from starting materials, purification steps and recrystallization to obtain crystalline form.	ST	
Production System Type	Chemical synthesis	CD	
Critical Process Version Number	1	INT	2)
Version	BBTH-001	ST	
Version Date	20170127	TS.Date	
Element Group: Organization			
Manufacturer ID	DUNS543210 (Artificial ID)	II	
Manufacturer Name	Company ZZ	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	

NOTE 1 This (Parent) Substance ID refers to the Substance Name: Penicillin G Benzathine.

NOTE 2 The Critical Process Number Version Number would change if a substantial change in the (synthetic) manufacturing process occurred. These would include a change in the chemistry, addition of elimination of a purification step.

Specified Substance Group 3 information level

The following table shows the elements captured at the Specified Substance Group 3 level for Benzathine Benzylpenicillin tetrahydrate, sterilized (USP).

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Table B.12 — Tabular format of the captured elements at the Specified Substance Group 3 level for Benzathine, Benzylpenicillin tetrahydrate, sterilized (USP)

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 3 [Benzathine Benzylpenicillin tetrahydrate, sterilized (USP)]			
Specified Substance Group 3 ID	JKHYR7865P (Artificial ID)	II	
Element Group: Substance Name			
Substance Type	Specified Substance Group 3	CD	
(Specified) Substance (Group 3) Name	Benzathine Benzylpenicillin tetrahydrate, sterilized-USP	ST	
Language	en	CD	
(Parent) Substance ID	GHFTE5643B (Artificial ID)	II	1)
Element Group: Grade			
Grade Type	USP	CD	
Grade Name	Benzathine Benzylpenicillin tetrahydrate sterilized	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP, Monograph USP38-NF33 Page 4781	ST	
NOTE This (Parent) Substance ID refers to the Substance Name: Penicillin G Benzathine.			

B.9 Radiopharmaceutical substance

B.9.1 Introduction

The ISO 11238 Substance Standard describes a nuclide and defines the Isotope Element Group based on the type of the underlying substance and not a type of the substance in and of itself.

Characteristics for each nuclide could at least include half-life, energy of emission, parent and daughter nuclides. The information model for structure and isotope is shown in Figure 10.

The registration of parent and daughter nuclides and registration of energy emission will be an issue of consideration probably to be discussed in a future edition of the Implementation Guide, Annex for Radiopharmaceutical substance/preparations and radionuclide generators.

From these substances one example is provided in compliance with the current ISO 11238 Standard e.g. Florbetapir ^{18}F, which is a diagnostic radiopharmaceutical drug substance.

For radiopharmaceutical products, this document can only provide very limited information due to the nature of these substances. The substances are produced, and not isolated separately, in a continuous process into the final product to be used either as a radiolabelling of a chemical substance or as a medicinal product e.g. solution for intravenous injection.

Special attention for these substances has to be paid to the purity of the radionuclide which is an integral aspect of the quality of the substance, which cannot be discussed here since this is confidential information.

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B.9.2 Example: Florbetapir ^{18}F

Florbetapir ^{18}F Solution for Injection is provided as a (non-carrier added) sterile solution for intravenous injection in a multi-dose vial. The proposed dose of Florbetapir ^{18}F Solution for Injection is 370 MBq at the time of injection. The maximum human dose is 370 MBq in 10 ml solution for injection containing not more than 50 µg Florbetapir ^{18}F. Florbetapir ^{18}F Solution for Injection is formulated in 10 %{v/v} ethanol, 0,45 % sodium ascorbate, 0,81 % sodium chloride sterile aqueous solution. The drug product may not be diluted by the end user.

General information

Florbetapir ^{18}F is a diagnostic radiopharmaceutical drug substance with a radioactive half-life of 109,77 minutes. Florbetapir ^{18}F, and Drug Product, Florbetapir ^{18}F Solution for Injection, are manufactured in one continuous process in which the Drug Substance is synthesized by nucleophilic radiofluorination of the Good Manufacturing Practice (GMP)-manufactured starting material (precursor). The ^{18}F radionuclide used for the manufacture of Florbetapir ^{18}F is produced from bombardment of [^{18}O] water with an intensive beam of accelerated protons in the cyclotron. The energy used for the nuclear reaction is a function of the type of cyclotron used. The nuclear reaction is represented as: ^{18}O(p,n)^{18}F. The ^{18}F-fluoride ion formed in the nuclear reactor remains dissolved in the target water and is transferred via a line through a shielded conduit located on a radiosynthesizer. In the synthesizer the ^{18}F-radiolabeling reaction takes place on the Florbetapir precursor and replacement of a specific group takes place by ^{18}F by means of a chemical substitution reaction. In the sense of the ISO 11238 model this reaction is a structural substitution by the nucleotide to form the final Florbetapir ^{18}F substance.

The Drug substance, Florbetapir ^{18}F, contains the radioactive isotope fluorine ^{18}F. ^{18}F undergoes radioactive decay primarily through emission of a positively-charged beta particle (positron; β+) having maximum and average energies of 635 and 249 keV respectively. A positron generated from ^{18}F travels in tissue until it collides with an electron and annihilates. The annihilation event produces 511 keV gamma photons which forms the basis for positron emission tomographic (PET) imaging. Decay schema details can be found on the web, see http://www.nucleide.org/DDEP_WG/Nuclides/F-18_tables.pdf. $^{18}_{9}$F decays to stable $^{18}_{8}$O.

The table below shows in tabular format the identity of material, combining the elements for Florbetapir ^{18}F at Substance and Specified Substance information levels.

Table B.13 — Identity of material, combining the elements for Florbetapir 18F, Substance information level

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	FLOR67453S (Artificial ID)	II	
Substance Type	Chemical	CD	
Element Group: Substance Name			
Substance Name	Florbetapir (^{18}F)	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	

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Element Name	Value	Data Format	Note #
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Recommended INN List	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	INN, WHO Drug information, Vol. 25, No. 1, 2011	ST	
Reference Source URL	http://www.who.int/medicines/publications/druginformation/innlists/PL103.pdf?ua=1	ST	
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Web page	CD	
Element Group: Substance Name (Repeat)			
Substance Name	(4-[(1E)-2-(6-{2-[2-(2-[18F]Fluoroethoxy)ethoxy]ethoxy}pyridin-3-yl)ethenyl]-N-methylbenzenamine	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Martindale	CD	
Reference Source Class	Official Name Source	CD	
Reference Source URL	https://www.medicinescomplete.com/mc/martindale/current/19185-l.htm?q=florbetapir%2018F&t=search&ss=text&p=1#_hit	ST	
Element Group: Substance Name (Repeat)			
Substance Name	4-[(1E)-2-(6-{2-[2-(2-[18F]fluoroethoxy)ethoxy]ethoxy} pyridine-3-yl)ethen-1-yl]-N-methylaniline.	ST	
Substance Name Type	Systematic Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	A123456 (Artificial ID)	ST	
Element Group: Substance Code			
Code	956103-76-7	CD.Code	

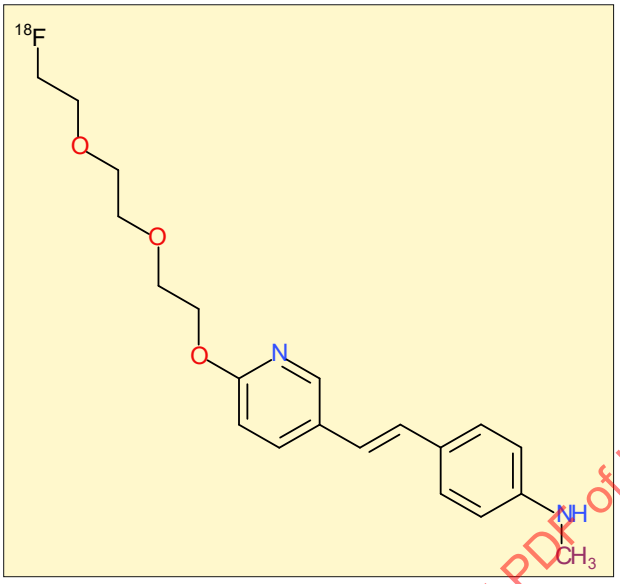
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Element Name	Value	Data Format	Note #
Element Name	Value	Data Format	Note #
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	6W15Z5R0RU	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	V09AX05	CD.Code	
Substance Classification Type	Florbetapir ^{18}F	ST	1)
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Literature	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=V09AX05&showdescription=yes	ST	
Element Group: Structure			
Stereochemistry	Achiral	CD	2)
Molecular Formula	$C_{20}H_{25}{}^{18}FN_2O_3$	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Recommended INN List	CD	
Reference Source Class	Official Name Source	CD	
Reference Source URL	http://www.who.int/medicines/publications/druginformation/innlists/PL103.pdf?ua=1	ST	

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Element Name	Value	Data Format	Note #
Element Group: Structural Representation			
Structural Representation Type	Full	CD	2)
Structural Representation Attachment	 **Figure B.9 — Structural representation of Florbetapir ^{18}F**	ED	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation	InChI=1S/C20H25FN2O3/c1-22-19-7-4-17(5-8-19)2-3-18-6-9-20(23-16-18)26-15-14-25-13-12-24-11-10-21/h2-9,16,22H,10-15H2,1H3/b3-2+/i21-1	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChemID*plus*	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://chem.sis.nlm.nih.gov/chemidplus/unii/6W15Z5R0RU	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	SMILES	CD	
Structural Representation	CNc1ccc(cc1)/C=C/c2ccc(nc2)OCCOCCOCC[18F]	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	Molfile	CD	

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Element Name	Value	Data Format	Note #
Structural Representation Attachment	TET below	ST	

Symyx 06091422092D 1 1.00000 0.00000 0
26 27 0 0 0 999 V2000
16.8468 -12.0230 0.0000 C 0 0 0 0 0 0 0 0 0 0
17.6255 -11.5734 0.0000 C 0 0 0 0 0 0 0 0 0 0
17.6255 -10.6741 0.0000 C 0 0 0 0 0 0 0 0 0 0
16.8468 -10.2244 0.0000 C 0 0 0 0 0 0 0 0 0 0
16.0679 -10.6741 0.0000 C 0 0 0 0 0 0 0 0 0 0
16.0679 -11.5734 0.0000 C 0 0 0 0 0 0 0 0 0 0
15.2891 -10.2244 0.0000 C 0 0 0 0 0 0 0 0 0 0
18.4044 -12.0230 0.0000 N 0 0 0 0 0 0 0 0 0 0
14.5103 -10.6741 0.0000 C 0 0 0 0 0 0 0 0 0 0
13.7315 -10.2244 0.0000 C 0 0 0 0 0 0 0 0 0 0
13.7315 -9.3251 0.0000 C 0 0 0 0 0 0 0 0 0 0
12.9527 -8.8755 0.0000 C 0 0 0 0 0 0 0 0 0 0
12.1739 -9.3251 0.0000 C 0 0 0 0 0 0 0 0 0 0
12.1739 -10.2244 0.0000 N 0 0 0 0 0 0 0 0 0 0
12.9527 -10.6741 0.0000 C 0 0 0 0 0 0 0 0 0 0
19.1832 -11.5734 0.0000 C 0 0 0 0 0 0 0 0 0 0
11.3950 -8.8755 0.0000 O 0 0 0 0 0 0 0 0 0 0
10.6162 -9.3252 0.0000 C 0 0 0 0 0 0 0 0 0 0
9.8374 -8.8755 0.0000 C 0 0 0 0 0 0 0 0 0 0
9.0586 -9.3251 0.0000 O 0 0 0 0 0 0 0 0 0 0
8.2798 -8.8755 0.0000 C 0 0 0 0 0 0 0 0 0 0
7.5009 -9.3251 0.0000 C 0 0 0 0 0 0 0 0 0 0
6.7221 -8.8755 0.0000 O 0 0 0 0 0 0 0 0 0 0
5.9433 -9.3251 0.0000 C 0 0 0 0 0 0 0 0 0 0
5.1645 -8.8755 0.0000 C 0 0 0 0 0 0 0 0 0 0
4.3857 -9.3251 0.0000 F -1 0 0 0 0 0 0 0 0 0
2 1 2 0 0 0
3 2 1 0 0 0
4 3 2 0 0 0
5 4 1 0 0 0
6 5 2 0 0 0
1 6 1 0 0 0
5 7 1 0 0 0
2 8 1 0 0 0
7 9 2 0 0 0
9 10 1 0 0 0
12 11 1 0 0 0

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Element Name	Value	Data Format	Note #
13 12 2 0 0 0 14 13 1 0 0 0 15 14 2 0 0 0 11 10 2 0 0 0 10 15 1 0 0 0 8 16 1 0 0 0 13 17 1 0 0 0 17 18 1 0 0 0 18 19 1 0 0 0 19 20 1 0 0 0 20 21 1 0 0 0 21 22 1 0 0 0 22 23 1 0 0 0 23 24 1 0 0 0 24 25 1 0 0 0 25 26 1 0 0 0 M ISO 1 26 18 M END			
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChemID*plus*	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://chem.sis.nlm.nih.gov/chemidplus/unii/6W15Z5R0RU	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document Type	Regulatory submission	CD	
Element Group: Isotope			
Nuclide ID	4M4WE5N2GE (UNII)	II	
Nuclide Name	^{18}F-Fluoride	CD	
Substitution Type	Specific	CD	
Nuclide Half-life	109,77	PQ	
Element Group: Amount			
Amount Type	Exact	CD	
Unit	Minutes	CD	

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Element Name	Value	Data Format	Note #
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	359,18	PQ	
Unit	g/mol	CD	
Element Group: Stoichiometric			
Number of Moieties	1	INT	

NOTE 1 ATC classification: An expert group from several EU-countries is responsible for the ATC classification of radiopharmaceuticals in V09 and V10. The group has also prepared the guidelines for classification of these products.

Radiopharmaceuticals for diagnostic use are classified in this group, while radiopharmaceuticals for therapeutic use are classified in V10. In general, the 3rd level are subdivided according to site of action or organ system, the 4th level according to radionuclide and the 5th level specifies the chemical substance. The ATC 5th level defines the actual form essential in nuclear medicine procedures, which includes radionuclide and carrier molecule. Therefore, products on the market that can often be regarded as intermediate products rather than ready-to-use radiopharmaceuticals can be given more than one (5th level) ATC code, e.g. Technetium (99mTc) exametazime (V09AA01) and technetium (99mTc) exametazime labelled cells (V09HA02).

NOTE 2 Ethynyl bond: E (trans) configuration.

Specified Substance Group 2 information level

The following elements are captured at the Specified Substance Group 2 level for Florbetapir (^{18}F).

Table B.14 —Specified Substance Group 2 level for Florbetapir (^{18}F)

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2 [Florbetapir (^{18}F)]			
Specified Substance Group 2 ID	HJFTE2345F (Artificial ID)	II	
Element Group: Substance Name			
(Specified) Substance (Group 2) Name	Florbetapir (18F)-Company Cyclotron ZZ	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	FLOR67453S (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Synthetic	CD	
Production Method Description	Nuclide production by bombardment of [^{18}O] by accelerated protons in a Cyclotron: 18O(p,n)^{18}F, followed by radiolabelling of a precursor substance by a chemical substitution on a radio synthesizer. The substance is not isolated during manufacturing.	ST	

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Element Name	Value	Data Format	Note #
Production System Type	Nuclide production by bombardment of a parent substance followed by radiolabelling.	CD	
Critical Process Version Number	1	INT	2)
Version	FLORF18	ST	
Version Date	20170127	TS.Date	
Element Group: Organization			
Manufacturer ID	DUNSNUCL78 (Artificial ID)	II	
Manufacturer Name	Company Cyclotron ZZ	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	

NOTE 1 This (Parent) Substance ID refers to the Substance Name: Florbetapir (^{18}F).

NOTE 2 The Critical Process Number Version Number would change if a substantial change in the manufacturing process occurred. The change in a version number is tied to the production system type.

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Annex C
(normative)

Protein substance

C.1 Introduction

Proteins are one of the five types of single substances described in ISO 11238. The fundamental property of peptides and proteins is that they consist of chains of alpha-amino acids brought together by a peptide bond. Peptides are typically relatively short polypeptide chains typically with a chain length of less than 40 amino acid residues. Chains longer than forty amino acid residues are typically considered to be proteins. In ISO 11238 peptides and proteins are defined in a similar manner. The amino-acid sequence shall be provided to define both peptides and proteins. The preferred format is a single letter Dayhoff code. Capital letters shall be used for L-amino acids and small letters for D-amino acids. When describing biosynthesized amino-acids the translated code should be used even for amino-acids that are modified by post-translational processes. The letter X can be used to represent amino-acids in synthetic peptides that are not part of the standard 22 single letter amino acid-codes used to represent amino-acids in proteins that are translated in cells.

Proteins or peptides that are modified will nearly always have the translated or natural amino-acid replaced with a fully modified alpha-amino acid. The attachment points will be assumed to be the alpha amino group and the adjacent acid. For substitution with beta-amino-acid, or if there is the possibility for ambiguity (e.g. isoaspartate), a residue containing the attachment point will be created. All substituted or replacement amino acids shall be registered as substances and will have a Substance ID.

EXAMPLE N-terminal modification of Glutamine or Glutamic acid to Pyroglutamic Acid, Substance ID: SZB83O1W42 (UNII).

Proteins often undergo extensive but variable post-translational modifications either within the cell or bioreactor, during processing, purification or the storage of the protein. As mentioned in the body of the implementation guide, there is no intention to capture microheterogeneity of proteins at the substance level. Post-translational modifications shall only be captured in detail if they are deemed to be essential for the functionality of the protein or if the protein is intentionally modified. The presence and sites of disulfide bonds and glycosylation will be captured at the substance level. The overall type of glycosylation will also be captured. More extensive information on glycosylation could be captured at the Specified Substance Group 1 level.

Non-ribosomal peptides, such as cyclosporines, bleomycins and vancomycin, will be defined as chemicals. Short peptides and derivatives of short ribosomal peptides (e.g. desmopressin) may be described by their sequence and a two-dimensional molecular structure. All dipeptides will be described as chemicals.

In the examples below, only elements that contain data will be shown for illustrative purposes. It should be noted that in addition to the formats presented below for structural representation of peptides and proteins, formats such as the Hierarchical Editing Language for Macromolecules (HELM) (see http://www.pistoiaalliance.org/projects/active-projects/hierarchical-editing-language-for-macromolecules-helm/) can be used. It should also be noted that the molfile format, which is not indicated below, may be the preferred format for transmitting structural information on small peptidic molecules. In Figure C.1, a detailed overview of the Protein Substance information is provided.

C.2 Scope

This document provides guidance to define elements that describe mandatory and conditional requirements/fields for peptides and proteins in order to generate ISO 11238 Substance Identifiers with

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respect to ISO 11238 and ISO/TS 19844 by providing examples of substances belonging to the class described above.

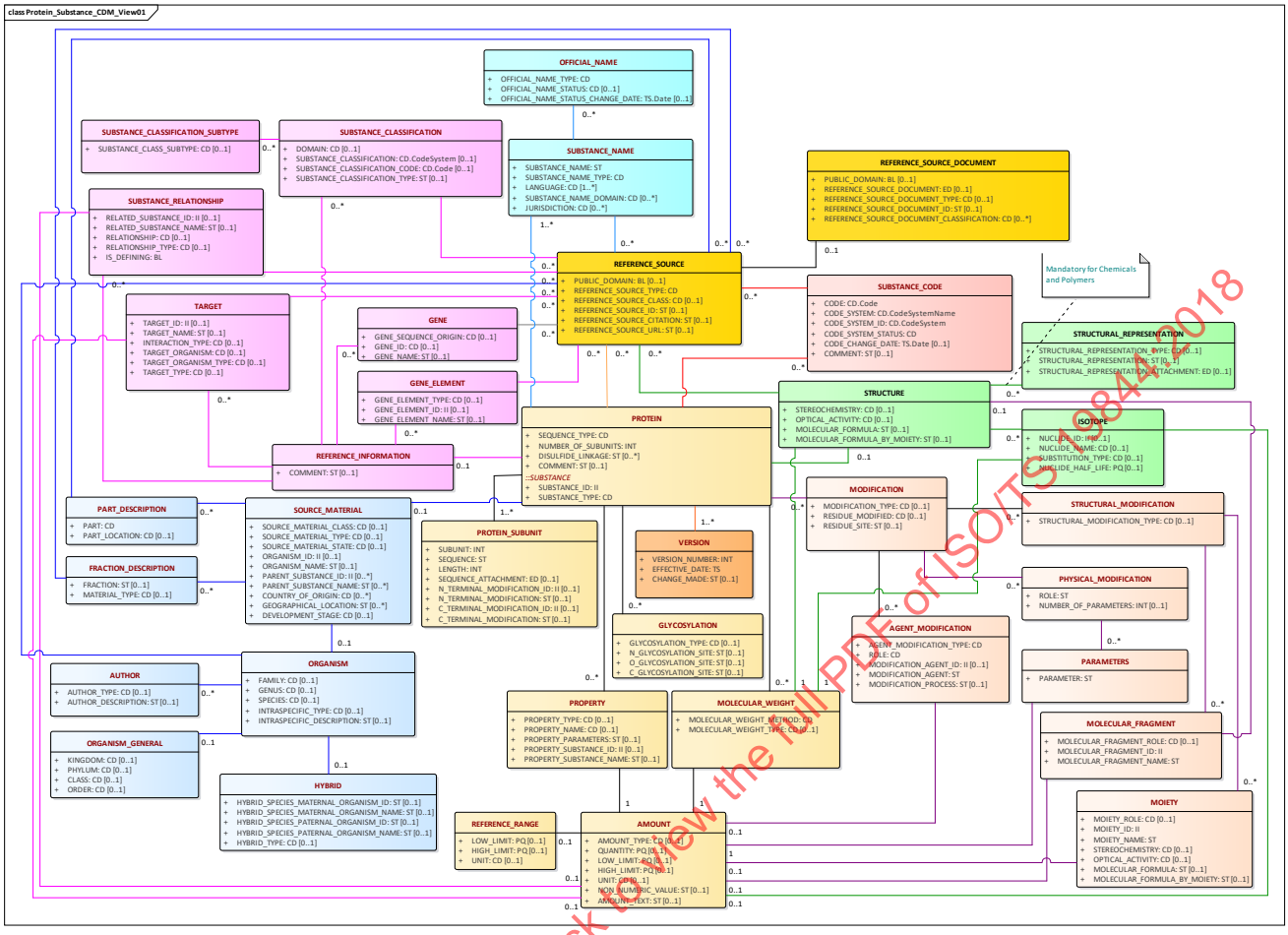


Figure C.1 — Detail overview of Protein Substance information

C.3 Terms and definitions

For the purposes of this document, both the terms and definitions given in ISO 11238 and the following apply.

C.3.1
protein substance

type of substance with a defined sequence of alpha-amino-acids connected through peptide bonds

Note 1 to entry: A protein consists of one or more chains with a length of more than 40 amino acids. A peptide is defined as a linear sequence consisting of 2 to 40 amino acid residues.

Note 2 to entry: Synthetic peptides and proteins with defined sequences, recombinant proteins and highly purified proteins extracted from biological matrices are described as protein substances. Sites of glycosylation, disulfide linkages and glycosylation type (e.g. fungal, plant, anthropoid, avian mammalian, human) are defining elements of protein substances, when known. A graphical molecular structure is also included in the definition of all peptides of 40 amino acid residues or less.

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Note 3 to entry: The absolute configuration at the a-carbon atom of the a-amino acids is designated by the prefixed small capital letter D or L to indicate a formal relationship to D- or L-serine and thus to D- or L-glyceraldehyde. The prefix 4 (Greek xi) indicates unknown configuration [13].

C.4 Peptide Substances

C.4.1 Example: Vasopressin

Vasopressin is a peptide hormone that causes the retention of water and vasoconstriction. In the US vasopressin has a USP monograph; there does not appear to be a monograph in either the Ph.Eur. or JP.

The elements needed to describe the substance will be presented in a tabular format.

Table C.1 — Protein Substance: Vasopressin

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	BDTDG7856V (Artificial ID)	II	
Substance Type	Protein	CD	
Element Group: Substance Name			
Substance Name	Vasopressin	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Susbstance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP, monograph 2017	ST	

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Element Name	Value	Data Format	Note #
Element Group: Substance Name (Repeat)			
Substance Name	Argipressin	ST	
Substance Name Type	Other Name (represents a synonym)	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Martindale	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Martindale: The complete Drug Reference, monograph Argipressin, last modification: March 8th, 2016	ST	
Reference Source URL	https://www.medicinescomplete.com/mc/martindale/current/ms-5948-j.htm#m5949-z	ST	1)
Element Group: Substance Name (Repeat)			
Substance Name	Vasopressin, 8-L-arginine-	ST	
Substance Name Type	Other Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	
Element Group: Substance Name (Repeat)			
Substance Name	1,2-Dithia-5,8,11,14,17-pentaazacycloeicosane-10-propionamide, 19-amino-13-benzyl-7-(carbamoylmethyl)-4-[2-[[1-[(carbamoylmethyl)carbamoyl]-4-guanidinobutyl]carbamoyl]-1-pyrrolidinylcarbonyl]-16-p-hydroxybenzyl-6,9,12,15,18-pentaoxo-	ST	
Substance Name Type	Systematic	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	

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Element Name	Value	Data Format	Note #
Element Group: Substance Code			
Code	113-79-1 (11000-17-2)	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	Y490706MFD	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Reference Information			
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	H01BA01	CD.Code	
Substance Classification Type	Vasopressin	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=H01BA01	ST	
Element Group: Structure			
Stereochemistry	Absolute	CD	
Optical Activity	(-)	CD	
Molecular Formula	$C_{46}H_{65}N_{15}O_{12}S_2$	ST	2)

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Element Name	Value	Data Format	Note #
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	3)
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	1 084,24	PQ	
Unit	g/mol	CD	
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment	See image below.	ED	

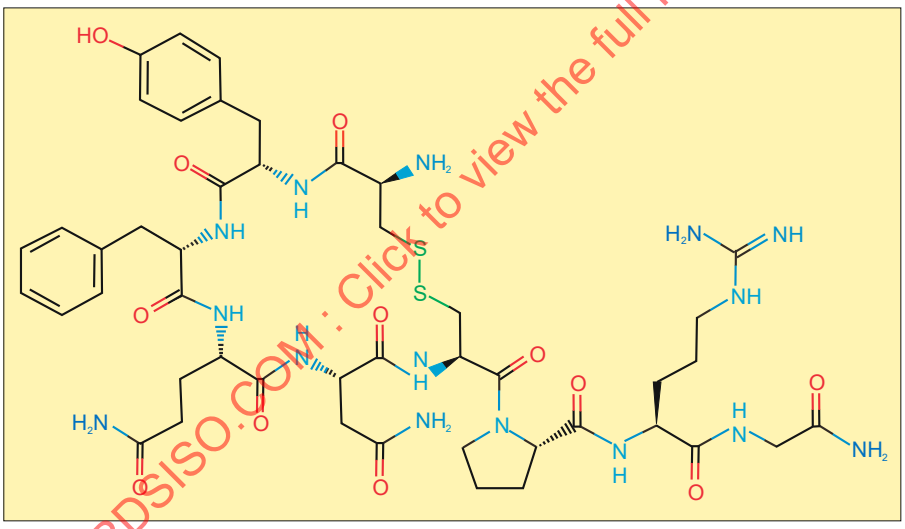


Figure C.2 — Structural representation of Vasopressin

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Element Name	Value	Data Format	Note #
Element Group: Structural Representation (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation	InChI=1S/C46H65N13O12S2/c47-17-5-4-9-29(40(65)52-22-38(51)63)54-45(70)35-10-6-18-59(35)46(71)34-24-73-72-23-28(48)39(64)55-31(20-26-11-13-27(60)14-12-26)43(68)56-32(19-25-7-2-1-3-8-25)42(67)53-30(15-16-36(49)61)41(66)57-33(21-37(50)62)44(69)58-34/h1-3,7-8,11-14,28-35,60H,4-6,9-10,15-24,47-48H2,(H2,49,61)(H2,50,62)(H2,51,63)(H,52,65)(H,53,67)(H,54,70)(H,55,64)(H,56,68)(H,57,66)(H,58,69)/t28-,29-,30-,31-,32+,33-,34-,35-/m0/s1	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Web	CD	
Reference Source URL	http://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:34543	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	SMILES	CD	
Structural Representation	c1ccc(cc1)C[C@@H]2C(=O)N[C@H](C(=O)N[C@H](C(=O)N[C@@H](CSSC[C@@H](C(=O)N[C@H](C(=O)N2)Cc3ccc(cc3)O)N)C(=O)N4CCC[C@H]4C(=O)N[C@@H](CCCCN)C(=O)NCC(=O)N)CC(=O)N)CCC(=O)N	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Web	CD	
Reference Source URL	http://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:34543	ST	
Element Group: Gene (Not applicable)			
Element Group: Protein			
Sequence Type	Complete	CD	
Number of Subunits	1	INT	
Disulfide Linkage	1_1-1_6	ST	4)

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Element Name	Value	Data Format	Note #
Element Group: Protein Subunit			
Subunit	1	INT	
Sequence	CYFQNCPRG	ST	
Length	9	INT	
C-Terminal Modification	Glycine	ST	
C-Terminal Modification ID	GLYU897654 (Artifical ID); [TE7660XO1C (UNII)]	II	
Element Group: Protein Subunit; C-terminal modification of Glycine shall be captured as a modification within the Structural Modification group			
Element Group: Modification			
Modification Type	Structural	CD	
Residue Modified	Glycine	CD	
Residue Site	1_9	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Molecular Fragment Role	C-Terminal Modification	CD	
Molecular Fragment ID	4JDT453NWO (UNII)	II	
Molecular Fragment Name	Glycinamide	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Amount Text	Complete	ST	

NOTE 1 This is a Subscription database.

NOTE 2 The molecular formula, as defined in 5.7.3 is to be specified in accordance with the Hill system. For a salt/hydrate the molecular formula of the base or the acid and the salt/hydrate part are separated by a dot per moiety, e.g. Desmopressin Monoacetate Trihydrate: Molecular formula by moiety (see 5.7.4): $C_{46}H_{64}N_{14}O_{12}S_2.C_2H_4O_2.3H_2O$ and by Molecular formula (see 5.7.3), following the Hill system: $C_{48}H_{74}N_{14}O_{17}S_2$.

NOTE 3 The molecular weight was implied as part of the Chemical Substance class in ISO 11238.

NOTE 4 This indicates there is a disulfide bond between residues 1 and 6; each subunit is numbered even if there is only one.

C.4.2 Example IIIb: Desmopressin

Desmopressin is a synthetic derivative of Vasopressin, the term is both an INN and BAN (British Approved Name) and a USAN name.

Table C.2 — Desmopressin

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Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	HJTFH3452D (Artificial ID)	II	
Substance Type	Protein	CD	
Element Group: Substance Name			
Substance Name	Desmopressin	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Recommended INN List	CD	
Reference Source Class	Official Name Source	CD	
Reference Source ID	040 (INN List, Artificial ID)	ST	
Reference Source Citation	INN List 33	ST	
Reference Source URL	https://mednet-communities.net/inn/db/media/docs/p-innlist33.pdf	ST	
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Journal	CD	
Element Group: Reference Source (Repeat)			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur. Monograph: 07/2009:0712	ST	
Reference Source URL	http://online6.edqm.eu/ep806/	ST	1)
Element Group: Substance Name (Repeat)			
Substance Name	Glycinamide, N-(3-mercapto-1-oxopropyl)-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-D-arginyl-, cyclic (1.fwdarw.5)-disulfide	ST	

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Element Name	Value	Data Format	Note #
Substance Name Type	Systematic Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	
Element Group: Substance Name (Repeat)			
Substance Name	1-{[(4R,7S,10S,13S,16S)- 7- (2-amino-2-oxoethyl)- 10- (3-amino-3-oxopropyl)- 13-benzyl-16- (4-hydroxybenzyl) 6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentaazacycloicosan-4-yl]carbonyl}-L-prolyl-D-arginylglycinamide	ST	
Substance Name Type	Systematic Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Chemspider	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://www.chemspider.com/Chemical-Structure.10481973.html	ST	
Element Group: Substance Name (Repeat)			
Substance Name	(3-Sulfanylpropanoyl)-l-tyrosyl-l-phenylalanyl-l-glutaminyl-l-asparaginyl-l-cysteinyl-l-prolyl-d-arginylglycinamide cyclic (1→6)-disulfide.	ST	
Substance Name Type	Systematic Name	CD	
Language	en	CD	

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Element Name	Value	Data Format	Note #
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur. monograph: 07/2009:0712	ST	
Reference Source URL	http://online6.edqm.eu/ep806/	ST	1)
Element Group: Substance Code			
Code	16679-58-6	CD.Code	
Code System	CAS Registry	CD.Code SystemName	
Code System ID	0049	CD.Code System	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	ENR1LLB0FP	CD.Code	
Code System	FDA GSRS (UNII)	CD.Code SystemName	
Code System ID	0050	CD.Code System	
Code System Status	Active	CD	
Element Group: Reference Information			
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.Code System	
Substance Classification Code	H01BA02	CD.Code	
Substance Classification Type	Desmopressin	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Public Database	CD	

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Element Name	Value	Data Format	Note #
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=H01BA02	ST	
Element Group: Structure			
Stereochemistry	Absolute	CD	
Optical Activity	(-)	CD	
Molecular Formula	$C_{46}H_{64}N_{14}O_{12}S_2$	ST	
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment	See image below	ED	

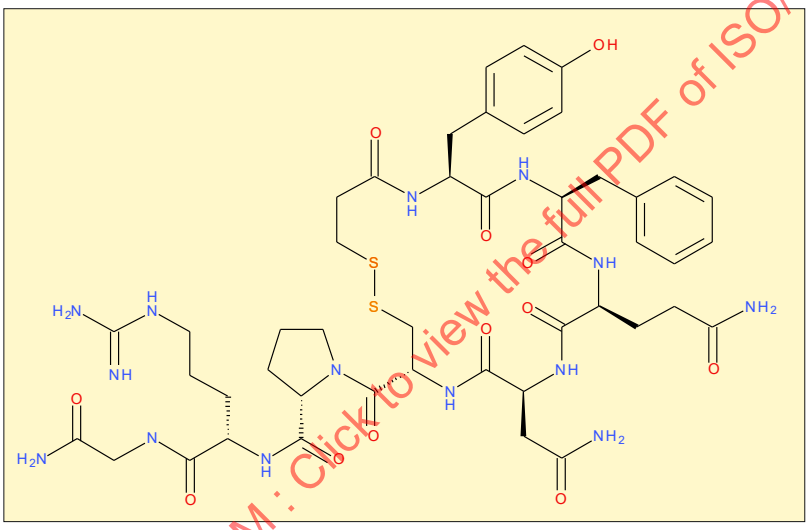


Figure C.3 — Structural representation of Desmopressin

Element Group: Structural Representation (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation	InChI=1S/C46H64N14O12S2/c47-35(62)15-14-29-40(67)58-32(22-36(48)63)43(70)59-33(45(72)60-18-5-9-34(60)44(71)56-28(8-4-17-52-46(50)51)39(66)53-23-37(49)64)24-74-73-19-16-38(65)54-30(21-26-10-12-27(61)13-11-26)41(68)57-31(42(69)55-29)20-25-6-2-1-3-7-25/h1-3,6-7,10-13,28-34,61H,4-5,8-9,14 24H2,(H2,47,62)(H2,48,63)(H2,49,64)(H,53,66)(H,54,65)(H,55,69)(H,56,71)(H,57,68)(H,58,67)(H,59,70)(H4,50,51,52)/t28-,29-,30-,31-,32-,33-,34-/m0/s1	ST	

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Element Name	Value	Data Format	Note #
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Web	CD	
Reference Source URL	http://www.chemspider.com/Chemical-Structure.10481973.html	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	SMILES	CD	
Structural Representation	C1C[C@H](N(C1)C(=O)[C@@H]2CSSCCC(=O)N[C@H](C(=O)N[C@H](C(=O)N[C@H](C(=O)N[C@H](C(=O)N2)CC(=O)N)CCC(=O)N)CC3=CC=CC=C3)CC4=CC=C(C=C4)O)C(=O)N[C@@H](CCCNC(=N)N)C(=O)NCC(=O)N	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Web	CD	
Reference Source URL	http://www.chemspider.com/Chemical-Structure.10481973.html	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	1 069,22	PQ	
Unit	g/mol	CD	
Element Group: Gene (Not applicable)			
Element Group: Protein			
Sequence Type	Complete	CD	
Number of Subunits	1	INT	
Disulfide Linkage	1_1-1_6	ST	2)

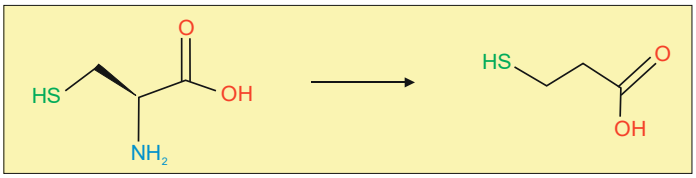
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Element Name	Value	Data Format	Note #
Element Group: Protein Subunit			
Subunit	1	INT	
Sequence	CYFQNCPrG (D-Arginine is represented by the smaller letter r)	ST	
Length	9	INT	
N-Terminal Modification	Cysteine	ST	
N-Terminal Modification ID	CYSTE67542 (Artificial ID); [K848JZ4886 (UNII)]	II	
C-Terminal Modification	Glycine	ST	
C-Terminal Modification ID	GLYU897654 (Artifical ID); [TE7660XO1C (UNII)]	II	
Element Group: Protein Subunit; There are two structural modifications; the N-terminal replacement of cysteine and the C-terminal modification of Glycine shall be captured as a modification within the Structural Modification group. In Case of N-Terminal and/or C-Terminal Modification of a Protein subunit the Modification class will be mandatory.			
Element Group: Modification (N-Terminal Modification)			
Modification Type	Structural Modification	CD	
Residue Modified	Cysteine	CD	
Residue Site	1_1	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Molecular Fragment Role	N-Terminal Modification	CD	
Molecular Fragment ID	MERC90876R (Artificial ID); [B03TJ3QU9M (UNII)]	II	
Molecular Fragment Name	3-Mercaptopropionic acid (The amino acid is replaced by thiol acid)	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Amount Text	Complete	ST	

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Element Name	Value	Data Format	Note #
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure C.4 — N-Terminal modification of Cysteine replaced by 3-Mercaptopropionic acid**	ED	
Element Group: Modification (Repeat) (C-Terminal Modification)			
Modification Type	Structural Modification	CD	
Residue Modified	Glycine	CD	
Residue Site	1_9	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Molecular Fragment Role	C-Terminal Modification	CD	
Molecular Fragment ID	GLYINAM786 (Artificial ID); [4JDT453NWO (UNII)]	II	
Molecular Fragment Name	Glycinamide	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Amount Text	Complete	ST	

NOTE 1 This is a Subscription database.

NOTE 2 Disulfide linkage is still between residue 1 and 6; cysteine is replaced with a structural modification capable of forming a disulfide linkage

C.4.3 Example: Desmopressin Acetate

In the US Desmopressin Acetate is defined as a monoacetate, trihydrate. In Japan, the English term Desmopressin Acetate Hydrate is also defined as a monoacetate, trihydrate.

Table C.3 — Desmopressin Acetate (USAN); Desmopressin Acetate Hydrate (JAN)

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	GFTDSR765T (Artificial ID)	II	

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Element Name	Value	Data Format	Note #
Substance Type	Protein	CD	
Element Group: Substance Name			
Substance Name	Desmopressin Acetate	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	US, EU	CD	
Element Group: Official Name			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP monograph	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Desmopressin Monoacetate Trihydrate	ST	
Substance Name Type	Other Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP monograph	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Desmopressin Acetate Hydrate	ST	
Substance Name Type	Official Name	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	JAN	CD	1)
Official Name Status	Current	CD	
Element Group: Reference Source			

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Element Name	Value	Data Format	Note #
Public Domain	Yes	BL	
Reference Source Type	JP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	JP monograph	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Desmopressin Monoacetate Trihydrate	ST	
Substance Name Type	Other Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	
Element Group: Substance Name (Repeat)			
Substance Name	Glycinamide, N-(3-mercapto-1-oxopropyl)-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-D-arginyl-, cyclic (1.fwdarw.5)-disulfide, acetate, hydrate (1:1:3)	ST	
Substance Name Type	Systematic Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	
Element Group: Substance Name (Repeat)			
Substance Name	1-{[(4R,7S,10S,13S,16S)-7-(2-amino-2-oxoethyl)-10-(3-amino-3-oxopropyl)-13-benzyl-16-(4-hydroxybenzyl)-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentaazacycloicosan-4-yl]carbonyl}-L-prolyl-D-arginylglycinamide acetate—water (1/3)	ST	
Substance Name Type	Systematic Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	ChEBI	CD	
Reference Source Class	Public Database	CD	

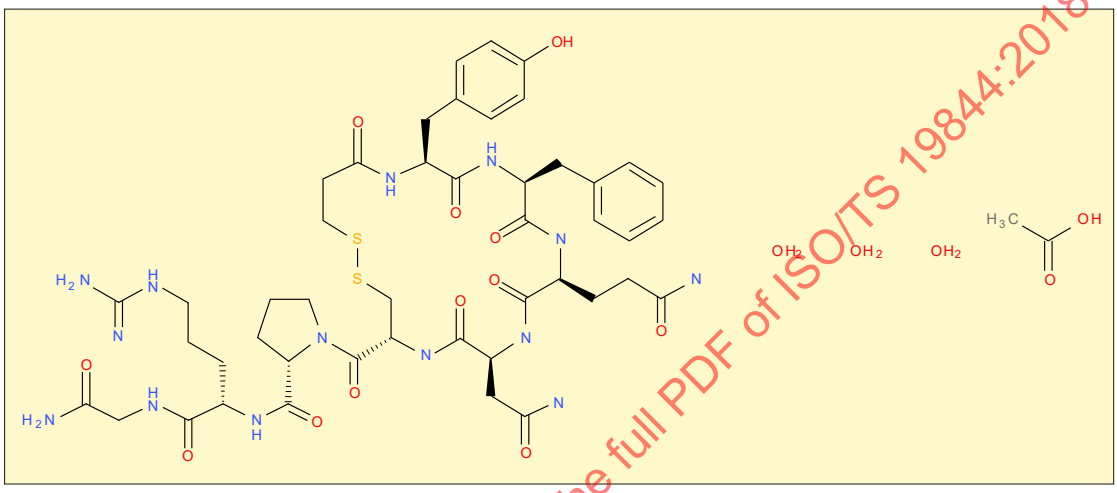
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Element Name	Value	Data Format	Note #
Reference Source URL	https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:59728	ST	
Element Group: Substance Code			
Code	16679-58-6	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	XB13HYU18U	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Reference Information			
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	H01BA02	CD.Code	
Substance Classification Type	Desmopressin	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Literature	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=H01BA02	ST	
Element Group: Structure			
Stereochemistry	Absolute	CD	
Optical Activity	(-)	CD	
Molecular Formula	$C_{48}H_{74}N_{14}O_{17}S_2$	ST	
Molecular Formula by Moiety	$C_{46}H_{64}N_{14}O_{12}S_2.C_2H_4O_2.3H_2O$	ST	

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Element Name	Value	Data Format	Note #
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment	In image below: The molecular structure has to provide a complete description of Desmopressin acetate hydrate moieties	ED	
 **Figure C.5 — Structural representation of Desmopressin Monoacetate trihydrate**			
The substance shall be defined using the sequence representation shown above along with two additional structural modifications for the salt and solvate			
Element Group: Structural Representation (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation	InChI=1S/C46H64N14O12S2.C2H4O2.3H2O/c47-35(62)15-14-29-40(67)58-32(22-36(48)63)43(70)59-33(45(72)60-18-5-9-34(60)44(71)56-28(8-4-17-52-46(50)51)39(66)53-23-37(49)64)24-74-73-19-16-38(65)54-30(21-26-10-12-27(61)13-11-26)41(68)57-31(42(69)55-29)20-25-6-2-1-3-7-25;1-2(3)4;;;/h1-3,6-7,10-13,28-34,61H,4-5,8-9,14-24H2,(H2,47,62)(H2,48,63)(H2,49,64)(H,53,66)(H,54,65)(H,55,69)(H,56,71)(H,57,68)(H,58,67)(H,59,70)(H4,50,51,52);1H3,(H,3,4);3*1H2/t28-,29-,30-,31-,32-,33-,34-;;;;/m0..../s1	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Web	CD	

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Element Name	Value	Data Format	Note #
Reference Source URL	http://www.chemspider.com/Chemical-Structure.19969319.html	ST	
Element Group: Structural Representation			
Structural Representation Type	SMILES	CD	
Structural Representation	O=C([C@H]1N(C([C@@H](NC([C@H](CC(N)=O)NC([C@H](CCC(N)=O)NC([C@H](CC2=CC=CC=C2)NC([C@H](CC3=CC=C(O)C=C3)N4)=O)=O)=O)=O)CSSCCC4=O)=O)CCC1)N[C@H](CCCNC(N)=N)C(NCC(N)=O)=O.CC(O)=O.[H]O[H].[H]O[H].[H]O[H]	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Web	CD	
Reference Source URL	http://www.chemspider.com/Chemical-Structure.19969319.htm	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	1 183,24	PQ	
Unit	g/mol	CD	
Element Group: Modification			
Modification Type	Structural modification	CD	
Element Group: Moiety			**2)**
Moiety Role	Salt molecule	CD	
Moiety ID	ACETA56341 (Artificial ID); [Q40Q9N063P (UNII)	II	
Moiety Name	Acetic Acid	ST	
Stereochemistry	Achiral	CD	
Molecular Formula	$C_2H_4O_2$	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	1	PQ	

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Element Name	Value	Data Format	Note #
Unit	{mol/mol}	CD	
Amount Text	Mole Ratio to Parent Substance	PQ	
Element Group: Moiety (Repeat)			
Moiety Role	Hydrate	CD	
Moiety ID	WATER89765 Artificial ID; 059QF0KO0R (UNII)	II	
Moiety Name	Water	ST	
Stereochemistry	Achiral	CD	
Molecular Formula	H_2O	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	3	PQ	
Unit	{mol/mol}	CD	
Amount Text	Mole Ratio to Parent Substance	PQ	
Element Group: Moiety (Repeat)			
Moiety Role	Parent	CD	
Moiety ID	HJTFH3452D (Artificial ID) [ENR1LLB0Fp (UNII)]	II	
Moiety Name	Desmopressin	ST	
Stereochemistry	Absolute	CD	
Optical Activity	(-)	CD	
Molecular Formula	$C_{46}H_{64}N_{14}O_{12}S_2$.	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	1	PQ	
Unit	{mol/mol}	CD	
Amount Text	Mole Ratio to Salt Hydrate	PQ	
Element Group: Reference Information			
Element Group: Substance Relationship			
Related Substance ID	HJTFH3452D (Artificial ID); [1J444QC288 (UNII)]	II	
Related Substance Name	Desmopressin	ST	
Relationship	Parent	CD	
Relationship Type	Ionic	CD	
Is Defining	Yes	BL	

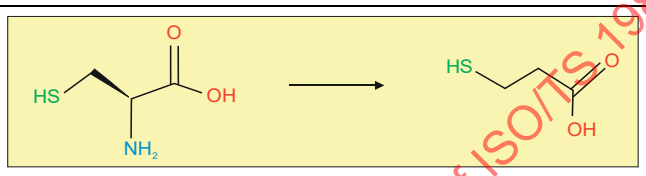
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Element Name	Value	Data Format	Note #
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	90,4	PQ	
Unit	% {w/w}	CD	
Amount Text	Equivalence Factor: 0,904 (Weight per cent to salt hydrate)	ST	
Element Group: Gene (Not applicable)			
Element Group: Protein			
Sequence Type	Complete	CD	
Number of Subunits	1	INT	
Disulfide Linkage	1_1-1_6	ST	3)
Element Group: Protein Subunit			
Subunit	1	INT	
Sequence	CYFQNCPrG (D-Arginine is represented by the smaller letter r)	ST	
Length	9	INT	
Element Group: Protein Subunit; There are two structural modifications; the N-terminal replacement of Cysteine and the C-terminal modification of Glycine shall be captured as a modification within the Structural Modification group. In case of N-Terminal and/or C-Terminal Modification of a Protein subunit the Modification class will be mandatory.			
N-Terminal Modification	Cysteine	ST	
N-Terminal Modification ID	CYST667542 (Artificial ID); [K848JZ4886 (UNII)]	II	
C-Terminal Modification	Glycine	ST	
C-Terminal Modification ID	GLYU897654 (Artifical ID); [TE7660XO1C (UNII)]	II	
Element Group: Modification (N-Terminal modification)			
Modification Type	Structural modification	CD	
Residue Modified	Cysteine	CD	
Residue Site	1_1	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Molecular Fragment Role	N-Terminal Modification	CD	
Molecular Fragment ID	MERC90876R (Artificial ID); [B03TJ3QU9M (UNII)]	II	

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Element Name	Value	Data Format	Note #
Molecular Fragment Name	3-Mercaptopropionic acid (The amino acid is replaced by thiol acid)	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Amount Text	Complete	ST	
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure C.6 — N-Terminal modification of Cysteine replaced by 3-Mercaptopropionic acid**	ED	
Element Group: Modification (Repeat) (C-Terminal Modification)			
Modification Type	Structural modification	CD	
Residue Modified	Glycine	CD	
Residue Site	1_9	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Molecular Fragment Role	C-Terminal Modification	CD	
Molecular Fragment ID	GLYINAM786 (Artificial ID); [4JDT453NWO (UNII)]	II	
Molecular Fragment Name	Glycinamide	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Amount Text	Complete	ST	

NOTE 1 JAN (Japanese Accepted Name); JP (Japanese Pharmacopoeia).

NOTE 2 For a protein substance all other molecular entities that are not covalently attached to the protein are captured as a moiety.

NOTE 3 Disulfide linkage is still between residue 1 and 6; cysteine is replaced with a structural modification capable of forming a disulfide linkage.

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C.4.4 Calcitonin Salmon

Calcitonin Salmon is a peptide hormone that lowers the plasma concentration of calcium by diminishing the rate of bone resorption. It can be made both synthetically or using recombinant DNA technology.

Table C.4 — Protein Substance: Calcitonin Salmon

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	CHJT8360JS (Artificial ID)	II	
Substance Type	Protein	CD	
Element Group: Substance Name			
Substance Name	Calcitonin Salmon	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	US	CD	
Element Group: Official Name			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP monograph	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Calcitonin (Salmon)	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	

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Element Name	Value	Data Format	Note #
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur. monograph: 01/2008:0471	ST	
Reference Source URL	http://online6.edqm.eu/ep806/	ST	1)
Element Group: Substance Name (Repeat)			
Substance Name	Calcitonin (Salmon)	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Recommended INN List	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	INN WHO Drug Information, Vol. 13, No. 1, 1999, Recommended INN list 41	ST	
Reference Source URL	http://whqlibdoc.who.int/druginfo/INN_1999_list41.pdf	ST	
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Journal	CD	
Element Group: Substance Name (Repeat)			
Substance Name	Salmon calcitonin	ST	
Substance Name Type	Other Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	

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Element Name	Value	Data Format	Note #
Element Group: Substance Name (Repeat)			
Substance Name	L-Prolinamide, L-cysteinyl-L-seryl-L-asparaginyl-L-leucyl-L-seryl-L-threonyl-L-cysteinyl-L-valyl-L-leucylglycyl-L-lysyl-L-leucyl-L-seryl-L-glutaminyl-L-.alpha.-glutamyl-L-leucyl-L-histidyl-L-lysyl-L-leucyl-L-glutaminyl-L-threonyl-L-tyrosyl-L-prolyl-L-arginyl-L-threonyl-L-asparaginyl-L-threonylglycyl-L-serylglycyl-L-threonyl-, cyclic (1.fwdarw.7)-disulfide	ST	
Substance Name Type	Systematic Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	
Element Group: Substance Code			
Code	47931-85-1	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	7SFC6U2VI5	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Reference Information			
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	H05BA01	CD.Code	

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Element Name	Value	Data Format	Note #
Substance Classification Type	Calcitonin (salmon synthetic)	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Web	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=H05BA01	ST	
Element Group: Structure			
Stereochemistry	Absolute	CD	
Optical Activity	(-)	CD	
Molecular Formula	$C_{145}H_{240}N_{44}O_{48}S_2$	ST	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	See image below.	ED	

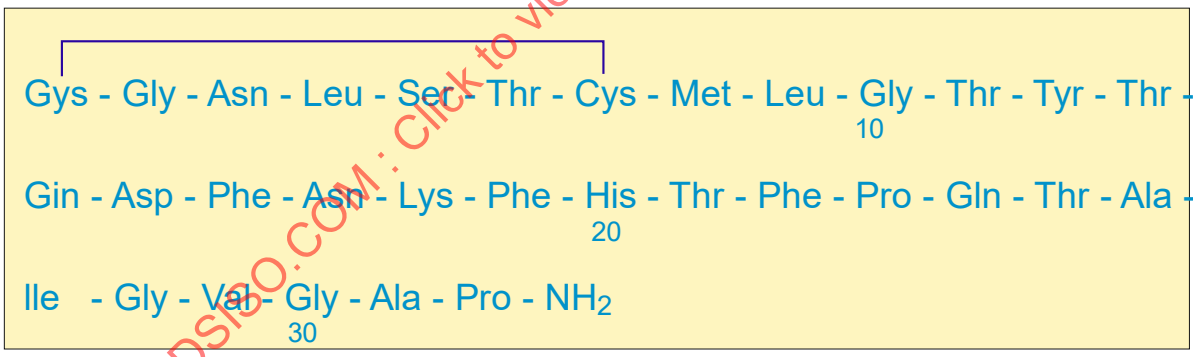


Figure C.7 — Structural representation of Calcitonin salmon

Element Group: Structural Representation(Repeat)			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	See image below	ED	

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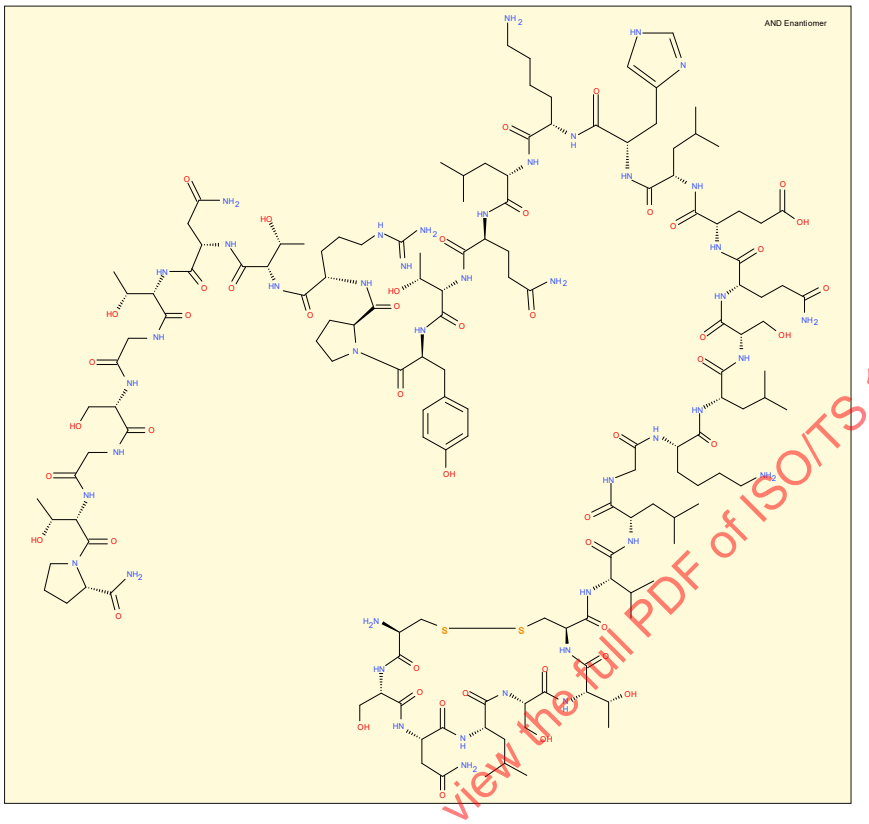
Element Name	Value	Data Format	Note #
			

Figure C.8 — Structural representation of Calcitonin salmon

Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Chemical Book	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://www.chemicalbook.com/ChemicalProductProperty_EN_CB2127316.htm	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation	See below	ST	

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Element Name	Value	Data Format	Note #
InChI=1S/C145H240N44O48S2/c1-65(2)45-86(175-139(232)110(70(11)12)183-136(229)99-63-239-238-62-79(148)117(210)178-96(59-191)134(227)174-92(52-104(151)202)131(224)172-90(49-69(9)10)129(222)180-98(61-193)135(228)187-114(74(16)197)142(235)181-99)118(211)158-55-106(204)162-80(25-18-20-40-146)120(213)169-89(48-68(7)8)128(221)179-97(60-192)133(226)167-83(34-37-102(149)200)122(215)165-85(36-39-109(207)208)123(216)171-88(47-67(5)6)127(220)173-91(51-77-54-156-64-161-77)130(223)164-81(26-19-21-41-147)121(214)170-87(46-66(3)4)126(219)166-84(35-38-103(150)201)125(218)186-113(73(15)196)141(234)177-94(50-76-30-32-78(199)33-31-76)143(236)189-44-24-29-101(189)137(230)168-82(27-22-42-157-145(154)155)124(217)185-112(72(14)195)140(233)176-93(53-105(152)203)132(225)184-111(71(13)194)138(231)160-56-107(205)163-95(58-190)119(212)159-57-108(206)182-115(75(17)198)144(237)188-43-23-28-100(188)116(153)209/h30-33,54,64-75,79-101,110-115,190-199H,18-29,34-53,55-63,146-148H2,1-17H3,(H2,149,200)(H2,150,201)(H2,151,202)(H2,152,203)(H2,153,209)(H,156,161)(H,158,211)(H,159,212)(H,160,231)(H,162,204)(H,163,205)(H,164,223)(H,165,215)(H,166,219)(H,167,226)(H,168,230)(H,169,213)(H,170,214)(H,171,216)(H,172,224)(H,173,220)(H,174,227)(H,175,232)(H,176,233)(H,177,234)(H,178,210)(H,179,221)(H,180,222)(H,181,235)(H,182,206)(H,183,229)(H,184,225)(H,185,217)(H,186,218)(H,187,228)(H,207,208)(H4,154,155,157)		
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	PubChem	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://pubchem.ncbi.nlm.nih.gov/compound/Salmon_calcitonin#section=Computed-Descriptors;	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	SMILES	CD	
Structural Representation	CC(C)CC1C(=O)NC(C(=O)NC(C(=O)NC(CSSCC(C(=O)NC(C(=O)NC(C(=O)N1)CC(=O)N)CO)N)C(=O)NC(C(C)C)C(=O)NC(CC(C)C)C(=O)NCC(=O)NC(CCCCN)C(=O)NC(CC(C)C)C(=O)NC(CO)C(=O)NC(CCC(=O)N)C(=O)NC(CCC(=O)O)C(=O)NC(CC(C)C)C(=O)NC(CC2=CN=CN2)C(=O)NC(CCCCN)C(=O)NC(CC(C)C)C(=O)NC(CCC(=O)N)C(=O)NC(C(C)O)C(=O)NC(CC3=CC=C(C=C3)O)C(=O)N4CCCC4C(=O)NC(CCCNC(=N)N)C(=O)NC(C(C)O)C(=O)NC(CC(=O)N)C(=O)NC(C(C)O)C(=O)NCC(=O)NC(CO)C(=O)NCC(=O)NC(C(C)O)C(=O)N5CCCC5C(=O)N)C(C)O)CO	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	PubChem	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://pubchem.ncbi.nlm.nih.gov/compound/Salmon_calcitonin#section=Canonical-SMILES	ST	
Element Group: Molecular Weight			

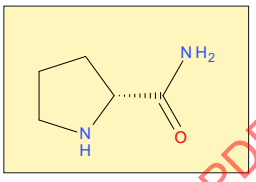
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Element Name	Value	Data Format	Note #
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	3431.85	PQ	
Unit	g/mol	CD	
Element Group: Gene (Not applicable)			
Element Group: Protein			
Sequence Type	Complete	CD	
Number of Subunits	1	INT	
Disulfide Linkage	1_1-1_7	ST	
Element Group: Protein Subunit			
Subunit	1	INT	
Sequence	CSNLSTCVLGKLSQELHKLQTYPRTNTGSGTP	ST	
Length	32	INT	
Element Group: Protein Subunit; There is one structural modification: The C-terminal modification of Proline shall be captured as a modification within the Structural Modification group			
C-Terminal Modification	Proline	ST	
C-Terminal Modification ID	PROLI56432 (Artificial ID) ; [9DLQ4CIU6V (UNII)]	II	
Element Group: Modification			
Modification Type	Structural Modification	CD	
Residue Modified	Proline	CD	
Residue Site	1_32	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino acid modification	CD	

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Element Name	Value	Data Format	Note #
Element Group: Molecular Fragment			
Molecular Fragment Role	C-Terminal Modification	CD	
Molecular Fragment ID	PROLI56432 (Artificial ID) ; [VD6PQK9DHG (UNII)]	II	
Molecular Fragment Name	Prolinamide	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Amount Text	Complete	ST	
Element Group: Structural Representation			
Structural Representation	Full	ST	
Structural Representation Attachment	 **Figure C.9 — Structural representation of Prolinamide**	ED	
NOTE This is a Subscription database.			

C.4.5 Example: Human Insulin

Human insulin is a polypeptide hormone consisting of two peptide chains or subunits that modulate the amount of carbohydrates in blood.

Table C.5 — Protein Substance: Human Insulin

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	HUI53427HT (Artificial ID)	II	
Substance Type	Protein	CD	
Element Group: Substance Name			
Substance Name	Insulin Human	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	USP	CD	

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Element Name	Value	Data Format	Note #
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP monograph	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Insulin Human	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Recommended INN List	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	WHO Drug Information Vol, 37, No.6, 1983, Recommended INN List 23	ST	
Reference Source URL	http://www.who.int/medicines/publications/druginformation/innlists/RL23.pdf?ua=1	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Insulin Human	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	

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Element Name	Value	Data Format	Note #
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur. monograph, 01/2011:0838 corrected 8.6	ST	
Element Group: Structure			
Stereochemistry	Absolute	CD	
Optical Activity	(+/-)	CD	
Molecular Formula	$C_{257}H_{383}N_{65}O_{77}S_6$	ST	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	 **Figure C.10 — Structural representation of Human Insulin**	ED	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	5 807,57	PQ	
Unit	g/mol	CD	.

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Element Name	Value	Data Format	Note #
Element Group: Gene (Not applicable)			
Element Group: Protein			
Sequence Type	Complete	CD	
Number of Subunits	2	INT	
Disulfide Linkage	1_7-2_7; 1_19-2_20; 2_6-2_11	ST	1)
Element Group: Protein Subunit			
Subunit (B)	1	INT	
Sequence	FVNQHLCGSHLVEALYLVCGERGFFYTPKT	ST	
Length	30	INT	
Element Group: Protein Subunit (Repeat)			
Subunit (A)	2	INT	
Sequence	GIVEQCCTSICSLYQLENYCN	ST	
Length	21	INT	
NOTE Each disulfide linkage listed in a single field separated by semi-colons.			

C.5 Element Group Protein, Specified Substance Group 1

Human Insulin combines with a number of other substances and has several different physical forms. Three examples below illustrate the use of Substances, Specified substances and physical form to define Specified Substance Group 1.

The Element Group 'Characteristic Attribute' is envisioned to be allocated at the Specified Substance Group 1 information level for the description of characteristics of a substance e.g. polymorphic form, particle size or additional information of properties not described at the substance information level, see Figure 35.

C.5.1 Example: Insulin Human Zinc Suspension (Amorphous), taken from Ph.Eur./USP Monographs for Zinc Suspensions

The physical form is a data element that will be captured at the Specified Substance Group 1 level. Insulin Human and the zinc are both captured.

Table C.6 — Insulin Human Zinc Suspension (Amorphous)

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Element Name	Value	Data Format	Note #
Element Group: Protein, Specified Substance Group 1			
Specified Substance Group 1 ID	HJGTD875G1 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Insulin Human Zinc Injectable Suspension (Amorphous)	ST	1)
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	US, EU	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur. monograph: 01/2008:0835 corrected 6.0	ST	
Reference Source URL	http://online6.edqm.eu/ep806/	ST	2)
Element Group: Constituent			
Constituent Substance ID	HUI53427HT (Artificial ID) ; [1Y17CTI5SR (UNII)]	II	
Constituent Substance Name	Insulin Human	ST	
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	100	PQ	
Unit	Insulin Units	CD	

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Element Name	Value	Data Format	Note #
Element Group: Constituent (Repeat)			
Constituent Substance ID	ZINC98765I (Artificial ID); [13S1S8SF37 (UNII)]	II	
Constituent Substance Name	Zinc Cation	ST	
Language	En	CD	
Substance Role	Stabilising ion	CD	
Is Defining	Yes	BL	
Element Group: Amount (Zinc Cation)			
Amount Type	Average	CD	
Quantity	0,19	PQ	
Unit	mg/100 Insulin Units	CD	3)
Element Group: Reference Range			
Low Limit	0,12	PQ	
High Limit	0,25	PQ	
Unit	mg/100 Insulin Units	CD	3)
Element Group: Physical Form (Insulin human)			
Physical State	Solid	CD	
Physical Form Type	Amorphous Powder	CD	
Element Group: Characteristic Attribute (Insulin human, Amorphous)			
Attribute Type	Physical	CD	
Attribute Name	Particle Size	ST	
Attribute Substance ID	HU53427HT (Artificial ID) ; [1Y17CTI5SR (UNII)]	II	
Attribute Substance Name	Insulin Human	ST	
Is Defining	Yes	BL	

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Element Name	Value	Data Format	Note #
Element Group: Amount			
Amount Type	NMT	CD	
Quantity	2	PQ	
Unit	Micrometre	CD	
Amount Text	Dimension along any axis	ST	

NOTE 1 The **(Specified) Substance (Group 1) Name** is given "**Insulin Human Zinc Injectable Suspension (Amorphous)**" based on the Pharmacopoeial definition of Insulin zinc injectable suspension (amorphous). It is a sterile neutral *(amorphous)* suspension of *bovine, porcine or human* insulin, complexed with a suitable zinc salt, the insulin is in a form which is practically insoluble in water. The (Specified) Substance (Group 3) Name and Pharmacopoeial Grade-Name is discussed in C.5.3.

NOTE 2 This is a Subscription database.

NOTE 3 **100** Insulin Units (IU) are equivalent to 3.47 mg human insulin, to 3.45 of porcine insulin and to 3.42 mg of bovine insulin. [Reference: Ph.Eur. 01/2002: 0854, footnote [29]]. **This means that the amount of mg Zinc cation can be expressed by the definition of a Unit:mg/100 Insulin Units.**

C.5.2 Example: Insulin Human Zinc Suspension (Crystalline), taken from Ph.Eur./USP Monographs for Zinc Suspensions

Table C.7 — Insulin Human Zinc Suspension (Crystalline)

Element Name	Value	Data Format	Note #
Element Group: Protein, Specified Substance Group 1			
Specified Substance Group 1 ID	JFGER7453P (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Insulin Human Zinc Injectable Suspension (Crystalline)	ST	1)
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	

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Element Name	Value	Data Format	Note #
Reference Source Citation	Ph.Eur. monograph, 01/2008:0836 corrected 6.0	ST	
Reference Source URL	http://online6.edqm.eu/ep806/	ST	2)
Element Group: Constituent			
Constituent Substance ID	HUI53427HT (Artificial ID) ; [1Y17CTI5SR (UNII)]	II	
Constituent Substance Name	Insulin Human	ST	
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	100	PQ	
Unit	Insulin Units	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	ZINC98765I (Artificial ID);[13S1S8SF37 (UNII)]	II	
Constituent Substance Name	Zinc Cation	ST	
Language	en	CD	
Substance Role	Stabilising ion	CD	
Is Defining	Yes	BL	
Element Group: Amount (Zinc Cation)			
Amount Type	Average	CD	
Quantity	0,19	PQ	
Unit	mg/100 Insulin Units	CD	
Element Group: Reference Range			
Low Limit	0,12	PQ	
High Limit	0,25	PQ	
Unit	mg/100 Insulin Units	CD	

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Element Name	Value	Data Format	Note #
Element Group: Physical Form (Insulin human)			
Physical State	Solid	CD	
Physical Form Type	Crystalline	CD	
Element Group: Characteristic Attribute (Insulin human)			
Attribute Type	Physical	CD	
Attribute Name	Particle Size	ST	
Attribute Substance ID	HUI53427HT (Artificial ID) ; [1Y17CTI5SR (UNII)]	II	
Attribute Substance Name	Insulin Human	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	NMT	CD	
Quantity	20	PQ	
Unit	Micrometre	CD	
Amount Type	Dimension along any axis	CD	
Element Group: Reference Range			
Low Limit	10	PQ	
High Limit	40	PQ	
Unit	Micrometre	CD	

NOTE 1 The (**Specified**) **Substance** (**Group** 1) **Name** is given "**Insulin Human Zinc Injectable Suspension (Crystalline)**" based on the Pharmacopoeial definition of Insulin zinc injectable suspension (Crystalline). It is a sterile neutral *(crystalline)* suspension of *bovine, porcine or human* insulin, complexed with a suitable zinc salt; the insulin is in a form which is practically insoluble in water. The (Specified) Substance (Group 3) Name and Pharmacopoeial Grade-Name are discussed in example C.5.3.

NOTE 2 This is a Subscription database.

C.5.3 Example: Insulin Human Zinc Suspension taken from Ph.Eur./USP Monographs for Zinc Suspensions, including discussion for Specified Substance Group 3 information

This example discusses a mixture of Zinc Insulin, amorphous (30 IU/ml) and Zinc Insulin, crystalline (70 IU/ml). It is considered as a multi-substance material and therefore captured at the Specified Substance Group 1 Information level with two parent substances: Insulin Human Zinc Injectable Suspension (Crystalline) and Insulin Human Zinc Injectable Suspension (Amorphous). The Specified Substance Group 3 information model is provided in Figure 38.

Table C.8 — Insulin Human Zinc Suspension

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Element Name	Value	Data Format	Note #
Element Group: Protein, Specified Substance Group 1			
Specified Substance Group 1 ID	HJGYD4532M (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Insulin Human Zinc Injectable Suspension	ST	1)
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur. monograph: 01/2008:0837 corrected 6.0	ST	
Reference Source URL	http://online6.edqm.eu/ep806/	ST	2)
Element Group: Official Name (Repeat)			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP monograph	ST	
Element Group: Constituent			
Constituent Substance ID	JFGER7453P (Artificial ID)	II	3)
Constituent Substance Name	Insulin Human Zinc Injectable Suspension (Crystalline)	ST	
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	

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Element Name	Value	Data Format	Note #
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	70	PQ	
Unit	% {w/w}	CD	
Amount Text	Weight Per cent of Total Insulin	ST	
Element Group: Constituent (Repeat)			
Constituent Substance ID	HJGTD875G1 (Artificial ID)	II	3)
Constituent Substance Name	Insulin Human Zinc Injectable Suspension (Amorphous)	ST	
Language	en	CD	
Substance Role	Active Specified Substance	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	30	PQ	
Unit	% {w/w}	CD	
Amount Text	Weight Per cent of Total Insulin	ST	
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	KHJTYE563P (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Insulin Human Zinc Injectable Suspension-Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	HJGYD4532M (Artificial ID)	II	4)
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name	Insulin Zinc Injectable Suspension	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia: 01/2008:0837 corrected 6.0	ST	
Element Group: Specified Substance Group 3 (Repeat)			

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Element Name	Value	Data Format	Note #
Specified Substance Group 3 ID	ASTEY6794F (Artificial ID)	II	
Substance Name	Insulin Human Zinc Injectable Suspension USP	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	HJGYD4532M (Artificial ID)	II	4)
Element Group: Grade			
Grade Type	USP	CD	
Grade Name	Insulin Zinc Suspension	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP37-NF32 pg.3349	ST	

NOTE 1 The (**Specified**) **Substance** (**Group 1**) **Name** is given "**Insulin Human Zinc Injectable Suspension**" based on the Pharmacopoeial definition of Insulin zinc injectable suspension. It is a sterile neutral suspension of *bovine insulin and/or porcine insulin or of human insulin* with a suitable zinc salt; the insulin is in a form which is practically insoluble in water. Insulin zinc injectable suspension is produced by mixing insulin zinc injectable suspension (crystalline) and insulin zinc injectable suspension (amorphous) in a ratio of 7 to 3.

NOTE 2 This a subscription database.

NOTE 3 The Constituent Substance ID and name refers to a Specified Substance Group 1.

NOTE 4 The (Parent) Substance ID refers to the (Specified) Substance (Group 1) Name: Insulin Human Zinc Injectable Suspension.

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C.6 Element Group Protein, Specified Substance Group 2

The ISO 11238 standard provides the possibility to go from the Substance information level to the Specified Substance Group 2 information level directly, see Figure 36.

In the next examples, the difference is described between synthetic and recombinant Calcitonin Salmon. Even when produced by the same manufacturer for both the synthetic and recombinant manufacturing process a separate CTD M3 regulatory dossier shall be submitted and separate SSG2 IDs will be generated. In the pharmacopoeial monographs for Calcitonin Salmon in Ph.Eur. and USP, different tests related to each manufacturing process are described and there is a different set of acceptance criteria related to the manufacturing process e.g. additional limits for impurities E, F and G when produced by the rDNA manufacturing process. Specified Substance Group 2 couples the manufacturer/manufacturing site with the (Specified) Substance.

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C.6.1 Example: Synthetic Calcitonin Salmon-Manufacturer Company Acme

Table C.9 — Synthetic Calcitonin Salmon-Manufacturer Company Acme

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	CHJT8360JS (Artificial ID)	II	
Substance Type	Protein	CD	
Element Group: Substance Name			
Substance Name	Calcitonin Salmon, Synthetic	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph. Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur. monograph: 01/2008:0471	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Acme Calcitonin Salmon	ST	
Substance Name Type	Brand	CD	
Language	en	CD	
Element Group: Reference Information			
Element Group: Substance Classification			
Further Element Groups: See Table C.4			
Substance Type: Specified Substance Group 2			
Specified Substance Group 2 ID	KHJR98675T (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Synthetic Calcitonin Salmon — Acme, site xxxx	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	CHJT8360JS (Artificial ID)	II	1)
Element Group: Manufacturing			

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Element Name	Value	Data Format	Note #
Manufacturing Type	Manufacturer	CD	
Production Method Type	Synthetic	CD	
Production Method Description	Chemical synthesis from starting materials, see enclosed document at Regulatory submission	ST	
Production System Type	Solid Phase Chemistry	CD	
Production System	FMOC Chemistry	CD	
Critical Process Version Number	1	INT	2)
Version	CALSYN-001	ST	
Version Date	20170127	TS.Date	
Element Group: Organization			
Manufacturer ID	DUNS78654A (Artificial ID)	II	
Manufacturer Name	Acme, site xxxx	ST	
Issuer of ID	Dun & Bradstreet	CD	
Manufacturing Role	Manufacturer	CD	

NOTE 1 This (Parent) Substance ID is referring to the Substance Name: Calcitonin Salmon, Synthetic.

NOTE 2 The version number would change if a substantial change in the (synthetic) manufacturing process occurred. These would include a change in the chemistry, addition or elimination of a purification step. A substantial change is a purification or processing step (i.e. changing a chromatographic matrix, changes in deprotection reagents etc.). The initial Critical Process Version Number is one and each subsequent number increases sequentially.

C.6.2 Example: Recombinant Calcitonin Salmon — Company Acme

There are instances when a company may switch from a synthetic substance to a substance produced using recombinant DNA technology.

Table C.10 — Recombinant Calcitonin Salmon — Company Acme

Element Name	Value	Data Format	Note #
Element Group: Substance			
Further Element Groups: See example Table C.9			
Substance Type: Specified Substance Group 2			
Specified Substance Group 2 ID	RDFS2341HL (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Recombinant Calcitonin Salmon — Acme, site yyyy	ST	

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Element Name	Value	Data Format	Note #
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	CHJT8360JS (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Recombinant Protein Production	CD	
Production Method Description	See attached document from Regulatory submission	ST	
Production System Type	Cell line or Cell Clone used for the production of the Protein	CD	
Production System	E. Coli AD494	CD	
Critical Process Version Number	1	INT	
Version	CALREC-001	ST	
Version Date	20170127	TS.Date	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Regulatory Submission	CD	
Reference Source Class	Process Method Description	CD	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	Production Method Description v1	ED	
Element Group: Organization			
Manufacturer ID	DUNS37245R (Artificial ID)	II	
Manufacturer Name	Acme, site yyyy	ST	
Issuer of ID	Dun & Bradstreet	CD	
Manufacturer Role	Manufacturer	CD	
NOTE 1 This (Parent) Substance ID is referring to the Substance Name: Calcitonin Salmon, Synthetic.			

Explanation: The ID of Specified Substance Group 2 has been appointed uniquely to the Specified Substance Group 2 Name, which couples the (Specified) Substance Name to the Manufacturer. In this case, there are two possibilities given by the description of the Pharmacopoeial monograph: Calcitonin Salmon, USP: Either it is produced from a synthetic process, and named “Synthetic Calcitonin Salmon” or processed by a microbial process, and named “Recombinant Calcitonin Salmon”. The result will be two different Specified Substance Group 2 IDs. In this case SSG2 names and SSG2 IDs will differ even if the same manufacturer is involved.

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The Version shall be tied to the Production System Type and will change if a critical process changes.

EXAMPLE A change in the production cell line will change the version number.

C.7 Element Group Protein, Specified Substance Group 3

For Calcitonin Salmon, there are two distinct production methods: one by chemical synthesis and the other uses rDNA technology. The method of production is required in labelling for both USP and Ph.Eur. monographs and there are separate specifications that are dependent on the methods of production. In this case two different Specified Substance Group 3 substances would be created for both Ph.Eur. and USP. JP does not distinguish material made synthetically or using rDNA technology and therefore just a single Specified Substance Group 3 would be created for JP. The Specified Substance Group 3 information data model is provided in Figure 38.

C.7.1 Example: Calcitonin Salmon (Synthetic) Specified Substance Group 3

Table C.11 — Calcitonin Salmon (Synthetic) SSG3

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	8SJUTVDF89 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Synthetic Calcitonin Salmon-USP	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	CHJT8360JS (Artificial ID)	II	1)
Element Group: Grade			
Grade Type	USP	CD	
Grade Name	Calcitonin Salmon	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP 38-NF-33; page 2525-2526	ST	
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	8RKHJT345P (Artificial ID)	II	
Element Group: Substance Name			

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Element Name	Value	Data Format	Note #
Substance Name	Synthetic Calcitonin Salmon-Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	CHJT8360JS (Artificial ID)	II	1)
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name	Calcitonin (Salmon)	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Resource Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoiea 8.6, monograph 1/2008:0471	ST	
NOTE 1 This (Parent) Substance ID is referring to the Substance Name: Calcitonin Salmon, Synthetic.			

C.7.2 Example: Calcitonin Salmon (Recombinant) Specified Substance Group 3

Table C.12 — Calcitonin Salmon (Recombinant) Specified Substance Group 3

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	GHHJGD6745 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Recombinant Calcitonin Salmon-USP	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	CHJT8360JS (Artificial ID)	II	1)
Element Group: Grade			
Grade Type	USP	CD	
Grade Name	Calcitonin Salmon	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	ST	
Reference Source Class	Official Name Source	CD	

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Element Name	Value	Data Format	Note #
Reference Source Citation	USP 38-NF-33; p. 2525-2526	ST	
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	HGDFR67453 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Recombinant Calcitonin Salmon-Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	CHJT8360JS (Artificial ID)	II	1)
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name	Calcitonin (Salmon)	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur. monograph, 01/2008:0471	ST	
NOTE This (Parent) Substance ID is referring to the Substance Name: Calcitonin Salmon, Synthetic.			

C.8 Example Protein Substance: Monoclonal Antibody Conjugated Toxin

Example: Identity of material, combining the elements for Brentuximab Vedotin

Brentuximab Vedotin is an IgG1 mouse-human chimeric toxin-conjugated monoclonal antibody that is targetted against theTNFRSF8 tumour necrosis factor receptor superfamily, member 8 [Homo sapiens (human)] receptor. It has been approved for the treatment of Hodgkin's lymphoma and systemic anaplastic large cell lymphoma (ALCL) after prior treatment failures. The antibody binds to cells expressing the antigen, undergoes endocytosis, and releases the toxin (MMAE) intracellularly following cleavage by a cathespin-like protease.

Brentuximab is a chimeric form of the murine monoclonal antibody AC10. It is expressed from the fusion of the heavy chain and light chain variable region genes (VH and VL, respectively) from the murine anti CD30 monoclonal antibody AC10 to the human immunoglobulin gamma 1(G1) and the kappa (k) constant region genes.

An Illustrative representation is presented below, see Figure C.11, showing the Brentuximab, chimeric CD30-directed antibody (cAC10 anti-CD30 antibody), and the highly potent anti-microtubule agent (toxin) monomethyl auristatin E(MMAE) (SGD-1010) connected with a protease-cleavable linker that covalently bonds MMAE (Vedotin) to brentuximab. The disulfide linkages are depicted in Figure C.12.

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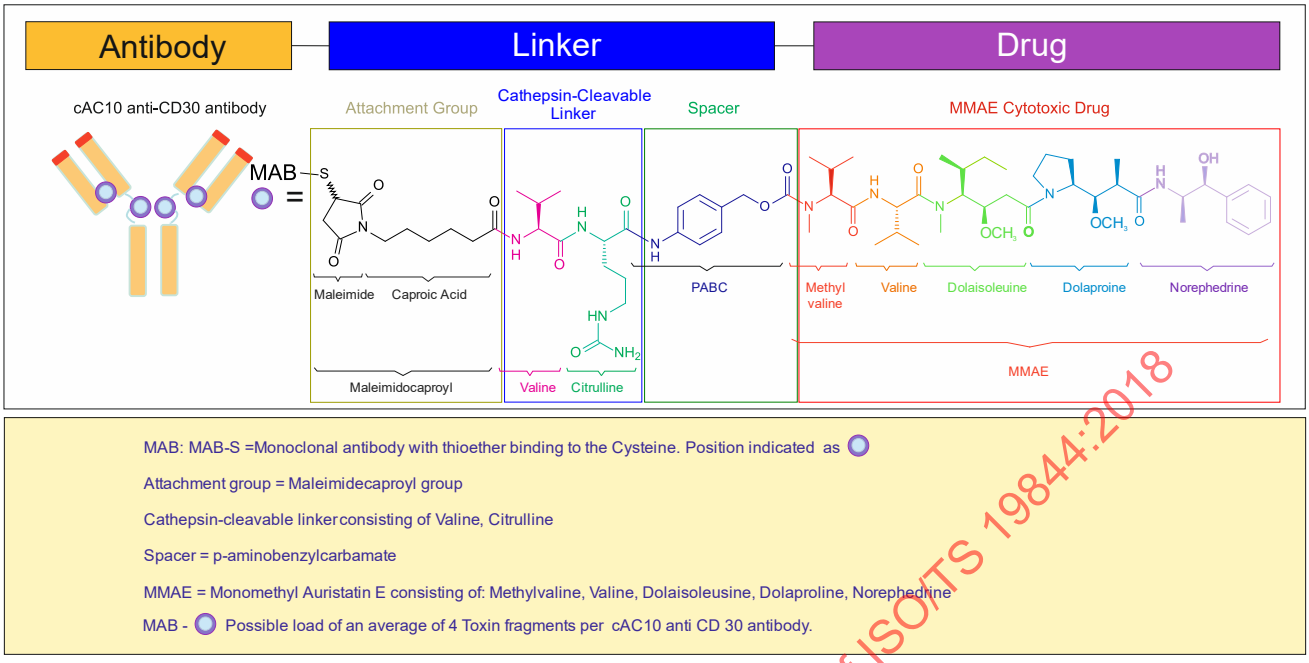
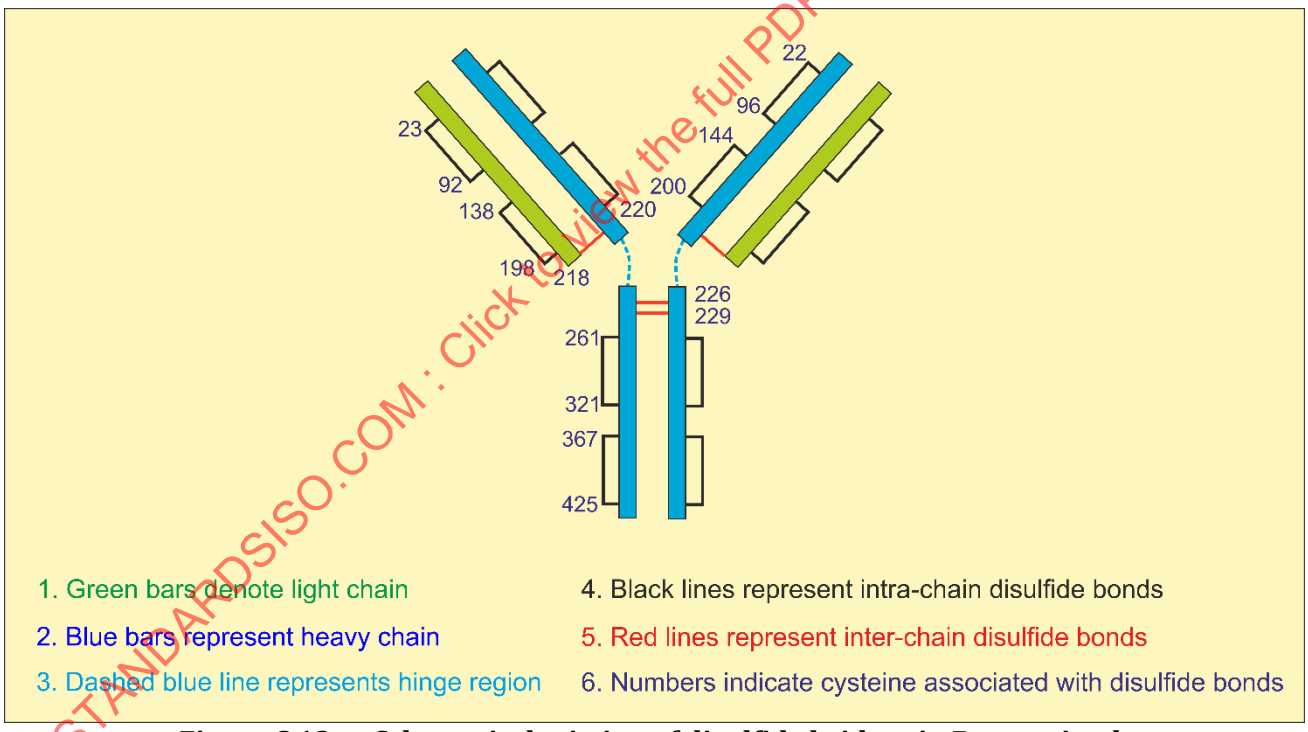


Figure C.11 — Structural representation of Brentuximab Vedotin



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Figure C.12 — Schematic depiction of disulfide bridges in Brentuximab

Table C.13 — Brentuximab Vedotin

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Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	JKHGYD6453 (Artificial ID)	II	
Substance Type	Protein	CD	
Element Group: Substance Name			
Substance Name	Brentuximab Vedotin	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Recommended INN list	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	INN, WHO Drug Information, Vol. 25, No. 1, 2011 Recommended INN: List 65	ST	1)
Reference Source URL	http://www.who.int/medicines/publications/druginformation/innlists/RL65.pdf?ua=1	ST	1)
Element Group: Substance Name (Repeat)			
Substance Name	Brentuximab Vedotin (genetically recombination)	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	JP	CD	
Element Group: Official Name			
Official Name Type	JP	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	JP	CD	

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Element Name	Value	Data Format	Note #
Reference Source Class	Official Name Source	CD	
Reference Source Citation	JP monograph	ST	
Element Group: Substance Code			
Code	914088-09-8	CD.Code	
Code System	CAS Registry	CD.CodeSystem Name	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	7XL5ISS668	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystem Name	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	fg10hd (Artificial Code)	CD.Code	
Code System	INN Biological Qualifier	CD.CodeSystem Name	
Code System ID	0051	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Structure			
Molecular Formula	$C_{6860}H_{10532}N_{1740}O_{2168}S_{40}$	ST	2)
Molecular Formula by Moiety	$C_{6588}H_{10108}N_{1696}O_{2108}S_{40}.4[C_{68}H_{106}N_{11}O_{15}]$	ST	2)
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	Brentuximab Vedotin structure.pdf\ (see Figure C.11)	ED	3)
Element Group: Structural Representation (Repeat)			
Structural Representation Type	Representative	CD	

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Element Name	Value	Data Format	Note #
Structural Representation Attachment	Brentuximab Vedotin disulfide linkage.pdf (see Figure C.12)	ED	3)
Element Group: Reference Information			
Element Group: Gene			
Gene Sequence Origin	Mouse-Human Chimeric	CD	
Gene ID	ghdftwu123	CD	
Gene Name (Heavy Chain)	*Mus musculus* VH(IGHV1-84*02 -(IGHD)-IGHJ3*01) [8.8.10] (1-117) - *Homo sapiens* IGHG1*01 CH3 K130>del (118-446)	ST	
Element Group: Gene (Repeat)			
Gene Sequence Origin	Mouse-Human Chimeric	CD	
Gene ID	glertwu456	CD	
Gene Name (Light Chain)	*Mus musculus* V-KAPPA(IGKV3-4*01 -IGKJ1*01) [10.3.9] (1'-111') - *Homo sapiens* IGKC*01(112'-218')	ST	
Element Group: Substance Classification			
Domain	Human	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	L01XC12	CD.Code	
Substance Classification Type	Brentuximab vedotin	ST	
Element Group: Substance Classification Subtype			
Substance Class Subtype	IgG1	CD	
Element Group: Target			
Target ID	943 (From NLM Gene)	II	
Target Name	TNFRSF8 tumour necrosis factor receptor superfamily, member 8 [*Homo sapiens* (human)] receptor	ST	
Interaction Type	Toxin Delivery	CD	
Target Organism	*Homo Sapiens*	CD	
Target Organism Type	Human	CD	
Target Type	Receptor	CD	
Element Group: Protein			

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Element Name	Value	Data Format	Note #
Sequence Type	Complete	CD	
Number of Subunits	4	INT	
Disulfide Linkage	1_22-1_96; 1_144-1_200; 1_220-3_218;1_226-2_226; 1_229-2_229; 1_261-1_321; 1_367-1_425; 2_22-2_96; 2_144-2_200; 2_220-4_218; 2_261-2_321; 2_367-2_425; 3_23-3_92; 3_138-3_198; 4_23-4_92; 4_138-4_1 98	ST	
Element Group: Protein Subunit			
Subunit	1	INT	
Sequence	pEIQLQQSGPEVVKPGASVKISCKASGYTFTDYYITWVKQ KPGQGLEWIGWIYPGSGNTKYNEKFKGKATLTVDTSSS TAFMQLSSLTSEDTAVYFCANYGNYWFAYWGQGTQVT VSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG	ST	4)
Length	446	INT	
Sequence Attachment	**Q**IQLQQSGPEVVKPGASVKISCKASGYTFTDYYITWVKQ KPGQGLEWIGWIYPGSGNTKYNEKFKGKATLTVDTSSS TAFMQLSSLTSEDTAVYFCANYGNYWFAYWGQGTQVT VSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG**K**	ED	5)
Element Group: Protein Subunit (Repeat)			
Subunit	2	INT	
Sequence	pEIQLQQSGPEVVKPGASVKISCKASGYTFTDYYITWVKQ KPGQGLEWIGWIYPGSGNTKYNEKFKGKATLTVDTSSS TAFMQLSSLTSEDTAVYFCANYGNYWFAYWGQGTQVT VSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP	ST	4)

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Element Name	Value	Data Format	Note #
	EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG		
Length	446	INT	
Sequence Attachment	**Q**IQLQQSGPEVVKPGASVKISCKASGYTFTDYYITWVKQ KPGQGLEWIGWIYPGSGNTKYNEKFKGKATLTVDTSSS TAFMQLSSLTSEDTAVYFCANYGNYWFAYWGQGTQVT VSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG**K**	ED	5)
Element Group: Protein Subunit (Repeat)			
Subunit	3	INT	
Sequence	DIVLTQSPASLAVSLGQRATISCKASQSVDFDGDSYMNW YQQKPGQPPKVLIYAASNLESGIPARFSGSGSGTDFTLNI HPVEEEDAATYYCQQSNEDPWTFGGGTKLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKV YACEVTHQGLSSPVTKSFNRGEC	ST	
Length	218	INT	
Element Group: Protein Subunit (Repeat)			
Subunit	4	INT	
Sequence	DIVLTQSPASLAVSLGQRATISCKASQSVDFDGDSYMNW YQQKPGQPPKVLIYAASNLESGIPARFSGSGSGTDFTLNI HPVEEEDAATYYCQQSNEDPWTFGGGTKLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKV YACEVTHQGLSSPVTKSFNRGEC	ST	
Length	218	INT	
N-Terminal Modification ID	0RH81L854J (UNII)	II	
N-Terminal Modification	Glutamine (Q)	ST	
C-Terminal Modification ID	K3Z4F929H6 (UNII)	II	

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Element Name	Value	Data Format	Note #
C-Terminal Modification	Lysine (K)	ST	
Element Group: Glycosylation			
Glycosylation Type	Mammalian	CD	
N-Glycosylation Site	1_297; 2_297	ST	
Element Group: Modification (N-Terminal modification)			
Modification Type	Structural Modification	CD	
Residue Modified	Glutamine (Q)	CD	
Residue Site	1_1; 2-1	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Molecular Fragment Role	N-Terminal Pyroglu Formation	CD	
Molecular Fragment ID	PYROG45321 (Artificial ID); [SZB83O1W42 (UNII)]	II	
Molecular Fragment Name	Pyroglutamic acid (pE)	ST	
Element Group: Modification (Repeat) (C-Terminal Modification)			
Modification Type	Structural Modification	CD	
Residue Modified	Lysine (K)	CD	
Residue Site	1-447; 2-447	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Removal	CD	6)
Element Group: Molecular Fragment			
Molecular Fragment Role	C-Terminal Lysine removal	CD	
Molecular Fragment ID	LYSIN67543R (Artificial ID); [K3Z4F929H6 (UNII)	II	
Molecular Fragment Name	Lysine (K)	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Low Limit	70	PQ	
High Limit	90	PQ	
Unit	%	CD	
Amount Text	70 % to 90 % removed, Incomplete	ST	

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Element Name	Value	Data Format	Note #
Element Group: Modification (Repeat)			
Modification Type	Structural modification	CD	
Residue Modified	Cysteine (C)	CD	
Residue Site	Variable	ST	7)
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	8)
Element Group: Molecular Fragment			
Molecular Fragment Role	Toxin Conjugation	CD	
Molecular Fragment ID	CYSMM12345 (Artificial ID); [6603L01WUR (UNII)]	II	
Molecular Fragment Name	Cysteine-VC-MMAE	ST	9)
Element Group: Amount			
Amount Type	Average	CD	
Quantity	4,0	PQ	
Low Limit	3	PQ	
High Limit	5	PQ	
Unit	Mol Ratio Toxin to Antibody	CD	
Element Group: Structural Representation			
Structural Representation Type (Molecular Fragment)	Full	CD	
Structural Representation Attachment (Molecular Fragment)	See image below	ED	

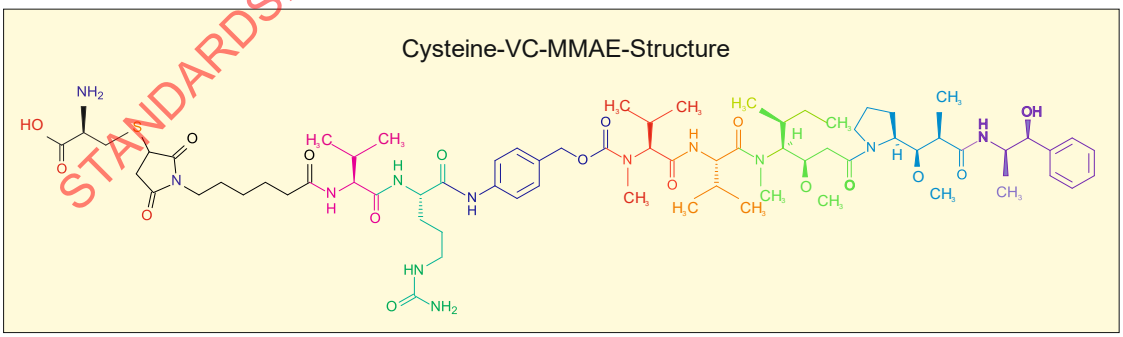


Figure C.13 — Structural representation of Cysteine-VC-MMAE

NOTE It is not required that both a Reference Source Citation and a Reference Source URL are transmitted but both are included here as an example.

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Element Name	Value	Data Format	Note #
[2] Calculations of molecular formula and molecular mass are based on one of the most abundant forms of the antibody and an average of 4 conjugated toxin groups. [3] Provision of a structural representation for proteins is not required, but they can be very useful for understanding the structure, so it may be provided. The structure in Figure C.11 can be provided as either a PDF or other supported image file formats, likewise with a representation of the disulfide linkage in Figure C.12 (also, see 5.7.6). [4] The attribute 'Sequence' represents the protein sequence after PTM (Post-Translational Modification). [5] The attribute 'Sequence Attachment' represents the protein sequence before PTM (Post-Translational Modification). [6] Additionally, the encoded C-terminal lysine of the heavy chain is typically partially post-translationally removed. Most monoclonal antibodies that are not intentionally treated with a carboxypeptidase enzyme can be defined as a mixture of three different proteins: the predominant form typically does not contain lysine on the C-terminus. [7] The value “variable” is provided since modification is not site specific. [8] The conjugation of the toxins to cysteine residues in the partially reduced antibody is the common form of modification for many antibodies. Typically, enough of the disulfide bonds are maintained for the antibody to retain its structure and the free sulfhydryl groups react with the maleimide conjugate. As with all amino acid modifications the amino acid cysteine is substituted with an amino acid containing the complete conjugate. [9] The molecular fragment may also need to be registered if it is not already defined and has a Substance ID.			

C.9 Addendum: Microheterogeneity

C.9.1 Microheterogeneity

Microheterogeneity is typically caused by differential post-translational modifications that lead to differences in the type and extent of glycosylation, phosphorylation, sulfation and/or other modifications throughout the ensemble of molecules of a given protein. Recently regulatory agencies are receiving more detailed information on the microheterogeneity of proteins in medicinal products. This information may be used to further distinguish proteins at the Specified Substance Group 1 level.

C.9.2 Introduction

Controlling and understanding the protein microheterogeneity of monoclonal antibodies (mAbs) both in a qualitative and quantitative manner represents one of the main focuses in the development and manufacturing of this class of therapeutics. Post-translational modification (PTM) on mAbs needs to be minutely characterized because it may affect antibody structure, efficacy, and potency, and its potential antigenicity or immunogenicity. The most widespread PTM occurring on mAbs is N-glycosylation. The nature of the glycan chains influences Fc-effector function and serum half-life. In particular, the lack of core fucosylation enhances Antibody Dependent Cellular Cytotoxicity (ADCC)[14]. The absence of fucose but not the presence of galactose or bisecting N-acetylglucosamine of human IgG1 complex-type oligosaccharides shows the critical role of enhancing ADCC, while the presence of (α2–6)-linked sialic acids (N-acetylneuraminic acids) may be beneficial for anti-inflammatory activity[15].

NOTE Quantitative PCR analysis indicated that YB2/0 cells had a lower expression level of FUT8 mRNA, which codes α1,6-fucosyltransferase, than CHO cells. Overexpression of FUT8 mRNA in YB2/0 cells led to an increase of fucosylated oligosaccharides and decrease of ADCC of the IgG1. These results indicate that the lack of fucosylation of IgG1 has the most critical role in enhancement of ADCC, although several reports have suggested the importance of Gal or bisecting GlcNAc and provide important information to produce the effective therapeutic antibody[14].

mAb glycosylation can be very diverse in nature, leading to an extensive molecular heterogeneity of the glycoprotein. Wild-type mAbs typically exist as a mixture of 3–5 different glycoforms, with their nature

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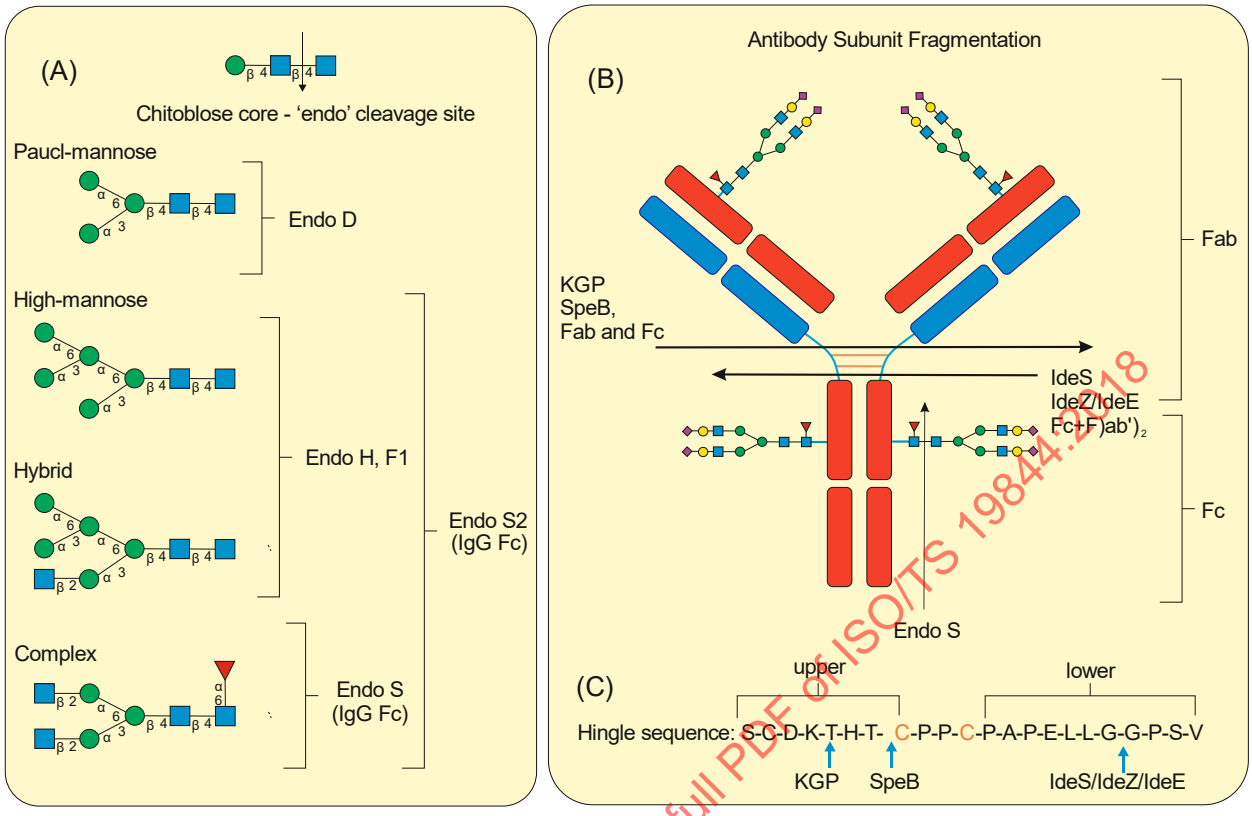
and abundance highly dependent on the cell line and expression system used. Human antibodies expressed in non-human cell lines can bear non-human carbohydrate chains (e.g. containing N-glycolylneuraminic acid, the galactose(α1–3) galactose epitope or xylose) that may trigger undesired immunogenic responses.

Glycosylation is an enzymatic reaction which occurs inside the cell. Oligosaccharide heterogeneity, which can cause monoclonal antibody heterogeneity, is most likely introduced during oligosaccharide synthesis and processing. All IgGs have the conserved N-linked oligosaccharides on the two conserved asparagine residues in the CH2 domain of the Fc region and approximately 15 % to 20 % also have N-linked oligosaccharides in the variable region, see Figure C.14. The variable region oligosaccharide could be on either the light chain, the heavy chain, or both. O-linked oligosaccharides have also been reported mostly located in the hinge region or possibly on Fc region. Low levels of non-glycosylated IgG were also observed, at least, for recombinant monoclonal antibodies. Wild type IgGs have a complicated oligosaccharide population on the conserved asparagine residues in the CH2 domains. Recombinant monoclonal antibodies expressed in various cell lines including CHO, NS0, hybridoma, and others normally have less complex oligosaccharide profiles. The common structures of oligosaccharides of recombinant monoclonal antibodies are biantennary complex with a core fucose with zero, one, or two terminal galactose, and various truncated structures with the loss of the core fucose, GlcNAc, or both, see Figure C.19, [16]. The structure of fucose is presented in Figure C.16. A glossary of the sugar abbreviations and representation is shown in Figure C.15.

NOTE Fucose is a hexose deoxy sugar with the molecular formula $C_6H_{12}O_5$. It is found on N-linked glycans on the mammalian, insect and plant cell surface. Two structural features distinguish fucose from other six-carbon sugars present in mammals: the lack of a hydroxyl group on the carbon at the 6-position (C-6) and the L-configuration. It is equivalent to 6-deoxy-galactose (3*S*,4*R*,5*R*,6*S*)-6-Methyltetrahydro-2*H*-pyran-2,3,4,5-tetraol), see Figure C.16. In the fucose-containing glycan structures, fucose can exist as a terminal modification or serve as an attachment point for adding other sugars. In human N-linked glycans, fucose is most commonly linked α-1,6 to the reducing terminal β-N-acetylglucosamine, see Figure C.17.

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NOTE Figure adapted from R. Duke and C. H. Taron [17] from Figure 2.

Figure C.14 — High-level types of Glycans and positions on the mAB[32]

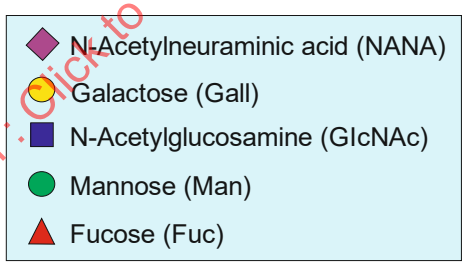


Figure C.15 — Abbreviations and notations of described saccharides in Figure C.19 and Figure C.20

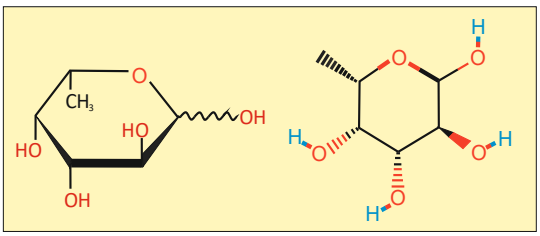


Figure C.16 — Structural representation of Fucose (6-deoxy-galactose)

[32] (A) Schematic summarising the general specificity of selected endoglycosidases. Endo S removes Fc N-glycans from IgG only, (B) Antibody fragmentation enzymes currently available [28].

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Oligosaccharides of high mannose have also been reported for several antibodies. Sialic acid is normally present at a very low level for Fc oligosaccharides [16].

NOTE Sialic acid is a generic term for the N- or O-substituted derivatives of neuraminic acid, a monosaccharide with a nine-carbon backbone [18]. It is also the name for the most common member of this group, N-acetylneuraminic acid (Neu5Ac or NANA, (6R)-5-Acetamido-3,5-dideoxy-6-[(1R,2R)-1,2,3-trihydroxypropyl]-beta-L-threo-hex-2-ulopyranosonic acid, $C_{11}H_{19}NO_9$, Mol. weight 309,3 g/mol.), see Figure C.17. Sialic acid structures are represented by a pink square in Figure C.14 (B). Sialic acids are found widely distributed in animal tissues and to a lesser extent in other organisms, ranging from plants and fungi to yeasts and bacteria, mostly in glycoproteins. They occur at the end of sugar chains connected to the surfaces of cells and soluble proteins. When sialic acid is attached to N-glycan structures it is negatively charged and in the α-anomeric form, see Figure C.18.

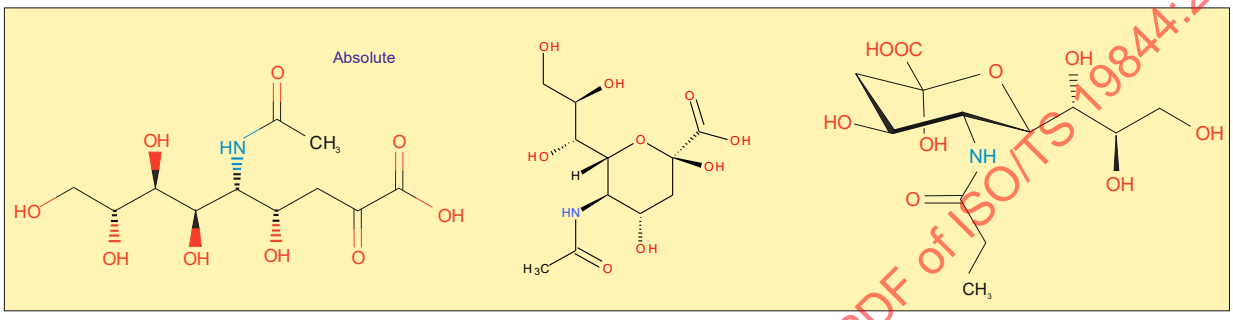
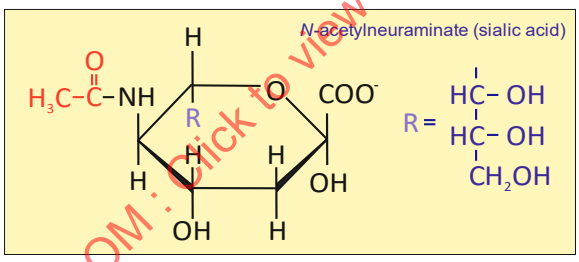


Figure C.17 — Structural representation of Sialic acid (N-acetyl-α-neuraminic acid)



N-acetylneuraminic acid (also called sialic acid) is often found as a terminal residue of oligosaccharide chains of glycoproteins. Sialic acid imparts negative charge to glycoproteins, because its carboxyl group tends to dissociate a proton at physiological pH, as shown here.

Figure C.18 — Structural representation of Sialic acid as negative charged ion

While different subtypes of IgGs and cell culture conditions can affect oligosaccharide structures, cell line is by far the most important factor that defines oligosaccharide structures. For example, recombinant monoclonal antibodies from cell lines of murine origin commonly contain Gala1-3Gal. This affects the *in vivo* half-life of these antibodies significantly because of the presence of natural antibodies that recognize Gala1-3Gal in the human body.

NOTE Size heterogeneity of monoclonal antibodies caused by different oligosaccharide structures can be readily detected by mass spectrometry. Chromatography is also very useful in separation of monoclonal antibodies with different oligosaccharides. Monoclonal antibodies with additional Fab oligosaccharides are more hydrophilic and have been shown as an earlier elution shoulder on a HIC column. The presence of sialic acids introduces additional negative charges and thus antibodies with sialic acids elute earlier on cation exchange chromatography. There are

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multiple interactions between the sugar moieties and the amino acids of the CH2 domains. Therefore, even neutral oligosaccharides may affect the chromatographic behaviour of monoclonal antibodies by modulating local surface charge.

Overview of some of the most extended glycan structures identified on the IgG mutant antibodies is provided on the database of 'GlyTouCan' https://glytoucan.org/ and Glycan structures can be found in the glycan section https://glytoucan.org/Structures.

In Figure C.20, typical examples of (sialylated) tri- and tetra-antennary N-glycans are presented. The inset shows the relationship between the structure of a tetra-sialylated tetra-antennary N-glycan and the used symbolic notation for such a structure, clarifying also the symbolic notation of diantennary and triantennary structures.

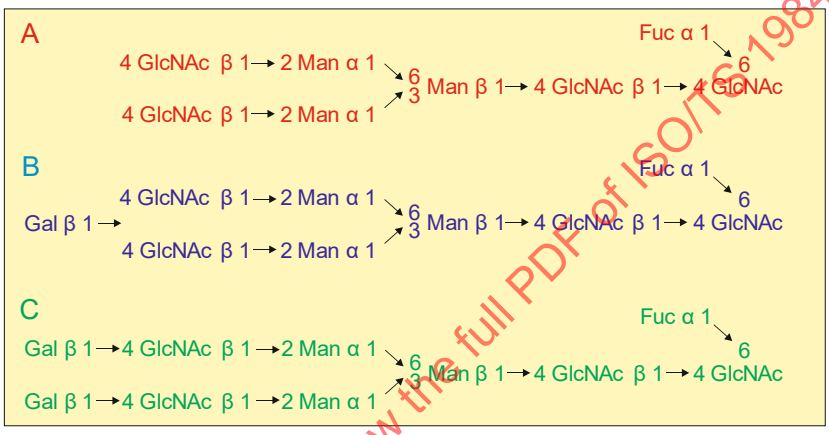


Figure C.19 — Structural representation of most common Glycan structures of Monoclonal Antibodies

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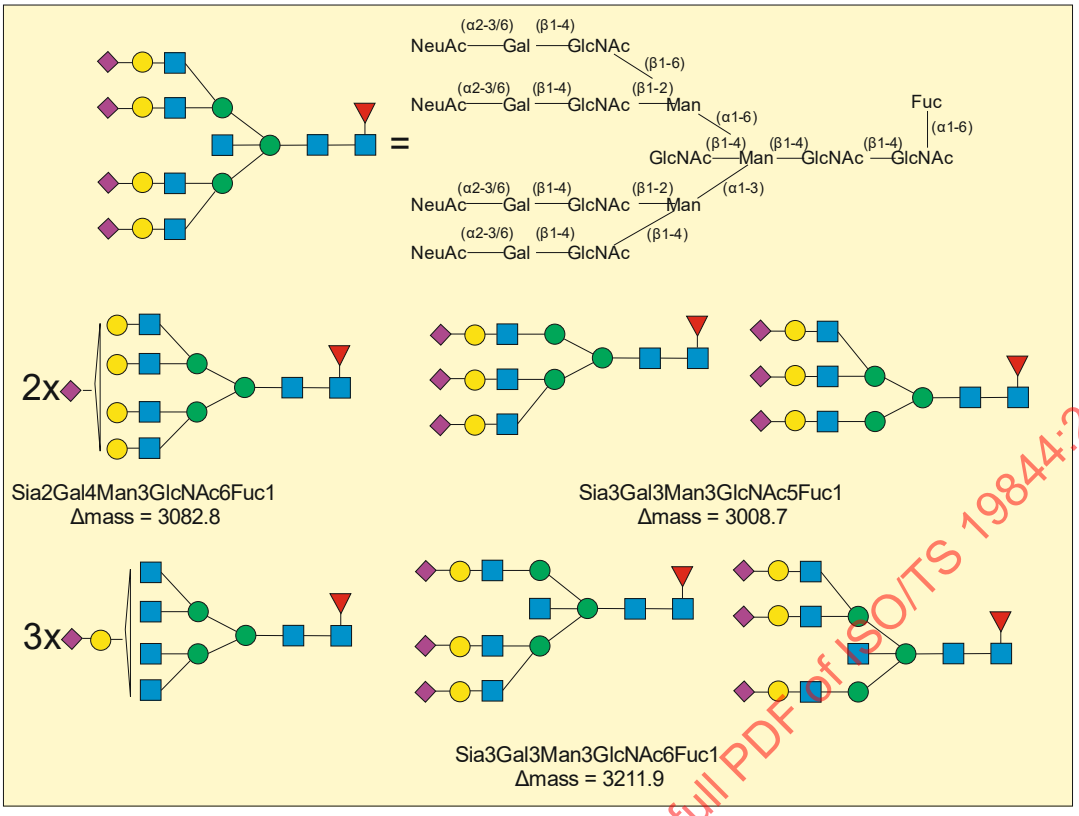


Figure C.20 — Examples of tri- and tetra-antennary N-Glycans and the relation with the representative notation

C.9.3 Brentuximab Glycans

There is one N-glycosylation site on the heavy chain (Asn297, 1_297; 2_297 in Table C.13 and it is predominantly occupied with a core fucosylated biantennary glycan, typically found with monoclonal antibodies produced by CHO (Chinese Hamster Ovary) cells, with 0, 1 or 2 terminal galactose residues, see Figure C.19 (A, B or C) as representative structures.

In Figure C.21 (Structure), abbreviation and glytoucan accession numbers of N-linked glycans found in Brentuximab Vedotin are presented. Specific linkages between GlcNac (blue squares) and mannose (green circles) groups are not shown. These linkages were described in the regulatory application dossier and coupled to the corresponding accession numbers. Red triangle = Fucose; White circle = Galactose.

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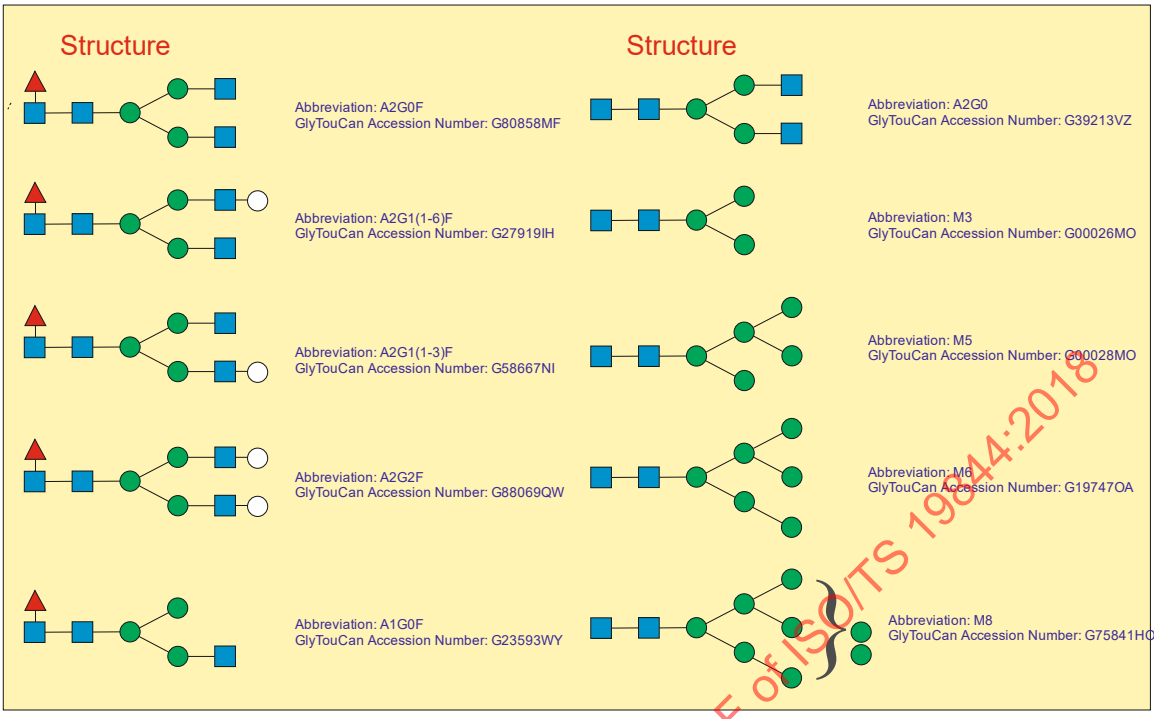


Figure C.21 — Representation of Brentuximab vedotin glycans

Entry of the GlyTouCan accession number for the predominate Glycan with the Code G80858MF in the GlyTouCan database gives the following result as provided in Figure C.22 (https://glytoucan.org/Structures/Glycans/G80858MF) giving the accession code, the representative structure, the calculated monoisotopic mass (Da) and the IUPAC Extended Systematic name: beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->3)[beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-beta-D-GlcpNAc(1->)

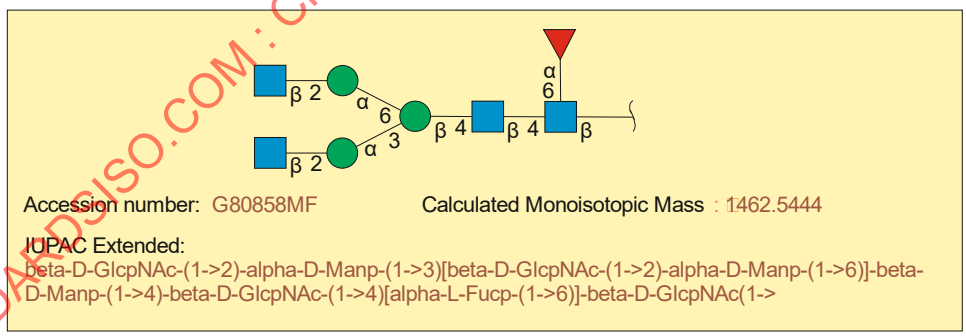


Figure C.22 — Display of the GlyTouCan accession number 80858MF[33]

C.9.4 Structuring Monoclonal Glycans at the Specified Substance Information level

The Specifed Substance Group 1 Information level is provided in Figure 35. The class 'Characteristic Attribute' will be used to describe the glycans typically present in mAbs. The element 'Attribute Type' has the values 'N-Glycan, O-Glycan'. The element 'Attribute Name' has the accession code used in the GlyTouCan, combined with the IUPAC Extended Systhematic name for individual glycans, or the value

[33] International Glycan Structure Repository. GlyTouCan; Accession Number=G80858MF, https://glytoucan.org/Structures/Glycans/G80858MF (accessed May. 25, 2017).

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'fucosylated' or 'afucosylated' (non-fucosylated) glycans. The element 'Attribute Substance ID' has the value of the (Parent) Substance ID of the mAb and the element 'Attribute Substance Name' is the name of the mAb e.g Brentuximab. The structure of the proposed glycan can be described by the Structural Representation inherited from the Substance information or with the use of the Element Group 'Modification', see Figure 20.

The glycan shall be registered as a molecular fragment.

In combination with the element group 'Amount' the percentage of the glycans can be described or the amount of fucosylated/ afucosylated glycans can be described.

The Specified Substance Group 1 Name could be composed of:

<Substance Name>, abbreviation of three lettered/numbers of GlyTouCan accession number> (as long as they differ from each other, e.g. Brentuximab Vedotin, [G80-G27-G58-G88-G23-G39-G00026MO-G00028MO-G19-G75].

Table C.14 — N-linked glycans described for Brentuximab Vedotin

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 1 (Protein)			
Specified Substance Group 1 ID	BRENSSG123 (Artificial ID)	II	
Element Group: Substance Name			
(Specified) Substance (Group 1) Name	Brentuximab Vedotin, [G80-G27-G58-G88-G23-G39-G00026MO-G00028MO-G19-G75]	ST	1)
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Biologic	CD	
Jurisdiction	US, EU	CD	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Element Group: Substance Name (Repeat)			
(Specified) Substance (Group 1) Name	Brentuximab Vedotin-SSG1-Glycans-Company XYZ	ST	1)
Substance Name Type	Specified Substance Group 1, Display Name	CD	
Language	en	CD	
Substance Name Domain	Biologic	CD	

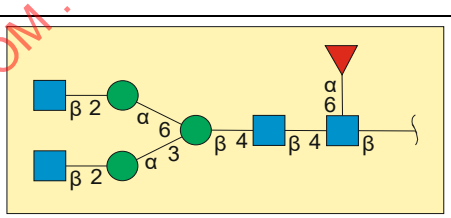
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Element Name	Value	Data Format	Note #
Jurisdiction	US, EU	CD	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Element Group: Reference Source			
Element Group: Constituent			
Constituent Substance ID	JKHGYD6453 (Artificial ID)	II	
Constituent Substance Name	Brentuximab Vedotin	ST	
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Characteristic Attribute			
Attribute Type	N-Glycan	CD	
Attribute Name	G80858MF- beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->3)[beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-beta-D-GlcpNAc(1->)	ST	2)
Attribute Substance ID	JKHGYD6453 (Artificial ID)	II	
Attribute Substance Name	Brentuximab Vedotin	ST	
Is Defining	Yes	BL	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	GlyTouCan	CD	
Reference Source Class	Public Database	CD	
Reference Source ID	G80858MF	ST	
Reference Source URL	https://glytoucan.org/Structures/Glycans/G80858MF	ST	
Element Group: Modification (Fc Modification)			
Modification Type	Structural Modification	CD	
Residue Modified	Asparagine (N)	CD	
Residue site	1_297 ; 2_297	ST	
Element Group: Structural Modification			

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Element Name	Value	Data Format	Note #
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Molecular Fragment Role	N-Glycan formation	CD	
Molecular Fragment ID	GLYCAN8754 (Artificial ID)	II	
Molecular Fragment Name	beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->3)[beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-beta-D-GlcpNAc(1->)	ST	3)
Element Group: Structure			4)
Element Group: Molecular weight (Fragment)			4)
Molecular Weight Method	LC/MS	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			4)
Amount Type	Exact	CD	
Quantity	1 462,54	PQ	5)
Unit	g/mol	CD	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	 **Figure C.23 — Structural representation of the molecular fragment beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->3)[beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-beta-D-GlcpNAc(1->)**	ED	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	N-Glycan	CD	
Attribute Name	G27919IH - beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->3)[beta-D-Galp-(1->4)-beta-D-GlcpNAc-(1->2)-alpha-D Manp-(1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-beta-D-GlcpNAc(1->	ST	2)

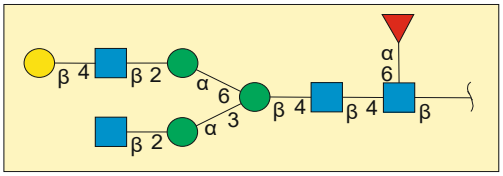
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Element Name	Value	Data Format	Note #
Attribute Substance ID	JKHGYD6453 (Artificial ID)	II	
Attribute Substance Name	Brentuximab Vedotin	ST	
Is Defining	Yes	BL	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	GlyTouCan	CD	
Reference Source Class	Public Database	CD	
Reference Source ID	G27919IH	ST	
Reference Source URL	https://glytoucan.org/Structures/Glycans/G27919IH	ST	
Element Group: Modification (Fc Modification)			
Modification Type	Structural Modification	CD	
Residue Modified	Asparagine (N)	CD	
Residue site	1_297 ; 2_297	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Molecular Fragment Role	N-Glycan formation	CD	
Molecular Fragment ID	GLYCAN6754 (Artificial ID)	II	
Molecular Fragment Name	beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->3)[beta-D-Galp-(1->4)-beta-D-GlcpNAc-(1->2)-alpha-D Manp-(1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-beta-D-GlcpNAc(1->	ST	3)
Element Group: Structure			4)
Element Group: Molecular weight (Fragment)			4)
Molecular Weight Method	LC/MS	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			4)
Amount Type	Exact	CD	
Quantity	1 624,59	PQ	5)
Unit	g/mol	CD	
Element Group: Structural Representation			

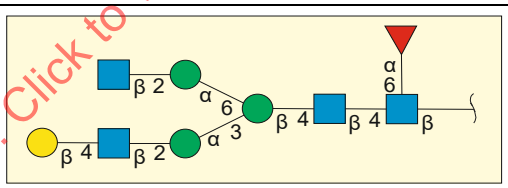
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Element Name	Value	Data Format	Note #
Structural Representation Type	Representative	CD	
Structural Representation Attachment	 **Figure C.24 — Structural representation of the molecular fragment beta-D-Galp-(1->4)-beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->3)[beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-beta-D-GlcpNAc(1->**	ED	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	N-Glycan	CD	
Attribute Name	G58667NI- beta-D-Galp-(1->4)-beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->3)[beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-beta-D-GlcpNAc(1->	ST	2)
Attribute Substance ID	JKHGYD6453 (Artificial ID)	II	
Attribute Substance Name	Brentuximab Vedotin	ST	
Is Defining	Yes	BL	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	GlyTouCan	CD	
Reference Source Class	Public Database	CD	
Reference Source ID	G58667NI	ST	
Reference Source URL	https://glytoucan.org/Structures/Glycans/G58667NI	ST	
Element Group: Modification (Fc Modification)			
Modification Type	Structural Modification	CD	
Residue Modified	Asparagine (N)	CD	
Residue site	1_297 ; 2_297	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			

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Element Name	Value	Data Format	Note #
Molecular Fragment Role	N-Glycan formation	CD	
Molecular Fragment ID	GLYCAN8976 (Artificial ID)	II	
Molecular Fragment Name	beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->3)[beta-D-Galp-(1->4)-beta-D-GlcpNAc-(1->2)-alpha-D Manp-(1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-beta-D-GlcpNAc(1->	ST	3)
Element Group: Structure			4)
Element Group: Molecular weight (Repeat) (Fragment)			4)
Molecular Weight Method	LC/MS	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			4)
Amount Type	Exact	CD	
Quantity	1 624,59	PQ	
Unit	g/mol	CD	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	 **Figure C.25 — Structural representation of the molecular fragment beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->3)[beta-D-Galp-(1->4)-beta-D-GlcpNAc-(1->2)-alpha-D Manp-(1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-beta-D-GlcpNAc(1->**	ED	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	N-Glycan	CD	
Attribute Name	G88069QW - alpha-D-NeupAc-(2->6)-beta-D-Galp-(1->4)-beta-D-GlcpNAc6S-(1->2)-alpha-D-Manp-(1->3)[alpha-D-Manp-(1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-?-D-GlcpNAc(1->	ST	2)
Attribute Substance ID	JKHGYD6453 (Artificial ID)	II	
Attribute Substance Name	Brentuximab Vedotin	ST	

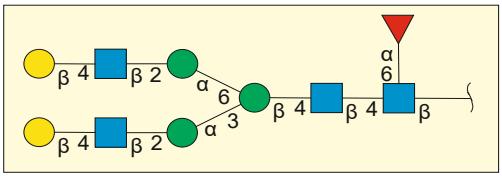
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Element Name	Value	Data Format	Note #
Is Defining	Yes	BL	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	GlyTouCan	CD	
Reference Source Class	Public Database	CD	
Reference Source ID	G88069QW	ST	
Reference Source URL	https://glytoucan.org/Structures/Glycans/G88069QW	ST	
Element Group: Modification (Fc Modification)			
Modification Type	Structural Modification	CD	
Residue Modified	Asparagine (N)	CD	
Residue site	1_297 ; 2_297	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Molecular Fragment Role	N-Glycan formation	CD	
Molecular Fragment ID	GLYCAN3425 (Artificial ID)	II	
Molecular Fragment Name	alpha-D-NeupAc-(2->6)-beta-D-Galp-(1->4)-beta-D-GlcpNAc6S-(1->2)-alpha-D-Manp-(1->3)[alpha-D-Manp-(1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-?-D-GlcpNAc(1->	ST	3)
Element Group: Structure			4)
Element Group: Molecular weight (Repeat) (Fragment)			4)
Molecular Weight Method	LC/MS	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			4)
Amount Type	Exact	CD	
Quantity	1 786,65	PQ	
Unit	g/mol	CD	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	

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Element Name	Value	Data Format	Note #
Structural Representation Attachment	 **Figure C.26 — Structural representation of the molecular fragment beta-D-Galp-(1->4)-beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->3)[beta-D-Galp-(1->4)-beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4))-[alpha-L-Fucp-(1->6)]-beta-D-GlcpNAc(1->**	ED	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	N-Glycan	CD	
Attribute Name	Core fucosylated Glycans	ST	
Attribute Substance ID	JKHGYD6453 (Artificial ID)	II	
Attribute Substance Name	Brentuximab Vedotin	ST	
Is Defining	No	BL	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	90	PQ	
Unit	%	CD	
Amount Text	Relative percentage of total glycans	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	N-Glycan	CD	
Attribute Name	Afucosylated Glycans	ST	
Attribute Substance ID	JKHGYD6453 (Artificial ID)	II	
Attribute Substance Name	Brentuximab Vedotin	ST	
Is Defining	No	BL	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	4,5	PQ	
Unit	%	CD	
Amount Text	Relative percentage of total glycans	ST	

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Element Name	Value	Data Format	Note #
NOTE 1 The (Specified) Substance (Group 1) Name consists of the Substance name extended with an abbreviation of the observed glycans as being coded in the GlyTouCan database (see Kinoshita K.A. *et al.* [19]). NOTE 2 The Attribute Name consists of the GlyTouCan identifier coupled with the IUPAC systematic name of the fragment. NOTE 3 The Molecular Fragment Name consists of the IUPAC systematic name of the fragment as described by the GlyTouCan identifier in the GlyTouCan database. This information is captured at the Molecular fragment ID [GLYCAN8754 (Artificial ID)] with the name 'beta-D-GlcpNAc-(1->2)-alpha-D-Manp-(1->3)[beta-D-GlcpNAc-(1->2)-alpha-D-Manp- (1->6)]-beta-D-Manp-(1->4)-beta-D-GlcpNAc-(1->4)[alpha-L-Fucp-(1->6)]-beta-D-GlcpNAc(1->)' which substance should be pre-registered before capturing the SSG1 information level of Brentuximab Vedotin. In general, all substance constituents and molecular fragments used to describe a characteristic attribute at the SSG1 information level should be pre-registered. Also preregistration for the molecular fragments GLYCAN6754 (Artificial ID), GLYCAN8976 (Artificial ID) and GLYCAN3425 (Artificial ID). NOTE 4 The Element Groups 'Structure' and 'Molecular Weight' with the 'Amount' are provided here for tutorial reason, since in general most of the molecular fragments used to describe characteristic attributes at the SSG1 information level are pre-registered (see also subclause 5.10.4.3.5).			

C.9.5 Example: Brentuximab Vedotin –Company XYZ.

High-level manufacturing information is provided by Specified Substance Group 2, see Figure 36.

Table C.15 — Recombinant Brentuximab Vedotin – Company XYZ

Element Name	Value	Data Format	Note #
Substance Type: Specified Substance Group 2			
Specified Substance Group 2 ID	GHDFW7856M (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Recombinant Brentuximab Vedotin—Company XYZ	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	JKHGYD6453 (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Recombinant Protein Production	CD	
Production Method Description	See attached document from Regulatory submission	ST	
Production System Type	Cell line or Cell Clone used for the production of the Protein	CD	
Production System	CHO cells	CD	
Critical Process Version Number	1	INT	
Version	BRENT-001	ST	
Version Date	20170125	TS.Date	

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Element Name	Value	Data Format	Note #
Element Group: Organization			
Manufacturer ID	DUNS37245R (Artificial ID)	II	
Manufacturer Name	Company XYZ, site abs	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	
NOTE The (Parent) Substantace ID refers to Brentuximab Vedotin.			

C.9.6 Brentuximab Vedotin–In-house Grade.

High-level Grade information is provided by Specified Substance Group 3, In-house specification, see Figure 38.

Table C.16 — Recombinant Brentuximab Vedotin –In-house specification

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	GHFTE8976H (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Brentuximab Vedotin-In-house	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
Parent Substance ID	JKHGYD6453 (Artificial ID)	II	1)
Element Group: Grade			
Grade Type	In-house	CD	
Grade Name	Brentuximab Vedotin-In-house-v002	ST	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory submission	CD	
Reference Source ID	Case 31452	ST	
NOTE The (Parent) Substantace ID refers to Brentuximab Vedotin.			

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Annex D
(informative)

Nucleic acid substance

D.1 Introduction

Nucleic acids are one of the five types of single substances described in ISO 11238. Nucleic acids are a type of substance that can be defined by a linear sequence of nucleosides typically linked through phosphate or phosphate-like diesters.

Nucleic acids will be defined by essentially three elements:

— the base;

— the base connected sugar or sugar-like element;

— the linkage element, typically a diester.

The goal for all monodisperse substances is to be able to have the ability to recreate the complete molecular structure of the substance from the data elements that define the substance.

Nucleic acids range from short oligonucleotides to whole chromosomes. Typically, short oligonucleotides can be represented by either a molecular structure or the three elements listed or both. Genes, gene elements, mRNA, plasmids and viral genomes shall be solely described as nucleic acids.

The base sequence will be captured using the common single letter codes A for Adenine, C for Cytosine, G for Guanine, I for Inosine, T for Thymine and U for Uracil. Sequences will always be captured in the standard 5'-3' direction. If modified bases are present, the sequence listed will be the unmodified sequence using the base which most closely resembles the modified base. If a base does not resemble a natural base an X can be used. Connection points will only be represented for modified bases if the linkage to the sugar or sugar-like moiety is other than the 1 position for pyrimidines or the 7 position for purines.

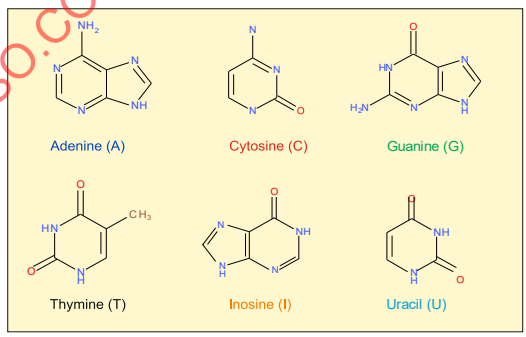


Figure D.1 — Nucleic acid bases

The Information model for Nucleic Acids is shown in Figure D.2 below.

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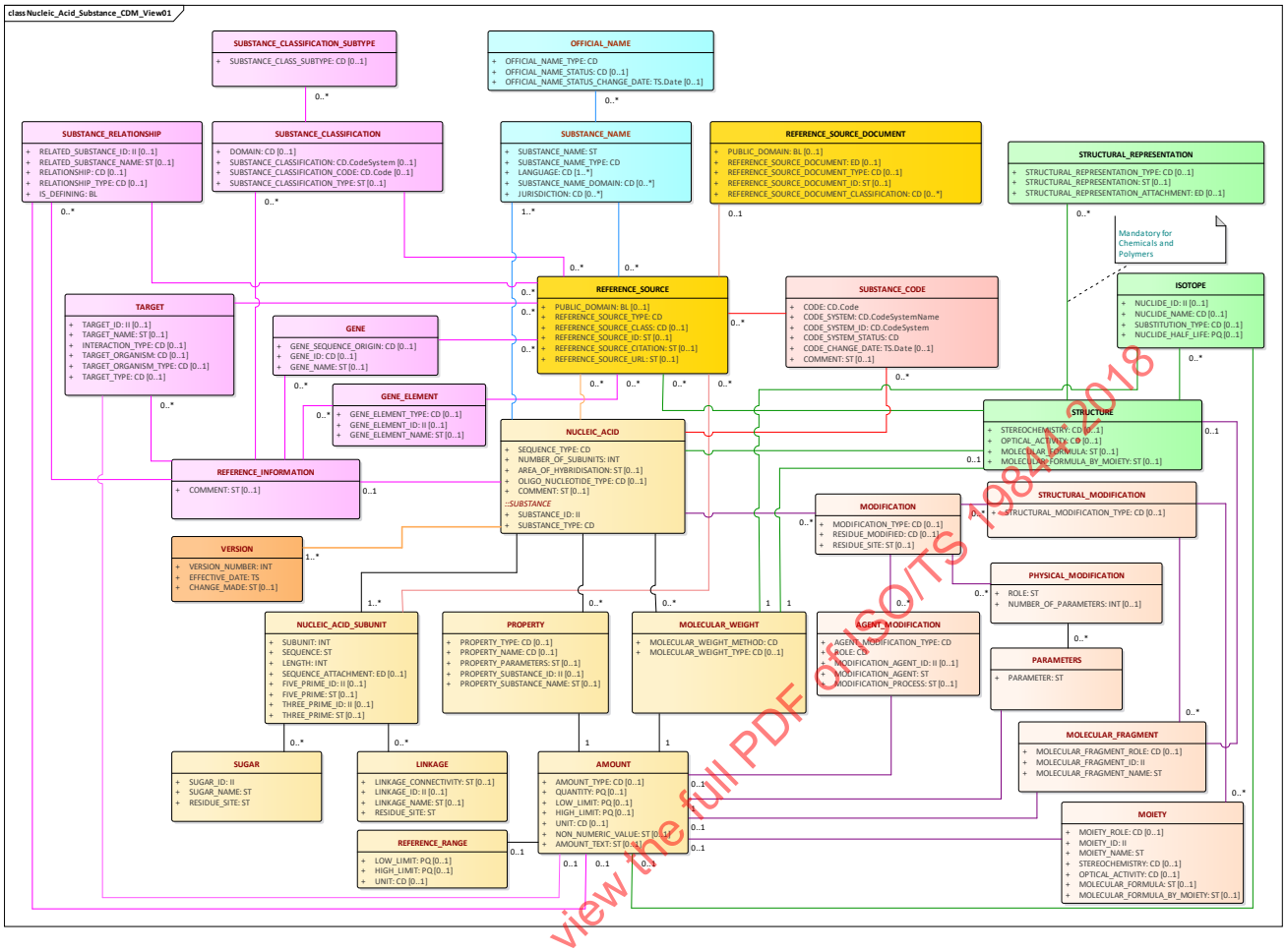


Figure D.2 —Detail overview of Nucleic Acid Substance information

D.2 Scope

This document provides guidance to define elements that describe mandatory and conditional requirements/fields for nucleic acids in order to generate ISO 11238 Substance Identifiers in view of ISO 11238 and ISO/TS 19844 by providing examples of substances belonging to the class described above.

D.3 Terms and definitions

D.3.1
nucleic acid substance

type of substance that can be defined by a linear sequence of nucleosides typically linked through phosphate or phosphate-like diester bonds

Note 1 to entry: The type of nucleic acid substance, e.g. ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), is also identified. Oligonucleotides and gene elements, e.g. promoters, enhancers, coding sequences and silencers, are defined as nucleic acid substances.

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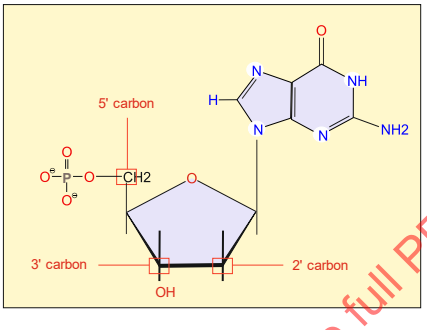
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D.4 Examples

D.4.1 Example: 5-Methylcytosine

5-Methylcytosine is a commonly observed modified base present in both oligonucleotides and the regulatory regions of many genes. The actual base sequence would still use C but there would be a site-specific base-substitution at every site where 5-Methylcytidine is present.

Sugar or sugar-like fragments are elements essential to the definition and structure of nucleic acids. A structure with a .beta.Furanose conformation will be used to indicate whether the nucleic acid contains ribose, deoxyribose or a related sugar and is typically connected to the base at the 1'-position, see Figure D.3, Figure D.4 and Figure D.5.

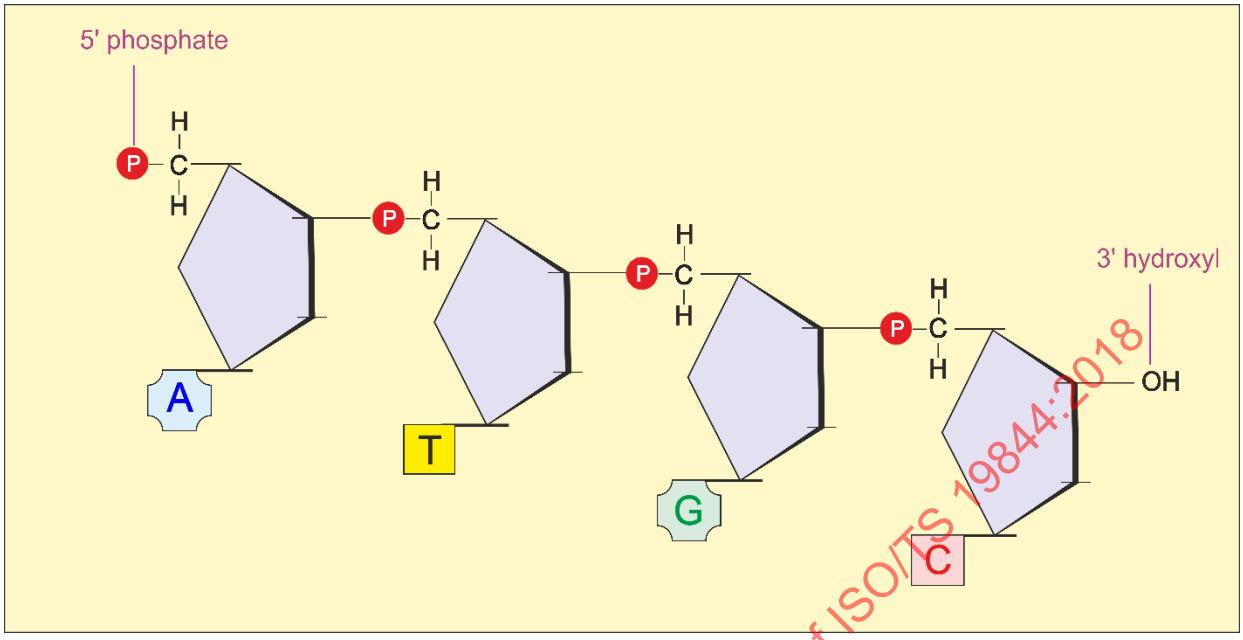


A nucleotide is made up of three components: a nitrogenous base (Guanine), a pentose sugar (deoxyriboase) and one of more phosphate groups. The Purine (or Pyrimidine) base is attached to the sugar at the 1st carbon position. Adenine and Guanine are classified as Purines, Cytosine, Thymine and Uracil are classified as Pyrimidines.

Figure D.3 — Representative structures of a nucleotide (1/3)

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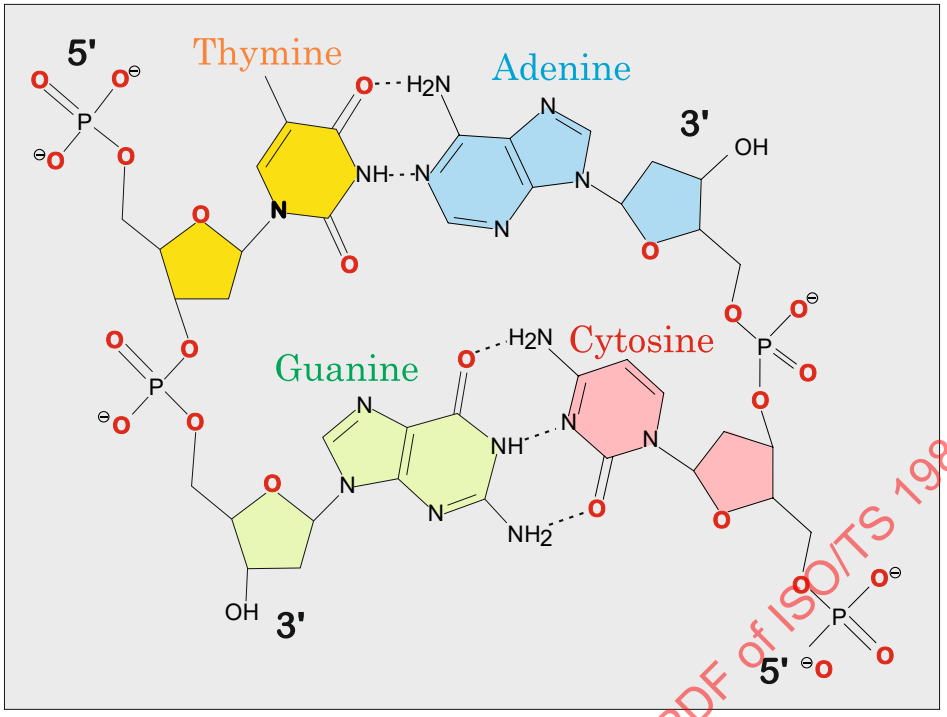


Short fragments of nucleic acids also are commonly produced without enzymes by oligonucleotide synthesizers. In all cases, the process involves forming of a phosphodiester bond between the 3' carbon of one nucleotide and the 5'carbon of another nucleotide. This leads to formation of the so-called 'sugar-phosphate backbone'. The key feature of all nucleic acids is that they have two distinctive ends: the 5' (5-prime) and the 3' (3-prime) ends. DNA and RNA polymerases add nucleotides to the 3' end of the previously incorporated base. Nucleic acids are synthesized in a 5'to 3' direction.

Figure D.4 — Representative structures of a nucleotide (2/3)

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In a double stranded DNA molecule, the two strands run antiparallel to one another so that one strand runs 5' to 3' and the other 3' to 5'. The phosphate backbone is located on the outside, and the bases are in the middle. Adenine forms hydrogen bonds (or base pairs) with Thymine, and Guanine base pairs with Cytosine.

Figure D.5 — Representative structures of a nucleotide (3/3)

Fragments with connection points will be used if bases are connected to a position other that 1' position. Common sugars are listed below:

Sugar ID: Z9I45OZ8PJ (UNII)
Sugar Name: .beta.-D-2-Deoxyribose

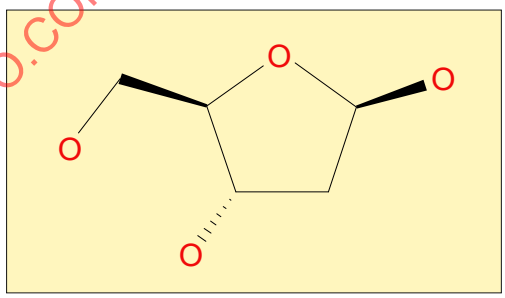


Figure D.6 — Structural representation of .beta.-D-2-Deoxyribose

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Sugar ID: IVV837V11N (UNII)

Sugar Name: .beta.-D-2-Ribose

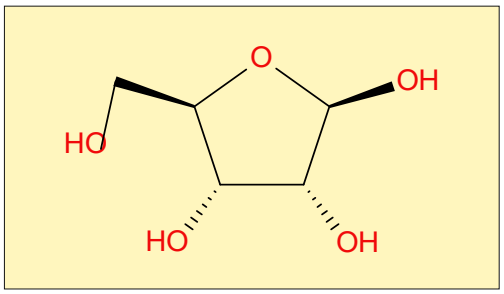


Figure D.7 — Structural representation of .beta.-D-2-Ribose

Sugar ID: AW90983458 (UNII)

Sugar Name: 2-O-Methyl-.beta.-D-ribofuranose

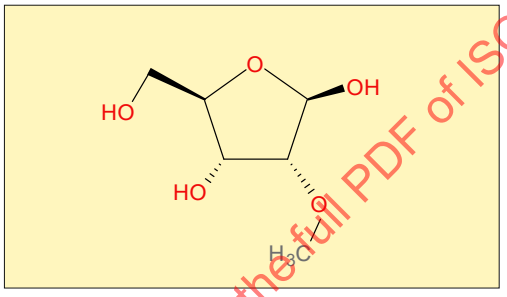


Figure D.8 — Structural representation of 2-O-Methyl-.beta.-D-ribofuranose

Sugar ID: 0K9V1SR8T9 (UNII)

Sugar Name: .beta.-D-Arabinofuranose

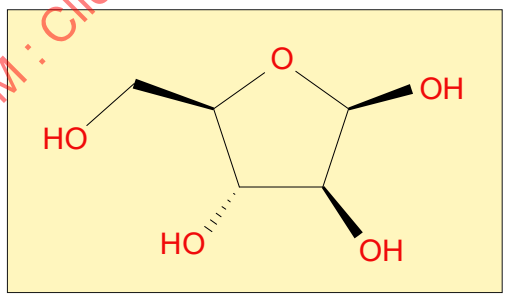


Figure D.9 — Structural representation of .beta.-D-Arabinofuranose

5’ and 3’ modified end-groups will be captured as a separate sugar fragment that contains the complete modification as a single unit.

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D.4.2 Example: A 5'-phosphate ribonucleotide

A 5'-phosphate ribonucleotide end-group can be captured through a sugar residue at position 1'.

Sugar ID: BVJ0IQF3T8 (UNII)
Sugar Name: .beta.-D-Ribose-5-phosphate

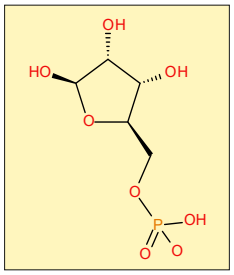


Figure D.10 — Structural representation of .beta.-D-Ribose-5-phosphate

The internucleotide linkages between sugars will be captured as a separate group of elements. The typical linkage is a phosphodiester linkage. Other common linkages include phosphothiorate; methylphosphonate salts will also be captured with the linkage.

D.4.3 Residues involved in the internucleotide linkage.

Typically, linkages will be numbered from the first 5'-residue involved in the linkage. Typically, linkages will begin at residue 2 and end at the 3' end of the strand.

The actual linkage which indicates the positions on each of the sugars involved in the linkage shall be captured. The typical linkage for nucleic acids will be 3' -> 5'.

Each linkage fragment shall have a name and ID and will be registered as a substance.

EXAMPLE

Linkage ID: 7Z7BK2GWOA (UNII)
Linkage Name: Phosphothioate linkage
Stereochemistry: Racemic

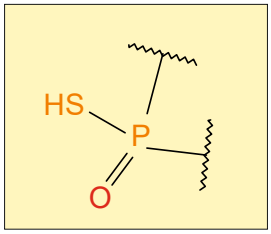


Figure D.11 — Structural representation of a Phosphothioate linkage

D.5 Substances

D.5.1 Example: Mipomersen sodium information

In addition to the elements listed above a graphical image of an oligonucleotide should be provided when appropriate. This is shown in Figure D.12 which is an attachment to the tabulated format information shown below.

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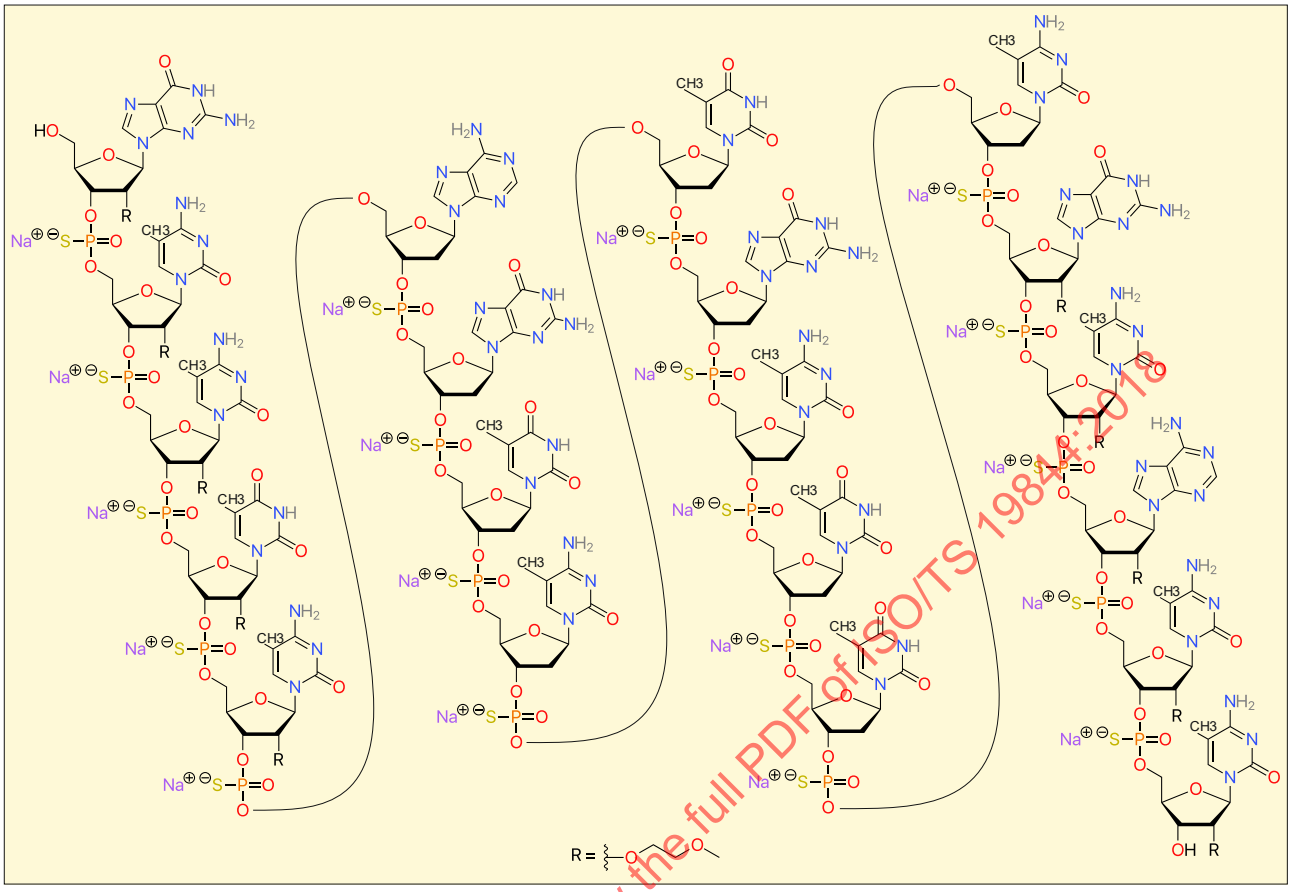


Figure D.12 — Structure of Mipomersen Sodium

D.5.2 Oligonucleotide Elements

Mipomersen sodium is a synthetic second-generation 2′-methoxyethyl antisense oligonucleotide inhibitor of the molecular target, apolipoprotein B-100.

D.5.2.1 Example Nucleic Acid Substance: Mipomersen sodium

Table D.1 — Mipomersen sodium

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	MIPO78654S (Artificial ID)	II	
Substance Type	Nucleic Acid	CD	
Element Group: Substance Name			
Substance Name	Mipomersen Sodium	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	

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Element Name	Value	Data Format	Note #
Element Group: Official Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Recommended INN List	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	WHO Drug Information Vol. 22, No 2, 2008	ST	1)
Reference Source URL	http://www.who.int/medicines/publications/druginformation/innlists/PL99.pdf?ua=1	ST	
Element Group: Substance Name (Repeat)			
Substance Name	2'-O-(2-methoxyethyl)-P-thioguanylyl-(3'→5')- 2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'→5')- 2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'→5')- 2'-O-(2-methoxyethyl)-5-methyl-P-thiouridylyl-(3'→5')- 2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'→5')- 2'-deoxy-P-thioadenylyl-(3'→5')- 2'-deoxy-P-thioguanylyl-(3'→5')- P-thiothymidylyl-(3'→5')- 2'-deoxy-5-methyl-P-thiocytidylyl-(3'→5')- P-thiothymidylyl-(3'→5')- 2'-deoxy-P-thioguanylyl-(3'→5')- 2'-deoxy-5-methyl-P-thiocytidylyl-(3'→5')- P-thiothymidylyl-(3'→5')- P-thiothymidylyl-(3'→5')- 2'-deoxy-5-methyl-P-thiocytidylyl-(3'→5')- 2'-O-(2-methoxyethyl)-P-thioguanylyl-(3'→5')- 2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'→5')- 2'-O-(2-methoxyethyl)-P-thioadenylyl-(3'→5')- 2'-O-(2-methoxyethyl)-5-methyl-P-thiocytidylyl-(3'→5')- 2'-O-(2-methoxyethyl)-5-methylcytidine, nonadecasodium	ST	
Substance Name Type	Systematic	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Recommended INN list	CD	
Reference Source Class	Official Name Source	CD	
Reference Source URL	http://www.who.int/medicines/publications/druginformation/innlists/PL99.pdf?ua=1	ST	

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Element Name	Value	Data Format	Note #
Element Group: Substance Name (Repeat)			
Substance Name	DNA, d(P-thio)([2′-O-(2-methoxyethyl)]rG-[2′-O-(2-methoxyethyl)]m5rC-[2′-O-(2-methoxyethyl)]m5rC-[2′-O-(2-methoxyethyl)]m5rU-[2′-O-(2-methoxyethyl)]m5rC-A-G-T-m5CT-G-m5C-T-T-m5C-[2′-O-(2-methoxyethyl)]rG-[2′-O-(2-methoxyethyl)]m5rC-[2′-O-(2-methoxyethyl)]rA-[2′-O-(2-methoxyethyl)]m5rC-[2′-O-(2-methoxyethyl)]m5rC), sodium salt(1:19)	ST	
Substance Name Type	Other Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	
Reference Source Citation	CAS Registry Name	ST	
Element Group: Substance Code			
Code	629167-92-6	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Reference Information			
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	C10AX11	CD.Code	
Substance Classification Type	Mipomersen	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Public Database	CD	

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Element Name	Value	Data Format	Note #
Reference Source URL	https://www.whocc.no/atc_ddd_index/?code=C10AX11&showdescription=yes	ST	
Element Group: Structure			
Stereochemistry	Chiral	CD	
Molecular Formula	$C_{230}H_{305}N_{67}Na_{19}O_{122}P_{19}S_{19}$	ST	
Molecular Formula by Moiety	N/A	ST	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	See Figure D.12 — Structure of Mipomersen Sodium	ED	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	7 594,9	PQ	
Unit	g/mol	CD	
Element Group: Nucleic Acid			
Sequence Type	Complete	CD	
Number of Subunits	1	INT	
Element Group: Nucleic Acid Subunit			
Subunit	1	INT	
Sequence	GCCUCAGTCTGCTTCGCACC	ST	
Length	20	INT	
Sequence Attachment	GCCUCAGTCTGCTTCGCACC	ED	1)
Five Prime ID	GUANI98765 (Artificial ID)	II	
Five Prime	Guanine (G)	ST	
Three Prime ID	CYTOS12345 (Artificial ID)	II	
Three Prime	Cytosine (C)	ST	

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Element Name	Value	Data Format	Note #
Element Group: Sugar			
Sugar ID	DEOX12345S (Artificial ID); [Z9I45OZ8PJ (UNII)]	II	
Sugar Name	.beta.-D-2-Deoxyribose	ST	
Residue Site	1_6-1_14	ST	
Element Group: Sugar (Repeat)			
Sugar ID	METHY76543 (Artificial ID);[FY7FL6G6HT (UNII)]	II	
Sugar Name	.beta.-D-2′-O-(2-methoxyethyl)ribose	ST	
Residue Site	1_1-1_5; 1_16-1_20	ST	
Element Group: Linkage			
Linkage Connectivity	3'→5'	ST	
Linkage ID	PHOSP13245 (Artificial ID); [1ST100S00F (UNII)]	II	
Linkage Name	Phosphothioate sodium linkage	ST	
Residue Sites	1_2-1_20	ST	
Element Group: Modification			
Modification Type	Structural modification	CD	
Residue Modified	Cytosine	CD	
Residue Site	1_2; 1_3; 1_5; 1_9; 1_12; 1_15 ;1_17; 1_19; 1_20	ST	
Element Group: Structural Modification			
Structural Modification Type	Nucleic acid base substitution	CD	
Element Group: Molecular Fragment			
Molecular Fragment Role	Nucleotide base modification	CD	
Molecular Fragment ID	MECYT67543 (Artificial ID); [6R795CQT4H (UNII)]	II	
Molecular Fragment Name	5-Methylcytosine	ST	2)
Element Group: Amount			
Amount Type	Exact	CD	
Amount Text	Complete	ST	
Element Group: Modification (Repeat)			
Modification Type	Structural modification	CD	

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Element Name	Value	Data Format	Note #
Element Group: Structural Modification			
Structural Modification Type	Salt formation	CD	
Element Group: Moiety			
Moiety Role	Salt	CD	
Moiety ID	NAYYY78654 (Artificial ID)	II	
Moiety Name	Sodium	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	19	PQ	
Unit	{mol/mol}	CD	
Amount Text	Mole Ratio to Parent Substance	ST	
Element Group: Moiety (Repeat)			
Moiety Role	Parent	CD	
Moiety ID	MEPO0564352 (Artificial ID)	II	
Moiety Name	Mipomersen	ST	
Element group: Amount			
Amount Type	Exact	CD	
Quantity	1	PQ	
Unit	{mol/mol}	CD	
Amount Text	Mole Ratio to Salt	ST	
Element Group: Reference Information			
Element Group: Substance Relationship			
Related Substance ID	MEPO0564352 (Artificial ID)	II	
Related Substance Name	Mipomersen	ST	
Relationship	Parent	CD	
Relationship Type	Ionic	CD	
Is Defining	Yes	BL	

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Element Name	Value	Data Format	Note #
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	94,2	PQ	
Unit	% {w/w}	CD	
Non Numeric Value	Equivalence Factor 0,942 (Weight per cent to salt)	ST	

[1] The underlined residues GCCUCAGTCTGCTTCGCACC are 2′-O-(2-methoxyethyl) nucleosides, all other residues are 2′-deoxynucleosides.

[2] The Molecular formula is provided for the 5-Methylcytosine. The Molecular Formula of the actual fragment is $C_5H_6N_3O$

D.5.2.2 Example: Nucleic Acid Substance: Litenimod

Litenimod is an oligonucleotide that is an agonist for the toll-9 receptor.

Table D.2 — Litenimod

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	PYTRS34526 (Artificial ID)	II	
Substance Type	Nucleic Acid	CD	
Element Group: Substance Name			
Substance Name	Litenimod	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Recommended INN List	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	WHO Drug Information, Vol. 21, No. 3, 2007 Recommended INN: List 58	ST	
Reference Source URL	http://mednet.who.int/inn/db/media/docs/r-innlist58.pdf	ST	
Element Group: Substance Name (Repeat)			
Substance Name	P-thiothymidylyl-(3'→5')-2'-deoxy-P-thioadenylyl-(3'→5')-2'-deoxy-P-thioadenylyl-(3'→5')-2'-deoxy-P-thioadenylyl-	ST	

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Element Name	Value	Data Format	Note #
	(3'→5')-2'-deoxy-P-thiocytidylyl-(3'→5')-2'-deoxy-P-thioguanylyl-(3'→5')-P-thiothymidylyl-(3'→5')-P-thiothymidylyl-(3'→5')-2'-deoxy-P-thioadenylyl-(3'→5')-P-thiothymidylyl-(3'→5')-2'-deoxy-P-thioadenylyl-(3'→5')-2'-deoxy-P-thioadenylyl-(3'→5')-2'-deoxy-P-thiocytidylyl-(3'→5')-2'-deoxy-P-thioguanylyl-(3'→5')-P-thiothymidylyl-(3'→5')-P-thiothymidylyl-(3'→5')-2'-deoxy-P-thioadenylyl-(3'→5')-P-thiothymidylyl-(3'→5')-2'-deoxy-P-thioguanylyl-(3'→5')-2'-deoxy-P-thioadenylyl-(3'→5')-2'-deoxy-P-thiocytidylyl-(3'→5')-2'-deoxy-P-thioguanylyl-(3'→5')-P-thiothymidylyl-(3'→5')-2'-deoxy-P-thiocytidylyl-(3'→5')-2'-deoxy-P-thioadenylyl-(3'→5')-thymidine		
Substance Name Type	Systematic Name	CD	
Language	en	CD	
Element Group: Substance Name (Repeat)			
Substance Name	DNA, d(P-thio)(T-A-A-A-C-G-T-T-A-T-A-A-C-G-T-T-A-T-G-A-C-G-T-C-A-T)	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	
Reference Source Citation	CAS Registry Name	ST	
Element Group: Substance Code			
Code	852313-25-8	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	303159CVH9	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Structure			
Stereochemistry	Chiral	CD	

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Element Name	Value	Data Format	Note #
Molecular Formula	$C_{256}H_{322}O_{129}P_{25}S_{25}$	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	FDA GSRS	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	https://fdasis.nlm.nih.gov/srs/auto/litenimod	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	8 369,20	PQ	
Unit	g/mol	CD	
Element Group: Nucleic Acid			
Sequence Type	Complete	CD	
Number of Subunits	1	INT	
Element Group: Nucleic Acid Subunit			
Subunit	1	INT	
Sequence	TAAACGTTATAACGTTATGACGTCAT	ST	
Length	26	INT	
Five Prime ID	TYMID87654 (Artificial IS); [JKUHT76541 (Artificial ID)]	II	
Five Prime	Thymine (T)	ST	
Three Prime ID	TYMID87654 (Artificial IS); [JKUHT76541 (Artificial ID)]	II	
Three Prime	Thymine (T)	ST	
Element Group: Sugar			
Sugar ID	DEOX12345S (Artificial ID); Z9I45OZ8PJ (UNII)	II	
Sugar Name	.beta.-D-2-Deoxyribose	ST	
Residue Site	1_1-1_26	ST	
Element Group: Linkage			
Linkage Connectivity	3'→5'	ST	
Linkage ID	PHOSP13245 (Artificial ID); [7Z7BK2GWOA (UNII)]	II	
Linkage Name	Phosphothioate linkage	ST	

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D.5.2.3 Example: Anti-sense RNA

TGF-.BETA.-2 ANTI-SENSE RNA (6-935) is an anti-sense RNA molecule that is expressed in allogenic tumour cells to reduce the amount of TGF-.BETA expression in allogenic target cells in order to increase the immunogenicity of the allogenic tumour cell vaccine. The RNA is defined as a substance in its own right.

Table D.3 — Anti-sense RNA

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	ANRNA67543 (Artificial ID)	II	
Substance Type	Nucleic Acid	CD	
Element Group: Substance Name			
Substance Name	TGF.beta.-2 Anti-sense RNA (6-935)	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	FDA GSRS	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	https://fdasis.nlm.nih.gov/srs/auto/tgf%252Ebeta%252E-2%20anti-sense%20rna%20(6-935)	ST	
Element Group: Substance Code			
Code	FUA17JE46Y	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Structure			
Element Group: Structural Representation			
Structural Representation Type	HELM	CD	1)
Structural Representation	RNA1{R©P.R(A)P.R(A)P.R(G)P.R(A)P.R(G)P.R(G)P.R(C)P.R(A)P.R(U)P.R(A)P.R(C)P.R(U)P.R(C)P.R(C)P.R(U)P.R(C)P.R(A)P.R(U)P.R(A)P.R(G)P.R(G)P.R(G)P.R(A)P.R(A)P.R(A)P.R(G)P.R(A)P.R(U)P.R(C)P.R(U)P.R(U)P.R(G)P.R(A)P.R(C)P.R(U)P.R(G)P.R(C)P.R(C)P.R(A)P.R(C)P.R(U)P.R(G)P.R(U)P.R(C)P.R(U)P.R	ST	1)

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Element Name	Value	Data Format	Note #
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Element Name	Value	Data Format	Note #
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Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	298 892,36	CD	
Unit	g/mol	CD	
Element Group: Nucleic Acid			

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Element Name	Value	Data Format	Note #
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Number of Subunits	1	INT	
Element Group: Nucleic Acid Subunit			
Subunit	1	INT	
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Length	930	INT	
Sequence Attachment	See below	ED	2)

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Element Name	Value	Data Format	Note #
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Element Group: Sugar			
Sugar ID	DRIBO98765 (Artificial ID); [Z9I45OZ8PJ (UNII)]	II	
Sugar Name	.beta.-D-Ribose	ST	
Residue Site	1_1-1_930	ST	

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Element Name	Value	Data Format	Note #
Element Group: Linkage			
Linkage Connectivity	3'→5'	ST	
Linkage ID	PHOSL45321 (Artificial ID0; [SSG1RX859B (UNII)]	II	
Linkage Name	Phosphoryl linkage	ST	
Residue site	1_1-1_930	ST	
NOTE 1 HELM: A hierarchical Notation Language for complex Biomolecule Structure Representation. The display of this structural representation is provided as a provisional set of data unsupported with a reference to a source. NOTE 2 FDA GSRS, https://tripod.nih.gov/ginas/app/substance/d1140dee			

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Annex E
(normative)

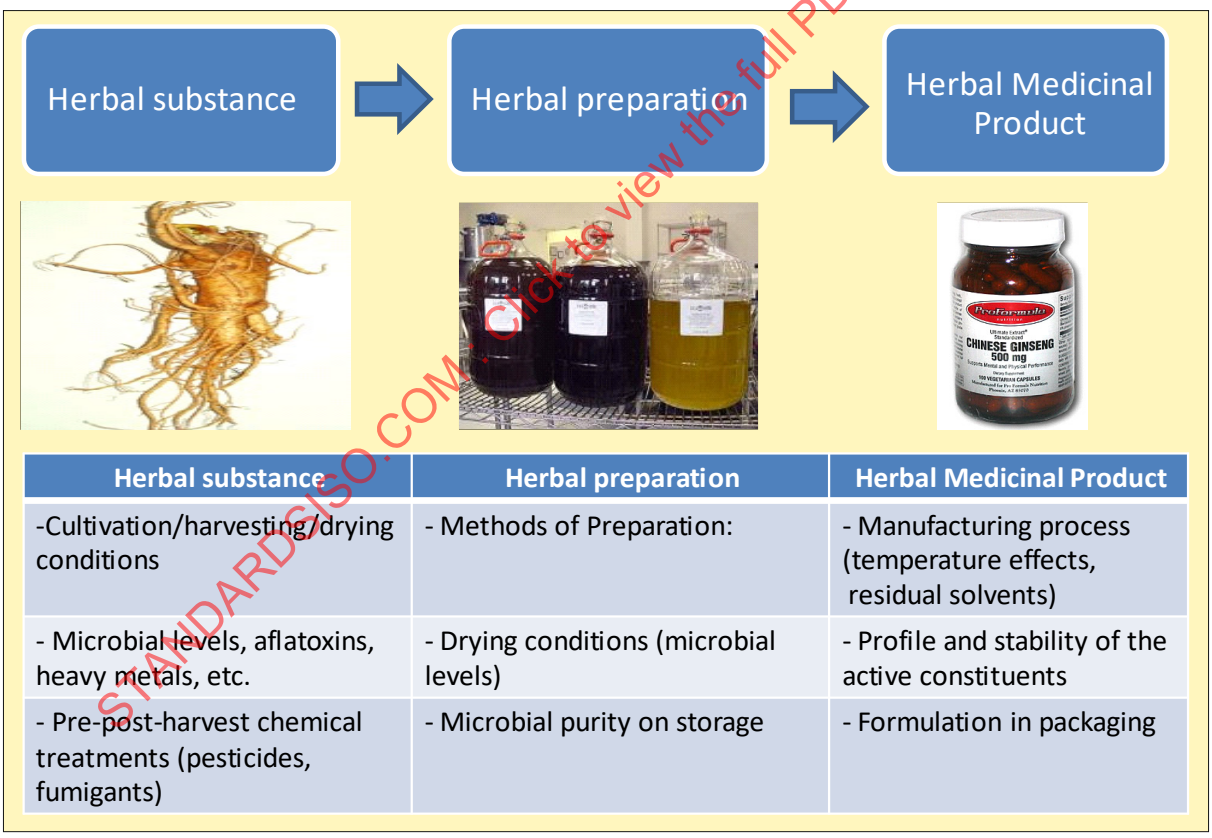
Structurally Diverse Substance — Herbal Substance/Herbal Specified Substance

E.1 Scope

This annex provides guidance to define elements that describe mandatory and conditional requirements/fields in order to generate ISO 11238 Substance Identifiers for Herbals, with respect to the ISO 11238 and ISO/TS 19844, by providing examples of generating identifiers for Herbal Substances (referred to as Herbal Drugs in this annex) and Herbal preparations.

E.2 Introduction

Legislation in jurisdictions such as the European Union provides a clear delineation between Herbal Drugs and Herbal preparations. This is illustrated in Figure E.1 below.



Herbal substance	Herbal preparation	Herbal Medicinal Product
-Cultivation/harvesting/drying conditions	- Methods of Preparation:	- Manufacturing process (temperature effects, residual solvents)
- Microbial levels, aflatoxins, heavy metals, etc.	- Drying conditions (microbial levels)	- Profile and stability of the active constituents
- Pre-post-harvest chemical treatments (pesticides, fumigants)	- Microbial purity on storage	- Formulation in packaging

Figure E.1 — Flow of the Herbal Information

NOTE Herbal Medicinal Products are not covered in detail by the ISO 11238. Herbal Medicinal Products are medicinal formulations of the Herbal Substance/Herbal Drug or Herbal preparations combined with excipients to formulate a Herbal Medicinal Product.

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The purpose of this Annex is to provide guidance on information that should be transmitted to a maintenance authority to assign an identifier to a given Herbal Drug or Herbal preparation.

ISO 11238 uses the terms 'Substance' and 'Specified Substance' in very specific ways.

2.1.58 substance: 'any matter of defined composition that has discrete existence, whose origin may be biological, mineral or chemical. Substances can be single substances, mixture or one of a group of Specified Substances'.

2.1.53 Specified Substances: 'group of elements which describe multi-substance materials and specify further information on substances and multi-substance materials relevant to the description of medicinal products'.

Within this document, the terms Substance and Specified Substance are used as defined by ISO 11238, whilst Herbal Drug and Herbal preparation are used as defined by pharmacopoeias.

Definitions for Herbal Drugs and Herbal preparations are presented in E.3.

This annex outlines that both Herbal Drugs and Herbal preparations, as used in pharmacopoeias, are captured as Substances within ISO 11238. In addition, a more basic unit, comprising unprocessed, fresh material of a single species or intraspecies (or occasionally a genus) and part, with no affiliation to any particular pharmacopoeia or medicinal product, will also be captured at the Substance level; for clarity, these will be referred to as Substance (fresh) in this annex.

There are five types of single substances in ISO 11238 (see 5.2.1), and Herbals are defined using the elements for a Structurally Diverse Substance (see Figure E.2 and 6.5 of this document) and in particular the source organism taxonomy, part and fraction.

The information model also accommodates fraction information at the Substance level which is captured at the Source Material information model (Figure 19). Fractions, such as oils and juices, are captured at this level; exudates such as gums and resins will also be treated as fractions in the same way as oils and juices. The element <Fraction> will correspond to two different Herbal preparations: <Oil, Exudate, Juice> or <Extract>, each requiring different information.

It is necessary to describe the Herbal preparation <Extract> in more detail compared with the Herbal preparation <Oil, Exudate, Juice> in order to comply with different jurisdictional legislation (e.g. European Union legislation) since marker substances shall be described and referred to for standardized and quantified Herbal preparations. Since the Constituent Group is captured at the Specified Substance Group 1 information level this information is captured here and as a consequence a Herbal preparation <Extract> has a Specified Substance Group 1 ID and along with the Substance Name Type, value 'Specified Substance Group 1' and further specifications described at the Specified Substance Group 1 (SSG1) level, such as the mass ratio Herbal Substance/Herbal extract (DER) as a Characteristic Attribute and the extraction solvent composition(s) by means of the element group Constituent.

Note, in this context, 'Herbal Substance' can be either a Substance (fresh) or a Herbal Drug.

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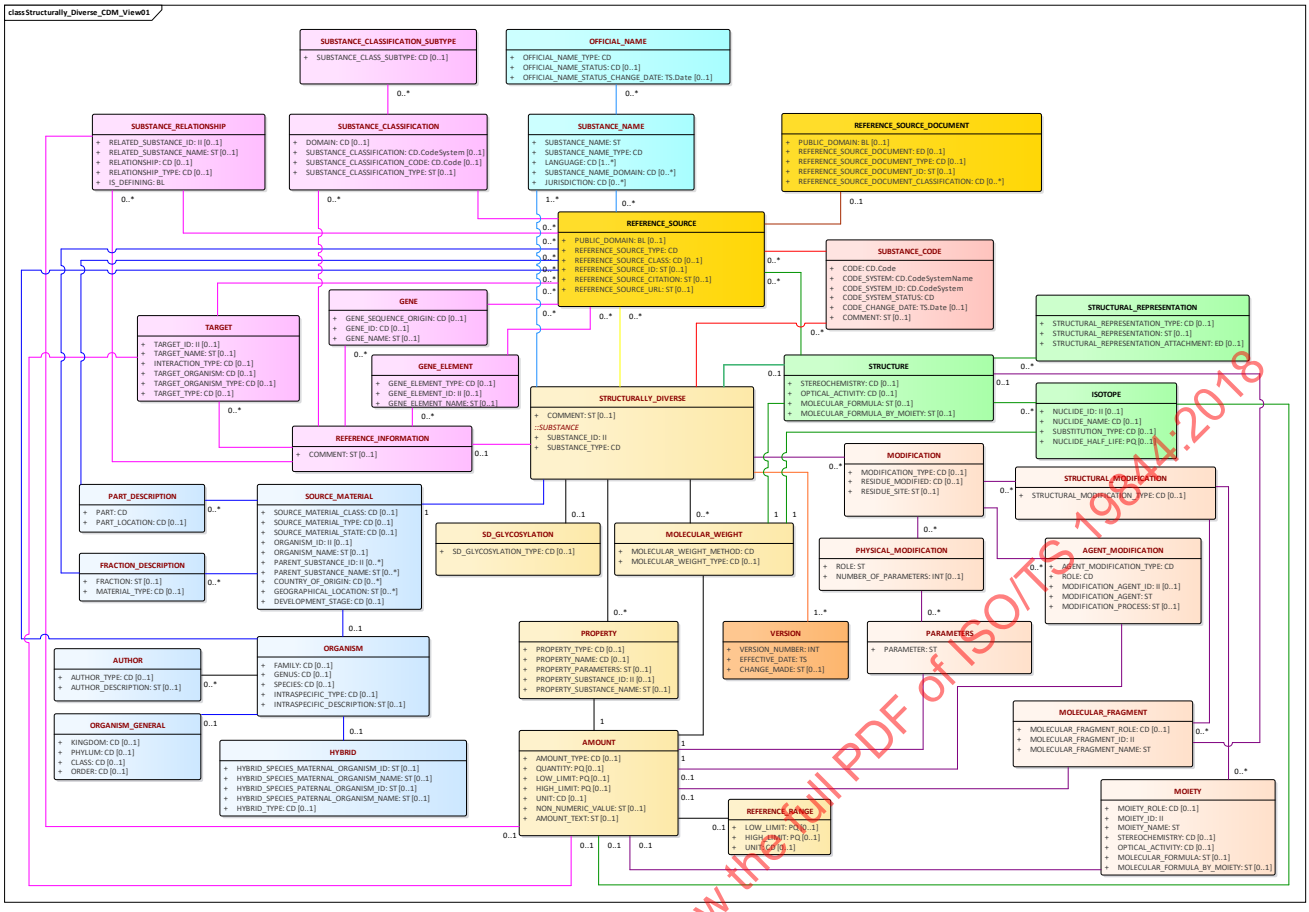


Figure E.2 — Detail overview of Structurally Diverse Substance information

For the Substance (fresh), Herbal Drug and Herbal preparation the information model shown above will be addressed as explained in Figure E.3.

The extended Fraction information, that is described by the Attribute Type 'Particular Herbal preparation' with the Attribute Name 'Drug Extract Ratio (DER)' in connection with the element group 'Amount' is not required at the Substance level but will be a defining element at the Specified Substance Group 1 information level (see Figure 35). Extended Fraction information regarding the extraction solvent composition is described by means of the element group Constituent in connection with the element group Amount.

Specified Substances include additional information for substances and multi-substance materials (multiple substances and/or Specified Substances of diverse origin used as a component in the formulation of a medicinal product). Herbal Drugs and Herbal preparations that are made from more than one plant species are multi-substance materials.

E.2.1 Structurally Diverse Substance type

Fresh plant material, Herbal Drugs and Herbal preparations, including extracts, will all be captured as Substances, defined using the elements of the structurally diverse substance type. The elements necessary for defining the source material of structurally diverse substances, i.e. organism, part and fraction, are illustrated in Figure 19.

This document should be referred to for user guidance and business rules for the various elements of the source material for structurally diverse substances as they apply to Herbals. Examples are given for Herbals derived from plant material, as well as material from algae and fungi, which are also classified as Herbals. Other types of natural materials, such as animals and minerals are also treated as Herbals in Kampo extracts and other systems of medicine.

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E.2.2 Organism Taxonomy

Substances of organic origin, such as plants and animals, should be defined simply by taxonomic information and the organism part. Taxonomic information, particularly the scientific name of a medicinal plant, is essential for defining herbal substances in medicinal products.

The Kew Gardens Medicinal Plant Names Services (MPNS) should be the authoritative source for all scientific names of plants and should also maintain a list of plant parts and fractions. A controlled vocabulary for medicinal plant taxonomy has been developed and will be maintained by the Kew Gardens Medicinal Plant Names Services. A submitter should choose the current accepted scientific name provided by MPNS. The MPNS Portal should be accessed via www.kew.org/mpns. The service should be contacted if the herbal substance material cannot be mapped to records in MPNS. It should be noted that many common and even pharmacopoeial names of plants often map to more than one plant species, but it is important that the actual herbal substance (defined as a particular species) is used in defining a substance.

The expert opinion for fungi should be obtained from Species Fungorum[34] which is managed and maintained by Kew Gardens[35]. Taxonomic information for most other organisms is available through Catalogue of Life (COL[36], currently 1,600,000+ organisms) and its 151 contributing source databases. The most notable contributors are Kew Gardens and the Integrated Taxonomic Information System[37]. COL has integrated the source datasets into a common seven level taxonomic tree using an eight-kingdom model and includes intraspecifics where relevant. For organisms omitted in the above sources, NCBI taxonomy[38] is the most useful source database.

The higher levels of taxonomy are useful but all levels above family are not required for organism definition. The primary definition of an organism is the combination of genus and species together with the describing author and family in that order providing validation. Intraspecific type, description and hybrid characteristics are also definitional where appropriate. Because taxonomy is continuously changing, new organism identifiers should only be generated after analysing potential collisions with existing identifiers using the above public datasets and/or conferring with appropriate taxonomic experts. Developmental stage, part and viral strain characteristics should be associated with separate identifiers that refer back to the whole organism parent substance.

E.2.3 Substance Names

This section describes and illustrates the elements associated with the name of a structurally diverse substance, which is defined by its scientific name, part and, where appropriate, fraction, as described below. There are three categories of Substance name.

E.2.3.1 Substance (fresh) Name

A Substance (fresh) is always a single species, or intraspecies, or is occasionally a single genus. It will have a Name which is composed of:

[<Scientific genus/binomial/trinomial with Author>,<Part(s)>]

The scientific element of the name is usually a binomial, but may be a trinomial or a genus, as appropriate, together with the author of the name. The Substance Name is not an Official name in any pharmacopoeia or other legislation, and the inclusion of the author is to ensure that it is not confused with the official

[34] http://www.speciesfungorum.org

[35] https://www.kew.org/

[36] http://www.catalogueoflife.org/col

[37] http://www.itis.gov

[38] http://www.ncbi.nlm.nih.gov/taxonomy

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names for Herbal Drugs and Herbal preparations that are derived from a single species. It can be written in any language and its jurisdiction can be restricted, thus the Substance Name Type has the value 'Other'.

The Part element of the name should be chosen from a controlled vocabulary (CV) consisting of a restricted number of terms with broad definitions, e.g. Root. More specific or detailed information about the parts used should be captured using the Part element of the Source Material class, e.g. Tuberous Root, or Root, peeled. This is illustrated by the Devil's Claw Root example 2, see E.4.3.

E.2.3.2 Substance (Herbal Drug)

[<Scientific genus/binomial/trinomial without Author>, <Part(s)>]

In terms of ISO 11238 such a Substance Name is equivalent to a Herbal Drug Name.

E.2.3.3 Substance (Herbal preparation)

[<Scientific genus/binomial/trinomial without Author>, <Part(s)>], [Fraction]

In terms of ISO 11238 such a Substance Name is equivalent to a Herbal preparation Name.

The Herbal preparation Name is used for several Herbal preparations, e.g. one for the Substance fraction: Oil, Exudate, Juice, and one for the Substance fraction: Extract. This is done to differentiate the Herbal preparation with Limited information with the one with Extended information.

The fraction (Herbal preparation) <Oil, Exudate, Juice> is prepared from one Substance (fresh).

NOTE Several Herbal preparations, e.g. Juices, can be a mixture of separately obtained juices obtained from the Herbal substances and mixed after expression. The final preparation is then a multi-substance material which is captured at the Specified Substance Group 1 level.

The fraction (Herbal preparation) <Extract> can be prepared from **one or more** Herbal Drug(s) and by **one or more** extraction step(s) and by **one or different** extraction solvent composition(s). Only the first extraction solvent composition as described by the Element Group 'Processing Material' is laid down. However, the extended Manufacturing information model (see Figure E.7) provides the possibility to use multiple manufacturing steps and the use of different solvent compositions by the class 'Processing Material'.

E.2.4 Examples of Substance (fresh) and Substance (Herbal Drug) Names

NOTE Examples provided for this subclause are further built upon in later subclauses. The numbering of the examples remains the same.

EXAMPLE 1

The Herbal Drug Ginkgo Leaf (Ph.Eur.) is defined as the whole or fragmented, dried leaf of *Ginkgo biloba* L., and is captured at the Substance level as the Substance (Herbal Drug) *Ginkgo biloba*, Leaf. Fresh leaf of *Ginkgo biloba* L. is also captured at the Substance level, and will be the parent substance of such a Herbal Drug.

Substance ID: 19FUJ2C58T
Substance (fresh) Name: *Ginkgo biloba* L., Leaf
Substance Name Type: Other

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The Scientific Name corresponds to: *Ginkgo biloba* L. (L. stands for the author Linnaeus) which comes from the Organism Name.

Plant Part: Leaf
The full taxonomy will also be captured in the elements groups Organism, Organism General, Author and Hybrid:

Element Group: Organism
Family: Ginkgoaceae
Genus: Ginkgo
Species: biloba

Element Group: Organism General
Kingdom: Plantae
Phylum: Tracheophyta
Class: Ginkgoopsida
Order: Ginkgoales

Element Group: Author
Author Type: Species Primary Author: L.
Author Description: L. (Linnaeus)

ISO 11238 doesn't make provision for synonyms of the scientific name (which would be synonyms at the level of Organism), so for now (for plants) such synonyms will be handled within the plant names controlled vocabulary. ISO 11238 does allow for non-scientific synonyms to be captured for Substances and Specified Substances. Synonyms of substances will be common names rather than official names from pharmacopoeias, and may or may not include reference to the part of the plant.

Synonyms:

Ginkgo: Name Type: Other
Language: en

Ginkgo biloba leaf: Name Type: Other
Language: en

Salisburia biloba leaf: Name Type: Other
Language: en

Maidenhair tree leaf: Name Type: Other
Language: en

Substance ID: 45SPM3HJ6Q
Substance (Herbal Drug) Name: *Ginkgo biloba*, Leaf
Parent Substance ID: 19FUJ2C58T
Parent Substance (fresh) Name: *Ginkgo biloba* L., Leaf

EXAMPLE 2

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The Herbal Drug Devil's Claw Root (Ph.Eur.), also known as Harpagophyti radix, is defined as cut and dried, tuberous secondary roots of *Harpagophytum procumbens* (Burch.) DC. ex Meisn. and/or *Harpagophytum zeyheri* Decne.

At the Substance level, Devil's Claw Root (Ph.Eur.) will be captured as two substances (Herbal Drug), each based on a different parent substance (fresh), i.e. the root of the species *Harpagophytum procumbens* (Burch.) DC. ex Meisn. Substance (fresh) Name: *Harpagophytum procumbens* (Burch.) DC. ex Meisn., Root and the root of the species *Harpagophytum zeyheri* Decne. Substance (fresh) Name: *Harpagophytum zeyheri* Decne., Root, both having the Substance Name Type, value Other. For each of these substances the plant Part (within the Source Material class) will be captured as the appropriate controlled vocabulary term, e.g. 'Tuberous root'.

Devil's Claw Root (Ph.Eur.) is captured as two separate substances (Herbal Drug), each with one of the species as a parent substance.

Substance (Herbal Drug) Name: *Harpagophytum procumbens*, Root
Substance Name Type: Other
Parent Substance (fresh) Name: *Harpagophytum procumbens* (Burch.) DC. ex Meisn., Root

Substance (Herbal Drug) Name: *Harpagophytum zeyheri*, Root
Parent Substance (fresh) Name: *Harpagophytum zeyheri* Decne, Root

NOTE "/" or "\" cannot be used in a name due to technical implementation requirements.

EXAMPLE 3

The Herbal Drugs Salvia Miltiorrhiza Root and Rhizome (BP) and Chinese Salvia (USP) are defined as the dried root and rhizome of *Salvia miltiorrhiza* Bunge. *Salvia Miltiorrhiza* Root and Rhizome (BP) and Chinese Salvia (USP) will be captured as substances (Herbal Drug) based on a single substance (fresh), the rhizome and root of *Salvia miltiorrhiza* Bunge (Substance Name: *Salvia miltiorrhiza* Bunge, Rhizome and Root). It is a single substance because the plant parts are contiguous and harvested together. They are listed alphabetically in the substance name. Salvia Miltiorrhiza Root and Rhizome (BP) and Chinese Salvia (USP) will be two separate Specified Substances Group 3 because the definitions in the BP and USP are slightly different.

EXAMPLE 4 (for further explanation see Annex B).

The Herbal preparation Olive Oil, Virgin (Ph.Eur.) is defined as the fatty oil obtained by cold expression or other suitable mechanical means from the ripe drupes of *Olea europaea* L.

Olive Oil, Virgin (Ph.Eur.) will be captured as a substance (Herbal preparation) based on a single substance (fresh), the fruit of *Olea europaea* L. (Substance Name: *Olea europaea* L., Fruit). Some fraction details for this oil will be captured at the Specified Substance Group 1 level, and at the Specified Substance Group 3 level when compared with other Olive Oil grades.

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E.2.5 Specified Substance Group 1, 2 and 3 information

Figure E.3 provides the example of capturing information for the Herbal Drug and Herbal preparation at the Substance level and additional information for the fraction (Herbal preparation) <Extract> at the Specified Substance level.

E.2.5.1 Specified Substance Group 1 Name:

The simplest Specified Substance Group 1 Name for a **Herbal Drug** will be composed of:

[Scientific genus/binomial/trinomial **without** Author] [Part(s)] [Dry/Fresh]

The name is not an official name in any pharmacopoeia or other legislation. However, it can be written in any language and its jurisdiction.

EXAMPLE 1 (cont.):

Specified Substance Group 1 ID (Herbal Drug): GINKSP1HD0 (Artificial ID)
Substance Name (Herbal Drug): *Ginkgo biloba*, Leaf, Dry
Substance Name Type: Specified Substance Group 1
Language: en
Substance Name Domain = botanical
Jurisdiction = EU, JP

Element Group: Constituent
Constituent Substance ID: [45SPM3HJ6Q]
Constituent Substance Name (Herbal Drug): *Ginkgo biloba*, Leaf
Language: en
Substance Role: Parent substance
Is Defining: Yes

EXAMPLE 2 (cont.):

Devil's Claw Root (Ph.Eur.) is the cut and dried tuberous roots of *Harpagophytum procumbens* (Burch.) DC. ex Meisn. and/or *Harpagophytum zeyheri* Decne. This will be captured as two separate Specified Substances Group 1, each with one Substance (Herbal Drug) of a single species as a parent substance.

Substance Name (Herbal Drug): *Harpagophytum procumbens*, Root, Dry
Substance Name Type: Specified Substance Group 1
Parent Substance (Herbal Drug): *Harpagophytum procumbens*, Root

Substance Name (Herbal Drug): *Harpagophytum zeyheri*, Root, Dry
Substance Name Type: Specified Substance Group 1
Parent Substance (Herbal Drug): *Harpagophytum zeyheri*, Root

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E.2.5.2 Specified Substance Group 2 Name:

EXAMPLE 1 (cont.):

The following elements relevant to Herbal Drugs are captured at the Specified Substance Group 2 level:

Details of the manufacturing/harvesting for the (parent) substance are described at this information level:
Specified Substance Group 2 ID (Herbal Drug): MANER7654M (Artificial ID)
Substance Name (Herbal Drug): *Ginkgo biloba*, Leaf, Dry – Company Aa.
Substance Name Type: Specified Substance Group 2
Language: en
(Parent) Substance ID: GINKSP1HD0 (Artificial ID)

Manufacturing details are described by the attributes of Manufacturing class in Figure 36:

Organizational details:
Manufacturer (Supplier) of the Herbal Drug (ID, Name/address/etc.) as per the Organization class defined in ISO 11615).

Other elements are detailed in Figure 36:.

E.2.5.3 Specified Substance Group 3 Name

For Herbal Drugs, which have been defined at the Substance or Specified Substance Group 1 level by reference to a pharmacopoeial monograph, the information about the grade of the substance will be captured at the Specified Substance Group 3 level. Also, reference can be made to an *In-House* specification.

Names of Herbal Drugs and Herbal preparations in pharmacopoeial monographs and legislation apply here. Examples include Ginkgo Leaf (Ph.Eur.) and Refined and Quantified Ginkgo Dry Extract (Ph.Eur.) which would be captured as separate Specified Substances Group 3. These are official names, and their language and jurisdiction should be captured.

There are three types of extracts described in the Ph.Eur.: Standardized, Quantified and Other.

The Standardized, and Quantified extracts will be distinguished by name from the other extracts.

EXAMPLE 1 (cont.):

Specified Substance Group 3 ID (Herbal Drug): HGTRW12345 (Artificial ID)
Substance Name (Herbal Drug): *Ginkgo biloba*, Leaf, Dry, [Standardized/Quantified]-Ph.Eur.
Substance Name Type: Specified Substance Group 3

Grade Type: Ph.Eur.
Grade Name: Ginkgo Leaf

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EXAMPLE 2 (cont.):

Where the Specified Substance is a multi-substance material, the name will be composed of the scientific name for each substance. For multi-substance materials composed of more than four plant species, a grouping term will be used, such as the genus, Herbal Drug, Herbal preparation or product name, whichever is most descriptive.

Substance Name (Herbal Drug): *Harpagophytum procumbens and_or Harpagophytum zeyheri,* Root, Dry, [Standardized/Quantified]- Ph.Eur.
Substance Name Type: Specified Substance Group 3

Grade Type: Ph.Eur.
Grade Name: Devil's Claw Root
(Parent) Substance Name (Herbal Drug): *Harpagophytum procumbens*, Root, Dry
(Parent) Substance Name (Herbal Drug): *Harpagophytum zeyheri*, Root, Dry

E.2.5.4 Overview of the Naming connections of the Botanical Material for the Substance and Specified Substance Group 1, 2, 3 Levels

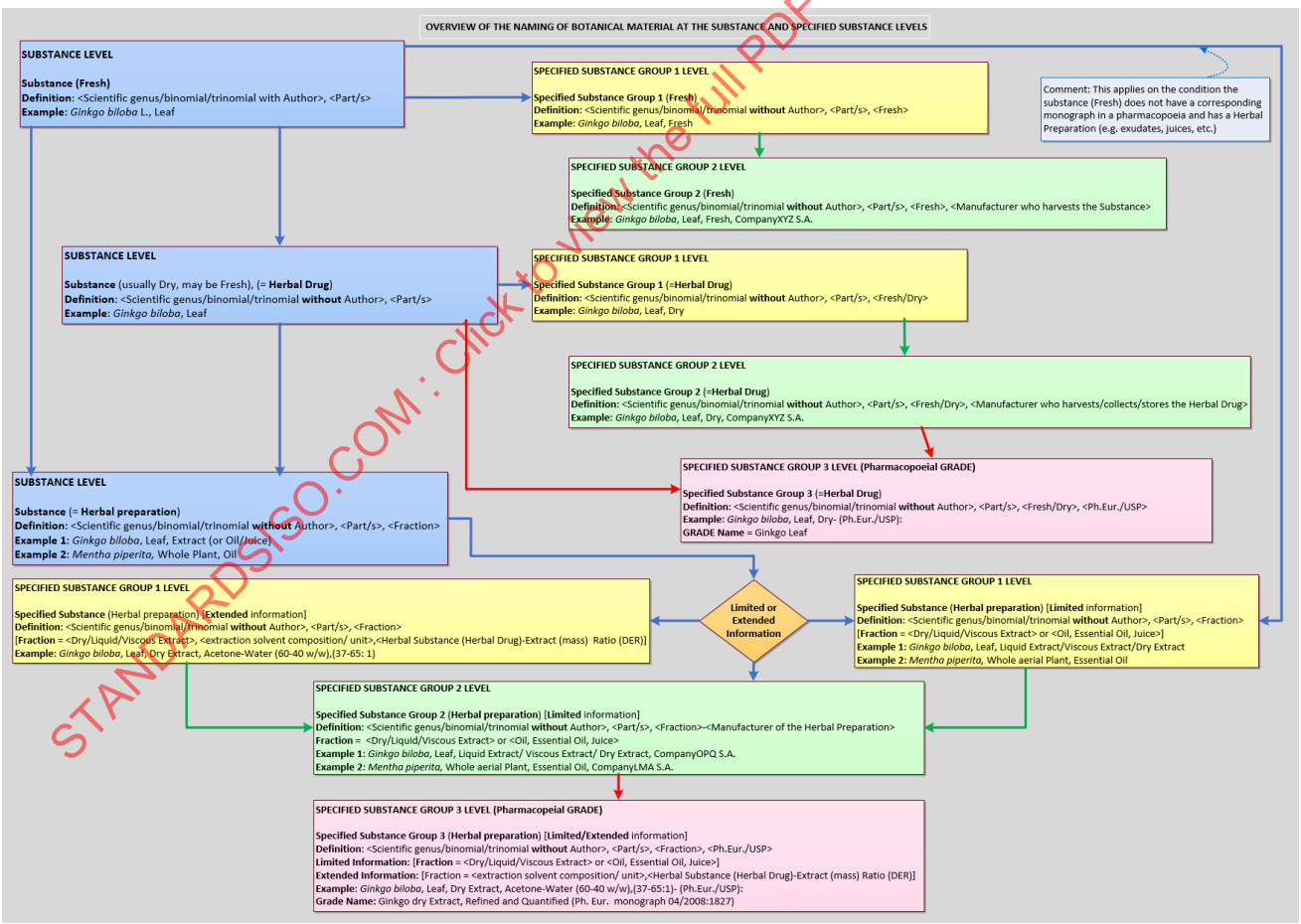


Figure E.3 — Overview of the Naming for Herbal Substance, Herbal Drug and Herbal preparation in relation to the Information levels

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E.2.6 Specified Substance Group 1 Information

The Specified Substance Group 1 (SSG1), (see 7.1) captures constituents (such as ranges of marker or signature substance(s), other substances that may have biological activity and extraction solvent, physical form and any characteristic attributes essential to the description of the material, see Figure 35. The defining and distinguishing elements for herbal **extracts** include the primary extraction solvent(s), amounts of major or specific constituents, and the ratio of the amount of starting material to the amount of dried extract isolated [e.g. Drug Extract Ratio, (DER)]. The marker substance(s) are captured in the Element Group 'Constituent' in connection with the Element Group 'Amount'. By doing so, the requirements for a standardized or quantified extract can be laid down.

NOTE 1 The attributes of the Element Group 'Characteristic Attribute', 'Attribute Type' with the value 'Particular Herbal' or 'Particular Herbal preparation' are to be used at the Specified Substance Group 1 information level for further description of the characteristics of the Substance (fresh) and Substance (Herbal Drug), see Figure 35. The attributes to be captured by the Attribute Type value 'Particular Herbal' are: Wild/Cultivated; Degree of comminution; Process state; Growth state; Harvesting condition; Decontamination process; Country of origin, Geographical location, Storage time and Storage conditions.

NOTE 2 Further information about the fraction (Herbal preparation) <Extract> such as, the Extraction solvent composition(s) is captured by the Element Group 'Constituent' in combination with the Element Group 'Amount' and the Herbal Substance/Herbal Preparation Mass Ratio (DER) which describes the quantity of native Herbal Substance that is used to prepare 1 g Herbal extract is described by the Element Group 'Characteristic Attribute', Attribute Type 'Particular Herbal Preparation' in connection with the Element Group 'Amount' In this context, 'Herbal Substance' can be either a Substance (fresh) or a Herbal Drug.

In Figure E.4 and Figure E.5 a rationale is provided showing the use of the defining Element Group 'Consituent' to describe the Extraction Solvent (Composition) and the use of the Element Group 'Characteristic Attribute' to describe the Drug Extract Ratio (DER).

Since the Herbal Substance (Substance (fresh) or Herbal Drug) is a complex botanical material the extraction solvent composition defines the qualitative and quantitative composition of the constituents present in the fraction (Herbal preparation) <Extract> as is shown in Figure 35. Depending on the composition and the polarity of the extraction solvent, in the range from water – up to water-ethanol mixtures up to acetone, different constituent components (qualitative difference) will be extracted into the botanical extract and with different amounts of the same constituent (quantitative difference). So, the marker strength (potency of the extract), and impurities and even unwanted constituents are heavily dependent on the extraction solvent composition and even the extraction process steps.

In Figure E.5 the influence of the extraction solvent composition on the dependency with the (Native) Herbal Substance/(Native) Herbal preparation is shown. In the experiment shown in Figure E.5 the optimal yield for the constituent Oleuropein is obtained by a solvent composition of ethanol 65 % {v/v} to 96 % {v/v}. Up to 90 % {v/v} ethanol the DER is about 3,2 – 3,6 parts to 1 part extract. When 96 % {v/v} ethanol is used 4,6 parts of the Herbal Substance is needed; even in this circumstance, a smaller amount of Oleuropein will be obtained. Thus, for a given extraction process the DER is a critical parameter in order to define the strength of the marker present in the extract.

The specifications of the marker(s) present in the herbal extract will be specified in the case of standardized, quantified or other herbal extract. These specifications can also be provided as an '*In-*

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House' specification document enclosed as a reference source document at Specified Substance Group 2 or at Specified Substance Group 3 information level.

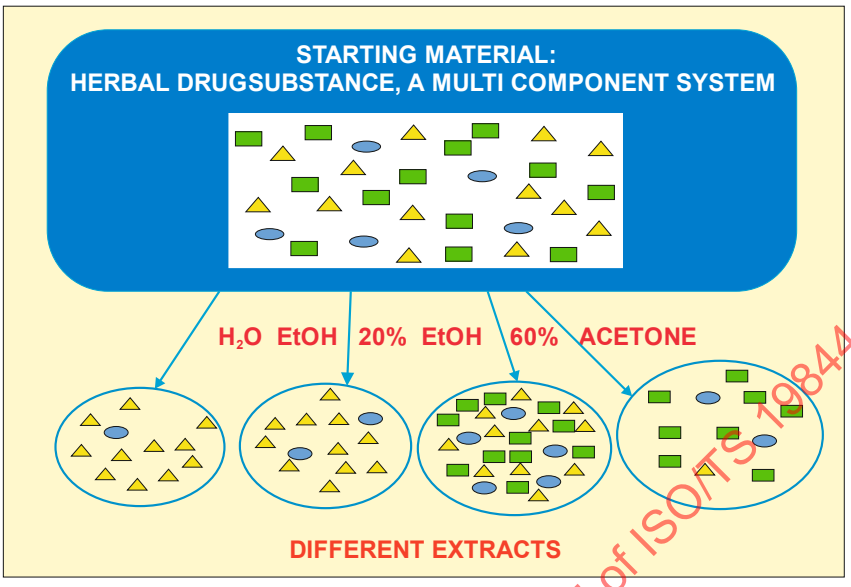


Figure E.4 — Difference of constituent content dependency on the extraction solvent composition. Herbal Substance in this figure can be either fresh plant material or a Herbal Drug

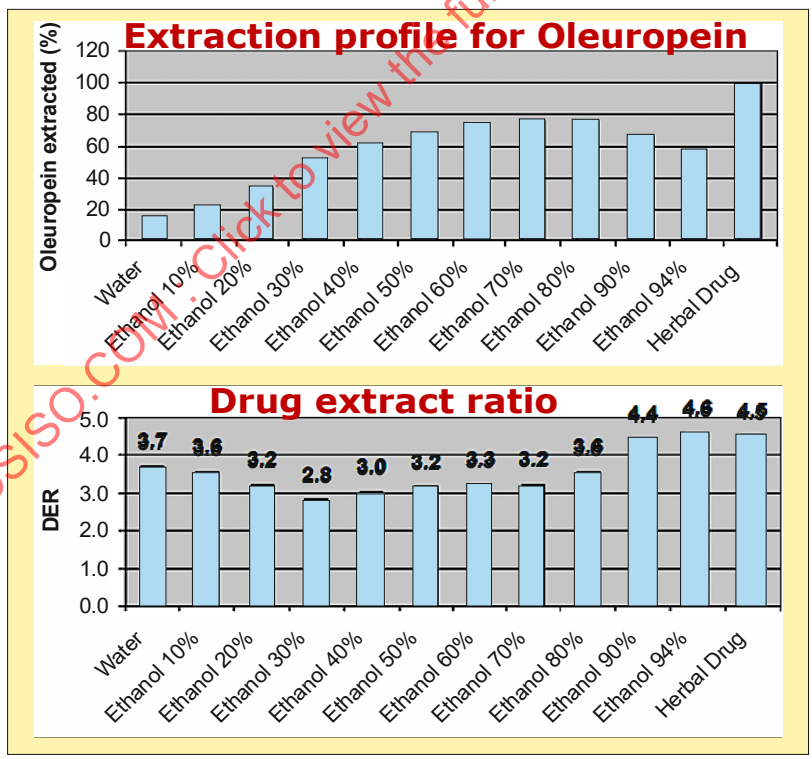


Figure E.5 — Extraction solvent composition range used to obtain the optimal constituent yield of Oleuropein in comparison with the minimum required amount of Herbal Substance (=Substance (fresh) or Herbal Drug)

In Figure E.6 an example is presented illustrating the content information for a Soft (semi-solid) Extract of the Herbal Drug Salvia miltiorrhiza, Rhizome and Root in which the primary extraction solvent

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composition is Ethanol (90 % {v/v})–Water (10 % {v/v}). Note that in the second extraction step the residue of the first extraction step is taken and extracted with water (100 % {v/v}) and finally combined with the ethanol extract, concentrated to a specified relative density.
The final extract has to contain Rosmarinic acid NLT 1.86 mg/g extract, named an 'other extract'. The DER in this example is: 4,5–6 g Herbal Drug material = 1 g Extract (dry, liquid, viscous).

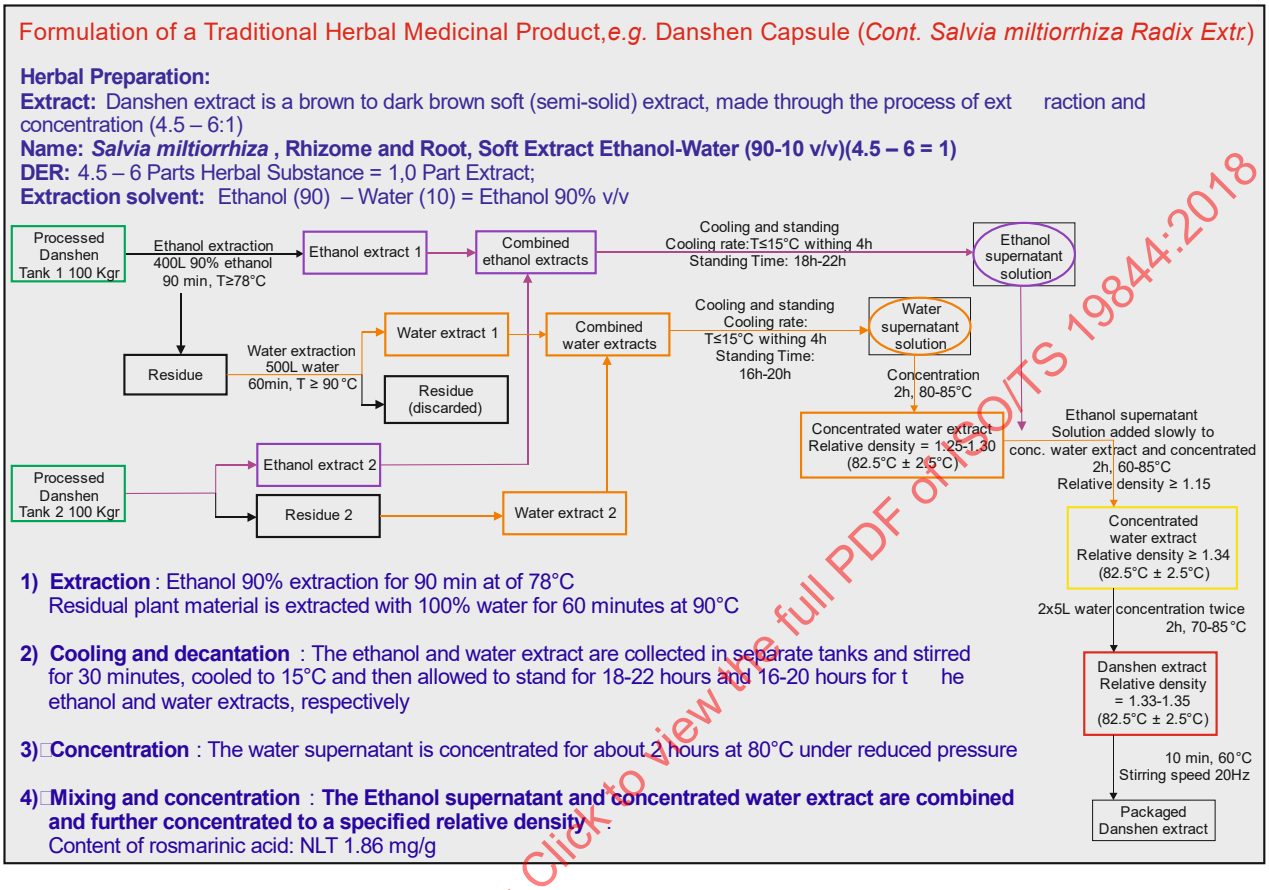


Figure E.6 — Example of Herbal preparation with two extraction solvent compositions

E.2.7 Specified Substance Group 2 Information

Specified Substance Group 2 (SSG2) shall capture manufacturer information, see Figure 36. For the Substance (fresh) this information will tie the manufacturer/farmer which grows and harvests or collects the fresh plant material. For the Herbal Drug this information will tie the manufacturer which processes (comminuted, cutting of the material) and stores the Herbal Drug. The manufacturer information should include the information about the manufacturing site, which can be sourced in accordance with the organizations in ISO 11615 as implemented within the regional requirements, e.g. for Europe this could be the EMA OMS service.

For the Herbal preparation, the manufacturer of the processed Herbal Drug or Substance (fresh) is captured. Although the details of the manufacturing are not part of the definition, they should be transmitted by the manufacturer because a significant change in the manufacturing process for these complex materials could result in a new Specified Substance Group 1 and/or Group 2 Name and ID for pharmacovigilance purposes, even if there are no apparent qualitative changes in the major constituents of the substance.

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The manufacturer is not necessarily the entity that holds the market authorization, but the entity that manufactures, collects, processes and stores the material.

If a substantial change in a critical manufacturing (extraction) process occurs, a new Specified Substance Group 2 ID shall be generated. This would result in a new version of the Specified Substance Group 2. For example: change of the extraction process by a significant change of extraction solvent composition, DER-ratio, addition of extraction steps by changing a chromatographic matrix or addition of percolation steps which could change the quantitative or qualitative composition of constituents or marker substances would result in a new critical process version number and in some cases in a new SSG2 ID. The critical process version number should be tied to the production system, see 7.2.7.4.

Figure E.7 provides a high-level simplified view of the Manufacturing Class for the Herbal preparation(s) (Extracts) since more information is needed to describe Standardized and Quantified Herbal preparations.

The Herbal Drug or Herbal Substance (fresh) is equivalent to the term 'Starting Material'. The extraction solvent composition will be captured in the Element Group 'Processing Material' and further described in the Element Group 'Manufacturing Material Substance' in combination with the 'Amount' class.

The Element Group 'Resultant Material' describes the crude extract or the obtained first extract which can be extracted again by a different extraction solvent composition as is shown in Figure E.6. The final extract is obtained by combining several intermediate extraction steps and is called the Resultant Substance in accordance with the description of the 'Resultant Material Type' (see relevant comment in Figure E.7).

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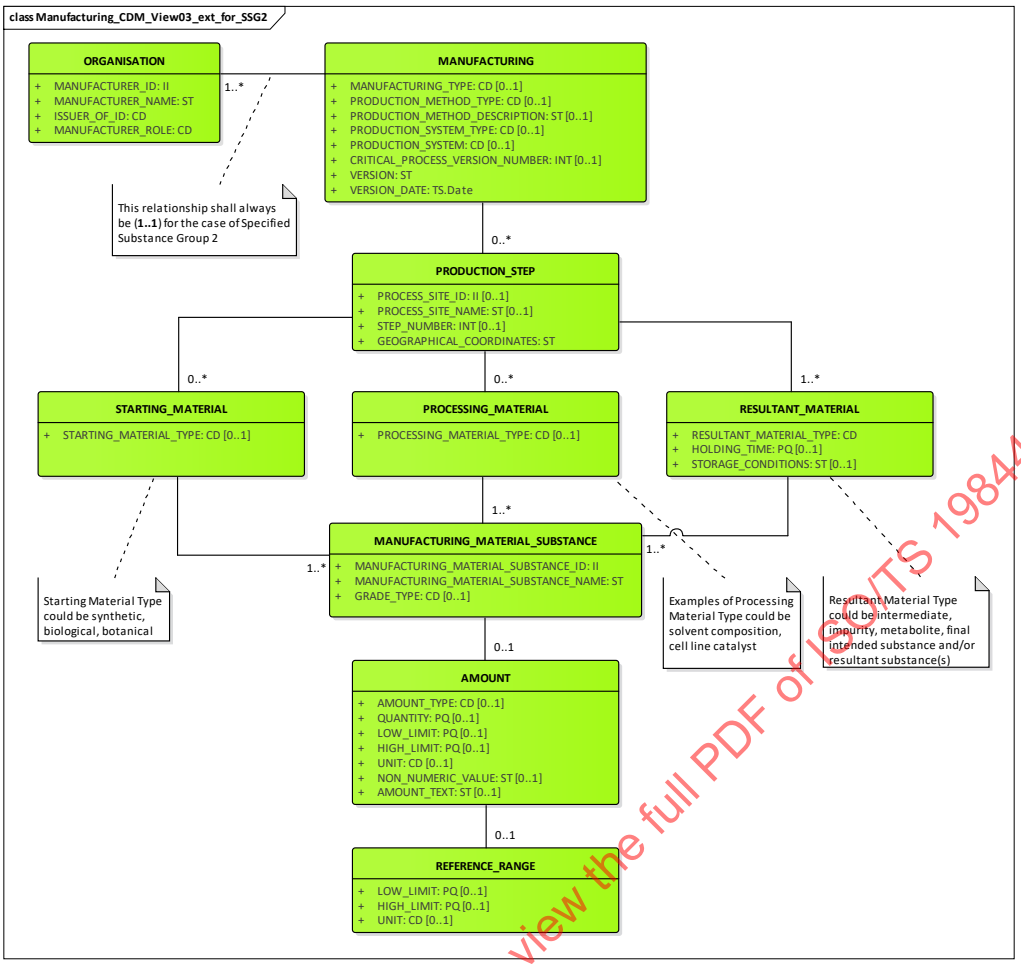


Figure E.7 — Manufacturing Information model with 'limited' extended information

E.2.8 Substance and Specified Substance information for *Iberis amara* L, Whole Plant and of the liquid extract. (Simplified example)

Table E.1 — Tabular format of the Substance and Specified Substance information for *Iberis amara* L, Whole Plant and of the liquid extract

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	HERBS78654 (Artificial ID)	II	
Substance Type	Structurally Diverse	CD	
Element Group: Substance Name			
Substance (fresh) Name	*Iberis amara* L., Whole Plant	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Substance Name Domain	Drug, Botanical	CD	
Jurisdiction	EU, US	CD	

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Element Name	Value	Data Format	Note #
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Element Group: Reference Source Document			
Reference Source Document	PDF Representation  **Figure E.8 — *Iberis amara* herba**	ED	
Reference Source Document Type	Journal article	CD	
Element Group: Source Material			
Source Material Class	Botanical	CD	
Source Material Type	Plant	CD	
Source Material State	Live	CD	
Organism ID	PLANT8764 (Artificial ID)	II	
Organism Name	*Iberis amara* L.	ST	
Parent Substance ID	N/A		
Parent Substance Name	N/A		
Development Stage	Mature plant stage	CD	
Element Group: Organism			
Family	Brassicaceae	CD	
Genus	Iberis	CD	
Species	amara	CD	

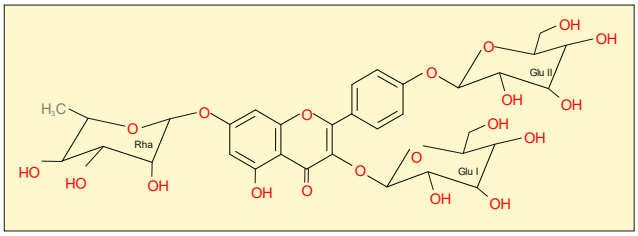
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Element Name	Value	Data Format	Note #
Element Group: Author			
Author Type	Primary Author	CD	
Author Description	L. (Linneaus)	ST	
Element Group: Part Description			
Part	Whole Plant	CD	
Herbal Substance (fresh) information captured at the Specified Substance Group 1 level			
Specified Substance Group 1 ID	HERB78654G1 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Iberis amara,* Whole Plant, Fresh	ST	
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug, Botanical	CD	
Jurisdiction	EU, US	CD	
Element Group: Constituent			
Constituent Substance ID	HERBS78654 (Artificial ID)	II	
Constituent Substance (fresh) Name	*Iberis amara* L., Whole Plant	ST	
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Constituent (Repeat)			
Constituent Substance ID	KAEM56231L (Artificial ID)	II	1)
Constituent Substance Name	Kaempferol-3,4' –O-β-diglucopyranoside-7-O-α-rhamnopyranoside	ST	
Substance Role	Marker	CD	
Is Defining	Yes	BL	
Element Group: Structure			**1)**
Stereochemistry	Chiral (Geometric Isomerism (Glycosidic bonds))	CD	
Optical Activity	(+/-)	CD	
Molecular Formula	$C_{33}H_{44}O_{20}$	ST	

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Element Name	Value	Data Format	Note #
Element Group: Structural Representation			**1)**
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.9 — Structural representation of Kaempferol-3,4' –O-β-diglucopyranoside-7-O-α-rhamnopyranoside**	ED	
Element Group: Molecular Weight 1)			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount 1)			
Amount Type	Exact	CD	
Quantity	756,38	PQ	
Unit	g/mol	CD	
Element Group: Characteristic Attribute			
Attribute Type	Particular Herbal	CD	
Attribute Name	Country of origin	ST	
Is defining	No	BL	
Element Group: Amount			
Non Numeric Value	Germany	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Harvest time	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Approximate	CD	
Non Numeric Value	June – August	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Harvesting method	ST	

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Element Name	Value	Data Format	Note #
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Non Numeric Value	Shock frozen directly after harvesting	ST	
Element Group: Attribute Parameter			
Attribute Parameter Name	Shock frozen condition	ST	
Attribute Parameter Value	Protected from light at –20 °C to –24 °C	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Storage time	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	24	PQ	
Unit	Month	CD	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Storage temperature	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	–22	PQ	
Low Limit	–24	PQ	
High Limit	–20	PQ	
Unit	Degree Celsius	CD	
NOTE The Element Groups 'Structure', 'Structural Representation', 'Molecular Weight' and 'Amount' are provided for tutorial reasons. This information is captured at the Substance ID of Kaempferol-3,4' –O-β-diglucopyranoside-7-O-α-rhamnopyranoside, which substance should be preregistered before capturing the SSG1 information level of *Iberis amara,* Whole Plant, Fresh. In general, all substance constituents described at the SSG1 information level are preregistered.			

Table E.2 — Tabular format of the Substance and Specified Substance Information for *Iberis amara*, Whole Plant, liquid extract (Extended Information).

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Herbal preparation information of the fraction: at the Substance information level: (Limited information)			
Substance ID (Herbal preparation)	EXTRA89765 (Artificial ID)	II	
Substance Type	Structurally Diverse	CD	
Element Group: Substance Name (Herbal preparation)			
Substance Name (Herbal preparation)	*Iberis amara*, Whole Plant, Extract	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Substance Name Domain	Drug, Botanical	CD	
Jurisdiction	EU, US	CD	
Element Group: Source Material			
Parent Substance ID	HERBS78654 (Artificial ID)	II	
Parent Substance Name	*Iberis amara* L., Whole Plant	ST	
Element Group: Part Description			
Part	Whole Plant	CD	
Element Group: Fraction Description			
Fraction	Extract	ST	
Material Type	Herbal extract	CD	
a) Herbal preparation information of the fraction at the Specified Substance Group 1 information: Liquid Extract (Limited information)			2)
Specified Substance Group 1 ID	SPHERP5643 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Iberis amara*, Whole Plant, Liquid Extract	ST	
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Fraction Description			
Fraction	Liquid Extract	ST	
Material Type	Liquid Herbal Extract	CD	
Element Group: Constituent			
Constituent Substance ID	EXTRA89765 (Artificial ID)	II	
Constituent Substance Name	*Iberis amara* L., Whole Plant	ST	
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	

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Element Group: Constituent (Repeat)			
Constituent Substance ID	KAEM56231L (Artificial ID)	II	1)
Constituent Substance Name	Kaempferol-3,4' –O-β-diglucopyranoside-7-O-α-rhamnopyranoside	ST	
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
b) Herbal preparation information of the fraction at the Specified Substance Group 1 information: Liquid Extract (Extended information)			2)
Specified Substance Group 1 ID	SPHERP2341(Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Iberis amara*, Whole Plant, Ethanol-Water Liquid Extract (50 – 50 v,v) (1 = 1.5 -2.5)	ST	
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Fraction Description			
Fraction	Ethanol-Water Liquid Extract (50 – 50 v,v)(1:1,5-2.5)	ST	
Material Type	Liquid Herbal Extract	CD	
Element Group: Constituent			
Constituent Substance ID	EXTRA89765 (Artificial ID)	II	
Constituent Substance Name	*Iberis amara*, Whole Plant, Extract	ST	
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Constituent (Repeat)			
Constituent Substance ID	ETHAN98765	II	
Constituent Substance Name	Ethanol	ST	
Language	en	CD	
Substance Role	Extraction solvent	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	PQ	
Quantity	50	PQ	
Unit	%{v/v}	CD	
Amount Text	Ethanol-Water Liquid Extract (50 – 50 v,v)	ST	

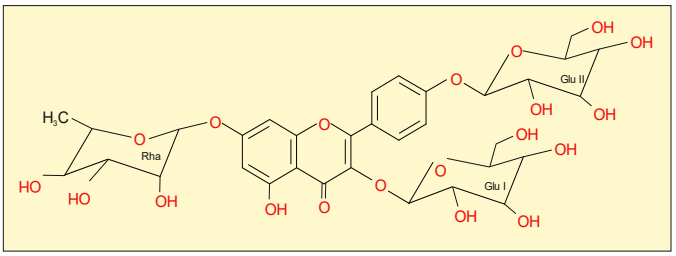
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Element Group: Constituent (Repeat)			
Constituent Substance ID	WATEP67543	II	
Constituent Substance Name	Water	ST	
Language	en	CD	
Substance Role	Extraction solvent	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	PQ	
Quantity	50	PQ	
Unit	%{v/v}	CD	
Amount Text	Ethanol-Water Liquid Extract (50 – 50 v,v)	ST	
Element Group: Constituent (Repeat)			
Constituent Substance ID	KAEM56231L (Artificial ID)	II	1)
Constituent Substance Name	Kaempferol-3,4' –O-β-diglucopyranoside-7-O-α-rhamnopyranoside	ST	
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	0,10	PQ	
Low Limit	0,05	PQ	
High Limit	0,15	PQ	
Unit	mg/ml	CD	
Element Group: Structure			1)
Stereochemistry	Chiral	CD	3)
Optical Activity	None	CD	
Molecular Formula	$C_{33}H_{44}O_{20}$	ST	

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Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.10 — Structural representation of Kaempferol-3,4' –O-β-diglucopyranoside-7-O-α-rhamnopyranoside**	ED	
Element Group: Molecular Weight			1)
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			1)
Amount Type	Exact	CD	
Quantity	756,38	PQ	
Unit	g/mol	CD	
Element Group: Characteristic Attribute			
Attribute Type	Particular Herbal preparation	CD	
Attribute Name	Drug Extract Ratio (DER)	ST	
Is defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Low Limit	1,5	PQ	
High Limit	2,5	PQ	
Unit	Part	CD	
Amount Text	1 part Herbal substance = 1,5 – 2,5 parts extract	ST	

[1] The element groups Structure, Structural Representation, Molecular Weight and Amount are provided for tutorial reasons. This information is captured at the Substance ID of Kaempferol-3,4' –O-β-diglucopyranoside-7-O-α-rhamnopyranoside, which substance should be preregistered before capturing the SSG1 information level of *Iberis amara,* Whole Plant, Fresh. In general, all substance constituents described at the SSG1 information level should be pre-registered.

[2] There is only one SSG1 possible: Either SSG1 for the Herbal preparation with limited information or SSG1 for the Herbal preparation with extended information. When the extended information is available in the regulatory submission documents, this information shall be mandatory.

[3] Geometric Isomerism (Glycosidic bonds).

E.2.9 Specified Substance Group 2 Information for *Iberis amara*, Whole Plant, liquid extract (Extended Information)

Table E.3 — Tabular format of the Specified Substance Group 2 Information for *Iberis amara*, Whole Plant, liquid extract (Extended Information)

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Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2			
Specified Substance Group 2 ID	JKHYR86461 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Iberis amara*, Whole Plant, Ethanol-Water Extract (50 – 50 v,v) (1 = 1,5 – 2,5)—Company ST GmbH	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	SPHERP2341 (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Extraction, Percolation	CD	
Production Method Description	Text written in Figure E.11: Extraction for 1 hour at 60 °C, Residual plant material is pressed and discarded. Total eluates of 5 percolators are mixed for 15 min. The extract is stored for 14 days at 20 °C before filtration and processed further into the Herbal product.	ST	
Critical Process Version Number	1	INT	2)
Version	001	ST	
Version Date	20171102	TS.Date	
Element Group: Organization			
Manufacturer ID	DUNS86745HF (Artificial ID)	II	
Manufacturer Name	Company ST GmbH	ST	3)
Issuer of ID	Dun & Bradstreet	CD	
Manufacturer Role	Harvester and Manufacturer of Botanical Material	CD	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	

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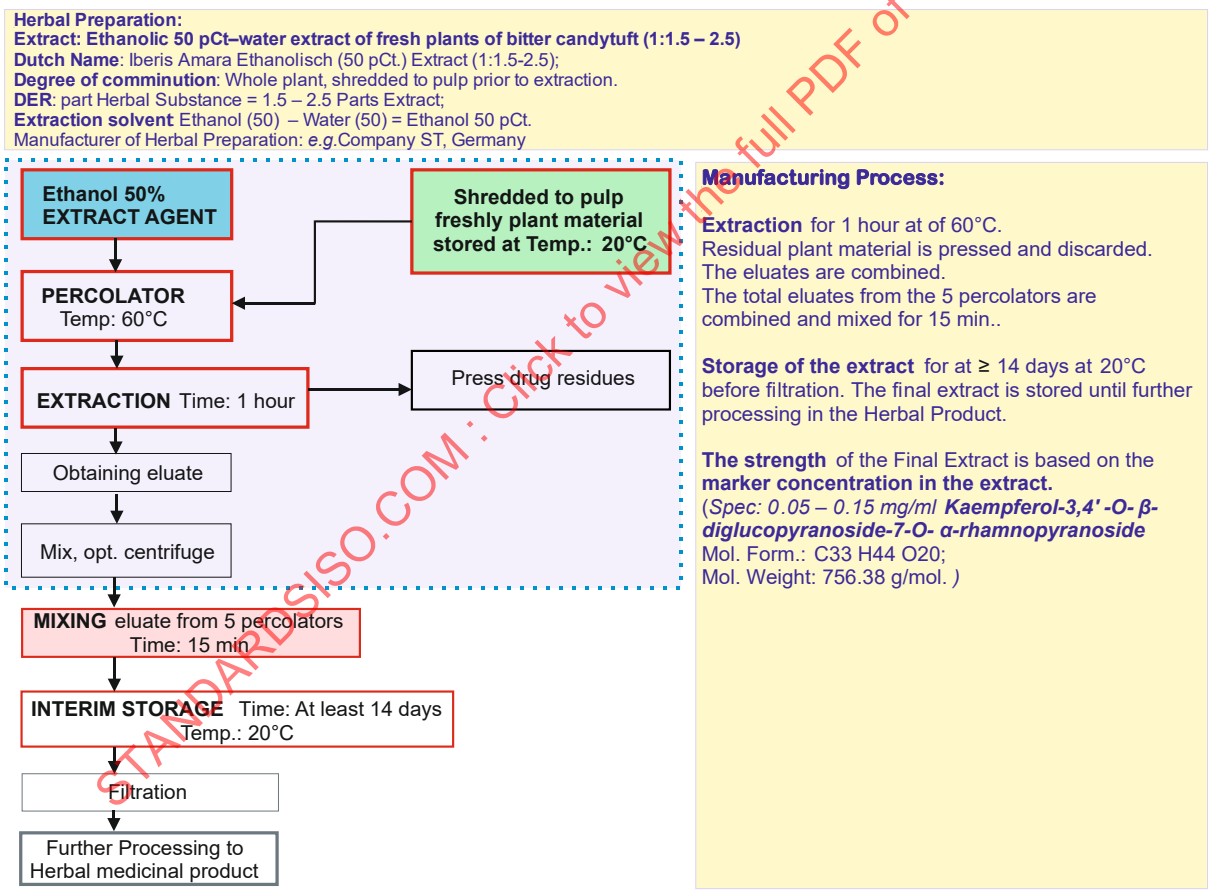
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Element Name	Value	Data Format	Note #
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	Text file, Release specification	ED	
Reference Source Document Type	Release Specification	CD	

NOTE 1 This (Parent) Substance ID corresponds to the (Specified) Substance (Group 1) Name: *Iberis amara*, Whole Plant, Ethanol-Water Extract (50 – 50 v,v) (1 = 1,5 – 2,5).

NOTE 2 The critical process version number would change if a substantial change in the manufacturing process occurred. These would include a change in the chemistry, addition or elimination of a purification step. A substantial change is a purification or processing step (i.e. changing the extraction solvent composition or add an additional extraction step etc.). The reason for a change in the version number is submitted along with a variation and tied to the Production System Type.

NOTE 3 Manufacturer identifications are defined with reference to Organizations in ISO 11615 and ISO/TS 20443. The process by which valid Manufacturer IDs/Name(s) are captured will be defined by Regional Guidance.



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Figure E.11 —Manufacturing information of the *Iberis Amara* Ethanolic Extract

In this Substance Class Specified Substance Group 2 the Element Group Reference Source Document is included. The Reference Source Document Type enables the manufacturer to submit the Release specification of the manufactured preparation.

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E.2.10 Specified Substance Group 3 Information

Specified Substance Group 3 will capture the grade of a given Substance or Specified Substance Group 1, where 'grade' refers to the overall quality or group of specifications of a given Substance or Specified Substance; it would also capture the specification outlined in monographs of a pharmacopoeia or approved by a given regulatory agency. In addition, this is where the names of Herbal Drugs and Herbal preparations in pharmacopoeias and other legislation are captured. The Ph.Eur. recognizes three types of Herbal Drugs/Herbal preparations Standardized, Quantified, and Other. Each will require the appropriate defining information. Standardized and quantified grades not covered in a pharmacopoeia, and also organic grades of material, would also be distinguished at this level, see Figure 38.

Later in this Annex examples at the substance and Specified Substance levels are provided.

E.3 Terms and definitions

The following terms and definitions are provided both as a general approach based on European Union jurisdiction and to support the ISO/TS 18062[20].

E.3.1 Definitions according to Directive 2001/83/EC and Directive 2004/24/EC, Title 1, Definitions

Article 30: Herbal medicinal product:

"Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more Herbal preparations, or one or more such herbal substances in combination with one or more such Herbal preparations."

NOTE Herbal Substances (as used in the definition above) are referred to as Herbal Drugs, mostly dry as defined by a pharmacopoeia, throughout this Annex in order to avoid confusion with the ISO 11238/ISO TS 19844 Substance information level.

In accordance with the Substance level the Herbal Drug is defined at the Substance level as a Substance (Herbal Drug) = [<Scientific genus/binomial/trinomial without Author>, <Part(s)>]. In addition, the unprocessed, fresh plant material is defined at the Substance level as a Substance (fresh) = [<Scientific genus/binomial/trinomial with Author>, <Part(s)>].

Article 31: Herbal Substances:

"All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances (= Herbal Drugs).

Herbal Substances (= Herbal Drugs) are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author)."

Article 32: Herbal preparations:

"Preparations obtained by subjecting herbal substances (= herbal drugs) to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include

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comminuted or powdered Herbal Substances (= Herbal Drugs), tinctures, extracts, essential oils, expressed juices and processed exudates."

NOTE 1 In accordance with the ISO Substance level the Herbal preparation is defined at the Substance level as a Substance (Herbal preparation) = [<Scientific genus/binomial/trinomial without Author>,<Part(s)>, <Fraction>].

NOTE 2 Herbal preparations such as oils and juices can be obtained from fresh plant material which has been captured at the Substance level as a Substance (fresh).

E.3.2 Definitions according to the European Pharmacopoeia

Ph.Eur.: DEFINITION HERBAL DRUG (01/2012:1433)

Herbal Drugs are mainly whole, fragmented, or broken plants, parts of plants, algae, fungi or lichen, in an unprocessed state, usually in dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be Herbal Drugs. Herbal Drugs are precisely defined by the botanical scientific name according to the binominal system (genus, species, variety and author).

Whole describes a Herbal Drug that has not been reduced in size and is presented, dried or undried, as harvested; for example: dog rose, bitter fennel or sweet fennel, Roman chamomile flower.

Fragmented describes a Herbal Drug that has been reduced in size after harvesting to permit ease of handling, drying and/or packaging; for example: cinchona bark, rhubarb, passion flower.

Broken describes a Herbal Drug in which the more-fragile parts of the plant have broken during drying, packaging or transportation; for example: belladonna leaf, matricaria flower, hop strobile.

Cut describes a Herbal Drug that has been reduced in size, other than by powdering, to the extent that the macroscopic description in the monograph of the Herbal Drug can no longer be applied. When a Herbal Drug is cut for a specific purpose that results in the cut Herbal Drug being homogeneous, for example when cut for herbal teas, it is a Herbal Drug preparation. Certain cut Herbal Drugs processed in this way may be the subject of an individual monograph.

A Herbal Drug that complies with its monograph and is subsequently cut for extraction shall comply in its cut form, except for its macroscopic description, with the monograph for that Herbal Drug, unless otherwise justified.

The term *Herbal Drug* is synonymous with the term *Herbal Substance* used in European Community legislation on herbal medicinal products.

Ph.Eur.: DEFINITION HERBAL DRUG PREPARATION (07/2010:1434)

Herbal Drug preparations are homogeneous products obtained by subjecting Herbal Drugs to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation.

Herbal Drug preparations include, for example, extracts, essential oils, expressed juices, processed exudates, and Herbal Drugs that have been subjected to size reduction for specific applications, for example Herbal Drugs cut for herbal teas or powdered for encapsulation.

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Herbal teas comply with the monograph Herbal teas (1435).

NOTE 1 The term comminuted used in European Community legislation on herbal medicinal products describes a Herbal Drug that has been either cut or powdered.

The term *Herbal Drug preparation* is synonymous with the term *Herbal preparation* used in European Community legislation on herbal medicinal products, see Figure E.3.

NOTE 2 In accordance with the ISO Substance level the Herbal preparation is defined as the Substance as [<Scientific genus/binomial/trinomial without Author>, Part(s)>, <Fraction>].

Quality requirements and naming of Herbal substances (= Herbal Drugs) in accordance to the Guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products (CPMP/QWP/2819/00 Rev 2[39]).

The quality of herbal medicinal products is determined by the quality of the starting plant material, in-process controls, GMP controls, process validation and by specifications applied to them throughout development and manufacture.

Consistent quality of products of herbal origin can only be assured if the starting plant material is defined in a rigorous and detailed manner, particularly the specific botanical identification of the plant material used. It is also important to know the geographical source and the conditions under which the Herbal Substance (= Herbal Drug) is obtained in order to ensure that the material is of consistent quality.

In accordance with European medicines legislation, the quality dossier should address potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, radioactive contamination, fumigants, etc. Thus, the potential for residues of fumigation agents should be fully considered; *and*

the 'Guideline on Good Agricultural and Collection Practice for starting materials of herbal origin' (Doc. Ref. EMEA/HMPC/246816/2005[40]) provides recommendations for an appropriate quality assurance system on the cultivation and harvesting of plant materials.

Constituents with known therapeutic activity: are chemically defined substances or groups of substances which are generally accepted to contribute substantially to the therapeutic activity of a Herbal Substance (= Herbal Drug), a Herbal preparation or a herbal medicinal product.

Drug extract ratio (DER): means the ratio between the quantity of Herbal Substance (= Herbal Drug) used in the manufacture of a Herbal preparation and the quantity of the Herbal preparation obtained. The number (given as the actual range) written before the colon is the relative quantity of the Herbal Substance (= Herbal Drug); the number written after the colon is the relative quantity of the Herbal preparation obtained.

Extraction solvents: are solvents which are used for the extraction process.

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[39] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/09/WC500113209.pdf

[40] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003362.pdf

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Genuine (Native) Herbal preparation: refers to the preparation without excipients, even if for technological reasons the genuine Herbal preparation is not available. However, for soft and liquid Herbal preparations the genuine Herbal preparation may contain variable amounts of (extraction) solvent.

Ratio of Herbal Substance (= Herbal Drug) to genuine Herbal preparation (DER genuine): is the ratio of the quantity of the Herbal Substance (= Herbal Drug) to the quantity of the resulting genuine Herbal preparation. The number (given as the actual range) written before the colon is the relative quantity of the Herbal Substance (= Herbal Drug); the number written after the colon is the relative quantity of the genuine Herbal preparation obtained.

Herbal teas: consist exclusively of one or more Herbal Substance(s) [= Herbal Drug(s)] intended for oral aqueous preparations by means of decoction, infusion or maceration. The preparation is prepared immediately before use. Herbal teas are usually supplied in bulk form or in sachets.

Markers: are chemically defined constituents or groups of constituents of a Herbal Substance (= Herbal Drug), a Herbal preparation or a herbal medicinal product which are of interest for control purposes independent of whether they have any therapeutic activity. Markers serve to calculate the quantity of Herbal Substance(s) (= Herbal Drug(s)) or Herbal preparation(s) in the Herbal Medicinal Product if the marker has been quantitatively determined in the Herbal Substance (= Herbal Drug) or Herbal preparations.

There are two categories of markers:

Active markers: are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.

Analytical markers: are constituents or groups of constituents that serve for analytical purposes.

Quantification: means adjusting the Herbal preparation to a defined range of constituents exclusively achieved by blending different batches of Herbal Substances (= Herbal Drugs) and/or Herbal preparations (e.g. quantified extracts).

Solvent: An inorganic or an organic liquid used for the preparation of solutions or suspensions in the manufacture of a Herbal preparation or the manufacture of a herbal medicinal product.

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a Herbal preparation/Herbal Substance (= Herbal Drug) or herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the Herbal preparation/Herbal Substance (= Herbal Drug) and/or herbal medicinal product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant.

Standardization: means adjusting the Herbal Substance (= Herbal Drug)/Herbal preparation to a defined content of a constituent or a group of constituents with known therapeutic activity respectively

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either by adding excipients or by blending batches of the Herbal Substance (= Herbal Drug) and/or Herbal preparation (e.g. standardized extracts).

Traditional herbal medicinal products: Medicinal Products for human use that fulfil the conditions laid down in article 16a (1) of Directive 2001/83/EC, as amended.

NOTE In accordance with the Ph.Eur. and the Herbal Guidelines Herbal Substances (= Herbal Drugs) are described as:

— **Standardized Herbal Substances (= Herbal Drugs)/Herbal preparations (extracts: Ph.Eur. monograph 04/2008:0765)**

are adjusted to a given content of constituents with known therapeutic activity within an acceptable tolerance.

Standardization is achieved by adjustment of the Herbal Substances (= Herbal Drugs) with excipients or by blending batches of Herbal Substances (= Herbal Drugs).

— **Quantified Herbal Substances (= Herbal Drugs)/Herbal preparations**

are adjusted to a defined range of constituents (active markers).

Adjustment is exclusively achieved by blending batches of Herbal Substances (= Herbal Drugs).

— **Other Herbal Substances (= Herbal Drugs)/Herbal preparations**

are active substances for which neither constituents with known therapeutic activity nor active markers are known. These Herbal Substances (= Herbal Drugs) are not adjusted to a defined content of an analytical marker. The minimum content for these analytical markers is given in an individual monograph)

See also: 'Declaration of Herbal Substances (= Herbal Drugs) and Herbal preparations in Herbal Medicinal Products/Traditional Herbal Medicinal Products in the SPC (EMEA/HMPC/CHMP/CVMP/287539/05Rev.)[41]

For the US jurisdiction see: 'Guideline for Assigning Titles to United States

Pharmacopoeia Herbal Medicines Compendium Monographs, Version 1.0: May 7, 2014', issued by the US: Pharmacopoeial Convention[42].

'Guidance for Industry: Botanical Drug Products', U.S. Department of Health and Human Services, FDA, Centre for Drug Evaluation and Research (CDER), June 2004[43].

For the Japanese jurisdiction f.i. Japanese Pharmacopoeia XVI, 2011, see:

'General Rules for Crude (Herbal) Drugs'; 'General Rules for Monographs for Preparations Related to Crude Drugs: Extract'.

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[41] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003272.pdf

[42] http://hmc.usp.org

[43] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf

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E.4 Documentation and Explanation of Example 1

E.4.1 Example *Ginkgo biloba*, leaf taken from the European Pharmacopoeia

This example describes one Herbal Drug of one Plant and, one Part of the Plant, which is the starting material for a Herbal preparation of one Herbal extract.

Table E.4 — Tabular Format Herbal Substance *Ginkgo biloba*: Description of the elements at the Substance information level and at the Specified Substance Group 1, 2 and 3.

Element Name	Value	Data Format	Note #
Element Group: Substance (Herbal Drug)			
Substance ID	45SPM3HJ6Q (Artificial ID)	II	
Substance Type	Structurally Diverse	CD	
Element Group: Substance Name			
Substance Name (Herbal Drug)	*Ginkgo biloba*, Leaf	ST	
Substance Name Type	Official	CD	
Language	en	CD	1)
Substance Name Domain	Drug, Botanical	CD	
Jurisdiction	EU, US	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur. monograph no: 01/2011:1828	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	 **Figure E.12 — Macroscopic characters of the Leaf** The upper surface of Ginkgo leaves is slightly darker than the lower surface. The petioles of the leaf are about 4 cm to 9 cm long. The lamina is about 4 cm to 10 cm wide, fan-shaped, usually bilobate or sometimes undivided.	ED	
Reference Source Document Type	Regulatory submission	CD	
Element Group: Substance Name (Repeat)			

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Element Name	Value	Data Format	Note #
Substance Name (Synonym)	Maidenhair tree leaf	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Source Material			
Source Material Class	Botanical	CD	
Source Material Type	Plant	CD	
Source Material State	Live	CD	
Organism ID	LH67543290 (Artificial ID)	II	
Organism Name	*Ginkgo biloba* L.	ST	2)
Parent Substance ID	19FUJ2C58T (Artificial ID)	II	
Parent Substance Name (fresh)	*Ginkgo biloba* L., Leaf	ST	
Development Stage	Mature plant stage	CD	
Element Group: Organism			
Family	*Ginkgoaceae*	CD	
Genus	*Ginkgo*	CD	
Species	*biloba*	CD	3)
Element Group: Author			
Author Type	Species Primary Author	CD	
Author Description	L.	ST	
Element Group: Organism General			
Kingdom	Plantae	CD	
Phylum	Tracheophyta	CD	
Class	Ginkgoopsida	CD	
Order	Ginkgoales	CD	
Element Group: Part Description			
Part	Leaf	CD	
Part Location	N/A		
Specified Substance Group 1 Information level for the Herbal Drug			
Specified Substance Group 1 ID	GINKSP1HD0 (Artificial ID)	II	
Element Group: Substance Name			

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Element Name	Value	Data Format	Note #
Substance Name	*Ginkgo biloba*, Leaf, Dry	ST	
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug, Botanical	CD	
Jurisdiction	EU, US	CD	
Element Group: Constituent			
Constituent Substance ID	45SPM3HJ6Q (Artificial ID)	II	
Constituent Substance Name	*Ginkgo biloba*, Leaf	ST	
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Characteristic Attribute			
Attribute Type	Particular Herbal	CD	
Attribute Name	Degree of Comminution	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Non Numeric Value	Cut, fragmented, sliced and sifted leaves	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Process State	ST	
Is Defining	No	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Amount Text	Natural dried at 20 °C for 6 hours	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Country of origin	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Non Numeric Value	China	ST	

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Element Name	Value	Data Format	Note #
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Geographical Location	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Non Numeric Value	Provinces Shandong, Jiangsu, Sichuan	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Wild/cultivated	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Non Numeric Value	Cultivated	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Growth state	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Approximate	CD	
Amount Text	Before leaves turn yellow	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Harvest time	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Approximate	CD	
Amount Text	June - October	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Storage Time	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	NMT	CD	

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Element Name	Value	Data Format	Note #
Quantity	6	PQ	
Unit	Month	CD	
Element Group: Attribute Parameter			
Attribute Parameter Name	Storage condition	ST	
Attribute Parameter Value	Stored protected from light at 0 °C, until processed	ST	
Element Group: Constituent (Repeat)			
Constituent Substance ID	KAEM56231L (Artificial ID)	II	
Constituent Substance Name	Kaempferol-3,4' –O-β-diglucopyranoside-7-O-α-rhamnopyranoside (see Structure in Figure E.9)	ST	4)
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	0,5	PQ	
Unit	%{w/w}	CD	
Amount Text	Weight per cent		
Element Group: Specified Substance Group 2 (Manufacturer who harvests/collects/stores the Herbal Drug)			
Specified Substance Group 2 ID	GHRC786543 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Ginkgo biloba*, Leaf, Dry—Company HARV, China	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	GINKSP1HD0 (Artificial ID)	II	5)
Element Group: Manufacturing			
Manufacturing Type	Harvester	CD	
Production Method Type	Harvesting	CD	
Production Method Description	Cutting, fragmenting	ST	
Critical Process Version Number	1	INT	
Version	001	ST	
Version Date	20160404	TS.Date	
Element Group: Organization			

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Element Name	Value	Data Format	Note #
Manufacturer ID	DUNS1234HF (Artificial ID)	II	
Manufacturer Name	Company HARV	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Harvester	CD	

NOTE 1 The Scientific name part has the language value la; see 5.3.2.

NOTE 2 The Organism ID and Name are provided by The Kew Gardens Medicinal Plant Names Services (MPNS).

NOTE 3 Species: biloba (only the specific epithet part of the name is captured here).

NOTE 4 The Substance Type Structurally Diverse is connected with the Element Groups Single Substance/Structure. All Structural information regarding Flavone Glycosides is captured/or supplemented at submission. (See Annex B, Chemical Substance).

NOTE 5 This (Parent) Substance ID is referring to the (Specified) Substance (Group 1) Name: *Ginkgo biloba*, Leaf, Dry.

E.4.2 Herbal preparation Ginkgo biloba extract, Limited information: Description of the elements at the Substance information level

Table E.5 — Tabular Format Herbal preparation Ginkgo biloba extract, Limited information: Description of the elements at the Substance information level

Element Name	Value	Data Format	Note #
Element Group: Substance (Herbal preparation) (Limited Information)			
Substance ID	HPR852369P (Artificial ID)	II	
Substance Type	Structurally Diverse, (Herbal preparation)	CD	
Element Group: Substance Name			
Substance Name	*Ginkgo biloba*, Leaf, Extract	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Substance Name Domain	Drug, Botanical	CD	
Jurisdiction	EU, US	CD	
Element Group: Substance Name (Repeat)			
Substance Name (Synonym)	Maidenhair tree leaf, extract	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Journal	CD	
Reference Source Class	Literature	CD	
Reference Source URL	http://europepmc.org/abstract/med/19702174	ST	

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Element Name	Value	Data Format	Note #
Element Group: Source Material			
Parent Substance ID	45SPM3HJ6Q (Artificial ID)	II	
Parent Substance Name	*Ginkgo biloba*, Leaf	ST	
Element Group: Part Description			
Part	Leaf	CD	
Element Group: Fraction Description			
Fraction	Extract	ST	
Material Type	Herbal, Extract	CD	
Element Group: Property			
Property Type	Physical	CD	
Property Name	Solubility	CD	
Property Parameters	1 mass part at 20 °C	ST	
Property Substance ID	SETHAN6098	II	
Property (Specified) Substance Name	Ethanol 60 % {v/v}	ST	1)
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	10	PQ	
Unit	g	CD	
NOTE Ethanol 60 % {v/v} is a Specified Substance Group 1 substance composed of Ethanol (60%{v/v}) and Water (40%{v/v}). It has a Specified Substance Group 1 ID of SETHAN6098 and the Specified Substance Group 1 has two Constituent Substances, Ethanol and Water.			

E.4.2.1 Herbal preparation Ginkgo biloba extract, Limited information: Description of the elements at the Specified Substance Group 1, 2 and 3.

Table E.6 — Tabular Format Herbal preparation Ginkgo biloba extract, Limited information: Description of the elements at the Specified Substance Group 1,2 and 3

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 1 (Herbal preparation Limited information)			
Specified Substance Group 1 ID	XYZ123456E (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Ginkgo biloba*, Leaf, Dry Extract	ST	

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Element Name	Value	Data Format	Note #
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	biologic	CD	
Jurisdiction	EU, US, JP	CD	
Element Group: Fraction			
Fraction	Dry Extract	ST	
Material Type	Dry Ethanolic Extract	CD	
Element Group: Constituent			
Constituent Substance ID	HPR852369P (Artificial ID)	II	
Constituent Substance Name	*Ginkgo biloba*, Leaf, Extract	ST	
Language	en	CD	
Substance Role	Parent substance	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	ETHAN98765 (Artificial ID)	II	
Constituent Substance Name	Ethanol	ST	
Language	en	CD	
Substance Role	Extraction solvent	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	60	PQ	
Unit	% {v/v}	CD	
Amount Text	Ethanol 60 % {v/v}	ST	
Element Group: Constituent (Repeat)			
Constituent Substance ID	WATERP67543 (Artificial ID)	II	
Constituent Substance Name	Water	ST	
Language	en	CD	
Substance Role	Extraction Solvent	CD	
Is Defining	Yes	BL	
Element Group: Amount			

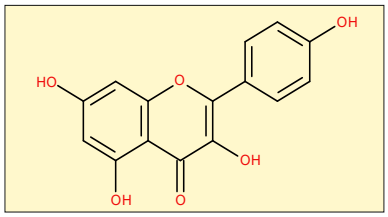
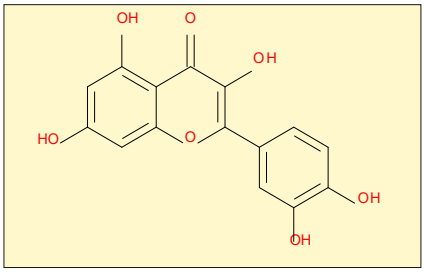
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Element Name	Value	Data Format	Note #
Amount Type	Exact	CD	
Quantity	40	PQ	
Unit	% {v/v}	CD	
Amount Text	Ethanol 60 % {v/v}	ST	
Element Group: Constituent (Repeat)			
Constituent Substance ID	FKLAV98765 (Artificial ID)	II	
Constituent Substance Name	Flavone Glycoside	ST	1)
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	25	PQ	
Low Limit	22	PQ	
High Limit	27	PQ	
Unit	% {w/w}	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	731P2LE49E (UNII)	II	
Constituent Substance Name	Kaempferol	ST	1)
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Structure			1)
Stereochemistry	Achiral	CD	
Molecular Formula	$C_{15}H_{10}O_6$	ST	
Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	

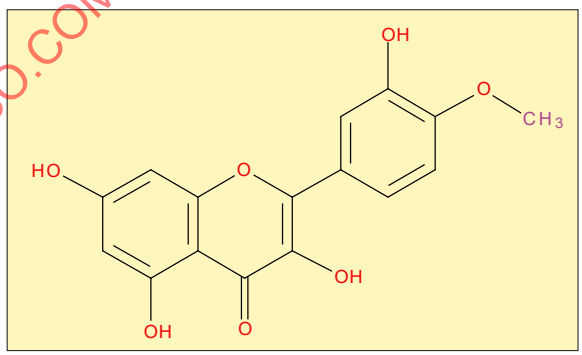
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Element Name	Value	Data Format	Note #
Structural Representation Attachment	 **Figure E.13 — Structural representation of Kaempferol**	ED	
Element Group: Molecular Weight			1)
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			1)
Amount Type	Exact	CD	
Quantity	286,23	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	9IKM0I5T1E (UNII)	II	
Constituent Substance Name	Quercetin	ST	1)
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Structure			1)
Stereochemistry	Achiral	CD	
Molecular Formula	$C_{15}H_{10}O_7$	ST	
Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.14 — Structural representation of Quercetin**	ED	

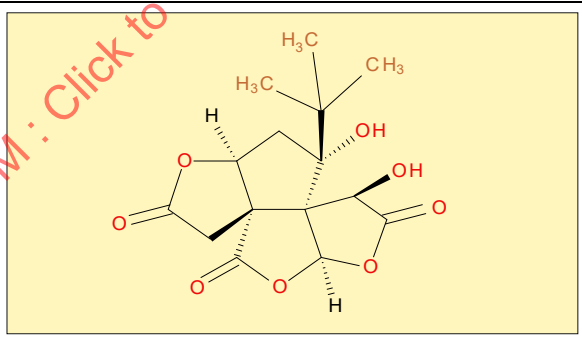
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Element Name	Value	Data Format	Note #
Element Group: Molecular Weight			1)
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			1)
Amount Type	Exact	CD	
Quantity	302,23	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	73WRA8Z8M8 (UNII)	II	
Constituent Substance Name	Isorhamnetin	ST	1)
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Structure			1)
Stereochemistry	Achiral	CD	
Molecular Formula	$C_{16}H_{12}O_7$	ST	
Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.15 — Structural representation of Isorhamnetin**	ED	
Element Group: Molecular Weight			1)
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			1)

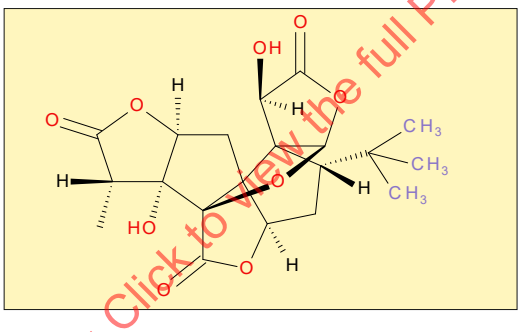
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Element Name	Value	Data Format	Note #
Amount Type	Exact	CD	
Quantity	316,26	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	M81D2O8H7U (UNII)	II	
Constituent Substance Name	Bilobalide	ST	1)
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Structure			1)
Stereochemistry	Chiral	CD	
Optical Activity	(-)	CD	
Molecular Formula	$C_{15}H_{18}O_8$	ST	
Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.16 — Structural representation of Bilobalide**	ED	
Element Group: Molecular Weight			1)
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			1)
Amount Type	Exact	CD	
Quantity	326,29	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			

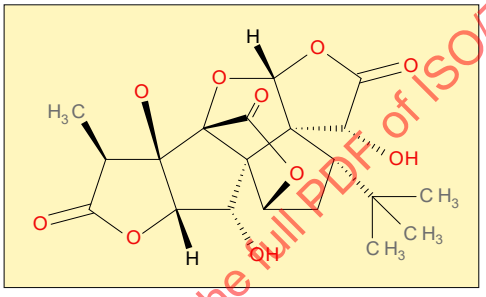
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Element Name	Value	Data Format	Note #
Constituent Substance ID	TAZ2DPR77B (UNII)	II	
Constituent Substance Name	Ginkgolide A	ST	1)
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Structure			1)
Stereochemistry	Chiral	CD	
Optical Activity	N/A	CD	
Molecular Formula	$C_{20}H_{24}O_9$	ST	
Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.17 — Structural representation of Ginkgolide A**	ED	
Element Group: Molecular Weight			1)
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			1)
Amount Type	Exact	CD	
Quantity	408,40	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	DF149B9460 (UNII)	II	
Constituent Substance Name	Ginkgolide B	ST	1)
Language	en	CD	

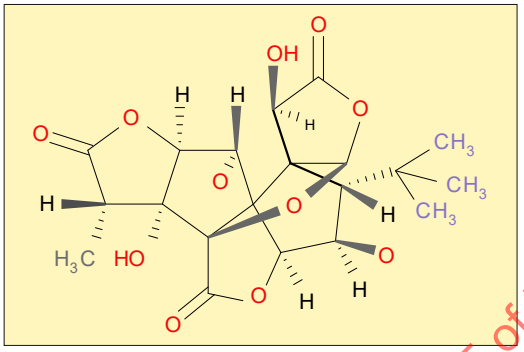
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Element Name	Value	Data Format	Note #
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Structure			1)
Stereochemistry	Chiral	CD	
Optical Activity	N/A	CD	
Molecular Formula	$C_{20}H_{24}O_{10}$	ST	
Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.18 — Structural representation of Ginkgolide B**	ED	
Element Group: Molecular Weight			1)
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount 1)			
Amount Type	Exact	CD	
Quantity	424,40	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	32ZQ957R4A (UNII)	II	
Constituent Substance Name	Ginkgolide C	ST	1)
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Structure			1)
Stereochemistry	Chiral	CD	

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Element Name	Value	Data Format	Note #
Optical Activity	N/A	CD	
Molecular Formula	$C_{20}H_{24}O_{11}$	ST	
Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.19 — Structural representation of Ginkgolide C**	ED	
Element Group: Molecular Weight 1)			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount 1)			
Amount Type	Exact	CD	
Quantity	440,40	PQ	
Unit	g/mol	CD	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Country of origin	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Non Numeric Value	China	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Geographical location	ST	
Is Defining	Yes	BL	

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Element Name	Value	Data Format	Note #
Element Group: Amount			
Non Numeric Value	Provinces Shandong, Jiangsu, Sichuan	ST	
Element Group: Specified Substance Group 2 (Manufacturer of the Herbal preparation) Extract Limited information			
Specified Substance Group 2 ID	GHTW12345 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Ginkgo biloba*, Leaf, Dry Extract—Company RGHS, Netherlands	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
Parent Substance ID	XYZ123456E (Artificial ID)	II	2)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Extraction	CD	
Production Method Description	Extraction with acetone-water followed by liquid-liquid extraction several washing steps, concentrating and drying of the final extract.	ST	
Critical Process Version Number	1	INT	
Version	001	ST	
Version Date	20160608	TS.Date	
Element Group: Organization			
Manufacturer ID	DUNS78544HP (Artificial ID)	II	
Manufacturer Name	Company RGHS	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	
Element Group: Specified Substance Group 3 Herbal preparation (Ph.Eur., Limited information)			
Specified Substance Group 3 ID	GHDMK123EP (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Ginkgo biloba*, Leaf, Dry Extract-Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	

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Element Name	Value	Data Format	Note #
(Parent) Substance ID	XYZ123456E (Artificial ID)	II	2)
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name (= Name of the Ph.Eur. monograph)	Ginkgo dry extract, refined and quantified	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph. Eur	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur., Monograph 04/2008:1827	ST	
NOTE 1 The Substance Type Structurally Diverse is connected with the Element Groups Single Substance/Structure. All Structural information regarding Flavone Glycosides is captured/or supplemented at submission (see Annex B, Chemical Substance). NOTE 2 This (Parent) Substance ID corresponds to the (Specified) Substance (Group 1) Name: *Ginkgo biloba*, Leaf, Dry Extract.			

E.4.2.2 Herbal preparation Ginkgo biloba extract, Extended information: Description of the elements at the Specified Substance Group 1, 2 and 3.

Table E.7 — Tabular Format Herbal preparation Ginkgo biloba extract, Extended information: Description of the elements at the Specified Substance Group 1, 2 and 3

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 1 (Herbal preparation Extended information)			
Specified Substance Group 1 ID	HERBP12345 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Ginkgo biloba*, Leaf, Dry Extract, Acetone-Water (60-40 w/w),(37-65:1)	ST	
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug, Botanical	CD	
Jurisdiction	EU, US	CD	
Element Group: Constituent			
Constituent Substance ID	HPR852369P (Artificial ID)	II	
Constituent Substance Name	*Ginkgo biloba*, Leaf, Extract	ST	
Language	en	CD	

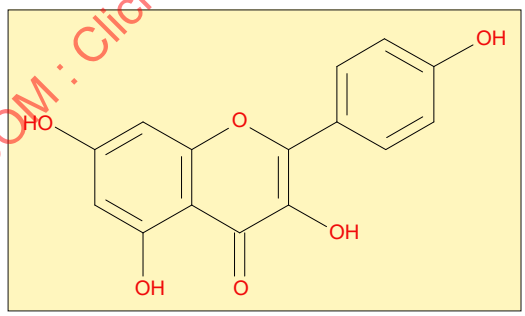
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Element Name	Value	Data Format	Note #
Substance Role	Parent Substance	CD	
Is Defining	Yes	BL	
Element Group: Fraction Description			
Fraction	Dry Extract, Acetone-Water (60-40 w/w),(37-65 = 1)	ST	
Material Type	Herbal, Leaf	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	ACETO98765 (Artificial ID)	II	
Constituent Substance Name	Acetone	ST	
Language	en	CD	
Substance Role	Extraction solvent	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	60	PQ	
Unit	%{w/w}	CD	
Amount Text	Acetone-Water (60-40 w/w)	ST	
Element Group: Constituent (Repeat)			
Constituent Substance ID	WATEP67543 (Artificial ID)	II	
Constituent Substance Name	Water	ST	
Language	en	CD	
Substance Role	Extraction Solvent	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	40	PQ	
Unit	%{w/w}	CD	
Amount Text	Acetone-Water (60-40 w/w)	ST	
Element Group: Constituent (Repeat)			
Constituent Substance ID	FKLAV98765 (Artificial ID)	II	
Constituent Substance Name	Flavone Glycoside	ST	1)
Language	en	CD	
Substance Role	Active Marker	CD	

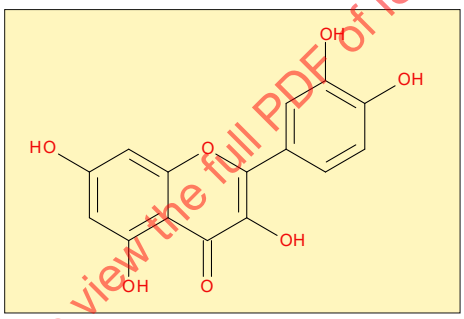
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Element Name	Value	Data Format	Note #
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	25	PQ	
Low Limit	22	PQ	
High Limit	27	PQ	
Unit	Mass per cent	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	731P2LE49E (UNII)	II	
Constituent Substance Name	Kaempferol	ST	1)
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Structure			1)
Stereochemistry	Achiral	CD	
Molecular Formula	$C_{15}H_{10}O_6$	ST	
Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.20 — Structural representation of Kaempferol**	ED	
Element Group: Molecular Weight			1)
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			1)
Amount Type	Exact	CD	
Quantity	286,23	PQ	
Unit	g/mol	CD	

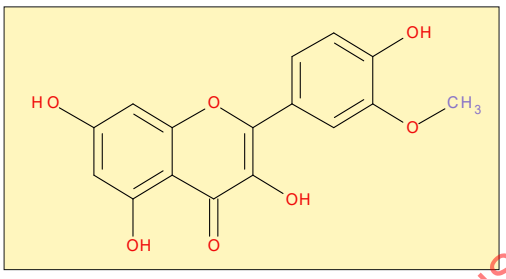
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Element Name	Value	Data Format	Note #
Element Group: Constituent (Repeat)			
Constituent Substance ID	9IKM0I5T1E (UNII)	II	
Constituent Substance Name	Quercetin	ST	1)
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Structure			1)
Stereochemistry	Achiral	CD	
Molecular Formula	$C_{15}H_{10}O_7$	ST	
Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.21 — Structural representation of Quercetin**	ED	
Element Group: Molecular Weight			1)
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			1)
Amount Type	Exact	CD	
Quantity	302,23	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	73WRA8Z8M8 (UNII)	II	
Constituent Substance Name	Isorhamnetin	ST	1)
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	

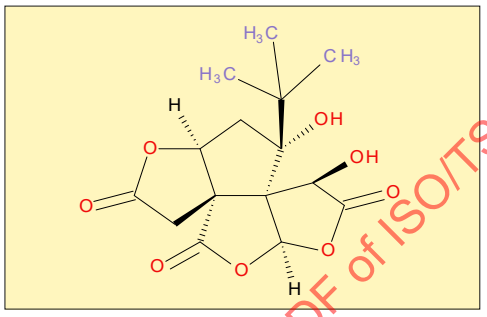
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Element Name	Value	Data Format	Note #
Element Group: Structure			1)
Stereochemistry	Achiral	CD	
Molecular Formula	$C_{16}H_{12}O_7$	ST	
Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.22 — Structural representation of Isorhamnetin**	ED	
Element Group: Molecular Weight			1)
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			1)
Amount Type	Exact	CD	
Quantity	316,26	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	M81D2O8H7U (UNII)	II	
Constituent Substance Name	Bilobalide	ST	1)
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	2,9	PQ	
Low Limit	2,6	PQ	
High Limit	3,2	PQ	
Unit	Mass per cent	CD	

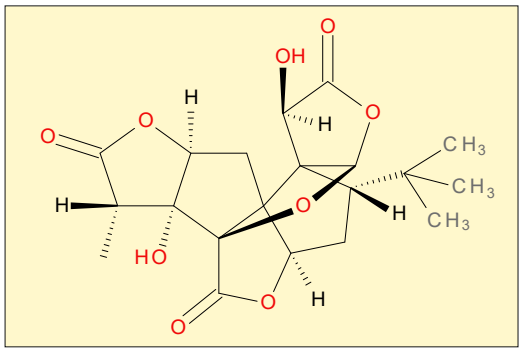
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Element Name	Value	Data Format	Note #
Element Group: Structure			1)
Stereochemistry	Chiral	CD	
Optical Activity	(-)	CD	
Molecular Formula	$C_{15}H_{18}O_8$	ST	
Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.23 — Structural representation of Bilobalide**	ED	
Element Group: Molecular Weight			1)
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			1)
Amount Type	Exact	CD	
Quantity	326,29	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	TAZ2DPR77B (UNII)	II	
Constituent Substance Name	Ginkgolide A	ST	1)
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Structure			1)
Stereochemistry	Chiral	CD	
Optical Activity	N/A	CD	
Molecular Formula	$C_{20}H_{24}O_9$	ST	

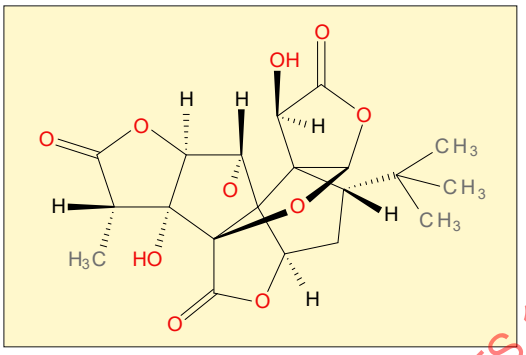
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Element Name	Value	Data Format	Note #
Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.24 — Structural representation of Ginkgolide A**	ED	
Element Group: Molecular Weight			1)
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			1)
Amount Type	Exact	CD	
Quantity	408,40	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	DF149B946O (UNII)	II	
Constituent Substance Name	Ginkgolide B	ST	1)
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Structure			1)
Stereochemistry	Chiral	CD	
Optical Activity	N/A	CD	
Molecular Formula	$C_{20}H_{24}O_{10}$	ST	

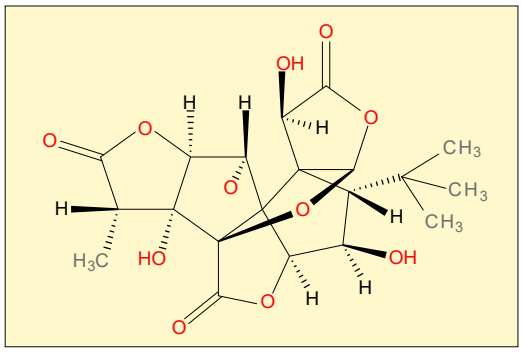
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Element Name	Value	Data Format	Note #
Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.25 — Structural representation of Ginkgolide B**	ED	
Element Group: Molecular Weight			1)
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			1)
Amount Type	Exact	CD	
Quantity	424,40	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Substance ID	32ZQ957R4A (UNII)	II	
Substance Name	Ginkgolide C	ST	1)
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Structure			1)
Stereochemistry	Chiral	CD	
Optical Activity	N/A	CD	
Molecular Formula	$C_{20}H_{24}O_{11}$	ST	

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Element Name	Value	Data Format	Note #
Element Group: Structural Representation			1)
Structural Representation Type	Full	CD	
Structural Representation Attachment	 **Figure E.26 — Structural representation of Ginkgolide C**	ED	
Element Group: Molecular Weight			1)
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			1)
Amount Type	Exact	CD	
Quantity	440,40	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	SUYTRE7854 (Artificial ID)	II	2)
Constituent Substance Name	Ginkgolide A, B, C	ST	
Language	en	CD	
Substance Role	Active Marker	CD	
Is Defining	Yes	BL	
Element Group: Amount (Constituents Ginkgolide A, B, C)			
Amount Type	Average	CD	
Quantity	3,1	PQ	
Low Limit	2,8	PQ	
High Limit	3,4	PQ	
Unit	%{w/w}	CD	

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Element Name	Value	Data Format	Note #
Element Group: Constituent (Repeat)			
Constituent Substance ID	32ZQ957R4A (UNII)	II	
Constituent Substance Name	Ginkgolic acid	ST	1)
Language	en	CD	
Substance Role	Toxic ingredient	CD	3)
Element Group: Amount (Constituent)			
Amount Type	NMT	CD	
Quantity	5	PQ	
Unit	ppm[44]	CD	
Element Group: Reference Source			
Reference Source Document	PDF	ED	
Reference Source Document Type	Journal article	CD	
Reference Source URL	http://onlinelibrary.wiley.com/enhanced/doi/10.1002/rcm.4086	ST	3)
Element Group: Characteristic Attribute			
Attribute Type	Particular Herbal preparation	CD	
Attribute Name	Drug Extract Ratio (DER)	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Low Limit	37	PQ	
High Limit	65	PQ	
Unit	g	CD	
Amount Text	37 – 65 parts Herbal Substance = 1 part Herbal Extract	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Country of origin	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Non Numeric Value	China	ST	

[44] Parts per million.

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Element Name	Value	Data Format	Note #
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular Herbal	CD	
Attribute Name	Geographical location	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Non Numeric Value	Provinces Shandong, Jiangsu, Sichuan	ST	
Element Group: Specified Substance Group 2 (Manufacturer of the Herbal preparation) Extract Extended information			
Specified Substance Group 2 ID	FGDWE56341 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Ginkgo biloba*, Leaf, Dry Extract, Acetone-Water (60-40 w/w),(37-65 = 1)—Company XYZ, Netherlands	ST	
Substance Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	HERBP12345 (Artificial ID)	II	4)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Extraction	CD	
Production Method Description	Extraction/absorption steps and final blending of the extract	ST	
Critical Process Version Number	1	INT	
Element Group: Reference Source			
Public Domain	No	CD	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	

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Element Name	Value	Data Format	Note #
Element Group: Reference Source Document			
Reference Source Document	Pdf. Document, Manufacturing flow overview	ED	
Reference Source Document Type	Regulatory Submission	CD	

Manufacturing overview, Herbal preparation, Dry Extract:

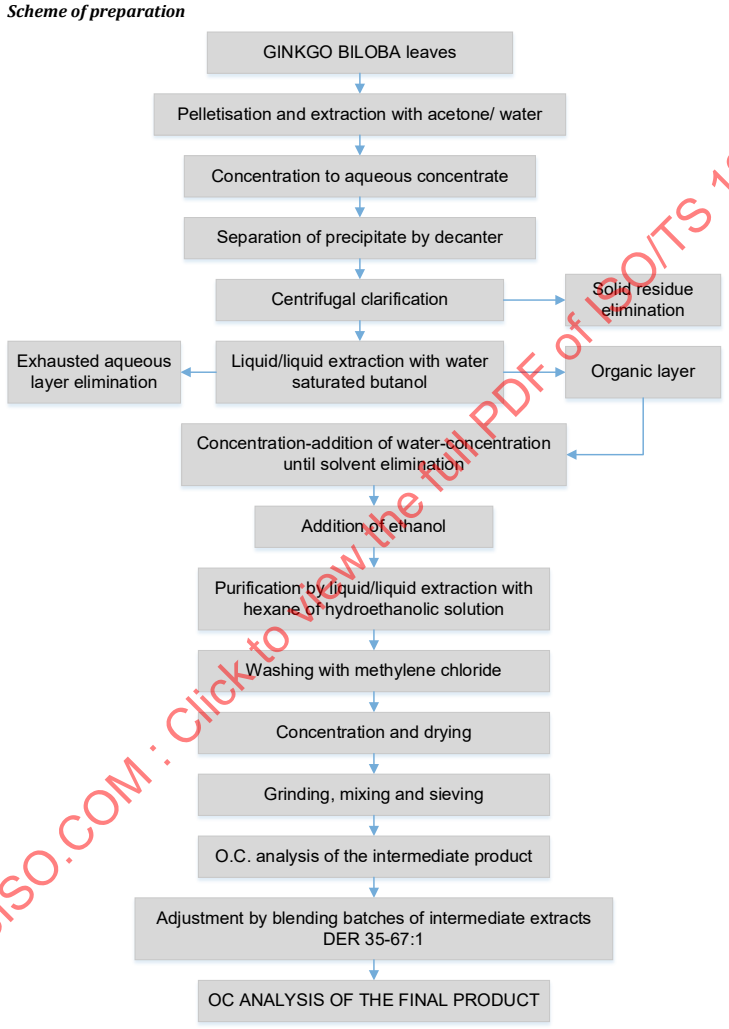


Figure E.27 — Schema of the manufacturing procedure of *Ginkgo biloba*, Leaf, Dry Extract

Element Group: Organization			
Manufacturer ID	DUNS6753HP (Artificial ID)	II	
Manufacturer Name	Company XYZ	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Harvester and Manufacturer of Botanical Material	CD	

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Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 3 Herbal preparation (Ph.Eur., Extended information)			
Specified Substance Group 3 ID	HJFGERA897 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Ginkgo biloba*, Leaf, Dry Extract, Acetone-Water (60-40 w/w),(37-65 = 1)-Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	HERBP12345 (Artificial ID)	II	4)
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name (= Name of the Ph.Eur. monograph)	Ginkgo dry extract, refined and quantified	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph. Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur., Monograph 04/2008:1827	ST	

NOTE 1 The Substance Type Structurally Diverse is connected with the Element Groups Single Substance/Structure. All Structural information regarding Flavone Glycosides should be captured/or supplemented at submission (see Annex B, Chemical Substance).

NOTE 2 SUYTRE7854 (Artificial ID) refers to Ginkgolide A, B, C which is a Multi-substance material composed of three substances. The ID is a specified substance ID.

NOTE 3 Reference for the Toxicity and allergenic activity of Ginkgo acids, in particular Ginkgolic acid, see Reference [21].

NOTE 4 This (Parent) Substance ID corresponds to (Specified) Substance (Group 1) Name: *Ginkgo biloba*, Leaf, Dry Extract, Acetone-Water (60-40 w/w),(37-65 = 1).

E.4.3 Example 2: Devil's Claw Root (Ph.Eur.), continued

This example is a submission for a Substance ID. The application is for a dry extract from the dried roots of *Harpagophytum procumbens* (Burch.) DC. ex Meisn. (1.5-3 = 1, w/w). Extraction solvent is ethanol 60 %{v/v}. The reference monograph also permits the use of *Harpagophytum zeyheri* Decne. and the substance IDs required for that species at the various levels are also included in this example in order to provide a full picture.

The information provided within subclauses E.4.3.1 and E.4.3.2 are as would be described in the regulatory submission and clause E.4.4 as per ISO 11238 and ISO/TS 19844.

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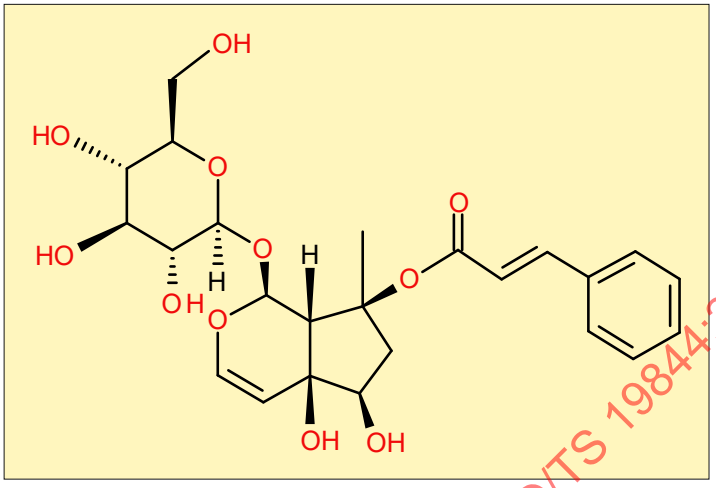
E.4.3.1 General Information Herbal Drug

Table E.8 — Devil's Claw Root

Provided information	Description
Description: Reference: Source: Plant, Part Dry Extract:	Devil's claw root consists of the cut and dried tuberous secondary roots of *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne. Note: Only one species is used. Content: minimum 1,2 per cent of harpagoside ($C_{24}H_{30}O_{11}$; Mr 494.5) (dried drug). European Pharmacopoeia ed. 8.6 Ph.Eur. monograph **01/2011:1095** Ph.Eur. monograph **01/2008:1871**
Process State, Wild/cultivated	For the production of the extract, Harpagophytum procumbens DC. from cultivations located in South Africa and Namibia is used. (Since in the area where the plant material is sourced Harpagophytum zeyheri Decne. is not common, it is extremely unlikely that this species is collected.)
Growth State	Crop-grown plants are harvested during the whole year after they have been cultivated for at least two growth periods.
Harvesting Conditions	Unwashed, undamaged tubers of good quality keep relatively well when stored under dry conditions. The tubers are cleaned dry and washed with clean water. Then they are cut into slices of 2-4 mm. The drying is carried out in a protected place but without further technical installation. The washed and cut roots are spread out on drying frames placed on trays. The natural air drying occurs indoors.
Decontamination Process	Special care is taken to ensure sufficient air circulation between the root slices (sufficient distance between the slices) and in the room (ventilation of the room by means of a ventilator, when necessary) in order to avoid mould formation. No post-harvesting treatment with ethylene oxide or other fumigant against pests is applied.
Storage Conditions	The well-dried drug is stored in dry bags indoors, protected from light.
Constituents	Devil's claw root characteristic constituents are: Iridoid glucosides, principally harpagoside together with small amounts of harpagide, 8-p-coumaroylharpagide, procumbide and its 6'-p-coumaroyl ester. The phenolic glycosides acteoside (verbascoside) and isoacteoside, and sugars, mainly the tetrasaccharide stachyose with smaller amounts of raffinose, sucrose and monosaccharides are also present.
Marker	Harpagoside is used as a quality marker for both the Herbal Drug and the Herbal preparation.
Marker Characterization: Molecular Formula: Molecular Weight:	CAS: 19210-12-9 (Harpagoside) UNII: 8KGS1DC5ZU $C_{24}H_{30}O_{11}$ 494,5 g/mol.

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Provided information	Description
Structural Information	See below  **Figure E.28 — Structural representation of Harpagoside**
Systematic Name:	*1S-(1α,4α,5α,7α(E),7α-1,4a,5,6,7,7a-Hexahydro-4a,5-dihydroxy-7-methyl-7-((allyl-1-oxo-3-phenyl)oxy)cyclopenta(c)pyran-1-yl-beta-D-glucopyranoside*
Marker Specification	Content: minimum 1,2 per cent
Substance ID	HARPO5643S (Artificial ID)
Characterization Macroscopic, Microscopic Examination	Characterization of the Herbal Drug is based on the monograph in the European Pharmacopoeia for Harpagophyti radix. Additionally, a selection of purity tests is carried out. The material is tested for pesticides, heavy metals, aflatoxins and microbial purity (cat 4A). In line with the Ph.Eur. Monograph specifications include an assay for Harpagoside. The Herbal Drug is examined macroscopically and using thin layer chromatography in line with the Ph.Eur. monograph.
Supplier of the Herbal Drug	Name Company, Address, Town, South Africa
Primary Process	Harvesting, cutting, drying

E.4.3.2 General Information Herbal preparation

Table E.9 — Devil's Claw Extract

Provided information	Description
Description: Reference: Dry Extract	Dry extract European Pharmacopoeia, ed. 8.6 Ph.Eur. monograph 01/2008:1871
Extraction Solvent	Ethanol – water [60-40, {v/v}].
Ratio Herbal Drug/Native Herbal preparation (DER)	1,5 – 3,0:1

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Provided information	Description
Marker Substance Marker Specification	Harpagoside, [$C_{24}H_{30}O_{11}$; Mr. 494.5) Minimum 1,5 per cent dried extract
Final Blending	Lactose monohydrate and Silicon Dioxide (Captured at the product level)
Manufacturer Name	Name, Address, Town, Country, Geographical coordinates
Manufacturing Process Description Storage	Step 1) Fluid extract: The roots are macerated with ethanol 60 %{v/v} while being processed through an extractor. The macerate is pressed/decanted from the resulting tincture after which the material is once more washed with ethanol 60 %{v/v}. Both tincture steps are purified from fine plant particles and are subjected to an ultra-heat treatment to reduce microbial burden. Step 2) Soft extract: The tincture is concentrated in two steps to a soft extract. Lactose monohydrate is mixed with the soft extract. Step 3) Dry extract: Drying is performed in a vacuum dryer. The dry extract is milled and mixed with Silicium dioxide to a concentration of 2,5 % relative to the finished extract preparation. The extract preparation is stored in PE drums with double PE foil liners.
Specifications final extract: Content Harpagoside Loss on drying Residual solvent	 1,5 to 2,5 per cent NMT[1] 5,0 per cent NMT[2] 0,5 per cent ethanol
NOTE 1 NMT equals to: Not More Than. NOTE 2 NLT equals to: Not Less Than.	

E.4.4 Organization of the information according to ISO 11238 and ISO/TS 19844

E.4.4.1 Information at the Substance level

The example is not organized in tabular format but the specific organization of the information for this Substance class is discussed. In addition, a tabular summary is provided in Table E.9.

E.4.4.2 Substance (Fresh)

This example describes the two species (*Harpagophytum procumbens* DC. and *Harpagophytum zeyheri* Decne.) described in the monograph of the Devil's claw root.

Element Group: Substance:

Substance (fresh) ID: DEVTYS543H (Artificial ID)
Substance Type: Structurally Diverse (Herbal Substance)

Element Group: Substance Name

Substance (fresh) Name: *Harpagophytum procumbens* (Burch.) DC. ex Meisn., Root
Substance Name Type: Other
Language: en
Substance Name Domain: Drug
Jurisdiction: EU, US

Element Group: Substance Name (Repeat)

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Substance Name: *Harpagophytum procumbens* (Burch.) DC. ex Meisn.
Substance Name Type: Scientific
Language : en

Element Group: Source Material
Organism ID: DSERW78654 (Artificial ID)
Organism Name: *Harpagophytum procumbens* (Burch.) DC. ex Meisn.

Element Group: Organism
Family: *Pedaliaceae*
Genus: Harpagophytum
Species: procumbens

Element Group: Author
Author Type: Species Parenthetical Author
Author Description: Burch.

Element Group: Author (Repeat)
Author Type: Species Primary Author
Author Description: DC. ex Meisn.

Element Group: Organism General
Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Lamiales

Element Group: Part Description
Part: Tuberous root

Element Group: Substance
Substance (fresh) ID: FGTE56432H (Artificial ID)
Substance Type: Structurally Diverse (Herbal Substance)

Element Group: Substance Name
Substance (fresh) name: *Harpagophytum zeyheri* Decne., Root
Substance Name Type: Other
Language: en

Element Group: Substance Name (Repeat)
Substance Name: *Harpagophytum zeyheri* Decne.
Substance Name Type: Scientific
Language: la
Substance Name Domain: Drug
Jurisdiction: EU, US
Element Group: Source Material

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Organism ID: YTREW8654Z (Artificial ID)
Organism Name: *Harpagophytum zeyheri* Decne.

Element Group: Organism
Family: *Pedaliaceae*
Genus: Harpagophytum
Species: zeyheri

Element Group: Author
Author Type: Species Primary Author
Author Description: Decne.

Element Group: Organism General
Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Lamiales

Element Group: Part Description
Part: Tuberous root

E.4.4.3 Substance (Usually Dry, may be Fresh as described in a Pharmacopoeia) = Herbal Drug

Element Group: Substance
Substance (Herbal Drug) ID: CCCCCCCCCC (Artificial ID)
Substance Type: Structurally Diverse (Herbal Substance)

Element Group: Substance Name
Substance Name (Herbal Drug): *Harpagophytum procumbens*, Root
Substance Name Type: Official
Language: en
Substance Name Domain: Drug
Jurisdiction: EU, US

Element Group: Official Name
Official Name Type: Ph.Eur.
Official Name Status: Current

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: Ph.Eur.
Reference Source Class: Official Name Source
Reference Source Citation: Ph.Eur. monograph 01/2011:1095

Element Group: Substance Name (Repeat) (Synonyms):
Substance Name: Harpagophyti radix – Substance Name Type: Other; Language: la
Substance Name: Teufelskrallenwurzel – Substance Name Type: Other; Language: de

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Substance Name: Devil's Claw Root – Substance Name Type: Official; Language: en

Element Group: Source Material
Parent Substance (fresh) ID: DEVTYS543H (Artificial ID)
Parent Substance (fresh) Name: *Harpagophytum procumbens* (Burch.) DC. ex Meisn., Root

Element Group: Part Description
Part: Tuberous root

Element Group: Substance
Substance Type: Structurally Diverse (Herbal Substance)
Substance (Herbal Drug) ID: DDDDDDDDDD (Artificial ID)

Element Group: Substance Name
Substance Name (Herbal Drug): *Harpagophytum zeyheri*, Root
Substance Name Type: Official
Language: en
Substance Name Domain: Drug
Jurisdiction: EU, US

Element Group: Official Name
Official Name Type: Ph.Eur.
Official Name Status: Current

Element Group: Reference Source
Public Domain: Yes
Reference: Ph.Eur.
Reference Source Class: Official Name Source
Reference Source Citation: Ph.Eur. Monograph: 01/2011:1095

Element Group: Substance Name (Repeat) (Synonyms):
Substance Name: Devil's Claw Root – Substance Name Type: Official; Language: en

Element Group: Source Material
Parent Substance (fresh) ID: FGTE56432H (Artificial ID)
Parent Substance (fresh) Name: *Harpagophytum zeyheri* Decne., Root

Element Group: Part Description
Part: Tuberous root

E.4.4.4 Substance, Herbal preparation

Element Group: Substance
Substance ID (Herbal preparation): EEEEEEEEEE (Artificial ID)
Substance Type: Structurally Diverse (Herbal Substance)

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Element Group: Substance Name
Substance Name (Herbal preparation): *Harpagophytum procumbens*, Root, Extract
Language: en
Substance Name Domain: Drug
Jurisdiction: EU, US

Element Group: Substance Name (Repeat) (Synonyms):
Substance Name: Devil's Claw Root Extract
Substance Name Type: Official
Language: en

Element Group: Reference Source
Public Domain: Yes
Reference: Ph.Eur.
Reference Source Class: Official Name Source
Reference Source Citation: Ph.Eur. Monograph: 01/2008:1871

Element Group: Source Material
Parent Substance ID: CCCCCCCCCC (Artificial ID)
Parent Substance Name (Herbal Drug): *Harpagophytum procumbens*, Root

Element Group: Part Description
Part: Tuberous root

Element Group: Fraction Description
Fraction: Extract
Material Type: Herbal

Element Group: Substance
Substance ID (Herbal preparation): FFFFFFFFFF (Artificial ID)
Substance Type: Structurally Diverse (Herbal Substance)

Element Group: Substance Name
Substance Name (Herbal preparation): *Harpagophytum zeyheri*, Root, Extract

Element Group: Substance Name (Repeat) (Synonyms):
Substance Name: Devil's Claw Root Extract – Substance Name Type: Official; Language: en

Element Group: Reference Source
Public Domain: Yes
Reference: Ph.Eur.
Reference Source Class: Official Name Source
Reference Source Citation: Ph.Eur. Monograph: 01/2008:1871

Element Group: Source Material
Parent Substance ID: DDDDDDDDDD (Artificial ID)

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Parent Substance Name (Herbal Drug): *Harpagophytum zeyheri*, Root

Element Group: Part Description
Part: Tuberous root

Element Group: Fraction Description
Fraction: Extract
Material Type: Herbal

E.4.4.5 Specified Substance Group 1 information level for the Herbal Drug

Element Group: Specified Substance Group 1
Specified Substance Group 1 ID (Herbal Drug): GHTDR6435H (Artificial ID)

Element Group: Substance Name
Substance Name (Herbal Drug): *Harpagophytum procumbens*, Root, Dry
Substance Name Type: Specified Substance Group 1
Language: en
Substance Name Domain: botanical
Jurisdiction: EU, US, South Africa, Namibia

Element Group: Substance Name (Repeat)
Official Name: Devil's Claw Root, Dry
Substance Name Type: Official
Language: en

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: Ph.Eur.
Reference Source Class: Official Name Source
Reference Source Citation: Ph.Eur. monograph 01/2011:1095

Element Group: Constituent
Constituent Substance ID (Herbal Drug): CCCCCCCCCC (Artificial ID)
Constituent Substance Name (Herbal Drug): *Harpagophytum procumbens*, Root
Language: en
Substance Role: Parent substance
(which in turn corresponds to the Parent Substance (fresh): *Harpagophytum procumbens* (Burch.) DC. ex Meisn., Root, with the Parent Substance (fresh) ID: DEVTYS543H (Artificial ID)
Is Defining: Yes

Element Group: Constituent (Repeat)
Constituent Substance ID: 8KGS1DC5ZU (Artificial ID)
Constituent Substance Name: Harpagoside ($C_{24}H_{30}O_{11}$; Mr. 494.5; Mr. 494.5), see Table E.9
Language: en
Substance Role: Active Marker

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Is Defining: Yes

Element Group: Amount
Amount Type: NLT
Quantity: 1,2
Unit: %{w/w}
Amount Text: Weight per cent

Other Constituents (Repeat) are:
Iridoid glucosides, principally Harpagoside together with small amounts of harpagide, 8-p-coumaroylharpagide, procumbide and its 6'-p-coumaroyl ester. The phenolic glycosides acteoside (verbascoside) and isoacteoside, and sugars, mainly the tetrasaccharide stachyose with smaller amounts of raffinose, sucrose and monosaccharides are also present.

Element Group: Characteristic Attribute
Attribute Type: Particular Herbal
Attribute Name: Country of origin
Is Defining: Yes

Element Group: Amount
Non Numeric Value: South Africa, Namibia

Element Group: Characteristic Attribute (Repeat)
Attribute Type: Particular Herbal
Attribute Name: Geographical location
Is Defining: Yes

Element Group: Amount
Non Numeric Value: Windhoek

Element Group: Specified Substance Group 1
Specified Substance Group 1 ID (Herbal Drug): TE84K152PR (Artificial ID)

Element Group: Substance Name
Substance Name (Herbal Drug): *Harpagophytum zeyheri*, Root, Dry
Substance Name Type: Specified Substance Group 1
Language: en

Element Group: Substance Name (Repeat)
Official Name: Devil's Claw Root, Dry
Substance Name Type: Official
Language: en

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: Ph.Eur.
Reference Source Class: Official Name Source

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Reference Source Citation: Ph.Eur. monograph 01/2011:1095

Element Group: Constituent
Constituent Substance ID (Herbal Drug): DDDDDDDDDD (Artificial ID)
Constituent Substance Name (Herbal Drug): *Harpagophytum zeyheri*, Root
Language: en
Substance Role: Parent substance
[which in turn has the Parent Substance (fresh): *Harpagophytum zeyheri* Decne., Root, with the Parent Substance ID: FGTE56432H (Artificial ID)]
Is Defining: Yes

Element Group: Constituent (Repeat)
Constituent Substance ID: 8KGS1DC5ZU (Artificial ID)
Constituent Substance Name: Harpagoside ($C_{24}H_{30}O_{11}$; Mr. 494.5; Mr. 494.5), see Table E.8.
Language: en
Substance Role: Active Marker
Is Defining: Yes

Element Group: Amount
Amount Type: NLT
Quantity: 1.2
Unit: %{w/w}
Amount Text: Weight per cent

Other Constituents (Repeat) are:
Iridoid glucosides, principally Harpagoside together with small amounts of harpagide, 8-p-coumaroylharpagide, procumbide and its 6'-p-coumaroyl ester. The phenolic glycosides acteoside (verbascoside) and isoacteoside, and sugars, mainly the tetrasaccharide stachyose with smaller amounts of raffinose, sucrose and monosaccharides are also present.

Element Group: Characteristic Attribute
Attribute Type: Particular Herbal
Attribute Name: Country of origin
Is Defining: Yes

Element Group: Amount
Non Numeric Value: South Africa, Namibia

Element Group: Characteristic Attribute (Repeat)
Attribute Type: Particular Herbal
Attribute Name: Geographical location
Is Defining: Yes

Element Group: Amount
Non Numeric Value: Windhoek

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Element Group: Characteristic Attribute (Repeat) (Herbal Drug), further laid out as shown in the tables
Attribute Type: Particular Herbal
Attribute Name:
Degree of Comminution: cut into slices of 2 cm to 4 cm.;
Process State: Dried indoors, well ventilated;
Wild/Cultivated: Cultivated;
Growth State: Mature plant;
Harvesting Time: Whole year
Storage Time: 2 years.
Is Defining: Yes

Element Group: Attribute Parameter (Herbal Drug)
Attribute Parameter Name: Harvesting condition
Attribute Parameter Value: Plants are harvested during the whole year after they have been cultivated for at least two growth periods

Element Group: Attribute Parameter (Repeat) (Herbal Drug)
Attribute Parameter Name: Storage Condition
Attribute Parameter Value: Undamaged tubers and stored under dry conditions

E.4.4.6 Specified Substance Group 2 information level for the Herbal Drug

Element Group: Specified Substance Group 2
Specified Substance Group 2 ID (Herbal Drug): PYFGS7654M (Artificial ID)

Element Group: Substance Name
(Specified) Substance (Group 2) Name (Herbal Drug): *Harpagophytum procumbens*, Root, Dry – Manufacturer AA.
Substance Name Type: Specified Substance Group 2
Language: en
(Parent) Substance Group 1 ID (Herbal Drug): GHTDR6435H (Artificial ID)

Element Group Manufacturing
Manufacturing Type: Harvester
Production Method Type: Harvesting
Production Method Description: Collecting and Harvesting, drying and storing of the Herbal Drug
Production System Type: N/A
Production System: N/A
Critical Process Version Number: 1
Version: 001
Version Date: 20161205

Element Group Organization
Manufacturer ID: MANDUNS452 (Artificial ID)
Manufacturer Name: Name
Issue of ID: EMA OMS Service
Manufacturer Role: Harvester and Manufacturer of Botanical Material

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Elemenet Group: Specified Substance Group 2
Specified Substance Group 2 ID (Herbal Drug): GJURT4523K (Artificial ID)

Elemenet Group: Substance Name
Substance Name (Herbal Drug): *Harpagophytum zeyheri*, Root, Dry – Manufacturer AA
Substance Name Type: Specified Substance Group 2
Language: en
(Parent) Substance ID (Herbal Drug): [TE84K152PR]

Element Group Manufacturing
Manufacturing Type: Harvester
Production Method Type: Harvesting
Production Method Description: Collecting and Harvesting, drying and storing of the Herbal Drug
Production System Type: N/A
Production System: N/A
Critical Process Version Number: 1
Version: 001
Version Date: 20161205

Element Group Organization
Manufacturer ID: MANDUNS452 (Artificial ID)
Manufacturer Name: Manufacturer AA
Issue of ID: EMA OMS Service
Manufacturer Role: Harvester and Manufacturer

E.4.4.7 Specified Substance Group 3 information level for the Herbal Drug

Element Group: Specified Substance Group 3
Specified Substance Group 3 ID (Herbal Drug): GGGGGGGGGG (Artificial ID)

Element Group: Substance Name
(Specified) Substance (Group 3) Name (Herbal Drug): *Harpagophytum procumbens and_or Harpagophytum zeyheri*, Root, Dry, Standardized
Substance Name Type: Specified Substance Group 3
Language: en
(Parent) Substance ID (Herbal Drug): GHTDR6435H (Artificial ID)
(corresponding to the Specified Substance Group 1 Name (Herbal Drug): *Harpagophytum procumbens*, Root, Dry)
(Parent) Substance ID (Herbal Drug): TE84K152PR (Artificial ID)
(corresponding to the Specified Substance Group 1 Name (Herbal Drug): *Harpagophytum zeyheri*, Root, Dry).

Element Group: Grade
Grade Type: Ph.Eur.
Grade Name: Devil's Claw Root

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Element Group: Reference Source
Public Domain: Yes
Reference Source Citation: Ph.Eur. monograph 01/2008:1095

E.4.4.8 Elements captured at the Specified Substance Group 1 level for the Herbal preparation (Extract, extended information)

Element Group: Specified Substance Group 1
Specified Substance Group 1 ID (Herbal preparation): EXCTER654E (Artificial ID)

Element Group: Substance Name
(Specified) Substance (Group 1) Name (Herbal preparation): *Harpagophytum procumbens*, Root, Dry Extract, Ethanol-Water (60-40 {v/v}) (1,5–3,0 = 1)
Substance Name Type: Specified Substance Group 1
Language: en
Substance Name Domain: Drug
Jurisdiction: EU, US

Element Group: Fraction Description
Fraction: Dry Extract, Ethanol-Water (60-40 {v/v}) (1,5–3,0 = 1)
Material Type: Herbal Extract

Element Group: Constituent
Constituent Substance ID: EEEEEEEEEE (Artificial ID
Constituent Substance Name: *Harpagophytum procumbens*, Root
Language: en
Substance Role: Parent Substance
Is Defining: Yes

Element Group: Constituent (Repeat)
Constituent Substance ID: ETHAN98765 (Artificial ID)
Constituent Substance Name: Ethanol
Language: en
Substance Role: Extraction solvent
Is Defining: Yes

Element Group: Amount
Amount Type: Exact
Quantity: 60
Unit: % {v/v}
Amount Text: Ethanol 60 % {v/v}

Element Group: Constituent (Repeat)
Constituent Substance ID: WATERP67543 (Artificial ID)
Constituent Substance Name: Water
Language: en
Substance Role: Extraction solvent

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Is Defining: Yes

Element Group: Amount
Quantity: 40
Unit: % {v/v}
Amount Text: Ethanol 60 % {v/v}

Element Group: Constituent (Repeat)
Constituent Substance ID: 8KGS1DC5ZU (Artificial ID)
Constituent Substance Name: Harpagoside, ($C_{24}H_{30}O_{11}$; Mr. 494.5)
Language: en
Substance Role: Active Marker
Is Defining: Yes

Element Group: Amount
Amount Type: NLT
Quantity: 1.2
Unit: %{w/w}

NOTE Marker specification: Minimum 1,5 per cent dried extract.
Final Blending: Lactose monohydrate, Silicium Dioxide.
Standardization: concentration of 2,5 % Harpagoside relative to the finished extract preparation.

Other Constituents (Repeat) are:
Iridoid glucosides, principally Harpagoside together with small amounts of harpagide, 8-p-coumaroylharpagide, procumbide and its 6'-p-coumaroyl ester. The phenolic glycosides acteoside (verbascoside) and isoacteoside, and sugars, mainly the tetrasaccharide stachyose with smaller amounts of raffinose, sucrose and monosaccharides are also present.

Element Group: Characteristic Attribute
Attribute Type: Particular Herbal preparation
Attribute Name: Drug Extract Ratio (DER)
Is Defining: Yes

Element Group: Amount
Amount Type: Exact
Low Limit: 1,5
High Limit: 3,0
Unit: g
Amount Text: 1,5 – 3,0 parts Herbal Substance = 1 part Herbal Extract

Element Group: Characteristic Attribute
Attribute Type: Particular Herbal
Attribute Name: Country of origin
Is Defining: Yes

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Element Group: Amount
Non Numeric Value: South Africa, Namibia

Element Group: Characteristic Attribute (Repeat)
Attribute Type: Particular Herbal
Attribute Name: Geographical location
Is Defining: Yes

Element Group: Amount
Non Numeric Value: Windhoek

An extract made from the Harpagophytum zeyheri would require a separate Specified Substance Group 1:

Element Group: Specified Substance Group 1
(Specified) Substance (Group 1) ID (Herbal preparation): UFR78E231Y (Artificial ID)

Element Group: Substance Name
(Specified) Substance (Group 1) Name (Herbal preparation): *Harpagophytum zeyheri*, Root, Dry Extract, Ethanol-Water (60-40 {v/v}) (1.5–3.0 = 1)
Substance Name Type: Specified Substance Group 1
Language: en
Substance Name Domain: Drug
Jurisdiction: EU, US

Element Group: Constituent
Constituent Substance ID: FFFFFFFFFF (Artificial ID)
Constituent Substance Name: *Harpagophytum zeyheri*, Root
Language: en
Substance Role: Parent substance
Is Defining: Yes

Element Group: Fraction Description
Fraction: Dry Extract
Material Type: Herbal

Element Group: Constituent
Constituent Substance ID: ETHAN98765 (Artificial ID)
Constituent Substance Name: Ethanol
Language: en
Substance Role: Extraction solvent
Is Defining: Yes

Element Group: Amount
Amount Type: Exact
Quantity: 60

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Unit: %{v/v}
Amount Text: Ethanol 60 %{v/v}

Element Group: Constituent (Repeat)
Constituent Substance ID: WATERP67543 (Artificial ID)
Constituent Substance Name: Water
Language: en
Substance Role: Extraction solvent
Is Defining: Yes

Element Group: Amount
Amount Type: Exact
Quantity: 40
Unit: % {v/v}
Amount Text: Ethanol 60 % {v/v}

Element Group: Constituent (Repeat)
Constituent Substance ID: 8KGS1DC5ZU (Artificial ID)
Constituent Substance Name: Harpagoside, ($C_{24}H_{30}O_{11}$; Mr. 494.5)
Language: en
Substance Role: Active Marker
Is Defining: Yes

Element Group: Amount
Amount Type: NLT
Quantity: 1,2
Unit: %{w/w}

NOTE Marker specification: Minimum 1,5 per cent dried extract.
Final Blending: Lactose monohydrate, Silicium Dioxide.
Standardization: concentration of 2,5 % Harpagoside relative to the finished extract preparation.

Other Constituents (Repeat) are:
Iridoid glucosides, principally Harpagoside together with small amounts of harpagide, 8-p-coumaroylharpagide, procumbide and its 6'-p-coumaroyl ester. The phenolic glycosides acteoside (verbascoside) and isoacteoside, and sugars, mainly the tetrasaccharide stachyose with smaller amounts of raffinose, sucrose and monosaccharides are also present.

Element Group: Characteristic Attribute
Attribute Type: Particular Herbal preparation
Attribute Name: Drug Extract Ratio (DER)
Is Defining: Yes

Element Group: Amount
Amount Type: Exact
Low Limit: 1,5

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High Limit: 3,0
Unit: g
Amount Text: 1,5 – 3,0 parts Herbal Substance = 1 part Herbal Extract

Element Group: Characteristic Attribute
Attribute Type: Particular Herbal
Attribute Name: Country of origin
Is Defining: Yes

Element Group: Amount
Non Numeric Value: South Africa, Namibia

Element Group: Characteristic Attribute (Repeat)
Attribute Type: Particular Herbal
Attribute Name: Geographical location
Is Defining: Yes

Element Group: Amount
Non Numeric Value: Windhoek

E.4.4.9 Elements captured at the Specified Substance Group 2 level for the Herbal preparation (Extract, extended information)

Element Group: Specified Substance Group 2
Specified Substance Group 2 ID (Herbal preparation): AGHFT4352E (Artificial ID)

Element Group: Substance Name
(Specified) Substance (Group 2) Name (Herbal preparation): *Harpagophytum procumbens*, Root, Dry Extract, Ethanol-Water (60-40 {v/v}) (1,5–3,0 = 1) – Manufacturer Ex.
Substance Name Type: Specified Substance Group 2
Language: en
(Parent) Substance ID (Herbal preparation): EXCTER654E (Artificial ID) (Corresponding to the (Specified) Substance (Group 1) (Herbal preparation) Name: *Harpagophytum procumbens*, Root, Dry Extract, Ethanol-Water (60-40 {v/v}) (1,5–3,0 = 1))

Element Group: Specified Substance Group 2
Specified Substance Group 2 ID (Herbal preparation): MZFTH564E (Artificial ID)

Element Group: Substance Name
(Specified) Substance (Group 2) Name (Herbal preparation): *Harpagophytum zeyheri*, Root, Dry Extract, Ethanol-Water (60-40 {v/v}) (1,5–3,0 = 1) – Manufacturer Ex.
Substance Name Type: Specified Substance Group 2
Language: en
Parent Substance Group 1 ID (Herbal preparation): TE84K152PR (Artificial ID)

Element Group: Manufacturing
Manufacturing Type: Manufacturer

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Production Method Type: Extraction
Production Method Description[45]: Maceration with ethanol 60 %, ultra-heat treatment, mixing with lactose monohydrate and blending with Silicium dioxide.
Production System Type: N/A
Production System: N/A
Critical Process Version Number: 1
Version: 001
Version Date: 20161108

NOTE If this process is changed by a change of the critical parameter based on a significant change to the production method (description), the SSG2-ID will change.

Element Group: Organization
Manufacturer ID: DUNS674521
Manufacturer Name: Company 'FGDSA' (Artificial Name)
Issuer of ID: EMA OMS
Manufacturer Role: Manufacturer

E.4.4.10 Elements captured at the Specified Substance Group 3 level for the Herbal preparation (Extract, extended information)

Substance Type: Specified Substance Group 3

Element Group: Specified Substance Group 3
Specified Substance Group 3 ID (Herbal preparation): YUTDR4267E (Artificial ID)

(Parent) Substance (Herbal preparation) ID: EXCTER654E (Artificial ID) (corresponding to the Specified Substance Group 1 (Herbal preparation) Name: *Harpagophytum procumbens*, Root, Dry Extract, Ethanol-Water (60-40 {v/v}) (1,5–3,0=1).
(Parent) Substance (Herbal preparation) ID: UFR78E23Y (Artificial ID) (corresponding to the Specified Substance Group 1 (Herbal preparation) Name: *Harpagophytum zeyheri*, Root, Dry Extract, Ethanol-Water (60-40 {v/v}) (1,5–3,0 = 1)

Element Group: Substance Name
Substance Name (Herbal preparation): *Harpagophytum procumbens* and/or *Harpagophytum zeyheri*, Root, Dry Extract, Ethanol-Water (60-40 {v/v}) (1,5–3,0 = 1)-Ph.Eur., Standardized.
Substance Name Type: Specified Substance Group 3
Language: en
Substance Name Domain: Drug

[45] Detailed Production Method Description:

The roots are macerated with ethanol 60 % {v/v} while being processed through a turbo extractor. The macerate is pressed/decanted from the resulting tincture after which the material is once more washed with ethanol 60 % {v/v}. Next both extracts are combined and subjected to ultra heat treatment (UHT) to reduce microbial burden. The UHT is triggered by the bioburden of the dried plant materials. The tincture is concentrated in two steps to a soft extract. Lactose monohydrate is mixed with the soft extract. Drying of the soft extract is performed in a vacuum dryer. The dry extract is milled and mixed with Silicium dioxide and blended to a concentration of 2,5 % relative to the finished extract preparation.

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Jurisdiction: US, EU

Element Group: Grade
Grade Type: Ph.Eur.
Grade Name: Devil's Claw Dry Extract

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: Ph.Eur.
Reference Source Class: Official Name Source
Reference Source Citation: Ph.Eur. monograph 01/2008:1871

E.4.5 Summary of the Organization of the information for Devil's Claw

Table E.10 — Substance and Specified Substance Information Devil's Claw Root, Part I

Structurally Diverse Substance, Substance (fresh) and Herbal Drug			
Substance information level A **Substance (fresh)** is always a single species, or intraspecies, or is occasionally a single genus. It will have a Name which is composed of: **[<Scientific genus/binomial/trinomial with Author>,<Part(s)>]**			
Substance ID	DEVTYS543H (Artificial ID)	Substance ID	FGTE56432H (Artificial ID)
Substance Type	Structurally Diverse (Herbal Substance)	Substance Type	Structurally Diverse (Herbal Substance)
Substance Name	*Harpagophytum procumbens* (Burch.) DC. ex Meisn., Root [a]	Substance Name	*Harpagophytum zeyheri* Decne., Root [b]
Element Group: Source Material		**Element Group: Source Material**	
Parent Substance Name	N/A	Parent Substance Name	N/A
Element Group: Organism (from which the Source Material is derived)		**Element Group: Organism (from which the Source Material is derived)**	
Family	*Pedaliaceae*	Family	*Pedaliaceae*
Genus	Harpagophytum	Genus	Harpagophytum
Species	procumbens	Species	zeyheri
Element Group: Author		**Element Group: Author**	
Species Parenthetical Author	Burch.	Species Parenthetical Author	
Species Primary Author	DC. ex Meisn.	Species Primary Author	Decne.
Element Group: Part Description		**Element Group: Part Description**	
Part	Tuberous root	Part	Tuberous root
Substance information level Information in accordance to a Pharmacopoeia (EP) for the Herbal Substance for which the ANNEX uses '**Herbal Drug**'. It will have a Name which is composed of: **[<Scientific genus/binomial/trinomial <u>without</u> Author>,<Part(s)>]**			
Substance Type	Structurally Diverse (Herbal Drug)	Substance Type	Structurally Diverse (Herbal Drug)
Substance ID	CCCCCCCCCC (Artificial ID)	Substance ID	DDDDDDDDDD (Artificial ID)

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Substance Name	*Harpagophytum procumbens,* Root	Substance Name	*Harpagophytum zeyheri*, Root
Element Group: Source Material		**Element Group: Source Material**	
Parent Substance ID	DEVTYS543H (Artificial ID)	Parent Substance ID	FGTE56432H (Artificial ID)
Parent Substance Name	*Harpagophytum procumbens* (Burch.) DC. ex Meisn., Root	Parent Substance Name	*Harpagophytum zeyheri* Decne., Root
Element Group: Part Description		**Element Group: Part Description**	
Part	Tuberous root	Part	Tuberous root
[a] The scientific part of the name is: *Harpagophytum procumbens (Burch.) DC. Ex Meisn.*		[b] The scientific part of the name is: *Harpagophytum zeyheri* Decne.	

Table E.11 — Substance and Specified Substance Information Devil's Claw Root, Part II

Specified Substance Group 1 information level Information in accordance to a Pharmacopoeia (EP) for the 'Herbal Drug'. It will have a Substance Name (Substance Name Type: SSG1) which is composed of: **[<Scientific genus/binomial/trinomial <u>without</u> Author>,<Part(s)><Fresh/Dry]**			
Specified Substance Group 1 ID	GHTDR6435H (Artificial ID)	Specified Substance Group 1 ID	TE84K152PR (Artificial ID)
Element Group: Substance Name		**Element Group: Substance Name**	
(Specified) Substance (Group 1) Name	*Harpagophytum procumbens*, Root, Dry	(Specified) Substance (Group 1) Name	*Harpagophytum zeyheri*, Root, Dry
Substance Name Type	Specified Substance Group 1	Substance Name Type	Specified Substance Group 1
Element Group: Substance Name (Repeat)		**Element Group: Substance Name (Repeat)**	
Substance Name (Herbal Drug)	Devil's Claw Root	Substance Name (Herbal Drug)	Devil's Claw Root
Substance Name Type	Official	Substance Name Type	Official
Element Group: Substance Name (Repeat)		**Element Group: Substance Name (Repeat)**	
Substance Name (Synonym)	Harpagophyti radix	Substance Name (Synonym)	Harpagophyti radix
Substance Name Type	Other	Substance Name Type	Other
Element Group: Constituent		**Element Group: Constituent**	
Constituent Substance ID	CCCCCCCCCC (Artificial ID)	Constituent Substance ID	DDDDDDDDDD (Artificial ID)
Consituent Substance Name	*Harpagophytum procumbens*, Root	Constituent Substance Name	*Harpagophytum zeyheri*, Root
Language	en	Language	en
Substance Role	Parent substance	Substance Role	Parent substance
Is Defining	Yes	Is Defining	Yes
Elements Captured at the Specified Substance Group 1 Information level for the Herbal Drug			

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— **See Element Group: Characteristic Attribute,** Attribute Type: Particular Herbal, Attribute Name: Degree of comminution; process state; wild/cultivated; growth state; harvesting time; decontamination process; country of origin; geographical location, storage time; storage condition; is defining: (Y/N) in combination with the element groups 'Amount' and 'Attribute Parameter' if appropriate.

— **See Element Group: Constituents:** Substance ID; Constituent Substance Name; Language; Substance Role (Markers), Is defining (Y/N) and the element group 'Amount'. Structural information of the constituents is inherited from the element group: Structure.

Table E.12 — Substance and Specified Substance Information Devil's Claw Root, Part III

Specified Substance Group 2 information level for the Herbal Drug The Substance Name (Substance Name Type SSG2) is composed of: SSG1-Name extended with the Manufacturer (Supplier) Name			
Specified Substance Group 2 ID	TYFGS7654M (Artificial ID)	Specified Substance Group 2 ID	GJURT4523K (Artificial ID)
(Specified) Substance (Group 2) Name	*Harpagophytum procumbens*, Root, Dry – Manufacturer AA	(Specified) Substance (Group 2) Name	*Harpagophytum zeyheri*, Root, Dry – Manufacturer AA
Substance Name Type	Specified Substance Group 2	Substance Name Type	Specified Substance Group 2
(Parent) Substance ID	GHTDR6435H (Artificial ID)	(Parent) Substance ID	TE84K152PR (Artificial ID)
(Parent Specified) Substance (Group 1) Name	*Harpagophytum procumbens*, Root, Dry	(Parent Specified) Substance (Group 1) Name	*Harpagophytum zeyheri*, Root, Dry
Element Group: Manufacturing		**Element Group: Manufacturing**	
Manufacturing Type	Collector and Harvester of Botanical Material	Manufacturing Type	Collector and Harvester of Botanical Material
Production Method Type	Harvesting	Production Method Type	Harvesting
Production Method Description	Collecting and Harvesting, drying and storing of the Herbal Drug	Production Method Description	Collecting and Harvesting, drying and storing of the Herbal Drug
Production System Type	N/A	Production System Type	N/A
Critical Process Version Number	N/A	Critical Process Version number	N/A
Element Group: Organization		**Element Group: Organization**	
Manufacturer ID	MANDUNS452 (Artificial ID)	Manufacturer ID	MANDUNS452 (Artificial ID)
Manufacturer Name	Company AA	Manufacturer Name	Company AA
Issuer of ID	Dun & Bradsteet	Issuer of ID	Dun & Bradstreet
Manufacturer Role	Harvester	Manufacturer Role	Harvester

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Table E.13 — Substance and Specified substance information Devil's Claw Root, Part IV

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Specified Substance Group 3 information level for the Herbal Drug **The Substance Name (Substance Name Type: SSG3) is composed of: (Specified) Substance (Group 1)-Name extended with the Pharmacopoeial Name**	
Specified Substance Group 3 ID	GGGGGGGGGG (Artificial ID)
(Specified) Substance (Group 3) Name	*Harpagophytum procumbens* and_*or* Harpagophytum *zeyheri*, Root, Dry-Ph. Eur.
Substance Name Type	Specified Substance Group 3
(Parent) Substance ID	GHTDR6435H (Artificial ID); TE84K152PR (Artificial ID)
(Parent Specified) Substance (Group 1) Name	*Harpagophytum procumbens*, Root, Dry; *Harpagophytum zeyheri*, Root, Dry
Element Group: Grade	
Grade Type	European Pharmacopoeia
Grade Name	Devil's Claw Root
Element Group: Reference Source	
Public Domain	Yes
Reference Source Type	Ph. Eur.
Reference Source Class	Official Name Source
Reference Source Citation	Ph.Eur. monograph 01/2008:1095

Table E.14 — Substance and Specified substance information Devil's Claw Extract, Part I

Structurally Diverse Substance, Herbal preparation (derived from Herbal Drug)			
Substance information level The **Herbal preparation** with **limited** information is captured at the Substance information level. It will have a Name which is composed of: **[<Scientific genus/binomial/trinomial with Author>,<Part(s)>,<Fraction>]**			
Substance ID	EEEEEEEEEE (Artificial ID)	Substance ID	FFFFFFFFFF (Artificial ID)
Substance Type	Structurally Diverse (Herbal preparation)	Substance Type	Structurally Diverse (Herbal preparation)
Substance Name	*Harpagophytum procumbens,* Root, Extract	Substance Name	*Harpagophytum zeyheri*, Root, Extract
Language	en	Language	en
Element Group: Source Material		**Element Group: Source Material**	
Parent Substance ID	CCCCCCCCCC (Artificial ID)	Parent Substance ID	DDDDDDDDDD (Artificial ID)
Parent Substance Name (Herbal Drug)	*Harpagophytum procumbens,* Root	Parent Substance Name (Herbal Drug)	*Harpagophytum zeyheri*, Root
Element Group: Fraction Description		**Element Group: Fraction Description**	
Fraction	Extract	Fraction	Extract
Specified Substance Group 1 information level The **Herbal preparation** with **limited** information can be further specified for addition information at the SSG1 information level. It will have a Substance Name which is composed of: **[<Scientific genus/binomial/trinomial <u>without</u> Author>,<Part(s)>,<Fraction>,<Dry/Liquid/Viscous>]**			
Substance ID	RGFSD7865L (Artificial ID)	Substance ID	JKHGR1234L (Artificial ID)

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(Substance Type)	Specified Substance Group 1	(Substance Type)	Specified Substance Group 1
Substance Name	*Harpagophytum procumbens,* Root, Dry Extract	Substance Name	*Harpagophytum zeyheri*, Root, Dry Extract
Substance Name Type	Specified Substance Group 1	Substance Name Type	Specified Substance Group 1
Element Group: Fraction Description		**Element Group: Fraction Description**	
Fraction	Dry Extract	Fraction	Dry Extract
Element Group: Constituent		**Element Group: Constituent**	
Constituent Substance ID	EEEEEEEEEE (Artificial ID)	Constituent Substance ID	FFFFFFFFFF (Artificial ID)
Constituent Substance Name (Herbal Preparation)	*Harpagophytum procumbens,* Root, Extract	Constituent Substance Name (Herbal Preparation)	*Harpagophytum zeyheri*, Root, Extract
Substance Role	Parent substance	Substance Role	Parent substance
Is Defining	Yes	Is Defining	Yes
Elements Captured at the Specified Substance Group 1 Information level for the Herbal preparation with **limited information** — **See Element Group: Constituents:** Extraction solvent composition (limited qualitative information) Substance ID; Substance Name; Language; Substance Role (Markers); and the element group Amount. Structural information of the constituents is inherited from the element group: Structure.			

Table E.15 — Specified substance Group 1 with extended information Devil's Claw Root Extract, Part II

Specified Substance Group 1 information level **The Herbal preparation with extended information can be further specified for addition information at the SSG1 information level. It will have a Name which is composed of:** [<Scientific genus/binomial/trinomial without Author>,<Part(s)>,<Fraction>,<Dry/Liquid/Viscous>,<extraction solvent composition>,<Herbal substance extract ratio (DER)>]			
Specified Substance Group 1 ID	EXCTER654E (Artificial ID)	Specified Substance Group 1 ID	UFR78E231Y (Artificial ID)
Substance Type	Specified Substance Group 1	Substance Type	Structurally Diverse (Herbal Drug)
Substance Name	*Harpagophytum procumbens,* Root, Dry Extract, Ethanol-Water (60-40 {v/v}), (1,5-3,0 = 1)	Substance Name	*Harpagophytum zeyheri*, Root, Dry Extract, Ethanol-Water (60-40 {v/v}), (1,5-3,0 = 1)
Substance Name Type	Specified Substance Group 1	Substance Name Type	Specified Substance Group 1
Element Group: Fraction Description		**Element Group: Fraction Description**	
Fraction	Dry Extract, Ethanol-Water (60-40 {v/v}), (1,5-3,0 = 1)	Fraction	Dry Extract, Ethanol-Water (60-40 {v/v}), (1,5-3,0 = 1)
Element Group: Constituent		**Element Group: Constituent**	
Constituent Substance ID	EEEEEEEEEE (Artificial ID)	Constituent Substance ID	FFFFFFFFFF (Artificial ID)
Constituent Substance Name (Herbal Preparation)	*Harpagophytum procumbens*, Root, Extract	Constituent Substance Name (Herbal Preparation)	*Harpagophytum zeyheri*, Root, Extract

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Language	en	Language	en
Substance Role	Parent substance	Substance Role	Parent substance
Is Defining	Yes	Is Defining	Yes
Element Group: Constituent		**Element Group: Constituent**	
Constituent Substance ID	ETHAN98765 (Artificial ID)	Constituent Substance ID	ETHAN98765 (Artificial ID)
Constituent Substance Name	Ethanol	Constituent Substance Name	Ethanol
Language	en	Language	en
Substance Role	Extraction solvent	Substance Role	Extraction solvent
Is Defining	Yes	Is Defining	Yes
Element Group: Amount		**Element Group: Amount**	
Amount Type	Exact	Amount Type	Exact
Quantity	60	Quantity	60
Unit	% {v/v}	Unit	% {v/v}
Amount Text	Ethanol-Water (60-40 {v/v})	Amount Text	Ethanol-Water (60-40 {v/v})
Element Group: Constituent (Repeat)		**Element Group: Constituent (Repeat)**	
Constituent Substance ID	WATEP67543 (Artificial ID)	Constituent Substance ID	WATEP67543 (Artificial ID)
Constituent Substance Name	Water	Constituent Substance Name	Water
Substance Role	Extraction solvent	Substance Role	Extraction solvent
Is Defining	Yes	Is Defining	Yes
Element Group: Amount		**Element Group: Amount**	
Amount Type	Exact	Amount Type	Exact
Average	40	Average	40
Unit	% {v/v}	Unit	% {v/v}
Amount Text	Ethanol-Water (60-40 {v/v})	Amount Text	Ethanol-Water (60-40 {v/v})
Element Group: Constituent (Repeat)		**Element Group: Constituent (Repeat)**	
Constituent Substance ID	HARPA89765 (Artificial ID)	Constituent Substance ID	HARPA89765 (Artificial ID)
Constituent Substance Name	Harpagoside	Constituent Substance Name	Harpagoside
Substance Role	Marker substance [a]	Substance Role	Marker substance [a]
Is Defining	Yes	Is Defining	Yes
Element Group: Amount		**Element Group: Amount**	
Amount Type	Average	Amount Type	Average
Low Limit	1,5	Low Limit	1,5
High Limit	2,5	High Limit	2,5
Unit	% {w/w}	Unit	% {w/w}

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Element Group: Characteristic Attribute		Element Group: Characteristic Attribute	
Attribute Type	Particular Herbal preparation	Attribute Type	Particular Herbal preparation
Attribute Name	Herbal Substance Extract Ratio (DER)	Attribute Name	Herbal Substance Extract Ratio (DER)
Is Defining	Yes	Is Defining	Yes
Element Group: Amount		**Element Group: Amount**	
Amount Type	Exact	Amount Type	Exact
Low Limit	1,5	Low Limit	1,5
High Limit	3,0	High Limit	3,0
Unit	Part	Unit	Part
Amount Text	1,5-3,0 Part Herbal Substance = 1 Part Extract	Amount Text	1,5-3,0 Part Herbal Substance = 1 Part Extract
Element Group: Characteristic Attribute (Repeat)		**Element Group: Characteristic Attribute (Repeat)**	
Attribute Type	Particular Herbal preparation	Attribute Type	Particular Herbal preparation
Attribute Name	Country of origin	Attribute Name	Country of origin
Is Defining	No	Is Defining	No
Element Group: Amount		**Element Group: Amount**	
Non Numeric Value	South Africa	Non Numeric Value	South Africa
Element Group: Characteristic Attribute (Repeat)		**Element Group: Characteristic Attribute (Repeat)**	
Attribute Type	Particular Herbal preparation	Attribute Type	Particular Herbal preparation
Attribute Name	Geographical location	Attribute Name	Geographical location
Is Defining	No	Is Defining	No
Element Group: Amount		**Element Group: Amount**	
Non Numeric Value	Windhoek	Non Numeric Value	Windhoek

Elements Captured at the Specified Substance Group 1 Information level for the Herbal preparation with **Extended information**

— **See Element Group: Constituent:** Extraction solvent composition (quantitative information) and Marker Substance (quantitative specification) in combination with the element group amount.

— Structural information of the constituents is inherited from the element group: Structure.

See Element Group: Characteristic Attribute: Herbal Drug Extract Ratio (DER) and e.g. Country of Origin in combination with the Element Group 'Amount'.

[a] The marker substance Harpagoside ($C_{24}H_{30}O_{11}$; Mw. 494,5) has the following specification: NLT 1,5 % dried extract; final blending: Lactose monohydrate, Silicium dioxide; Standardization: concentration of 2,5 % Harpagoside relative to the finished extract preparation. This is formation is mandatory in order to decide at Specified Substance Group 3 information level that the extract is a standardized extract.

Table E.16 — Specified Substance Group 1 with extended information Devil's Claw Root Extract, Part III

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Specified Substance Group 2 information level for the Herbal preparation with extended information The Substance Name (Substance Name Type SSG2) is composed of: (Specified) Substance (Group 1)-Name extended with the Manufacturer (Supplier) Name			
Specified Substance Group 2 ID	AGHFT4352E (Artificial ID)	Specified Substance Group 2 ID	MZFTH564E (Artificial ID)
(Specified) Substance (Group 2) Name	*Harpagophytum procumbens,* Root, Dry Extract, Ethanol-Water (60-40 {v/v}), (1,5-3,0:1) –Manufacturer AA	Substance Name	*Harpagophytum zeyheri*, Root, Dry Extract Ethanol-Water (60-40 {v/v}), (1,5-3,0:1)– Manufacturer AA
Substance Name Type	Specified Substance Group 2	Substance Name Type	Specified Substance Group 2
(Parent) Substance ID	EXCTER654E (Artificial ID)	(Parent) Substance ID	TE84K152PR (Artificial ID)
(Parent Specified) Substance (Group 1) Name	*Harpagophytum procumbens,* Root, Dry Extract, Ethanol-Water (60-40 {v/v}), (1,5-3,0 = 1)	(Parent Specified) Substance (Group 1) Name	Harpagophytum zeyheri, Root, Dry Extract Ethanol-Water (60-40 {v/v}), (1,5-3,0 = 1)
Element Group: Manufacturing		**Element Group: Manufacturing**	
Manufacturing Type	Manufacturer	Manufacturing Type	Manufacturer
Production Method Type	Extraction	Production Method Type	Extraction
Production Method Description	Maceration with ethanol 60 %, ultra-heat treatment, mixing with lactose monohydrate and blending with Silicium dioxide	Production Method Description	Maceration with ethanol 60 %, ultra-heat treatment, mixing with lactose monohydrate and blending with Silicium dioxide
Production System Type	N/A	Production System Type	N/A
Production System	N/A	Production System	N/A
Critical Process Version Number	1	Critical Process Version number	1
Element Group: Organization		**Element Group: Organization**	
Manufacturer ID	DUNS674521 (Artificial ID)	Manufacturer ID	DUNS674521 (Artificial ID)
Manufacturer Name	Company BB	Manufacturer Name	Company BB
Issuer of ID	EMA OMS Service	Issuer of ID	EMA OMS Service
Manufacturer Role	Harvester and Manufacturer of Botanical Material	Manufacturer Role	Harvester and Manufacturer of Botanical Material

Specified Substance Group 3 information level for the Herbal preparation The Substance Name (Substance Name Type: SSG3) is composed of: (Specified) Substance (Group 1)-Name extended with the Pharmacopoeial Name	
Specified Substance Group 3 ID	YUTDR4267E (Artificial ID)
(Specified) Substance (Group 3) Name	*Harpagophytum procumbens and_or* Harpagophytum *zeyheri*, Root, Dry Extract, Ethanol-Water (60-40 {v/v}), (1,5-3,0:1), Standardized-Ph.Eur.
Substance Name Type	Specified Substance Group 3
(Parent Specified) Substance (Group 1) ID	EXCTER654E (Artificial ID) UFR78E231Y (Artificial ID)
(Parent) Substance Name	*Harpagophytum procumbens, Root,* Dry Extract, Ethanol-Water (60-40 {v/v}),(1,5-3,0 =1)

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	Harpagophytum zeyheri, Root, Dry Extract, Ethanol-Water (60-40 {v/v}),(1,5-3,0 =1)
Element Group: Grade	
Grade Type	Ph.Eur.
Grade name	Devil's Claw Root Dry Extract
Element Group: Reference Source	
Public Domain	Yes
Reference Source Type	Ph. Eur.
Reference Source Class	Official Name Source
Reference Source Citation	Ph.Eur. monograph 01/2008:1871

E.5 Documentation and Explanation of Example 3

E.5.1 Example 3: Salvia Miltiorrhiza Root and Rhizome (BP=Ph.Eur.) and Chinese Salvia (USP), *continued*.

E.5.1.1 Specifications according to the USP and Ph.Eur.:

Chinese Salvia is defined in the USP as:

Chinese Salvia consists of the dried roots and rhizomes of Salvia miltiorrhiza Bunge, also known as Danshen (Fam. Lamiaceae).

It contains NLT 0,1 % of Tanshinone IIA; NLT 0 2 % of total Tanshinones, calculated as the sum of Cryptotanshinone, Tanshinone I, and Tanshinone IIA; and NLT 3 0 % of Salvianolic acid B; all calculated on the dried basis. It is collected in spring or fall.

Salvia Miltiorrhiza Root and Rhizome is defined in the Ph.Eur. as:

Dried, whole or fragmented rhizome and root of Salvia miltiorrhiza Bunge, collected in spring or autumn. It contains

— Substance Name: Salvianolic acid B ($C_{36}H_{30}O_{16}$; Mr 719): minimum 3,0 per cent (dried drug);

— Substance ID: C1GQ844199 (See below for structure E.5.3.2);

— Substance Name: Tanshinone IIA ($C_{19}H_{18}O_3$; Mr 294.3): minimum 0,12 per cent (dried drug);

— Substance ID: 4GPC9FQG6L (See below for structure E.5.3.2).

The specifications of the markers are slightly different and therefore there will be two different Specified Substances Group 1 and Group 3.

NOTE 1 Two different SSG1 IDs are not necessary if the extraction method captures both the Ph.Eur. and USP specifications captured in SSG3 (e.g. Tanshinone IIA NLT 0,12%; Total Tanshinones NLT 0,2 % and Salvianolic acid B NLT 3,0 %). If this is not the case an extraction method needs to be defined capturing the Ph.Eur. specifications and Grade at SSG3 and a separate extraction method needs to be defined covering the USP specifications and Grade at SSG3. In this case two SSG1 and SSG3 IDs are needed depended on the extraction method used. A different SSG1 is caused by a difference in extraction solvent composition or extraction method or by both.

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NOTE 2 For the extraction process a more complex method is used. The method uses two extraction solvent compositions, one for the first extraction process on the Herbal Drug material (ethanol 90 %) and one for the residue which is extracted again (water 100 %). Both supernatant solutions are combined and concentrated to give the final viscous extract. For detailed information see Figure E.6.

NOTE 3 Explanation: Rules for a new SSG1 ID and a new SSG3 ID are as follows:

New SSG3: Every reference to a specific Pharmacopoeial Grade generates a new SSG3
Each pharmacopoeial monograph lists its own specifications. When an applicant/sponsor refers to two pharmacopoeial monographs and the specifications are different for the marker than an In-house specification are to be laid down covering both maker specifications.
Example: Marker A, pharmacopoeia 1, specification for the extract is ≥2,0 mg/g extract.
Marker A, pharmacopoeia 2, specification for the extract is ≥2,5 mg/g extract.
In-house specification is defined as: Marker A is ≥2,5 mg/g extract.
SSG3 ID (1) refers to pharmacopoeia 1
SSG3 ID (2) refers to pharmacopoeia 2
The In-house specification can be attached as a reference document, in both cases.

New SSG1: In the example described for the Salvia miltiorrhiza extract the ethanol supernatant and concentrated water extract are combined and further concentrated to a relative density of 1,33 to 1,35, with a specification for the marker: Rosmarinic acid: NLT (≥) 1,86 mg/g.

The extraction solvent composition is a defining element for the SSG1 ID since the solvent composition determines whether or not a marker will be extracted from the parent material and with which amount the maker will be extracted. The DER determines if the requirements will be met and whether or not batches of the parent material shall be blended in order to comply to the minimal amount of marker present in the extract.

If another solvent composition or extraction method will be used the SSG1 will be changed.

The applicant/sponsor may change the solvent composition and/or the DER as long as the requirement for the marker in the extract will be met (Specification: Rosemarinic acid: NLT 1,86 mg/g).

Conclusion: Solvent composition 1 + DER 1 gives SSG1 ID (1); solvent composition (2) + DER 1 gives SSG1 ID (2);

solvent composition 1 + DER 2 gives SSG1 ID (3); solvent composition 2 + DER 2 gives SSG1 ID (4).

E.5.1.2 Submitted Data

Herbal Drug: Salvia miltiorrhiza
Description:
Salvia miltiorrhiza, also known as red sage, tan shen, or danshen, is a perennial plant of the genus Salvia, highly valued for its roots in traditional Chinese medicine. Native to China and Japan, it grows at 90 to 1,200 m (300 to 3,900 ft) elevation, preferring grassy places in forests, hillsides, and along stream banks.

A sample of the Root and Rhizome. Cylindrical, slightly curved segments, 5 cm long. The external surface is reddish brown, rough with longitudinal striations, see Figure E.29.

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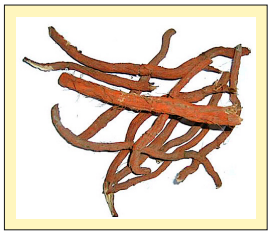


Figure E.29 — Root and Rhizome of Salvia miltiorrhiza

The Scientific Name is: *Salvia miltiorrhiza* Bunge; Family: Labiatae (*Lamiaceae*)

Parts of the plant: Dried, fragmented root and rhizome, cut pieces NMT 5 cm.

Harvest time, Cultivated plants: In the autumn of the next year after seeding when the aerial parts of the plants are wilting (Shaanxi province of China). The harvested material is dried at 50 °C to 60 °C as soon as possible after harvesting (loss on drying ≤13 %) and stored in closed PP bags under low relative humidity conditions.

Marker Substance for specification:

— Salvianolic acid B (Molecular formula: C_{36} H_{30} O_{16}; *Mr*: 718,6 g/mol); NLT 3,0 %

— Tanshinone IIA (Molecular formula: C_{19} H_{18} O_3; *Mr*: 294,3 g/mol); NLT 0,12 %

Analytical marker: Rosmarinic acid BP-spec.: NLT 0,17 %

CAS Registry Name: Benzenepropanoic acid, .alpha.-[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]-3,4-dihydroxy-, (.alpha.R)-

CAS No.: 20283-92-5; Molecular formula: C_{18} H_{16} O_8; *Mr*: 360,3 g/mol.

E.5.2 Herbal preparation: Salvia Miltiorrhiza Extract provided information

Extract Description: Danshen extract is a brown to dark brown soft (semi-solid) extract, made through the process of extraction and concentration DER (4.5 – 6.0:1)

Name: *Salvia miltiorrhiza*, Rhizome and Root, Ethanolic (90)-Water (10), Soft Extract (4,5-6,0:1)

DER: 4,5 – 6,0 Parts Herbal Drug = 1.0 Part Extract;

Extraction solvent: Ethanol (90) – Water (10) = Ethanol 90 %{v/v}.

Manufacturing information:

Production Method Description:

1) Extraction: The plant material is extracted with Ethanol 90 % extract and the residue of the plant material is extracted once more with 100 % water.

2) Cooling and decantation: The ethanol 90% and water extracts are collected in separate tanks, stirred and cooled to 15 °C and allowed to stand for 20 hours.

3) Concentration: The water supernatant is concentrated for several hours at 80 °C under reduced pressure.

4) Mixing and further concentration: The Ethanol supernatant and concentrated water extract are combined and further concentrated to a relative density of 1,33 to 1,35.

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Specification: Analytical marker: Rosmarinic acid: NLT 1,86 mg/g

Organization information:

Manufacturer of Herbal preparation: Manufacturer GHT.

E.5.3 Organization of the information according to ISO 11238 and ISO/TS 19844

E.5.3.1 Substance information level

E.5.3.1.1 Substance (fresh)

Substance ID: SALV7356YS (Artificial ID)
Substance Type: Structurally Diverse (Herbal Substance)

Element Group: Substance Name
Substance (fresh) Name: *Salvia miltiorrhiza* Bunge, Rhizome and Root
Substance Name Type: Other
Language: en

Element Group: Substance Name (Repeat)
Substance Name: *Salvia miltiorrhiza* Bunge
Substance Name Type: Scientific
Language: la

Element Group: Source Material:
Organism ID: SALVI765432 (Artificial ID)
Organism Name: *Salvia miltiorrhiza* Bunge

Element Group: Organism
Family: *Lamiaceae*
Genus: Salvia
Species: miltiorrhiza

Element Group: Author
Author Type: Species Primary Author
Author Description: Bunge

Element Group: Organism General
Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Lamiales

Element Group: Part Description
Part: Rhizome; Root

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E.5.3.1.2 Substance (Herbal Drug)

Substance (Herbal Drug) ID: HHHHHHHHHH (Artificial ID)
Substance Type: Structurally Diverse (Herbal Drug)

Element Group: Substance Name
Substance (Herbal Drug) Name: *Salvia miltiorrhiza*, Rhizome and Root
Substance Name Type: Official
Language: en

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: Ph.Eur.
Reference Source Class: Official Name Source
Reference Source Citation: Ph.Eur.: 04/2013:2663

Element Group: Reference Source (Repeat)
Public Domain: Yes
Reference Source Type: USP, Dietary Supplements
Reference Source Class: Official Name Source

Element Group: Substance Name (Repeat)
Substance (Herbal Drug) Name: Chinese Salvia
Substance Name Type: Other
Language: en

Element Group: Substance Name (Repeat)
Substance (Herbal Drug) Name: Danshen
Substance Name Type: Other
Language: en

Element Group: Source Material
Parent Substance ID: SALV7356YS (Artificial ID)
Parent Substance (fresh) Name: *Salvia miltiorrhiza* Bunge, Rhizome and Root

Element Group: Part Description
Part: Rhizome and Root

E.5.3.1.3 Substance (Herbal preparation)

Substance Type: Structurally Diverse
Substance (Herbal preparation) ID: KKKKKKKKKK (Artificial ID)

Element Group: Substance Name
Substance (Herbal preparation) Name: *Salvia miltiorrhiza*, Rhizome and Root, Extract
Substance Name Type: Other
Element Group: Source Material

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Parent Substance ID (Herbal Drug): HHHHHHHHHH (Artificial ID)
Parent Substance Name (Herbal Drug): *Salvia miltiorrhiza*, Rhizome and Root

Element Group: Part Description
Part: Rhizome and Root

Element Group: Fraction Description
Fraction: Extract
Material Type: Herbal

E.5.3.2 Specified Substance Group 1 information level (Herbal Drug)

Substance Type: Specified Substance Group 1
Specified Substance Group 1 ID: HJYTRE876S (Artificial ID)

Element Group: Substance Name
(Specified) Substance (Group 1) Name: *Salvia miltiorrhiza*, Rhizome and Root, Dry
Substance Name Type: Specified Substance Group 1
Language: en
Substance Name Domain: Botanical
Jurisdiction: EU, US

Element Group: Substance Name (Repeat)
Substance Name: Salvia miltiorrhiza Root and Rhizome
Substance Name Type: Official
Language: en
Substance Name Domain: Botanical
Jurisdiction: EU, US

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: Ph.Eur.
Reference Source Class: Official Name Source
Reference Source Citation: Ph.Eur.: 04/2013:2663

Element Group: Substance Name (Repeat)
Substance Name: Chinese Salvia
Substance Name Type: Official
Language: en

Element Group: Reference Source (Repeat)
Public Domain: Yes
Reference Source Type: USP, Dietary Supplements
Reference Source Class: Official Name Source

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Element Group: Constituent
Constituent Substance ID (Herbal Drug): HHHHHHHHHH (Artificial ID)
Constituent Substance Name (Herbal Drug): *Salvia miltiorrhiza*, Rhizome and Root
Language: en
Substance Role: Parent substance
Is Defining: Yes

Element Group: Characteristic Attribute
Attribute Type: Particular Herbal
Attribute Name:
Degree of Comminution: Fragmented, cut in pieces NMT 5 cm
Process State: Dried
Wild/Cultivated: Cultivated
Growth State: When the aerial parts of the plants are wilting
Harvesting Time: In Autumn of the next year after seeding
Country of Origin: China
Geographical Location: Shaanxi Province
Storage Time: N/A
Storage Conditions: The harvested material is dried at 50 °C to 60 °C as soon as possible after harvesting (loss on drying ≤13 %) and stored in closed PP bags under low relative humidity conditions.

Element Group: Constituent
Marker Substances and specification (amount):

Constituent Substance ID: C1GQ844199 (Artificial ID)
Constituent Substance Name: Salvianolic acid B (Mol. Form.: $C_{36}H_{30}O_{16}$; Mr: 718.6)
Language: en
Substance Role: Marker
Is Defining: Yes

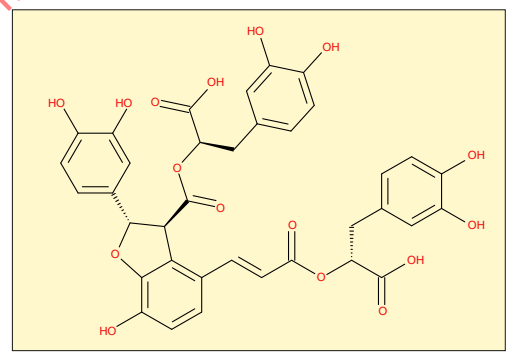


Figure E.30 — Structural representation of Salvianolic acid B

Element Group: Amount
Amount Type: NLT
Quantity: 3,0
Unit: %{w/w}
Amount Text: NLT 3 %
Element Group: Constituent

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Constituent Substance ID: 4GPC9FQG6L (UNII)
Constituent Substance Name: Tanshinone IIA (Mol. Form.: C_{19} H_{18} O_3; Mr: 294.3)
Language: en
Substance Role: Marker
Is Defining: Yes

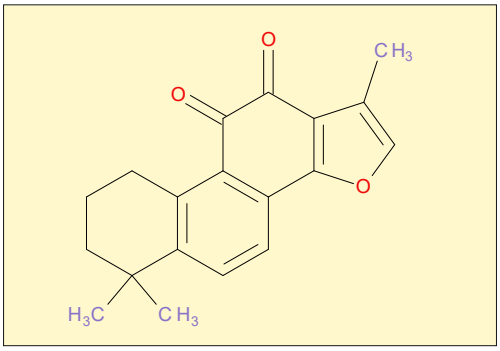


Figure E.31 — Structural representation of Tanshinone IIA

Element Group: Amount
Amount Type: NLT
Quantity: 0,12
Unit: %{w/w}
Amount Text: NLT 0,12 %

Element Group: Constituent (Repeat)
Constituent Substance ID: MQE6XG29YI (UNII)
Constituent Substance Name: Rosmarinic acid, Mol. Form.: C_{18} H_{16} O_8; Mr: 360,3 g/mol.
Language: en
Substance Role: Marker
Is Defining: Yes

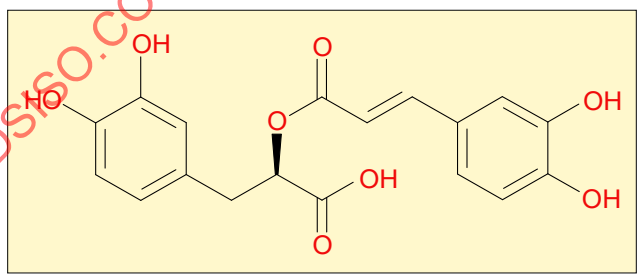


Figure E.32 — Structural representation of Rosmarinic acid

Systematic Name: Benzenepropanoic acid,.alpha. [[(2E)-3-(3.4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]-3,4-dihydroxy-, (.alpha.R)-

Element Group: Amount
Amount Type: NLT
Quantity: 0,17
Unit: -%{w/w}
~~A~~mount Text: NLT 0,17 %

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Other Constituents: Potential bioactive constituents include: Salvianolic acid B, Tanshinone IIA, Cryptotanshinone, Tanshinone I, Danshensu, Lithospermic acid and Rosmarinic acid. Rosmarinic acid was chosen as analytical marker due to its stability in the extract preparation. These additional constituents should also be captured.

Element Group: Constituent (Repeat)
Constituent Substance ID: 5E9SXT166N (UNII)
Constituent Substance Name: Cryptotanshinone
Language: en
Substance Role: Marker
Is Defining: Yes

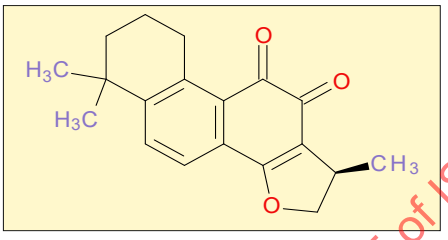


Figure E.33 — Structural representation of Cryptotanshinone

Element Group: Constituent (Repeat)
Constituent Substance ID: 03UUH3J385 (UNII)
Constituent Substance Name: Tanshinone I
Language: en
Substance Role: Marker
Is Defining: Yes

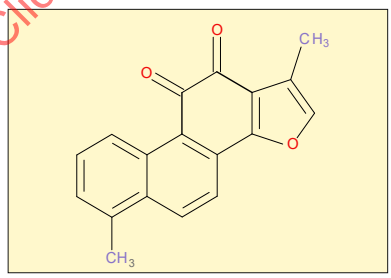


Figure E.34 — Structural representation of Tanshinone I

Element Group: Constituent (Repeat)
Constituent Substance ID: 4GF33A5PAJ (UNII)
Constituent Substance Name: Danshensu
Language: en
Substance Role: Marker
Is Defining: Yes

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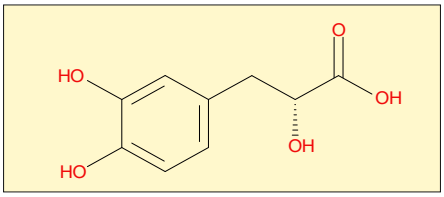


Figure E.35 — Structural reprepsentation of Danshensu

Element Group: Constituent (Repeat)
Constituent Substance ID: 100IP83JAC (UNII)
Constituent Substance Name: Lithospermic acid
Language: en
Substance Role: Marker
Is Defining: Yes

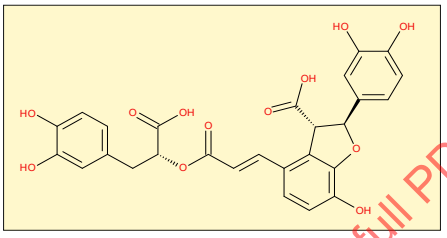


Figure E.36 — Structural representation of Lithospermic acid

E.5.3.3 Specified Substance Group 2 information level (Herbal Drug)

Specified Substance Group 2 (Herbal Drug) ID: TYGD6754UY (Artificial ID)
Substance Type: Specified Substance Group 2

Element Group: Substance Name
Substance (Herbal Drug) Name: *Salvia miltiorrhiza*, Rhizome and Root, Dry-Manufacturer GHT
Substance Name Type: Specified Substance Group 2
(Parent) Substance ID: HJYTRE876S (Artificial ID), (Herbal Drug, SSG1)

Element Group: Manufacturing
Manufacturing Type: Harvester
Production Method Type: Harvesting
Production Method Description: Collecting and Harvesting, drying and storing of the Herbal Drug

Element Group: Organization
Manufacturer ID: DUNS654321 (Artificial ID)
Manufacturer Name: Name
Issuer of ID: EMA OMS
Manufacturer Role: Harvester/ Manufacturer

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E.5.3.4 Specified Substance Group 3 information level (Herbal Drug)

Specified Substance Group 3 ID (Herbal Drug): HJGFDT67EP (Artificial ID)

Element Group: Substance Name
Substance Name: *Salvia miltiorrhiza*, Rhizome and Root, Dry, Quantified-Ph.Eur.
Substance Name Type: Specified Substance Group 3
Language: en
(Parent) Substance ID: HJYTRE876S (Artificial ID), (Herbal Drug, SSG1)

Element Group: Grade
Grade Type: Ph.Eur.
Grade Name: *Salvia Miltiorrhiza* Root and Rhizome

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: Ph. Eur.
Reference Source Class: Official Name Source
Reference Source Citation: Ph.Eur. monograph 04/2013:2663

Substance Type: Specified Substance Group 3
Specified Substance Group 3 ID (Herbal Drug): GHFTE653US (Artificial ID)

Element Group: Substance Name
(Specified) Substance (Group 3) Name (Herbal Drug): *Salvia miltiorrhiza*, Rhizome and Root, Dry, Quantified–USP
Substance Name Type: Specified Substance Group 3
Language: en
Parent Substance ID: HJYTRE876S (Artificial ID), (Herbal Drug, SSG1)

Element Group: Grade
Grade Type: USP
Grade Name: Chinese Salvia

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: USP
Reference Source Class: Official Name Source
Reference Source Citation: USP, Dietary Supplements

NOTE Reference is made to the same Parent Specified Substance ID assuming that both specifications (Grades) are met with the same extraction method.

E.5.4 Specified Substance Group 1 information level of Herbal preparation (Extract, extended information)

Substance Type: Specified Substance Group 1
Specified Substance Group 1 (Herbal preparation) ID: SAJT6754DS (Artificial ID)

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(Specified) Substance (Group 1) Name (Herbal preparation): *Salvia miltiorrhiza*, Rhizome and Root, Soft Extract, Ethanol-Water (90-10 {v/v}) (4,5–6,0 = 1)

NOTE The term "soft" extract has to be added to the controlled vocabulary (CV) and is distinct from "liquid" and "dry" extract.

Business rule(s): When 2 extraction solvent compositions are used in a Herbal preparation only the first solvent composition is formulated in the ISO/TS 19844 at the Specified Substance Group 1 Name of the Herbal preparation. If more solvent compositions are needed to lay down, these compositions should be described at the Specified Substance Group 2 information level, Manufacturing.

Element Group: Constituent
Constituent Substance ID: KKKKKKKKKK (Artificial ID)
Constituent Substnace Name: *Salvia miltiorrhiza*, Rhizome and Root, Soft Extract
Language: en
Substance Role: Parent substance
Amount Type: N/A

Element Group: Fraction Description
Fraction: Soft Extract
Material Type: Herbal

Element Group: Constituent (Repeat)
Constituent Substance ID: ETHAN98765 (Artificial ID)
Constituent Substance Name: Ethanol
Language: en
Substance Role: Extraction solvent
Is defining: Yes

Element Group: Amount
Amount Type: Exact
Quantity: 90
Unit: %{v/v}
Amount Text: Ethanol 90 %{v/v}

Element Group: Constituent (Repeat)
Constituent Substance ID: WATER67543 (Artificial ID)
Constituent Substance Name: Water
Substance Role: Extraction solvent

Element Group: Amount
Amount Type: Exact
Quantity: 10
Unit: %{v/v}
Amount Text: Ethanol 90 %{v/v}

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Element Group: Constituent (Repeat)
Constituent Substance ID: C1GQ844199 (UNII)
Constituent Substance Name: Salvianolic acid B [Mol. Form.: $C_{36}H_{30}O_{16}$; Mol. Weight: Mr 719]
Language: en
Substance Role: Marker
Is Defining: Yes

Element Group: Amount
Amount Type: NMT
Quantity: 1,5
High Limit: 3,0
Unit: %{w/w}

Element Group: Constituent (Repeat)
Constituent Substance ID: 4GPC9FQG6L (UNII)
Constituent Substance Name: Tanshinone IIA [Mol. Form.: $C_{19}H_{18}O_3$; Mol. Weight: Mr 294.3]
Language: en
Substance Role: Marker
Is Defining: Yes

Element Group: Amount
Amount Type: NLT
Quantity: 0,12
Unit: %{w/w}

Element Group: Constituent (Repeat)
Constituent Substance ID: MQE6XG29YI (UNII)
Constituent Substance Name: Rosmarinic acid
Language: en
Substance Role: Analytical marker
Is Defining: Yes

Element Group: Amount
Amount Type: NLT
Quantity: 1,86
Unit: mg/g
Amount Text: NLT 1,86 mg/g

Element Group: Characteristic Attribute
Attribute Type: Particular Herbal preparation
Attribute Name: Drug Extract Ratio (DER)
Is Defining: Yes
Element Group: Amount
Amount Type: Average
Low Limit: 4,5
High Limit: 6,0

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Unit: Part
Amount Text: 4,5 – 6,0 parts Herbal Substance = 1 part Herbal preparation

Element Group: Characteristic Attribute
Attribute Type: Particular Herbal
Attribute Name: Country of origin
Is Defining: Yes

Element Group: Amount
Non Numeric Value: China

Element Group: Characteristic Attribute
Attribute Type: Particular Herbal
Attribute Name: Geographical location
Is Defining: Yes

Element Group: Amount
Non Numeric Value: Shaanxi Province

E.5.4.1 Specified Substance Group 2 information level of the Herbal preparation (Extract, extended information)

Specified Substance Group 2 ID (Herbal preparation): SALTU2345M (Artificial ID)

Element Group: Substance Name
Substance (Herbal preparation) Name: *Salvia miltiorrhiza*, Rhizome and Root, Soft Extract, Ethanol-Water (90-10 {v/v}) (4,5–6,0 = 1)-Manufacturer FDC
Substance Name Type: Specified Substance Group 2
Language: en
(Parent Specified) Substance (Group 1 (Herbal preparation)) ID: [SAJT6754DS (Artificial ID)]

Element Group: Manufacturing
Manufacturing Type: Soft Extract
Production Method Type: Extraction
Production Method Description[46]: (Figure E.6)
Version: EXTR-002

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[46] Manufacturing Method:

a) Extraction: Ethanol 90 % extract and the residue of the plant material is extracted once more with 100 % water.

b) Cooling and decantation: The ethanol 90 % and water extracts are collected in separate tanks, stirred and cooled to 15 °C and allowed to stand for 20 hours.

c) Concentration: The water supernatant is concentrated for several hours at 80 °C under reduced pressure.

d) Mixing and further concentration: The Ethanol supernatant and concentrated water extract are combined and further concentrated to a specified density.

Specification: Analytical marker: Rosmarinic acid: NLT 1,86 mg/g

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Version Date: 20170224
NOTE A flow chart of the extraction method used in for the Herbal preparation is provided in Figure E.6. See also Figure 37.

Element Group: Organization
Manufacturer ID: D.U.N.S.89765M (Artificial ID)
Manufacturer Name: Manufacturer FDG
Issuer of ID: EMA OMS
Manufacturer Role: Manufacturer

E.5.4.2 Specified Substance Group 3 information level (Herbal preparation)

Specified Substance Group 3 ID (Herbal preparation): LLLLLLLLLL (Artificial ID)

Element Group: Substance Name
(Specified) Substance (Group 3 (Herbal preparation)) Name: *Salvia miltiorrhiza*, Rhizome and Root, Soft Extract, Ethanol-Water (90-10 {v/v}) (4,5–6,0:1), Quantified
Substance Name Type: Specified Substance Group 3
(Parent Specified) Substance (Group 1) ID (Herbal preparation): SAJT6754DS (Artificial ID)

Element Group: Grade
Grade type: In-house
Grade Name: Salvia Miltiorrhiza Extract

Element Reference information
Public Domain: Yes
Reference Source Type: In-house
Reference Source Class: Regulatory Submission

E.6 Documentation and Explanation of Example 4

E.6.1 Herbal preparations Olive Oil, Virgin (Ph.Eur.) and Olive Oil, Refined (Ph.Eur.)

At the Specified Substance Group 3 level, vegetable oils are captured as described in several Pharmacopoeial monographs e.g. Olive Oil, Virgin and Olive Oil, Refined.

The Herbal preparation Olive Oil, Virgin (Ph.Eur.) is defined as the fatty oil obtained by cold expression or other suitable mechanical means from the ripe drupes of *Olea europaea* L.

E.6.1.1 Olive Oil, Virgin (Ph.Eur.)

Olive Oil, Virgin (Ph.Eur.) is defined as a Herbal preparation (because it has been obtained by expression). There is no defined Herbal Drug for this Herbal preparation, but instead its source material is a Substance (fresh), the ripe drupes (fruit) of *Olea europaea* L.

The Herbal preparation relashionship to the Substance (fresh) is a two-way relationship. The fraction <Oil, Exudate, Juice> is prepared from one Substance (fresh).

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NOTE Several Herbal preparations, e.g. Juices, can be a mixture of separately obtained juices obtained from the Herbal Substances and mixed after expression. The final preparation is then a multi-substance material which is captured at the Specified Substance Group 1 level.

E.6.1.2 Elements to be described at the Substance (fresh) and Substance (Herbal preparation) level

Substance (fresh) ID: OLIJF5643S (Artificial ID)
Substance (fresh) Name: *Olea europaea* L., Fruit
Substance Name Type: Other

Substance ID (Herbal preparation): HJFTE78543 (Artificial ID)
Substance (Herbal preparation) Name: *Olea europaea*, Fruit, Oil
Substance Name Type: Other

Substance Name: Olive Oil, Virgin
Substance Name Type: Official

NOTE For further elements see B.7.8.1.

Common Name: Olive Oil.
(Other names and synonyms may be captured here)
e.g. Crude Olive Oil

Element Group: Source Material
Parent Substance (fresh) ID: OLIJF5643S (Artificial ID)
Parent substance Name: *Olea europaea* L., Fruit

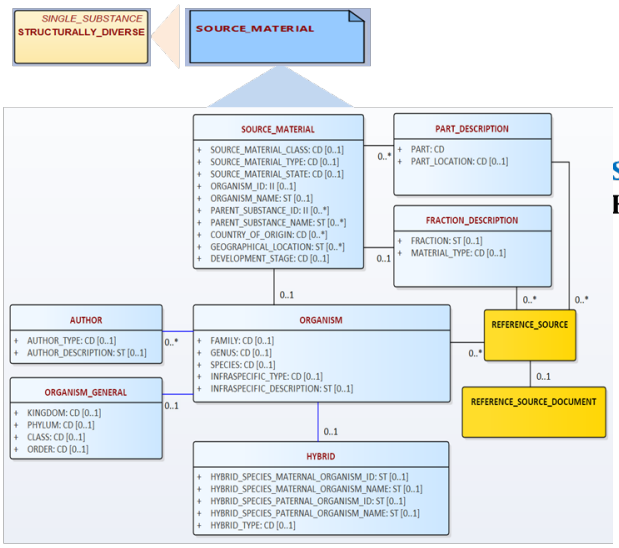
Element Group: Part Description
Part: Fruit
Element Group: Fraction Description
Fraction: Oil
Material Type: Herbal

NOTE The value Oil is appropriate here. The fraction (Herbal preparation) is valid for: Oil, Exudate, Juice (see also Figure E.37).

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ISO/TS 19844 Information model for the unique identification of the Substance Type: Structurally Diverse, Herbal Substance/Herbal preparation



Herbal Substance ID: OLIJF5643S
Substance Name (fresh):
[<Scientific genus/binomial/trinomial with Author>,<Part(s)>]: *Olea europaea* L., Fruit
Substance Name Type: Other

Substance Information Level:
Herbal Substance (Herbal Drug)

For information only:
Herbal Substance ID:
Substance Name (Herbal Drug):
[<Scientific genus/binomial/trinomial without Author>,<Part(s)>]
Parent Substance ID:

Substance Information Level:
Herbal Preparation Type: Oil, Exudate, Juice

Substance ID: HJTE78543
Herbal preparation Name:
[<Scientific genus/binomial/trinomial without Author>,<Part(s)>,<Fraction>] *e.g. Olea europaea* L., Fruit, Oil
Substance Name Type: Other
Parent ID: OLIJF5643S
Parent Substance Name: *Olea europaea* L., Fruit

Figure E.37 — The relationships between the ISO 11238, ISO/TS 19844 Structurally diverse description and the Substance (fresh) and Substance (Herbal preparation) for Olive Oil, Virgin

NOTE There is no Herbal Drug defined for the Herbal preparation 'Olive Oil, Virgin' Therefore the Parent substance for this Herbal preparation is the Substance (Fresh) *Olea europaea* L., Fruit.

Additional information for more elements at the Substance level for the Substance *Olea europaea* L., Fruit and the Herbal preparation Olive Oil, Virgin can be described at the Element Group "Property" which is is to be used at the Substance or Specified Substance Group 1 information level for the description of the characteristics of the Olive Oil.

Properties to be captured related to liquids (oils) and the description as per ISO 11238 can be found in Figure B.31 and in Figure B.32.

E.6.1.3 Elements to be described at the Specified Substance Group 3 Information level (Herbal preparation).

At the Specified Substance Group 3 level the Pharmacopoeial Grade of a substance is captured as a specification for Olive Oil, Virgin, with the (Specified) Substance (Group 3) name of Olive Oil, Virgin-Ph.Eur.

Specified Substance Group 3 ID (Herbal preparation): JFGDRW4526 (Artificial ID)
Substance Name Type: Specified Substance Group 3

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NOTE The (Parent) Substance Name (Herbal preparation): *Olea europaea*, Fruit, Oil, is related to the (Parent) Substance (fresh) Name: *Olea europaea* L., Fruit, and corresponding (Parent) Substance (fresh) ID: OLIJF5643S (Artificial ID).

Element Group: Grade
Grade Type: Ph.Eur.
Grade Name: Olive Oil Virgin

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: Ph. Eur.
Reference Source Class: Official Name Source
Reference Source Citation: Ph.Eur. monograph 07/2011:0518

Further information regarding vegetable oils is provided in the Annex B, Chemical Substance of this Document including tabular examples of Olive Oil, Virgin and Olive Oil, Refined (Ph.Eur.), see B.7.2.

E.7 Documentation and Explanation of Example 5

E.7.1 JP XVI monograph Shakuyakukanzoto Extract, see Figure E.38.

It consists of the two Herbal Drugs Peony Root (JP) and Glycyrrhiza (JP).

The Extract is prepared from 5 g to 6 g of both the "Crude" Drugs and is finally quantified to 50 mg to 150 mg Peoniflorin ($C_{23}H_{28}O_{11}$, Mr 480,5) and 50 mg to 150 mg Glycyrrhizic acid ($C_{42}H_{62}O_{16}$, Mr = 822,9). It should be prepared as directed under the General Monograph Extracts, see Figure E.38.

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Shakuyakukanzoto Extract

芍薬甘草湯エキス

Shakuyakukanzoto Extract contains not less than 50 mg and not more than 150mg of peoniflorin ($C_{23}H_{28}O_{11}$: 480.46), and not less than 50mg and not more than 150mg of glycyrrhizic acid ($C_{42}H_{62}O_{16}$: 822.93), per extract prepared with the amount specified in the Method of preparation

Method of preparation

	1)	2)
Peony Root	6 g	5 g
Glycyrrhiza	6 g	5 g

Prepare a dry extract of viscous extract as directed under Extracts, according to the prescription 1) or 2), using the crude drugs shown above.

Description Shakuyakukanzoto Extract occurs as a light brown to brown, powder or viscous extract. It has slightly an odour and a sweet taste.

Figure E.38 — Display of the Shakuyakukanzoto Extract with reference to the Japanese pharmacopoeia XVI

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E.7.2 JP Monograph for Preparations Related to Crude Drugs, I. Extract

(1) Extracts are preparations, prepared by concentrating extractives of crude drugs. There are the following two kinds of extracts:

(i) Viscous extracts;

(ii) Dry extracts.

(2) Unless otherwise specified, extracts are usually prepared as follows.

(i) Crude drugs, pulverized to suitable sizes, are extracted for a certain period of time with suitable solvents by means of cold extraction or warm extraction, or by percolation as directed in (ii) of (2) under 6. Tinctures. The extractive is filtered, and the filtrate is concentrated or dried by a suitable method to make a millet jelly-like consistency for the viscous extracts, or to make crushable solid masses, granules or powder for the dry extracts.

Extracts, which specify the content of marker substance(s), are prepared by assaying marker substance(s) in a portion of sample and adjusting, if necessary, to specified strength with suitable diluents.

(ii) Weigh crude drugs, pulverized to suitable sizes, according to the prescription and heat for a certain period of time after adding 10 to 20 times the amount of water. After separating the solid and liquid by centrifugation, the extractive is concentrated or dried by a suitable method to make a millet jelly-like consistency for the viscous extracts, or to make crushable solid masses, granules or powder for the dry extracts.

(3) Extracts have odour and taste derived from the crude drugs used.

Conclusion: Extraction solvent is Water

The final extract has to comply with both the content markers and strength mentioned above. The extract may be blended by batches or by excipients to comply with the marker strength.

E.7.3 JP Monograph of the Crude Drugs (starting materials) JP monograph Peony Root and Glycyrrhiza

Peony Root
Peaeoniae Radix
シャクヤク

Peony Root is the root of Paeonia lactiflora Pallas (*Paeoniaceae*). It contains not less than 2,0 % of Peoniflorin ($C_{23}H_{28}O_{11}$, 480,46), calculated on the dried basis.

Description: Cylindrical root, 7 cm to 20 cm in length, 1 cm to 2,5 cm in diameter; externally brown to light greyish brown, with distinct longitudinal wrinkles, with warty scars of lateral roots, and with laterally elongated lenticels; fractured surface dense in texture, light greyish brown, and with light brown radial lines in xylem.

Odour, characteristic; taste, slightly sweet at first, followed by an astringency and a slight bitterness.

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Identification: (1) Shake 0,5 g of pulverized Peony Root with 30 mL of ethanol (95) for 15 min, and filter. Shake 3 mL of the filtrate with 1 drop of iron (III) chloride TS: a blue-purple to blue-green colour is produced, and it changes to dark blue-purple to dark green. (etc.)

Glycyrrhiza
Glycyrrhizae Radix

カンゾウ
Glycyrrhiza is the root and stolon, with (unpeeled) or without (peeled) the periderm, of *Glycyrrhiza uralensis* Fisher or *Glycyrrhiza glabra* Linne (*Leguminosae*).

It contains not less than 2,5 % of glycyrrhizic acid ($C_{42}H_{62}0_{16}$: 822,93), calculated on the basis of dried material.

Description: Nearly cylindrical pieces, 0,5 cm to 3,0 cm in diameter, over 1 m in length. Glycyrrhiza is externally dark brown to red-brown, longitudinally wrinkled, and often has lenticels, small buds and scaly leaves; peeled Glycyrrhiza is externally light yellow and fibrous. The transverse section reveals a rather clear border between phloem and xylem, and a radial structure which often has radiating splits; a pith in Glycyrrhiza originates from stolon, but no pith from root; odour, slight; taste, sweet.

Under a microscope: the transverse section reveals several layers of yellow-brown cork layers, and 1- to 3 cellular layers of cork cortex inside the cork layer; the cortex exhibiting medullary rays and obliterated sieve portions radiated alternately; the phloem exhibiting groups of phloem fibers with thick but incompletely lignified walls and surrounded by crystal cells; peeled Glycyrrhiza sometimes lacks periderm and a part of the phloem; the xylem exhibiting large yellow vessels and medullary rays in 3 to 10 rows radiated alternately; the vessels accompanied with xylem fibers surrounded by crystal cells, and with xylem parenchyma cells; the parenchymatous pith in Glycyrrhiza originated only from stolon. The parenchyma cells contain starch grains and often solitary crystals of calcium oxalate.

Identification: To 2 g of pulverized Glycyrrhiza add 10 mL of a mixture of ethanol 95 % and water (7:3), heat by shaking in a water bath for 5 min, cool, filter, and use the filtrate as the sample solution. Separately, dissolve 5 mg of Glycyrrhizic acid RS in 1 mL of a mixture of ethanol 95 % and water (7:3), and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <2,03 (etc.).

E.7.4 Organization of the information in accordance to ISO 11238 and ISO/TS 19844

NOTE Due to different jurisdictional requirements (e.g. Japanese jurisdictional regulations) some elements normally captured at the Specified Substance level will be optional (e.g. the Element Group 'Characteristic Attribute'). In addition, the JP “Kampo Code” is always mandatory in the JP jurisdiction.

E.7.4.1 Information captured at the Substance level for Glycyrrhiza (JP)

Since one of two species may be used in Glycyrrhiza (JP), information for both species [as the Substance (fresh)] are provided in this example, but it will be assumed that Glycyrrhiza glabra L. has been used to create the Shakuyakukanzoto Extract.

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E.7.4.2 Substance (Fresh)

Element Group: Substance
Substance ID: HGTDE7634F (Artificial Code)
Substance Type: Structurally Diverse (Herbal Substance)

Element Group: Substance Name
Substance (fresh) Name: *Glycyrrhiza glabra* L., Root and Stolon
Substance Name Type: Other
Language: en
Substance Name Domain: Drug
Jurisdiction: EU, US, JP

Element Group: Substance Name (Repeat)
Substance name: *Glycyrrhiza glabra* L.
Substance Name Type: Scientific
Language: la

Element Group: Source Material
Organism ID: GLYZ897650 (Artificial ID)
Organism Name: *Glycyrrhiza glabra* L.

Element Group: Organism
Family: *Fabaceae* (*Leguminosae*)
Genus: *Glycyrrhiza*
Species: *glabra*
Element Group: Author
Author Type: Species Primary Author
Author Description: L.

Element Group: Organism General
Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Fabales

Element Group: Part Description
Part: Root and Stolon

NOTE Root and Stolon with (unpeeled) or without (peeled) periderm.

Element Group: Substance Code
Code: TRE4 (Artificial code)
Code System: Kampo Code
Code System ID: 0051
Code System Status: Active

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E.7.4.2.1 Substance (Fresh)

Element Group: Substance
Substance ID: GHTE8976OF (Artificial Name)
Substance Type: Structurally Diverse (Herbal Substance)

Element Group: Substance Name
Substance (fresh) Name: *Glycyrrhiza uralensis* Fisch. ex DC., Root and Stolon
Substance Name Type: Other
Language: en
Substance Name Domain: Drug
Jurisdiction: EU, US, JP

Element Group: Substance Name (Repeat)
Substance Name: *Glycyrrhiza uralensis* Fisch. ex DC.
Substance Name Type: Scientific

Element Group: Source Material
Organism ID: BLYZ89765U (Artificial ID)
Organism Name: *Glycyrrhiza uralensis* Fisch. ex DC.

Element Group: Organism
Family: *Fabaceae* (*Leguminosae*)
Genus: *Glycyrrhiza*
Species: *uralensis*

Element Group: Author
Author Type: Species Primary Author
Author Description: Fisch. ex DC.
Element Group: Organism General
Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Fabales

Element Group: Part Description
Part: Root and Stolon

NOTE Root and Stolon with (unpeeled) or without (peeled) periderm.

E.7.4.3 Substance (Herbal Drug)

Element Group: Substance
Substance ID: MMMMMMMMMM (Artificial ID)
Substance Type: Structurally Diverse (Herbal Substance)

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Element Group: Substance Name
Substance (Herbal Drug) name: *Glycyrrhiza glabra*, Root and Stolon
Substance Name Type: Official
Language: en
Substance Name Domain: Drug
Jurisdiction: EU, US, JP

Element Group: Official Name
Official Name Type: JP
Official Name Status: Current

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: JP
Reference Source Class: Official Name Source
Reference Source Citation: Japanese Pharmacopoeia XVI

Element Group: Substance Name (Repeat)
Substance Name: Glycyrrhiza
Substance Name Type: Other
Language: en

Element Group: Substance Name (Repeat)
Substance Name: Chinese liquorice
Substance Name Type: Other
Language: en

Element Group: Source Material
Parent Substance ID: HGTDE7634F (Artificial Code)
Parent Substance (fresh) Name: *Glycyrrhiza glabra* L., Root and Stolon

Element Group: Part Description
Part: Root and Stolon

NOTE Root and Stolon with (unpeeled) or without (peeled) periderm.

Element Group: Substance Code
Code: TRE3 (Artificial code)
Code System: Kampo Code
Code System ID: 0051
Code System Status: Active

E.7.4.4 Information captured at the Group 1 Specified Substance level for the Herbal Drug Glycyrrhiza (JP)

NOTE Only the information that would be captured for *Glycyrrhiza glabra* L. is presented here.

Specified Substance ID: GAKYT5643S (Artificial ID)
Substance Type: Specified Substance Group 1

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Element Group: Substance Name
Substance Name (Herbal Drug): Glycyrrhiza *glabra*, Root and Stolon, Dry

Substance Name Type: Specified Substance Group 1
Language: en
Substance Name Domain: Botanical
Jurisdiction: EU, US, JP

Element Group: Substance Name (Repeat)
Substance Name: *Glycyrrhiza radix*
Substance Name Type: Official
Language: la

Element Group: Official Name
Official Name Type: JP
Official Name Status: Current

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: JP
Reference Source Class: Official Name Source
Reference Sourse Citation: JP, ed. XVI

Element Group: Constituent
Constituent Substance ID: MMMMMMMMMM (Artificial ID)
Constituent Substance Name: *Glycyrrhiza glabra*, Root and Stolon
Language: en
Substance Role: Parent substance
Is Defining: Yes

Element Group: Constituent (Repeat)
Constituent Substance ID: 6FO62043WK (UNII)
Constituent Substance Name: Glycyrrhizic acid [Mol. Form.: $C_{42}H_{62}O_{16}$; Mol. Weight: Mw = 822.9]
Language: en
Substance Role: Marker

Element Group: Amount
Amount Type: NLT
Quantity: 2,5
Unit: %{w/w}

Element Group: Structure (presented for tutorial reason)
Stereochemistry: Chiral
Optical Activity: N/A
Molecular Formula: $C_{42}H_{62}O_{16}$

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Element Group: Molecular Weight
Molecular Weight Method: Calculated
Molecular Weight Type: Number average

Element Group: Amount
Amount Type: Exact
Quantity: 822,9
Unit: g/mol

Element Group: Structural Representation
Structural Representation Type: Full
Structural Representation Attachment: See image below.

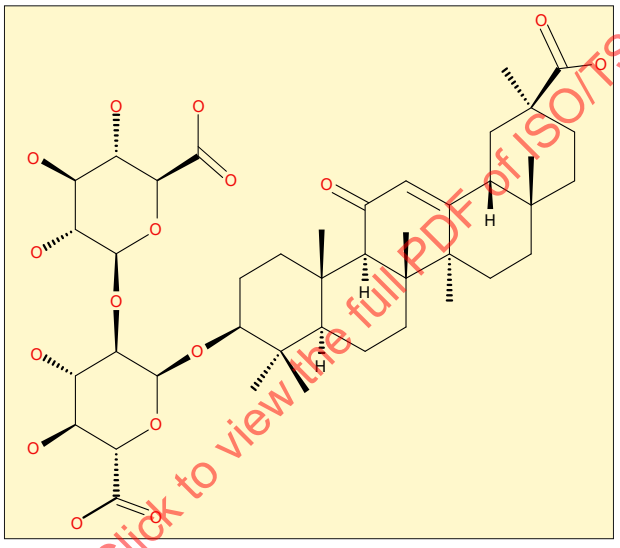


Figure E.39 — Structural representation of Glycyrrhizic acid

In addition to marker substances additional constituents of each herbal extract should be captured and linked to the extract if significant biological activity has been attributed to them. The two substances below are substances from liquorice root shown to have oestrogenic activity.

— Constituent Substance ID: C6Y321Q75O (Artificial ID)

— Constituent Substance Name: Glabrene

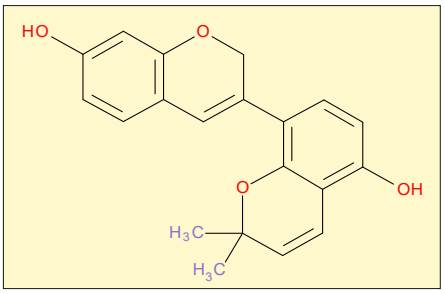


Figure E.40 — Structural representation of Glabrene

— Constituent Substance ID: HOC5567T41 (Artificial ID)

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— Constituent Substance Name: Glabridin

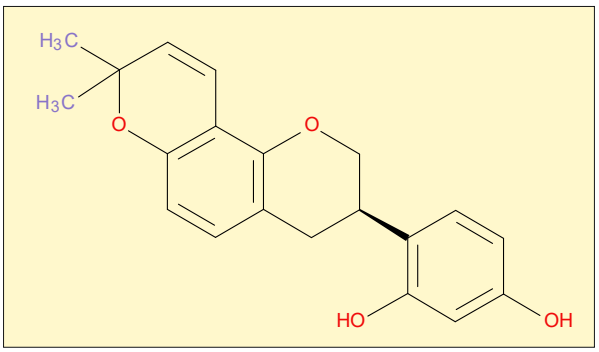


Figure E.41 — Structural representation of Glabridin

E.7.4.5 Information captured at the Substance level for Peony Root (JP)

Element Group: Characteristic Attribute
Attribute Type: Particular Herbal
Attribute Name: Process state
Is Defining: No

NOTE This class is conditional based on Jurisdictional regulation. For example, this class is optional in the JP jurisdiction.

Element Group: Amount
Amount Type: Exact
Amount Text: Dry or fresh, processed peeled or unpeeled Roots and Stolons

Element Group: Characteristic Attribute (Repeat)
Attribute Type: Particular Herbal
Attribute Name: Wild/ Cultivated; Countries of Origin; Growth State; Harvesting time are optional for the Japanese Jurisdiction
Is Defining: No

Capturing a marker specification of NLT 2,5 %, calculated on basis of the dried material of Glycyrrhizic acid is shown below:

Element Group: Constituent
Constituent Substance ID: MMMMMMMMMM (Artificial ID)
Constituent Substance Name: *Glycyrrhiza glabra*., Root and Stolon
Language: en
Substance Role: Parent substance
Is Defining: Yes

Element Group: Constituent (Repeat)
Constituent Substance ID: 6FO62043WK (UNII)
Constituent Substance Name: Glycyrrhizic acid [Mol. Form.: $C_{42}H_{62}O_{16}$; Mol. Weight: Mw = 822,9]

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Language: en
Substance Role: Marker

Element Group: Amount
Amount Type: NLT
Quantity: 2,5
Unit: %{w/w}

Structural information of Glycyrrhizic acid is presented above.

E.7.4.6 Information captured at the Substance level for Peony Root (JP)

Element Group: Substance (fresh)
Substance ID: PEOGHDR78S (Artificial ID)
Substance Type: Structurally Diverse (Herbal Substance)

Element Group: Substance Name
Substance (fresh) name: *Paeonia lactiflora* Pall., Root
Substance Name Type: Other
Language: en
Substance Name Domain: Drug
Jurisdiction: JP

Element Group: Substance Name (Repeat)
Substance Name: *Paeonia lactiflora* Pall.
Substance Name Type: Scientific
Language: la

Element Group: Source Material
Organism ID: KLJIR78634 (Artificial ID)
Organism Name: *Paeonia lactiflora* Pall.

Element Group: Organism
Family: *Paeoniaceae*
Genus: *Paeonia*
Species: *lactiflora*

Element Group: Author
Author Type: Species Primary Author
Author Description: Pall.

Element Group: Organism General
Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Saxifragales

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Element Group: Part Description
Part: Root

Element Group: Substance (Herbal Drug)
Substance ID: PPPPPPPPPP (Artificial ID)
Substance Type: Structurally Diverse (Herbal Drug)

Element Group: Substance Name
Substance name (Herbal Drug): *Paeonia lactiflora*, Root
Substance Name Type: Other
Language: en
Substance Name Domain: Drug
Jurisdiction: JP

Element Group: Substance Name (Repeat)
Substance Name: Peony Root
Substance Name Type: Official
Language: en

Element Group: Official Name
Official Name Type: JP
Official Name Status: Current

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: JP
Reference Source Class: Official Name Source
Reference Source Citation: Japanese Pharmacopoeia XVI

Element Group: Substance Name (Repeat)
Substance Name: Baishao
Substance Name Type: Other
Language: cn

Element Group: Substance Name (Repeat)
Substance Name: White Peony
Substance Name Type: Other
Language: en

Element Group: Substance Name (Repeat)
Substance Name: Red Peony Root
Substance Name Type: Other
Language: en

Element Group: Source Material
Parent Substance ID: PEOGHDR78S (Artificial ID)

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Parent Substance (fresh) Name: *Paeonia lactiflora* Pall., Root

Element Group: Substance Code
Code: PAE1 (Artificial code)
Code System: Kampo Code
Code System ID: 0051
Code System Status: Active

E.7.4.7 Information captured at the Group 1 Specified Substance level for the Herbal Drug Peony Root (JP)

Specified Substance ID: YUTD65489P (Artificial ID)
Substance Type: Specified Substance Group 1

Element Group: Substance Name
Substance Name (Herbal Drug): *Paeonia lactiflora*, Root, Dry

Element Group: Constituent
Constituent Substance ID: PPPPPPPPPP (Artificial ID)
Constituent Substance Name (Herbal Drug): *Paeonia lactiflora*, Root
Language: en
Substance Role: Parent substance
Is Defining: Yes

Capturing a Marker specification of Peoniflorin of NLT 2,0 %, calculated on the basis of the dried material is shown below:

Element Group: Constituent (Repeat)
Constituent Substance ID: 21AIQ4EV64 (Artificial ID)
Constituent Substance Name: Peoniflorin [Mol. Form.: $C_{23}H_{28}O_{11}$, Mol. Weight: Mr 480.46]
Language: en
Substance Role: Marker
Is Defining: Yes

Element Group: Amount
Amount Type: NLT
Quantity: 2,0
Unit: %{w/w}

Element Group: Structure (presented for tutorial reason)
Stereochemistry: Chiral
Optical Activity: Unknown
Molecular Formula: $C_{23}H_{28}O_{11}$

Element Group: Molecular Weight
Molecular Weight Method: Calculated
Molecular Weight Type: Number average

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Element Group: Amount
Amount Type: Exact
Quantity: 480,46
Unit: g/mol

Element Group: Structural Representation
Structural Representation Type: Full
Structural Representation Attachment: See image below:

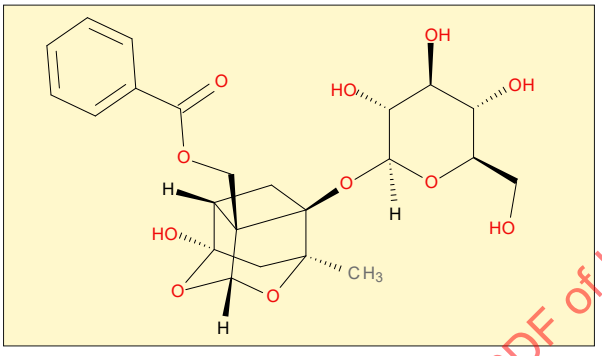


Figure E.42 — Structural representation of Peoniflorin

Element Group: Characteristic Attribute[47]
Attribute Type: Particular Herbal
Attribute Name: Process state
Is Defining: No

Element Group: Amount
Amount Type: Exact
Non Numeric Value: Dry or fresh, processed peeled or unpeeled Roots and Stolons

Element Group: Characteristic Attribute (Repeat)
Attribute Type: Particular Herbal
Attribute Name: Wild/cultivated (N/A); Countries of origin (N/A); Growth state (N/A); Harvesting time (N/A) are optional for the Japanese Jurisdiction.

Element Group: Substance Code
Code: YTRW2 (Artificial code)
Code System: Kampo Code
Code System ID: 0051
Code System Status: Active

E.7.4.8 Information captured at the Substance level for the Herbal preparation Shakuyakukanzoto Extract

Substance (Herbal preparation)

[47] This class is conditional based on Jurisdictional regulations. For example, this class will be optional in the JP jurisdiction.

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Substance ID: RRRRRRRRRR (Artificial ID)
Substance Type: Structurally Diverse (Herbal Substance)

Element Group: Substance Name
Substance Name (Herbal preparation): Shakuyakukanzoto Extract
Substance Name Type: Official
Language: en
Substance Name Domain: Drug
Jurisdiction: JP

Element Group: Official Name
Official Name Type: JP
Official Name Status: Current

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: JP
Reference Source Class: Official Name Source
Reference Source Citation: Japanese Pharmacopoeia XVI

Element Group: Source Material
Parent Substance ID: MMMMMMMMMM (Artificial ID)
Parent Substance Name (Herbal Drug): *Glycyrrhiza glabra*, Root and Stolon
Parent Substance ID: PPPPPPPPPP (Artificial ID)
Parent Substance Name (Herbal Drug): *Paeonia lactiflora*, Root

Element Group: Substance Code
Code: SHE3 (Artificial code)
Code System: Kampo Code
Code System ID: 0051
Code System Status: Active

E.7.4.9 Information captured at the Group 1 Specified Substance level for Shakuyakukanzoto Extract (JP)

Specified Substance ID: EUYTS6725C (Artificial ID)
Substance Type: Specified Substance Group 1

Element Group: Substance Name
Substance Name: Shakuyakukanzoto Dry or Viscous Aqueous Extract[48]
Substance Name Type: Specified Substance Group 1
Language: en
Substance Name Domain: Drug

[48] In the EU and US jurisdictions, the Specified Substance Group 1 Name should read: Shakuyakukanzoto, Dry or Viscous Aqueous Extract corresponding to 50 mg to 150 mg Peoniflorin and Glycyrrhizic Acid per 5 g to 6 g Peony Root and 5 g to 6 g Glycyrrhiza. In this example, only Glycyrrhiza glabra, root and stolon is supposed to be used.

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Jurisdiction: JP

Element Group: Constituent
Constituent Substance ID: RRRRRRRRRR (Artificial ID)
Constituent Substance Name (Herbal preparation): Shakuyakukanzoto Extract
Substance Role: Parent substance
Amount: N/A

Element Group: Constituent (Repeat)
Constituent Substance ID: WATER67543 (Artificial ID)
Constituent Substance Name: Water
Language: en
Is Defining: Yes

Element Group: Constituent (Repeat)[49]
Constituent Substance ID: 21AIQ4EV64 (Artificial ID)
Constituent Substance Name: Peoniflorin ($C_{23}H_{28}O_{11}$, Mr 480.46)
Language: en
Substance Role: Marker
Amount Type: Numeric Value

Element Group: Amount
Amount Type: Average
Low Limit: 8,3
High Limit: 30
Unit: mg

Element Group: Constituent (Repeat)
Constituent Substance ID: 6FO62043WK (UNII)
Constituent Substance Name: Glycyrrhizic acid [Mol. Form.: $C_{42}H_{62}O_{16}$; Mol. Weight: Mw = 822,9]
Language: en
Substance Role: Marker
Element Group: Amount
Amount Type: Average
Low Limit: 8,3
High Limit: 30
Unit: mg

Element Group: Characteristic Attribute

[49] Information on the markers:
Peoniflorin ($C_{23}H_{28}O_{11}$, Mr= 480.5); Glycyrrhizic acid ($C_{42}H_{62}O_{16}$, Mr = 822.9)
Marker Specification:
50 mg to 150 mg Peoniflorin per 5 g to 6 g Peony Root
50 mg to 150 mg Glycyrrhizic acid per 5 g to 6 g Glycyrrhiza

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Drug Extract Ratio (DER): N/A (Optional)[50]

Element Group: Fraction Description
Fraction: Dry or Viscous Aqueous Extract
Material Type: Botanical, Herbal

E.7.4.10 Information captured at the Specified Substance Group 2 level for Shakuyakukanzoto Extract (JP)

Specified Substance Group 2 ID: [HGTSIY876H]

Element Group: Substance Name
Substance Name: Shakuyakukanzoto Dry or Viscous Aqueous Extract–Manufacturer THP
Substance Name Type: Specified Substance Group 2
Language: en
(Parent) Substance ID: EUYTS6725C (Artificial ID)

NOTE The (Parent) Substance ID EUYTS6725C (Artificial ID) corresponds to the (Parent Specified) Substance (Group 1) Name: Shakuyakukanzoto Dry or Viscous Aqueous Extract.

Element Group: Manufacturing
Production Method Type: Extraction
Production Method Description: Extraction, and preparing a dry or viscous aqueous extract in accordance to section, XI.1.1., JP, Monograph for Preparations Related to Crude Drugs, I. Extract
Production System Type: N/A
Production System: N/A
Critical Process Version number: 1
Version: EXTR-001
Verson Date: 20170402

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: JP
Reference Source Class: Official Name Source
Reference Source Citation: Japanese Pharmacopoeia XVI

Element Group: Manufacturing
Manufacturer ID: DUNS987654 (Artificial ID)
Manufacturer Name: Manufacturer THP
Issuer of ID: EMA OMS
Manufacturer Role: Manufacturer

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[50] This element is optional for the Japanese jurisdiction.

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E.7.4.11 Information captured at the Group 3 Specified Substance level for Shakuyakukanzoto Extract (JP)

Specified Substance Group 3 ID: GHFTE8675G (Artificial ID)

Element Group: Substance Name
Substance Name: Shakuyakukanzoto, Dry or Viscous Aqueous Extract-JP
Substance Name Type: Specified Substance Group 3
(Parent) Substance ID: EUYTS6725C (Artificial ID)

NOTE The (Parent) Substance ID EUYTS6725C (Artificial ID) corresponds to the (Parent Specified) Substance (Group 1) Name: Shakuyakukanzoto Dry or Viscous Aqueous Extract.

Element Group: Grade
Grade Type: JP, ed. XVI
Grade Name: Shakuyakukanzoto Extract

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: JP
Reference Source Class: Official Name Source
Reference Source Citation: Japanese Pharmacopoeia XVI

E.8 General Information on the use of Glycyrrhiza species and their constituents

On the website of the European Medicines Agency there is an assessment report[51] on *Glycyrrhiza glabra* L. and/or *Glycyrrhiza inflata Bat*. and/or *Glycyrrhiza uralensis* Fisch., radix; Rapporteur: Marisa Delbò: Assessors: Gioacchino Calapai, Marisa Delbò.

Reference: EMA/HMPC/571122/2010 Corr.1, Committee on Herbal Medicinal Products (HMPC), 12 March 2013[52]

List of references: List of references supporting the assessment of *Glycyrrhiza glabra* L. and/or *Glycyrrhiza inflata* Bat. and/or *Glycyrrhiza uralensis* Fisch, radix[53]

EMA/HMPC/571121/2010 Corr.1 Committee on Herbal Medicinal Products (HMPC), 12 March 2013

Some sections out of this assessment report will be discussed here regarding the constituents.

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[51] Assessment report: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2012/08/WC500131285.pdf

[52] Reference: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/herbal/medicines/herbal_med_000132.jsp&mid=WC0b01ac058001fa1d)

[53] List of References: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_List_of_references_supporting_the_assessment_report/2012/08/WC500131286.pdf

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Herbal preparation(s):

a) Comminuted Herbal Drug;
b) Soft extract (1: 0,4-0,5), extraction solvent water;
c) Soft extract (3:1), extraction solvent water;
d) Dry extracts that correspond to preparations mentioned under b) and c).

Pharmaceutical forms

Herbal preparations in solid or liquid dosage forms for oral use.
Comminuted Herbal Drug as a herbal tea for oral use.

Herbal Drug(s)

Liquorice root consists of the dried unpeeled or peeled, whole or cut root and stolons of *Glycyrrhiza glabra* L. and/or of *Glycyrrhiza inflata* Bat. and/or *Glycyrrhiza uralensis* Fisch. It contains not less than 4,0 per cent of 18 β-glycyrrhizic acid ($C_{42}H_{62}O_{16}$, Mr 823), calculated with reference to the dried drug (European Pharmacopoeia 2010), see Figure E.43.



LIQUORICE ROOT

Liquiritiate radix

DEFINITION

Dried, unpeeled or peeled, whole or cut root and stolons of *Glycyrrhiza glabra* L. and/or of *Glycyrrhiza inflata* Bat. and/or *Glycyrrhiza uralensis* Fisch.

Content: minimum 4.0 per cent of 18β-glycyrrhizic acid ($C_{42}H_{62}O_{16}$;M_r 823 g/mol) (dried drug)

Ph.Eur. monograph no. 277

Figure E.43 — Description of Liquorice root

Description:

Glycyrrhiza glabra is a perennial herb native to central and south-western Asia and the Mediterranean region. It is cultivated in the Mediterranean basin of Africa, in southern Europe, and in India. It is a medicinal plant in China and India, and cultivated for this purpose [22].

The genus *Glycyrrhiza* (Leguminosae) consists of about 30 species native to Europe, Asia, North and South America as well as Australia, including *G. glabra, G. uralensis, G. inflata, G. aspera, G. korshinskyi* and *G. eurycarpa. G. glabra* includes three varieties: Persian and Turkish liquorices assigned to *G. glabra var. violacea*, Russian liquorice is *G. glabra var. gladulifera*, and Spanish and Italian liquorices are *G. glabra var. typical*[23]. *G. uralensis, G. inflata and G. glabra* are the only species mentioned in the Chinese Pharmacopoeia. The Chinese name is *gan-cao* which means “sweet herb”.

Constituents:

Saponins

Liquorice root contains triterpenoid saponins (4 % to 20 %), mostly glycyrrhizin, a mixture of potassium and calcium salts of 18β-glycyrrhizic acid (also known as glycyrrhizic or glycyrrhizinic acid and a

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glycoside of glycyrrhetinic acid), which is 50 times sweeter than sugar. Other triterpenes present are liquiritic acid, glycyrretol, glabrolide, isoglaborlide and liquorice acid[24].

18β-glycyrrhizic acid (3-O-(2-O-β-d-glucopyranuronosyl–α-d-glucopyranurosyl)-3-β-hydroxy-11-oxo-18β,20β-olean-12-en-29-oic acid) was isolated for the first from the roots of *Glycyrrhiza glabra* by Ronbiquet (1809) who called it glycyrrhizin. The name of glycyrrhizic acid was given later by Roussin (1876), see Reference [25]. It is a monodesmoside, which on hydrolysis releases two molecules of D-glucuronic acid and the aglycone 18β-glycyrrhetic (glycyrrhetinic) acid (enoxolone)[22]. The name glycyrrhizin has been more strictly maintained for the potassium, calcium and magnesium salts, which are in liquorice roots as well as the ammonium salt, which is in the common commercial preparations[25].

Glycyrrhizin is the major bioactive compound in the underground parts of Glycyrrhiza (liquorice) plants which possesses a wide range of pharmacological properties and is used worldwide as a natural sweetener. Because of its economic value, the biosynthesis of glycyrrhizin has received considerable attention. Glycyrrhizin is most likely derived from the triterpene β-amyrin, an initial product of the cyclization of 2,3 oxidosqualene. The subsequent steps in glycyrrhizin biosynthesis are believed to involve a series of oxidative reactions at the C-11 and C-30 positions, followed by glycosyl transfers to the C-3 hydroxyl group[26].

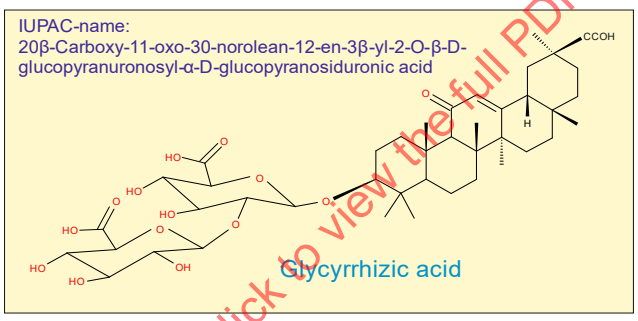


Figure E.44 — Representative Structure of Glycyrrhizic acid

Flavonoids

More than 300 flavonoids have been isolated from Glycyrrhiza species. These flavonoids belong to various types, including flavanones or flavanonols, chalcones, isoflavans, isoflavenes, flavones or flavonols, isoflavones and isoflavanones. Amongst them, flavanones and chalcones are the main types[27].

Flavonoids are responsible for the yellow colour of liquorice. They include liquiritin, liquiritigenin, rhamnoliquiritin, neoliquiritin, chalcones, isoliquiritin, isoliquiritigenin, neoisoliquiritin, licuraside, glabrolide and licoflavonol[28]. The compounds 5,8-dihydroxy-flavone-7-O-beta-D-glucuronide, glychionide A, and 5-hydroxy-8-methoxyl-flavone-7-O-beta-D-glucuronide, glychionide B were also isolated from the roots of G. glabra[29].

In liquorice, the isoflavones glabridin, galbrene, glabrone, shinpterocarpin, licoisoflavones A and B, formononetin, glyzarin, kumatakenin, have been found. Other isoflavones present are hispaglabridin A, hispaglabridin B, 4'-O-methyl glabridin, 3'-hydroxy-4'-O-methyl glabridin, glabroisoflavanone A and B glabroiso-flavanone B.

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Coumarins

Coumarins include liqcoumarin, glabrocoumarone A and B, herniarin, umbelliferone, glycyrin, glycocoumarin, licofuranocoumarin, licopyranocoumarin and glabrocoumarin[30].

Other compounds

Minor components occur in amounts that vary depending on the species and geographical location[22]. The dihydrostilbenes, dihydro-3,5-dihydroxy-4'-acetoxy-5'-isopentenylstilbene, dihydro-3,3',4'-trihydroxy-5-O-isopentenyl-6-isopentenylstilbene, dihydro-3,5,3'-trihydroxy-4'-methoxystilbene and dihydro-3,3'-dihydroxy-5β-d-O-glucopyranosyloxy-4'-methoxystilbene were isolated from the leaves of G. glabra grown in Sicily[31]. Moreover, fatty acids (C2– C16) and phenols (phenol, guaiacol), together with common saturated linear γ-lactones (C6–C14). 4-Methyl-γ-lactones, 4-ethyl-γ-lactones in trace amounts, as well as asparagines, glucose, sucrose, starch, polysaccharides (arabinogalactants) and sterols (β-sitosterol, dihydrostigmasterol) have also been found[32].

E.8.1 Herbal preparation, Liquorice extract

There are about 14 species known, although most commercial liquorice is extracted from varieties of G. *glabra* grown in southern and central Europe (var. typica), in central and southern Russia (*var.glandulifera*), and in Iran and Iraq (*var. violacea*). Commercial liquorice products are derived from extracts of the root[24].

The harvesting of liquorice root occurs in the autumn of its third or fourth year of growth. The roots are dug up, washed and transported to warehouses for baling, sorting and drying. The dried roots are crushed by millstones and the pulp is boiled to make the extract. After removal of the solids, the extract is vacuum dried to a dark paste, which is cast into blocks or short sticks, or may be dried to a powder[33].

The European Pharmacopoeia reports the following liquid and dry extracts:

Liquorice ethanolic liquid extract, standardized (*Liquiritiae extractum fluidum ethanolicum normatum*), which is produced from the Herbal Drug by a suitable procedure for liquid extracts using ethanol (70 % {v/v}) and contains 3 % to 5 % of 18 β-glycyrrhizic acid. The extract is a clear liquid, dark brown, with a faint characteristic odour and a sweet taste.

Liquorice dry extract for flavouring purposes (*Liquiritiae extractum siccum ad saporandum*) produced from the cut liquorice root by a suitable procedure using water, and contains: 5 % to 7 % of 18 β-glycyrrhizic acid. The dry extract is a yellowish-brown or brown powder with a very sweet taste.

Markers

At the levels of Specified Substance Group 1 and Group 2 only the markers and analytical markers are used with the specification in order to control the manufacturing process of the extract. Other constituents may be mentioned qualitatively, but do not form part of the assessment and control of the Herbal preparation manufacturing process.

An example of a multistep extraction process of liquorice root in which the first eluate is enriched by extracting the drug residue again is shown in Figure E.45, in which the eluates of several percolators are combined.

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Extraction solvent: Ethanol –Water (30 – 70 {v/v});

DER: 2.5 – 3.5 Parts Herbal Drug = 1.0 Part Extract;

The specified content of the Final Extract is based on the marker in the extract: 7 -12 mg/ml glycyrrhizic acid.

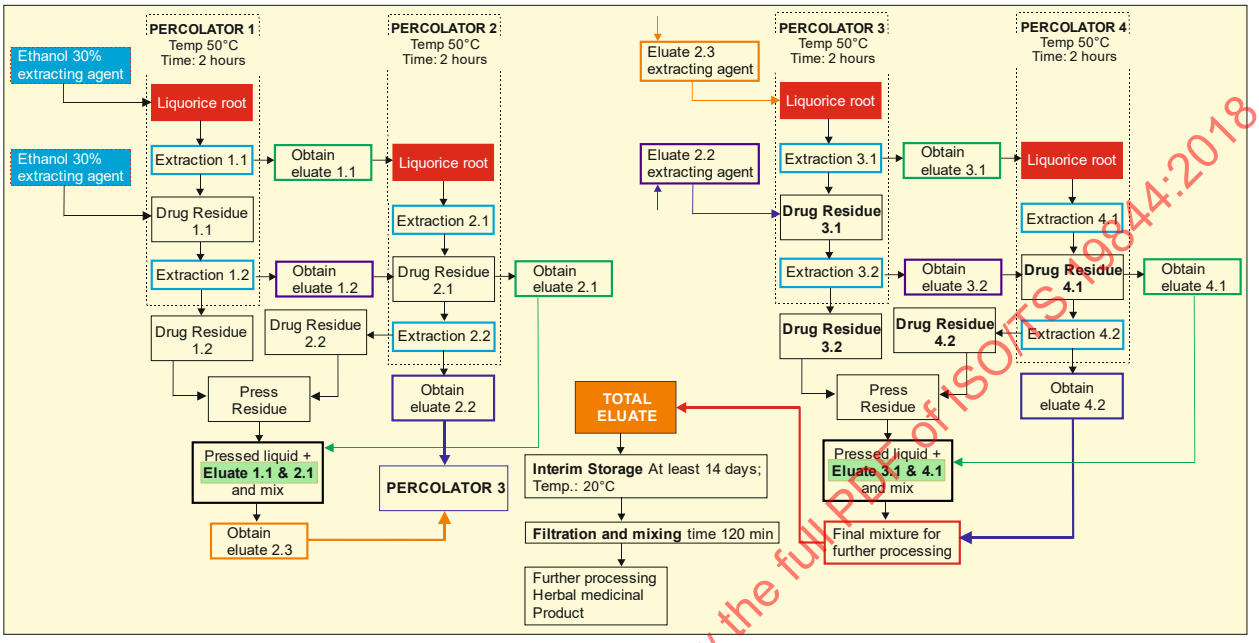


Figure E.45 — Example of multi-step extraction procedure for Liquorice root

E.9 Exudates

Definitions according to Directive 2001/83/EC and Directive 2004/24/EC, Title 1, Definitions:

Article 31: *Herbal Substances* (*this Annex refers to these as Herbal Drugs*): describes for "exudates": Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances (= Herbal Drugs).

Article 32: *Herbal preparations*: describes for "exudates":

These include comminuted or powdered herbal substances (= Herbal Drugs), tinctures, extracts, essential oils, expressed juices and processed exudates."

This means that exudates are considered to be Herbal Drugs when the treatment is not 'specific', meaning only e.g. cutting the bark of a tree to let the material flow out of the tree and drying in the sun. When more handling occurs, e.g. mechanical heat treatment or extensive drying, exudates are considered to be Herbal preparations.

However, within the structure of ISO 11238, fractions, including all exudates, are captured at the Substance (Herbal preparation) information level with the Substance Name composed of:

[Scientific genus/binomial/trinomial **without** Author] [Part(s)] [**Fraction**] (= Herbal preparation)

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with reference to the (**Parent**) Substance (Fresh) name composed of:

[Scientific genus/binomial/trinomial **with Author**] [Part(s)] (= Substance (Fresh))

All processing details including Air-drying for the Herbal preparation will be captured at the Group 1 Specified Substance level in which Air-drying will be considered as a 'natural process', so that 'No specific treatment exudates' and 'processed exudates' are considered as 'natural processed' which are captured at the Substance information level and '(mechanical) processed exudates', respectively, captured by the definition of "fraction" at the Group 1 Specified Substance information level.

E.9.1 Examples

E.9.1.1 Peru balsam, Ph.Eur. monograph 01/2008:0754

DEFINITION

Balsam obtained from the scorched and wounded trunk of *Myroxylon balsamum* (L.) Harms var. *pereirae* (Royle) Harms.

Content: 45,0 per cent mass fraction to 70,0 per cent mass fraction of esters, mainly benzyl benzoate and benzyl cinnamate.

CHARACTERISTICS

Appearance: dark brown, viscous liquid which is transparent and yellowish-brown when viewed in a thin layer; it is not sticky, non-drying and does not form threads.

Solubility: practically insoluble in water, freely soluble in anhydrous ethanol, not miscible with fatty oils, except for castor oil.

E.9.1.2 Production of Peru Balsam

Production of Peru balsam is carried out after the rains in November/December until May, by fire-scorching and wounding the bark of the tree, leaving approximately 1 week, before slashing and removing rectangular strips of outer layers of bark (typically some 30 cm × 15 cm), which are crushed, boiled into hot water and pressed giving ´Balsam of Cascara´, Balsam of the Bark.

As well as the bark, the tree is also worked – according to Poucher (1936), after the outer layers of bark are removed, exposing the wood. The wood is covered with cloths or rags to collect the exudates over 15 to 20 days, the cloths or rags being subsequently boiled to recover the balsam and pressed in a rope press, giving 'Balsam de Pañal', the major part of the yield.

In a few days, a third exudation ('Balsam de Contrapique o Tacuazonte') is collected with cloths that are boiled and pressed to recover the resin. In the pressing process the balsam sinks to the bottom (S.G. 1,150 to 1,170) and the water is decanted off and the resin strained.

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A combination of these three tappings in definite proportions is a ´Raw Balsam´ that is then boiled to evaporate the residual water[54] (this called the ¨Purification Process¨) and gives the Peru balsam as we know it commercially.

The tree may be tapped in this way at fortnightly intervals up to 8 to 9 months per year. Average yields have been reported to be between 0,25 kg to 0,50 kg per tree per annum, with trees around 60 years of age giving maximum yields.

E.9.1.3 Tolu balsam, Ph.Eur. monograph 01/2008:1596

DEFINITION

Oleo-resin obtained from the trunk of *Myroxylon balsamum* (L.) Harms var. *balsamum*.

NOTE There are no longer any recognized varieties for this species, so the type variety (autonym) is no longer valid. However, to be consistent with the classification that this Annex is following for Peru Balsam, the type variety, var. balsamum, will be used here for Tolu Balsam.

Content: 25,0 per cent to 50,0 per cent of free or combined acids, expressed as cinnamic acid ($C_9H_8O_2$; Mr 148.2) (dried drug).

CHARACTERISTICS

Appearance: hard, friable, brownish to reddish-brown mass; thin fragments are brownish-yellow when examined against the light.

Reminiscent odour of vanillin.

Solubility: practically insoluble in water, very soluble to freely soluble in alcohol, practically insoluble in light petroleum.

E.9.1.4 Production of Tolu Balsam

To obtain the gum a V-shaped notch is cut through the bark. Below the point of the notch the bark and wood are hollowed out to insert a cup to collect the drips. Incisions are made at many points up and down the trunk, but in such a way as to not girdle the tree.

When the tree is scarred as far as one can reach from the ground, scaffolds are sometimes rigged around it, so that the same process can be repeated farther up. As many as 20 incisions may be made up the side of a tree. Gum is collected from the cups by gatherers who make their rounds of the trees with a pair of rawhide bags slung over the backs of donkeys (burros). Contents of the cups are emptied into bags, and the cups replaced for more gum. The bags are emptied into tin export containers. The collection season continues over an 8-month period from July to March or April.

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[54] Peru Balsam 'Oil' is generally encountered as ex-molecular distillation or very high vacuum distillation of the crude Peru Balsam, which offers yields of >50 %.

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Because of the number of incisions per tree and the length of the collection of the gum are indefinite, data vary. Average of 8 kg to 10 kg balsam/tree.

After collection, the gum dries to resin. It is collected in gourds and transported by donkeys. It is soft and pliable inside the tree, and becomes brittle and hard after it dries due to air exposure. The aroma is at its strongest when it is fresh, then gradually becomes weaker as it dries.

Tolu Balsam is more fluid than Peru balsam when fresh because it has greater quantities of phellandrene and alcohols, such as guaiacol and cresol. Part of the characteristic fragrance of both resins is due to the coumarins.

E.9.2 Conclusion

The harvesting of Peru Balsam is obtained by fire-scorching and wounding the bark of the tree made on one side of the tree and the balsam is collected over three rounds to get an average quality of gum-resin. The resin is boiled in water to recover the balsam.

This process can be seen as a manufacturing process of the fraction of the tree which can be captured at the Substance information level, Herbal preparation.

Detailed information regarding the Element Group 'Herbal Substance Particulars' can be captured at the Specified Substance Group 1 level and Manufacturing/Harvesting/Collection and Processing information at the Specified Substance Group 2 information level.

The harvesting of Tolu Balsam is obtained by a different way of making V-shaped incisions. 20 incisions are made at many points up and down the trunk, but in such a way as to not girdle the tree. The resin is collected over time and drying in the air to a hard-dry gum. Since it is soft and pliable inside the tree the chemical composition changes after drying. The gum-resin is to be considered 'natural processed' and a Herbal preparation.

E.10 Peru Balsam/Tolu Balsam structuring information

E.10.1 Capturing information for Peru Balsam (Ph.Eur.) at the Substance information level

E.10.1.1 Substance (Fresh)

Substance ID: PERU3451GP (Artificial ID)

Substance Type: Structurally Diverse (Herbal Substance)

Element Group: Substance Name

Substance (fresh) Name: *Myroxylon balsamum* (L.) Harms var. *pereirae* (Royle) Harms, Trunk

Substance Name Type: Other

Language: en

Substance Name Domain: Drug

Jurisdiction: EU, US

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Element Group: Substance Name (Repeat)

Substance Name: *Myroxylon balsamum* (L.) Harms var. *pereirae* (Royle) Harms

Substance Name Type: Scientific

Language: la

Element Group: Source Material

Organism ID: MYRO786543 (Artificial ID)

Organism Name: *Myroxylon balsamum* (L.) Harms var. *pereirae* (Royle) Harms

Element Group: Part Description

Part: Trunk

E.10.1.2 Substance (Herbal preparation)

Substance ID (Herbal preparation): GHFTE7856B (Artificial ID)

Substance Type: Structurally Diverse (Herbal Substance)

Element Group: Substance Name

Substance Name (Herbal preparation): *Myroxylon balsamum* var. *pereirae*, Trunk, Balsam

Substance Name Type: Official

Language: en

Substance Name Domain: Drug

Jurisdiction: EU, US

Element Group: Official Name

Official Name Type: Ph. Eur.

Official Name Status: Current

Element Group: Reference Source

Public Domain: Yes

Reference Source Type: Ph. Eur.

Reference Source Class: Official Name Source

Reference Source Citation: Ph P.Eur. monograph 01/2008:0754

Element Group: Substance Name (Repeat)

Substance Name: Peru balsam

Substance Name Type: Common Name

Language: en

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Element Group: Source Material

Parent Substance (fresh) ID: PERU3451GP (Artificial ID)

Parent Substance Name: Substance (fresh) Name: *Myroxylon balsamum* (L.) Harms var. *pereirae* (Royle) Harms, Trunk

Element Group: Part Description

Part: Trunk

Element Group: Fraction Description

Fraction: Balsum

Material Type: Herbal

E.10.2 Capturing information for Peru Balsam (Ph.Eur.) at the Specified Substance information level

E.10.2.1 Element Group: Specified Substance Group 1

Specified Substance Group 1 ID: TTTTTTTTTT (Artificial ID)

Element Group: Substance Name

(Specified) Substance (Group 1) Name (Herbal preparation): *Myroxylon balsamum* var. *pereirae*, Trunk, Balsam, Dry

Substance Name Type: Specified Substance Group 1

Language: en

Substance Name Domain: Drug

Jurisdiction: EU, US

Element Group: Constituent

Constituent Substance ID: GHFTE7856B (Artificial ID)

Constituent Substance Name (Herbal preparation): *Myroxylon balsamum var. pereirae*, Trunk, Balsam

Language: en

Substance Role: Parent substance

Is Defining: Yes

Element Group: Constituent (Repeat)

Constituent Substance ID: (Artificial ID)

Constituent Substance Name (Herbal preparation): Benzyl benzoate

Language: en

Substance Role: Marker

Is Defining: Yes

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Element Group: Constituent (Repeat)
Constituent Substance ID: BENZB45321 (Artificial ID)
Constituent Substance Name (Herbal preparation): Benzyl cinnamate
Language: en
Substance Role: Marker
Is Defining: Yes

Element Group: Amount
Amoung Type: Average
Low Value: 45
High Value: 70
Unit: %{w/w}
Amount Text: esters of Benzyl benzoate and Benzyl cinnamate

Element Group: Characteristic Attribute
Attribute Type: Particular Herbal preparation
Attribute Name: Country of origin
Is Defining: No

Element Group: Amount
Non Numeric Value: Jamaica

Element Group: Characteristic Attribute (Repeat)
Attribute Type: Particular Herbal preparation
Attribute Name: Country of origin
Is Defining: No

Element Group: Amount
Non Numeric Value: El Salvador

Element Group: Characteristic Attribute (Repeat)
Attribute Type: Particular Herbal preparation
Attribute Name: Country of origin
Is Defining: No

Element Group: Amount
Non Numeric Value: Sri Lanka

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E.10.2.2 Element Group: Specified Substance Group 2

Specified Substance Group 2 ID: MANUF67543 (Artificial ID)

(Parent Specified) Substance (Group 1) ID: TTTTTTTTTT (Artificial ID)

Element Group: Substance Name

(Specified) Substance (Group 2) Name (Herbal preparation): *Myroxylon balsamum* var. *pereirae*, Trunk, Balsam, Dry—Manufacturer ZZ

Substance Name Type: Specified Substance Group 2

Language: en

Element Group: Manufacturing

Manufacturing Type: Harvester and Manufacturer

Production Method Type: Harvesting and Manufacturing

Production Method Description: Collecting and Harvesting, drying and storing of the Exudate

Production System Type: N/A

Production System: N/A

Critical Process Version Number: 1

Version: HARV-001

Version Date: 20161021

Element Group: Organization

Manufacturer ID: D.U.N.S. 7654 (Artificial ID)

Manufacturer Name: Name, address, town, country (Brazil), Geographical coordinates

Issuer of ID: EMA OMS

Manufacturing Role: Harvester

E.10.2.3 Element Group: Specified Substance Group 3

Specified Substance Group 3 ID: DFSW9876HJ (Artificial ID)

Element Group: Substance Name

(Specified) Substance (Group 3) Name (Herbal preparation): *Myroxylon balsamum* var. *pereirae*, Trunk, Balsam, Dry—Ph.Eur.

Substance Name Type: Specified Substance Group 3

Element Group: Grade

Grade Type: Ph.Eur.

Grade Name: Peru Balsam

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Element Group: Reference Source

Public Domain: Yes

Reference Source Type: Ph. Eur.

Reference Source Class: Official Name Source

Reference Source Citation: Ph.Eur., monograph 01/2008:0754

E.10.3 Capturing information for Tolu Balsam (Ph.Eur.)

E.10.3.1 Substance (Fresh)

Substance ID: GHFTE5643O (Artificial ID)

Substance Type: Structurally Diverse (Herbal Substance)

Element Group: Substance Name

Substance (fresh) Name: *Myroxylon balsamum* (L.) Harms var. *balsamum*, Trunk

Substance Name Type: Other

Language: en

Substance Name Domain: Drug

Jurisdiction: EU, US

Element Group: Substance Name (Repeat)

Substance Name: *Myroxylon balsamum* var. *balsamum*

Substance Name Type: Scientific

Language: la

Element Group: Part Description

Part: Trunk

E.10.3.2 Substance (Herbal preparation)

Substance ID (Herbal preparation): JFGW9876UT (Artificial ID)

Substance Type: Structurally Diverse (Herbal Substance)

Element Group: Substance Name

Substance Name (Herbal preparation): *Myroxylon balsamum* var. *balsamum*, Trunk, Balsam

Substance Name Type: Official

Language: en

Substance Name Domain: Drug

Jurisdiction: EU

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Element Group: Official Name

Official Name Type: Ph. Eur.

Official Name Status: Current

Element Group: Reference Source

Public domain: Yes

Reference Source Type: Ph. Eur.

Reference Source Class: Official Name Source

Reference Source Citation: Ph.Eur. monograph 01/2008:1596

Element Group: Substance Name (Repeat)

Substance Name: Tolu balsam

Substance Name Type: Common Name

Language: en

Element Group: Source Material

Parent Substance (fresh) ID: TOLUP78654 (Artificial ID)

Parent Substance Name: Substance (fresh) Name *Myroxylon balsamum* (L.) Harms var. *balsamum*, Trunk

Element Group: Part Description

Part: Trunk

Element Group: Fraction Description

Fraction: Balsum

Material Type: Herbal

E.10.4 Specified Substance information level

E.10.4.1 Element Group: Specified Substance Group 1

Specified Substance Group 1 ID: RRRRRRRRRR (Artificial ID)

Element Group: Substance Name

(Specified) Substance (Group 1) Name (Herbal preparation): *Myroxylon balsamum* var. *balsamum*, Trunk, Balsam, Dry

Substance Name Type: Specified Substance Group 1

Language: en

Substance Name Domain: Botanical

Jurisdiction: US

Element Group: Constituent

Constituent Substance ID: JFGW9876UT (Artificial ID)

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Constituent Substance Name (Herbal preparation): *Myroxylon balsamum* var. *balsamum*, Trunk, Balsam
Language: en
Substance Role: Parent substance
Is Defining: Yes

Element Group: Constituent (Repeat)
Constituent Substance ID: CINN078563 (Artificial ID)
Constituent Substance Name (Herbal preparation): Cinnamic acid ($C_9H_8O_2$; M_r 148.2)
Language: en
Substance Role: Marker
Is Defining: Yes

Element Group: Amount
Amount Type: Average
Low Value: 25
High Value: 50
Unit: %{w/w}
Amount Text: free or combined acids, expressed as Cinnamic acid
Element Group: Characteristic Attribute
Attribute Type: Particular Herbal preparation
Attribute Name: Country of origin
Is Defining: No

Element Group: Amount
Non Numeric Value: Colombia (CO)

Element Group: Characteristic Attribute (Repeat)
Attribute Type: Particular Herbal preparation
Attribute Name: Country of origin
Is Defining: No

Element Group: Amount
Non Numeric Value: Peru (PE)

Element Group: Characteristic Attribute (Repeat)
Attribute Type: Particular Herbal preparation
Attribute Name: Country of origin
Is Defining: No

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Element Group: Amount

Non Numeric Value: Venezuela (VE)

E.10.4.2 Element Group: Specified Substance Group 2

Specified Substance Group 2 ID: MANUF67543 (Artificial ID)

(Parent Specified) Substance (Group 1) ID: RRRRRRRRRR (Artificial ID)

Element Group: Substance Name

Substance Name (Herbal preparation): *Myroxylon balsamum* var. *balsamum*, Trunk, Balsam, Dry—Manufacturer ZZ

Substance Name Type: Specified Substance Group 2

Element Group: Manufacturing

Manufacturing Type: Harvester

Production Method Type: Harvesting and Manufacturing

Production Method Description: Collecting and Harvesting, drying and storing of the Exudate

Production System Type: N/A

Production System: N/A

Critical Process Version Number: 1

Version: 001

Version Date: 20160502

Element Group: Organization

Manufacturer ID: D.U.N.S. 8976 (Artificial ID)

Manufacturer Name: Company 'GHTR'

Issuer of ID: EMA OMS

Manufacturing Role: Harvester and Manufacturer

Element Group: Specified Substance Group 3

Specified Substance Group 3 ID: HJGFD453Y (Artificial ID)

(Parent) Specified Substance Group 1 ID: RRRRRRRRRR (Artificial ID)

Element Group: Substance Name

Substance Name (Herbal preparation): *Myroxylon balsamum* var. *balsamum*, Trunk, Balsam, Dry—Ph.Eur.

Substance Name Type: Specified Substance Group 3

Language: en

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Element Group: Grade

Grade Type: Ph. Eur.

Grade Name: Tolu Balsam

Element Group: Reference Source

Public Domain: Yes

Reference Source Type: Ph. Eur.

Reference Source Class: Official Name Source

Reference Source Citation: Ph.Eur., monograph 01/2008:1596

E.11 Comparison table

The table below is used to clarify terms used in a Pharmacopoeia and to compare them with the terms used in the ISO 11238 and this document.

Pharmacopoeia term	N/A	Ph.Eur. 'Herbal Substance' for which the Annex uses 'Herbal Drug'	Ph.Eur. 'Herbal preparation'
Level captured at in ISO	ISO 'Substance level'	ISO 'Specified Substance (Herbal Drug) levels'	ISO 'Specified Substance (Herbal preparation) levels'
Term used in Annex	1) Substance (fresh) 2) Substance (Herbal Drug) 3) Substance (Herbal preparation)	1: SSG1 2: SSG1 3: SSG1	1: SSG1 2: SSG1 3: SSG1
Simple example ->	1) *Arnica montana* L., Flower 2) *Arnica montana*, Flower 3) *Arnica montana*, Flower, Tincture	1: *Arnica montana*, Flower, Dry 2: *Arnica montana*, Flower, Dry---Manufacturer 3: Arnica Flower (Ph.Eur.)	1: *Arnica montana*, Flower, Tincture 2: *Arnica montana*, Flower, Tincture ---Manufacturer 3: Arnica Tincture (Ph.Eur.)
	1) *Ginkgo biloba* L., Leaf 2) *Ginkgo biloba*, Leaf 3) *Ginkgo biloba*, Leaf, Dry Extract	1: *Ginkgo biloba*, Leaf, Dry 2: *Ginkgo biloba*, Leaf, Dry – Company Aa 3: Ginkgo Leaf (Ph.Eur.)	1: *Ginkgo biloba*, Leaf, Dry Extract, Acetone-Water (60-40 w/w) (37-65:1) 2: *Ginkgo biloba*, Leaf, Dry Extract, Acetone-Water (60-40 w/w) (37-65:1)—Manufacturer Cc 3: *Ginkgo biloba*, Leaf, Dry Extract, Acetone-Water (60-40 w/w/) (37-65:1), Refined and Quantified 3: Refined and Quantified Ginkgo Dry Extract (Ph.Eur.)

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	1) *Harpagophytum procumbens* (Burch.) DC. ex Meisn., Root 2) *Harpagophytum procumbens*, Root 3) Harpagophytum procumbens, Root, Dry Extract	1: *Harpagophytum procumbens*, Root, Dry 2: *Harpagophytum procumbens*, Root, Dry---Company Bb 3: Devil's Claw Root (Ph.Eur.)	1: *Harpagophytum procumbens and/or Harpagophytum zeyheri*, Root, Dry Extract Ethanol-Water (60-40 {v/v}) (1,5–3,0:1) 3: *Harpagophytum procumbens and/or Harpagophytum zeyheri*, Root, Dry Extract Ethanol-Water (60-40 {v/v}) (1,5–3,0:1), Standardized 3: Devil's Claw Dry Extract
	1) *Harpagophytum zeyheri* Decne., Root 2) *Harpagophytum zeyheri*, Root 3) *Harpagophytum zeyheri*, Root, Dry Extract	1: *Harpagophytum zeyheri*, Root, Dry 2: *Harpagophytum zeyheri*, Root, Dry---Company Bb 3: Devil's Claw Root (Ph.Eur.)	As above
	1) *Salvia miltiorrhiza* Bunge, Rhizome and Root 2) *Salvia miltiorrhiza*, Rhizome and Root 3) *Salvia miltiorrhiza*, Rhizome and Root, Soft Extract	1: *Salvia miltiorrhiza*, Rhizome and Root, Dry 3: Salvia Miltiorrhiza Root and Rhizome (BP) 3: Chinese Salvia (USP)	1: *Salvia miltiorrhiza*, Rhizome and Root, Soft Extract Ethanol-Water (90-10 {v/v}) (4,5–6,0:1)
	1) *Olea europaea* L., Fruit 3) *Olea europaea*, Fruit, Oil		1: *Olea europaea*, Fruit, Oil 3: Olive Oil, Virgin (Ph.Eur.) 3: Olive Oil, Refined (Ph.Eur.)

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Annex F
(informative)

Structurally Diverse Substance, Homeopathic substance

F.1 Introduction

F.1.1 Introduction

Homeopathic medicines are prepared from materials of botanical, chemical, mineral, or zoological origin. They are prepared, in Europe in accordance with a homeopathic manufacturing procedure described in the official pharmacopoeias currently used in the European Member States, - originally the French and the German national pharmacopoeia, now increasingly in the European Pharmacopoeia. The British Homeopathic Pharmacopoeia is also used in the UK. In the United States, homeopathic methods are established in the Homeopathic Pharmacopoeia of the United States (HPUS). Homeopathic medicines are also widely used in India (according to the Homeopathic Pharmacopoeia of India) and in Pakistan. Mexico has the Farmacopea Homeopática Mexicana and, Brazil the Farmacopeia Homeopática Brasileira. Homeopathy is also practiced in Australia and New Zealand.

F.1.2 Homeopathy and the use of homeopathic medicinal products

Homeopathy is a therapeutic system based on the so-called Similia-principle or the Law of Similars. It was founded by Samuel Hahnemann (1755-1843). He published this theory in the "Organon of the Healing Art". Homeopathic therapy and the production of homeopathic medicinal products has a long tradition in Europe (with development in Germany and in France), in the United States of America, India and in South America.

F.1.3 Legislation and regulatory requirements

Legislation and regulatory requirements are applied in different jurisdictions. For example, all Member States of the European Union are obliged to register homeopathic medicines pursuant to Directive 2001/82/EC (veterinary use) and 2001/83/EC (human use) - amended by Directive 2004/28/EC and Directive 2004/27/EC respectively - on the Community Code relating to medicinal products. Single homeopathic medicines that have been diluted above 1:10,000 may be registered according to a simplified registration procedure while more concentrated homeopathic medicines and those with specific therapeutic indications shall follow the market authorization regulation in a similar way to conventional drugs.

In the European Union in Directive 2001/83/EC on the Community Code relating to medicinal products for human use, a homeopathic medicinal product is defined as:

"Any medicinal product prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States. A homeopathic medicinal product may contain a number of principles".

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F.2 Manufacturing of homeopathic medicinal products/homeopathic references

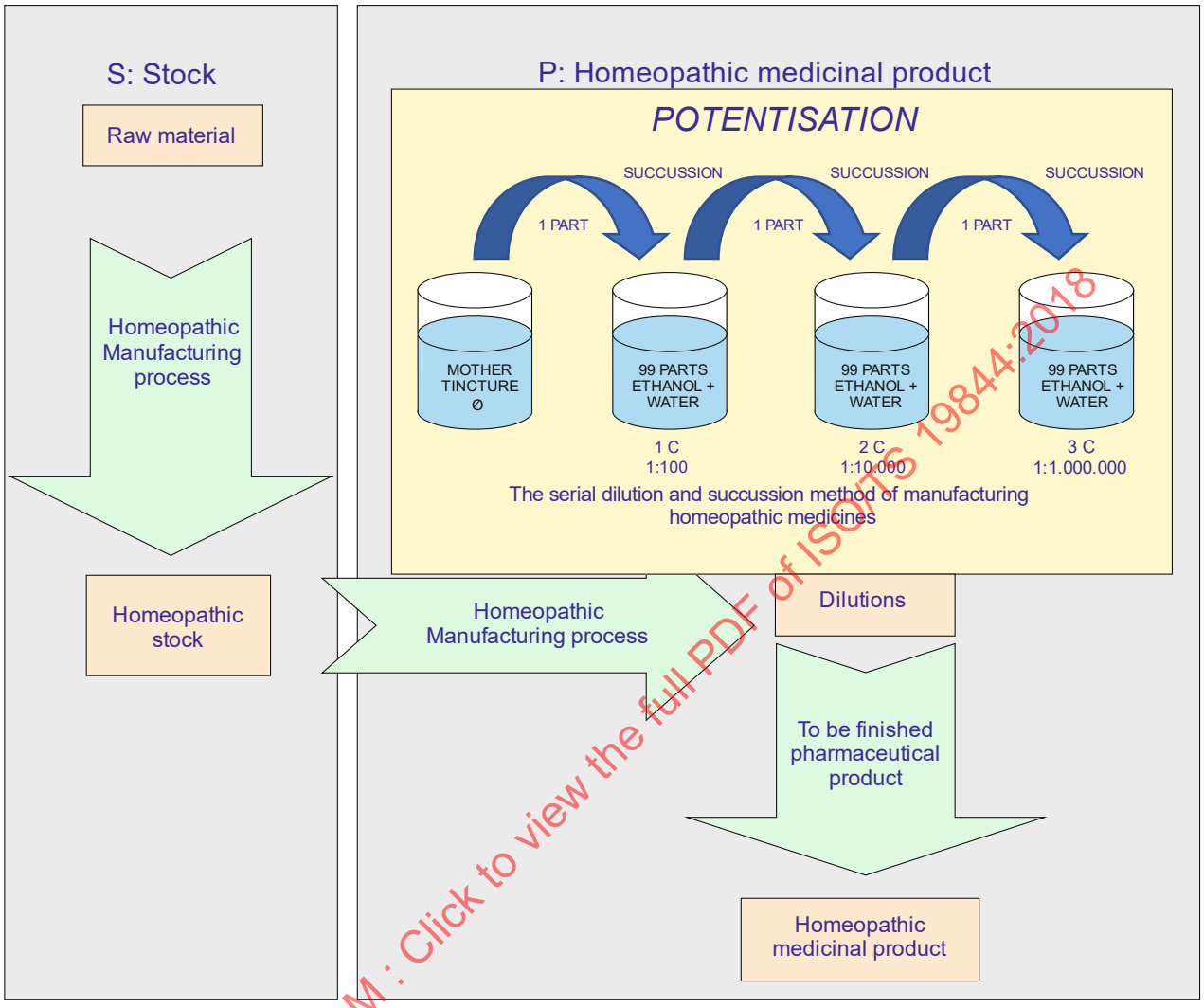


Figure F.1 — Preparation of Homeopathic medicinal product

F.2.1 Legislation and regulatory requirements

Some medicines in their crude state may be potentially toxic, and source materials are substantially diluted using a procedure known as potentization or dynamization.

This process involves successive dilutions and vigorous shaking (succussion) for liquid preparations and successive grinding (trituration) for solid preparations. The potentization process can be performed in various ways. Homeopathic potencies are usually designated by the combination of a number and a letter. The number refers to the number of successive dilutions to which the starting material has been subjected within a manufacturing procedure to prepare that remedy.

The letter refers to the scale on which the dilution has been carried out. There are several different scales, of which the decimal (1:10) and centesimal (1:100) scales are the most widely used. The letter D or X denotes the decimal method (i.e. 1 part of liquid is added to 9 parts of purified water, ethanol, glycerol or lactose). The letter C indicates the centesimal method (1 part added to 99 parts of diluent). Ø, MT or TM denotes mother tincture, the initial homeopathic preparation made from a source material from herbal or animal origin; this may be further potentized but may itself be used as a homeopathic medicine. Clean

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glassware (test tube and pipettes) is used for each dilusional stage. Other dilutional scales are also used. In the Korsakovian method (denoted K), a single piece of glassware is used; this is emptied and refilled, the liquid adhering to the walls of the vessel in which it is diluted – it is otherwise similar to the method above. In the 50 millesimal or quinquagintamillesimal dilution method (denoted LM or Q), dilution is in steps of approximately 1: 50 000; this is achieved by absorbing the dilution on to small lactose granules, which are then redissolved.

The process of potentization decreases the toxic properties. Although it is advisable to restrict the protracted use of low potencies (below D4 or C2) of some homeopathic medicines, homeopathic medicines in diluted form generally are considered safe to take and free of side effects (side effects should not be confused with homeopathic aggravation based on homeopathic theory: a transient harmless exacerbation of symptoms in response of treatment). Most homeopathic medicines by the nature of their non-toxicity are, in some countries, available over the counter, i.e. without a prescription.

F.3 Specific Definitions of Homeopathic Manufacturing

F.3.1 Homeopathic Stocks

Substances, products of preparations used as starting materials for the production of homeopathic preparations.

Note 1 to entry: A stock is usually one of the following: a mother tincture or a glycerol macerate, for raw materials of botanical, zoological or human origin, or the substance itself, for raw materials of chemical or mineral origin. [European Pharmacopoeia, monograph 1038, Homoeopathic preparations].

F.3.2 Homeopathic preparation

Preparations prepared from substances, products or preparations called stocks, in accordance with a homeopathic manufacturing procedure.

Note 1 to entry: A homeopathic preparation is usually designated by the Latin name of the stock, followed by an indication of the degree of dilution. For the purpose of dosage forms for homeopathic use, “active substances” are considered to be “dilutions or triturations of homeopathic stocks”. [European Pharmacopoeia, monograph 1038, Homoeopathic preparations].

F.3.3 Homeopathic Dilutions

process by which dilutions and triturations are obtained from homeopathic stocks in accordance with a homeopathic manufacturing procedure: this means successive dilutions and successions, or successive appropriate triturations, or a combination of the two processes

Note 1 to entry: The number of potentization steps defines the degree of dilution; for example, “D3”, “3DH” or “3X” means three decimal potentization steps (diluted 1:1000), and “C3” or “3CH” means three centesimal potentization steps (diluted 1: 1.000.000).

F.3.3.1 Decimal dilution/decimal potencies

The potentization steps are: 1 part of the stock plus 9 parts of the vehicle: designated as “D”, “DH” or “X” (decimal). Manufacturing methods are described in the European Pharmacopoeia monograph 2371

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(Methods of preparation of homoeopathic stocks and potentization), and in the Homeopathic Pharmacopoeia of the United States as "Decimal scale of attenuation".

F.3.3.2 Centesimal dilution/centesimal potencies

The potentization steps are: 1 part of the stock plus 99 parts of the vehicle: designated as "*C*" or "*CH*" (centesimal). Manufacturing methods are described in the European Pharmacopoeia monograph 2371 (*Methods of preparation of homoeopathic stocks and potentization*), and in the Homeopathic Pharmacopoeia of the United States as "*Centesimal scale of attenuation*".

F.3.3.3 LM – potencies

The LM potencies (symbol "LM") were the last scale of potencies developed by Samuel Hahnemann (1755-1842). They are also known as Q-potencies (*symbol* "*Q*") and 50 Millesimal potencies. The scale represents a serial dilution of 1:50,000 with each subsequent potency. The LM potencies are usually available in dry globules and the potency range is from LM1 to LM30. Unlike the mother tinctures that are used to prepare the first Decimal and Centesimal scale potencies, the first LM potency is prepared from the 3C trituration of the original drug substance. Potencies are made with a 50,000 dilution factor by alternate steps of liquid dilution and impregnation of sucrose pillules. Manufacturing methods are described in the German Homeopathic Pharmacopoeia - Homöopathisches Arzneibuch (HAB), and in the Homeopathic Pharmacopoeia of the United States as "*Fifty millesimal scale of attenuation*".

F.3.3.4 Korsakovian potencies

Homeopathic preparations that have been prepared using the so-called Korsakovian method: In the process of serial dilution/potentization only one container is used throughout the process. Each dilution factor corresponds to a ratio 1:100. Symbol: *K, CK*[55]. The manufacturing method is described in the Homeopathic Pharmacopoeia of the United States as "*Korsakovian attenuations – Single flask method of preparation*".

Table F.1

30 K	30 times 1:100 one glass method
200 K	200 times 1:100 one glass method
M K	1 000 times 1:100 one glass method
10M K (XMK)	10 000 times 1:100 one glass method
50M K (LMK)	50 000 times 1:100 one glass method
CMK	100 000 times 1:100 one glass method

[55] CK is described in British Homoeopathic Pharmacopoeia.

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F.3.3.5 Methods of preparation of homeopathic stocks and potentization

Definitions and description of methods of preparation of stocks and potentization are currently described in monograph 2371 of the European Pharmacopoeia (Methods of preparation of homoeopathic stocks and potentization) or in a pharmacopoeia currently used officially in one of the European Union Member States, e.g. the German Homeopathic Pharmacopoeia –or in the French Pharmacopoeia – Pharmacopée française. In the United States of America, corresponding methods are established in the HPUS. However, on a global scale, methods of preparation of homeopathic stocks and potentization are not fully harmonized.

NOTE

— There are several methods described in the Ph.Eur. monograph no 2371 under Ph.Eur. section 1.1.1 – 1.1.11 using mixtures of expressed juice and different percentages of ethanol as vehiculum to obtain the mother tincture or mixtures of fresh plant latex with ethanol mixtures.

— Methods described under Ph.Eur. section 2.1 – 2.2.4 using glycerol macerates used for maceration of raw materials of animal or herbal origin in glycerol (85 per cent).

— Methods described under Ph.Eur. section 3.1 – 3.1.3, 3.2.1 -3.2.3 using liquid dilutions used for dissolution of any suitable inorganic or organic starting material for minerals and venoms and which allows additives as mineral and organic acids when precipitation is observed in the final solutions or from triturations D4 and higher.

— Methods described under Ph.Eur. section 4.1 – 4.2 used for triturations, that is solid dilutions of raw materials or mother tinctures and solutions and a solid dry vehiculum, in most cases lactose monohydrate.

— Methods described under Ph.Eur. section 5.1 used for preparations by co-potentising 2 or more stocks and/or dilutions thereof, where co-potentization consists of mixing several stocks or dilutions of stocks then potentising them together in one or more potentization steps.

F.3.3.6 Mother Tincture

Mother tinctures for homeopathic preparations (*symbols: MT* from Mother tincture; *TM* from the French Teinture-mère; and the symbol Ø is the German Urtinktur) are liquid preparations obtained by the solvent action of a suitable vehicle upon raw materials. The raw materials are usually in the fresh form but may be dried. Mother tinctures for homeopathic preparations may also be obtained from plant juices, with or without the addition of a vehicle. For some preparations, the matter to be extracted may undergo a preliminary treatment. [Ph.Eur., monograph 2019 *Mother tinctures for homoeopathic preparations*]. In the Homeopathic Pharmacopoeia of the United States defined as *Tinctures or alcoholic solutions*.

F.3.3.7 Nosode

Homeopathic preparations made from products of human or animal disease processes, from pathogens or their metabolic products, from the decomposition products of animal organs, or from cultured micro-organisms (according to: *Points to consider on Safety of Homeopathic medicinal products from Biological origin, and to the German Homeopathic Pharmacopoeia, Chapter H, 5-2-5*).

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F.3.3.8 Potentization

Dilutions and triturations are obtained from stocks by a process of potentization in accordance with a homeopathic manufacturing procedure: this means successive dilutions and successions, or successive appropriate triturations, or a combination of the two processes.

F.3.3.9 Raw material

Raw materials for the manufacturing of homeopathic preparations may be of natural (botanical, zoological, mineral or human), or of synthetic origin (chemical). A raw material of botanical, zoological or human origin may be used either in the fresh state, or in the dried state. Raw materials of chemical or mineral origin are, at the same time, themselves considered as the homeopathic stock, according to the European Pharmacopoeia (*monograph Homeopathic preparations*).

F.3.3.10 Succussion

Process of agitating a liquid preparation in the manufacturing of homeopathic medicinal products.

Note 1 to entry: As intermediate step in the process of serial dilution, it is part of the potentization process.

F.3.3.11 Vehicle

Vehicles are excipients used for the preparation of certain stocks or for the potentization process.

Note 1 to entry: They may include, for example: purified water, ethanol of a suitable concentration, glycerol 85 per cent and lactose monohydrate. In Europe, vehicles comply with any requirement of the relevant monographs of the European Pharmacopoeia. [European Pharmacopoeia, monograph 1038 *Homoeopathic preparations*].

Note that ethanol of a suitable concentration is not to be considered as an extraction solvent when used to prepare a mother liquid. The mother liquid is defined as a liquid preparation obtained by the solvent action of a suitable vehicle.

Note 2 to entry: Vehicle description is in reference to homeopathy formulations and not in relation to other vehicles which are carriers or inert media used as solvent (diluent) in medicinally active agent formulations and or their administration.

F.3.4 Dosage Forms

A dosage form of a homeopathic preparation complies with any relevant dosage form monograph of the European Pharmacopoeia with the general Ph.Eur. Monograph 1038 Homoeopathic preparations, and with the following.

— For the purpose of dosage forms for homeopathic use, "*active substances*" are considered to be dilutions or triturations of homeopathic stocks or the stocks themselves.

— These dosage forms are prepared using appropriate excipients.

Homeopathic medicinal products are available in a range of oral dose forms: Tablets made of impregnated milk sugar (lactose); Globuli (pillules or granules) may be made of milk sugar or sucrose; Liquid preparations are solutions of the medication in water with some amount of alcohol added as a preservative.

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Other dosage forms used are: creams, gels, ointments, oral drops solutions, oral powders. In several countries, homeopathic medicinal products are also marketed as eye drops, ear drops, nasal sprays, suppositories or as solution for injection.

F.3.5 Homeopathic Stocks and Raw Materials

To estimate the exact number of substances and materials used for the manufacturing of homeopathic stocks is frankly impossible. This could be several thousands. The number of different stocks which can be considered well-known by homeopathic practitioners lies between 1 500 and 1 800. The number of different homeopathic remedies which are available and registered by regulatory authorities in the European Union is between 600 – 800. In homeopathic practice 200 – 400 different remedies are used on a regular basis.

F.3.6 Classification of Homeopathic Stocks and Homeopathic Dilutions (in accordance with ISO 11238 and ISO/TS 19844)

F.3.6.1 Homeopathic starting material

All homeopathic starting materials are considered as a substance belonging to one of the five Substances Types. The most important Substance Types for homeopathic substances are Chemical and Structurally Diverse material which are Herbals and Animal-derived material.

The Homeopathic Name as a synonym is captured at the substance information level with the Substance Name Type 'Homeopathic'.

The Homeopathic Name including the Homeopathic dilution shall be repeated at the Specified Substance Group 1 information level as a synonym with the Substance Name Type 'Specified Homeopathic.

F.3.6.2 Capturing Information at the Specified Substance Group 1 information level

All homeopathic stocks and dilutions are further described at the Specified Substance Group 1 information level with additional information regarding the Vehicle composition and the Dilution/Potentization.

F.3.6.3 Substance Dilution Potentization

Decimal, Centimal dilutions and LM dilutions shall be included in the Specified Substance Group 1 Information level.

F.3.6.3.1 Decimal dilution/decimal potencies

The potentization steps are: 1 part of the stock plus 9 parts of the vehicle: designated as "D", "DH" or "X" (decimal).

Reference: Manufacturing methods are described in the European Pharmacopoeia monograph 2371 (Methods of preparation of homoeopathic stocks and potentization) and in the Homeopathic Pharmacopoeia of the United States as "Decimal scale of attenuation".

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F.3.6.3.2 Centesimal dilution/centesimal potencies

The potentization steps are: 1 part of the stock plus 99 parts of the vehicle: designated as "C" or "CH" (centesimal).

Reference: Manufacturing methods are described in the European Pharmacopoeia monograph 2371 (Methods of preparation of homoeopathic stocks and potentization), and in the Homeopathic Pharmacopoeia of the United States as "Centesimal scale of attenuation".

F.3.6.3.3 LM – potencies

The LM potencies (*symbol* "*LM*"). They are also known as Q-potencies (*symbol* "*Q*") and 50 Millesimal potencies. The scale represents a serial dilution of 1:50 000 with each subsequent potency. The LM potencies are usually available in dry globules and the potency range is from LM1 to LM30. The first LM potency is prepared from the 3C trituration of the original drug substance. Potencies are made with a 50 000 dilution factor by alternate steps of liquid dilution and impregnation of sucrose pillules.

Reference: Manufacturing methods are described in the German Homeopathic Pharmacopoeia, and in the Homeopathic Pharmacopoeia of the United States as "*Fifty millesimal scale of attenuation*".

F.3.6.4 Vehicle

Definition: Vehicles are excipients used for the preparation of certain stocks or for the potentization process.

Valid values: e.g. purified water, ethanol of a suitable concentration, glycerol 85 per cent and lactose monohydrate.

Reference: Vehicle, as described under "Manufacturing methods in the European Pharmacopoeia monograph 2371 (*Methods of preparation of homoeopathic stocks and potentization*), and in the Homeopathic Pharmacopoeia of the United States as "Centesimal scale of attenuation", or as described in the Homöopathisches Arzneibuch, or in the French Pharmacopoeia (Pharmacopée Française).

Homeopathic stocks examples are provided in Table F.2 classified to the origin.

Table F.2 — Examples

Homeopathic stocks[a]	Scientific name	Homeopathic name
Botanical origin (Plantae):		
Chlorophyta (Green Algae) Rhodophyta (Red Algae)	*Fucus vesiculosus* L.	Fucus
Trachyophyta		
Equisetopsida (Horsetails)	*Equisetum arvense* L.	Equisetum arvense
Ginkgoopsida	*Ginkgo biloba* L.	Ginkgo biloba
Pinopsida (Conifers)	*Thuja occidentalis* L.	Thuja
Pinus	Oleum terebintinae	Terebintina

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Homeopathic stocks[a]	Scientific name	Homeopathic name
Gnetopsida	*Ephedra distachyia* L.	Ephedra vulgaris
Magnoliopsida	*Anamirta cocculus* (L.) Wight & Arn.	Cocculus
Fungi:		
Basidiomycota	*Amanita muscaria* (L.) Lam. (syn. Agaricus muscarius L.)	Agaricus muscarius
Ascomycota *Nosodes of Plants* (fungal pathogen of plants)	*Neonectria ditissima* (Tul. & C. Tul.) Samuels & Rossman (syn. Nectria ditissima Tul. & Tul.)	Nectrianium
Microbiological origin:		
Bacteria *Bacterial nosodes*	*Escherichia coli* (Migula 1895), Castellani and Chalmers 1919	Colibacillium
Viri (Viruses):[b] Orthopoxvirus:	Vaccinia virus, Cowpox virus	Vaccinium
Zoological origin (Animalia):[c]		
Porifera (Sponges)	*Spongia officinalis Linnaeus*, 1759 (syn. *Euspongia officinalis Linnaeus*, 1759)	Spongia tosta
Cnidaria(Coelenterata)	*Aurelia aurita Linnaeus*, 1758	Medusa
Annelida (Jointed Worms)	*Hirudo medicinalis Linnaeus*, 1758	Hirudo officinalis
Echinodermata (Echinoderms)	*Asterias rubens Linnaeus*, 1758	Asterias rubens
Arthropoda (Arthopodes)	*Araneus diadematus* Clerck, 1757	Aranea
Chordata (Vertebrates)	*Bufo bufo Linnaeus*, 1758	Bufo
Nosodes from zoological origin:	Horse Grease	Malandrinum
Chemical origin:		
Inorganic chemical substance	Kaliumdichromat	Kalium bichromicum
Organic chemical substance	Acidum aceticum	Aceticum acidum
Hormones	Cortisone	Cortisonum
Farmaca	Diazepam	Diazepam
Mineral origin:		
Natural minerals	Pyrit	Pyrit
Vulcanic lava	Ashes from Mount Hecla	Hekla lava
Mineral Waters	Seawater Water from a well	Aqua marina e.g. Carlsbad aqua
Mineral preparations	Black gunpowder	Gunpowder
Gemstones	Diamond	Adamas

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Homeopathic stocks[a]	Scientific name	Homeopathic name
Imponderabilia:		
Physical radiation	Moonlight	Luna

[a] See Bolte Angelika, Wichmann Jörg 2006 [34].

[b] http://ictvonline.org/virusTaxonomy.asp; (Vaccinia virus and Cowpox virus are separate species in the genus Orthopoxvirus).

[c] Zoologists use a different set of author abbreviations (e.g. Linnaeus rather than L.) and also include the date. Sometimes the author and date are in brackets, and sometimes not, even within the same database.

F.3.6.5 Organism Taxonomy of Structural Diverse Substance Type, e.g. Herbal and Zoological Organism

Substances of organic origin, such as plants and animals, should be defined simply by taxonomic information and the organism part. Taxonomic information, particularly the scientific name of an organism, is essential for defining such substances in medicinal products.

The Kew Gardens Medicinal Plant Names Services (MPNS) should be the authoritative source for all scientific names of plants and should also maintain a list of plant parts and fractions. A controlled vocabulary for medicinal plant taxonomy has been developed and will be maintained by the Kew Gardens Medicinal Plant Names Services.

The higher levels of taxonomy are useful but all levels above family are not required for organism definition. The primary definition of organism is the combination of genus and species together with describing author and family in that order providing validation. Intraspecific type and description and hybrid characteristics are also definitional where appropriate. The organism should be described as whole with no other characteristics. Because taxonomy is continuously changing, new organism identifiers should only be generated after analysing potential collisions with existing identifiers using the above public datasets and/or conferring with appropriate taxonomic experts. Developmental stage, part and viral strain characteristics should be associated with separate identifiers that refer back to the whole organism parent substance.

For Herbals, the organism and part defines the source material at the Substance information level, Element Group Source Material.

A Substance is always a single species, or intraspecies, or is occasionally a single genus. The fresh, unprocessed plant material is captured as the Substance (fresh), with a name which is composed of: [Scientific genus/binomial/trinomial with Author], [Part(s)]. It has no affiliation to any particular pharmacopoeia or medicinal product.

The Herbal Drug, which is minimally processed, usually dried or sometimes fresh is the Substance (Herbal Drug), with a name composed of: [Scientific genus/binomial/trinomial without author], [Part(s)].

The processed Herbal preparation is the Substance (Herbal preparation), with a name composed of: [Scientific genus/binomial/trinomial without author], [Part(s)], [Fraction].

NOTE The terminology 'Herbal preparation' is not used as such in the terminology of homeopathic substances, but the description of the vehicle and the potentization is captured in the Specified Substance Group 1 Name used for Homeopathic substances.

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The Herbal Drug Ginkgo Leaf (Ph.Eur.) is defined as the whole or fragmented, dried leaf of *Ginkgo biloba* L., and is captured at the Substance level as the Substance (Herbal Drug) *Ginkgo biloba*, Leaf. Fresh leaf of *Ginkgo biloba* L. is also captured at the Substance level, and is the parent substance of such a Herbal Drug.

Example of a Substance (fresh):

Substance ID: 19FUJ2C58T (Artificial ID)
Substance (fresh) Name: *Ginkgo biloba* L., Leaf
The scientific name part (from the Organism Name) is: *Ginkgo biloba* L. [L. stands for the author Linnaeus]

Element Group: Part Description
Part: Leaf

The full taxonomy is captured by the elements of the classes Organism, Organism General and Author:
Element Group: Organism
Family: Ginkgoaceae
Genus: Ginkgo
Species: Biloba

Element Group Author:
Author Type: Species Primary Author
Author Description: L. (Linnaeus)

Element Group: Organism General
Kingdom: Plantae
Phylum: Tracheophyta
Class: Ginkgoopsida
Order: Ginkgoales

Example of a Substance described in a pharmacopoeia (Herbal Drug):

Substance ID: 45SPM3HJ6Q (Artificial ID)
Substance (Herbal Drug) Name: *Ginkgo biloba*, Leaf
Parent Substance ID: 19FUJ2C58T
Parent Substance (fresh) Name: *Ginkgo biloba* L., Leaf
For further information and examples see Annex E.

F.3.7 Capturing of the Homeopathic medicine (Stock. Dilution Grade, Dilution method)

F.3.7.1 Substance information level: (Homeopathic Substance)

— **Substance (fresh) ID**

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— **Substance (fresh) Name**: In accordance with the Substance Types Structurally diverse and chemical

e.g. Scientific Name with Author, and Part (see Annex E) or Chemical Name when appropriate. For Botanical derived source material, this will be read as:

<Scientific genus/binomial/trinomial with Author>, <Part(s)>

— Element Group: Source Material: (Capturing Homeopathic Raw Material)

— Element Group: Organism

— Element Group: Part Description (when applicable).

— **Substance (Herbal/Homeopathic Drug) ID**

— **Substance (Herbal/Homeopathic Drug) Name**: In accordance with the Substance Types Structurally diverse and chemical e.g.

Scientific Name without Author, and Part (See Herbal Annex E) or Chemical Name when appropriate.

For Botanical derived source material, this will be as:

<Scientific genus/binomial/trinomial without Author>,<Part(s)>

Substance Name (Repeat):

Homeopathic Name with the Name Type value 'Homeopathic' for the US/EU Jurisdiction

Element Group: Source Material: (Capturing Homeopathic stock)

Element Group: Code

F.3.7.2 Specified Substance Group 1: (Herbal)

— **Specified Substance Group 1 ID**

— **Specified Substance Group 1 Name (Botanical origin)**:

<Scientific Name without Author> <Part>< Dry/Fresh><vehicle>< dilution method>

< dilution>

or:

Specified Substance Group 1 Name (Chemical):

<Chemical Name, mineral> <vehicle><dilution method><dilution>

Substance Name (Repeat):

Specified Homeopathic Name with the Name Type value 'Specified Homeopathic' for the US/EU Jurisdiction.

Vehicle is described as a Substance Role in the element group Constituent.

Element Group: Constituent

Constituent Substance ID: [this is the ID of the Substance (Homeopathic drug) or Substance (fresh) or the substance used as a vehicle].

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Constituent Substance Name: [this is the Name for the Substance (Homeopathic drug) or Substance (fresh) or name of the substance used as vehicle].

Substance Role: [this is the role of the substance and may have the value 'Parent' or Vehicle].

Is Defining (yes/no): [this element is to specify if the Constituent described is considered defining element for the Specified Substance].

Homeopathic Dilution/ Potentization

The Substance Dilution (potentization) grade is described as a Characteristic Attribute Name with the value 'Substance Dilution Grade' and in combination with the Element Group Amount, see Figure 35 and the tables with examples in clause F.4.

Element Group: Characteristic Attribute

The 'Attribute Type' for homeopathic substances has the value 'Particular Homeopathic'. The 'Attribute Name' for this attribute type value is 'Substance Dilution Potentization Grade' and in combination with the Element Group 'Amount', the homeopathic strength is described by 'amount' (number of dilution) and by 'unit' (Dilution method e.g. DH (Decimal), see Figure 35.

F.3.7.3 Specified Substance Group 2

— **Specified Substance Group 2 ID**

— **Specified Substance Group 2 Name (Herbal/Homeopathic substance or specified substance in a 1:1 relation with the manufacturer of the substance or specified substance):**

<Scientific Name without Author> <Part>< Dry/Fresh><vehiculum>< dilution method>

< dilution>– Manufacturer

Or:

Specified Substance Group 2 Name (Chemical):

<Chemical Name, mineral> <vehiculum><dilution method><dilution> - Manufacturer)

Element Group: Manufacturing

— Manufacturing high-level information and sometimes details

— Production Method Description

NOTE When the manufacturing information is within the Public Domain, then the Public Domain attribute has the value <Yes> in the Element Group Reference Source information attached to the Specified Substance Group 2 information. When the manufacturing information is confidential the value of the Public Domain attribute has the value <No> in the Element Group Reference Source information attached to the Specified Substance Group 2 information. Manufacturing information as published in a Pharmacopoeia or in literature is considered public information; see the Specified Substance Group 2 example in F.4.2.

Element Group: Organization

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The information is sourced in accordance with the organizations in ISO 11615 as implemented within the regional requirements, e.g. for Europe this could be the EMA OMS service and for the US the Chamber of Commerce. See Figure 36.

F.3.7.4 Specified Substance Group 3:

Specified Substance Group 3 ID

Specified Substance Group 3 Name (Herbal/Homeopathic substance or specified substance):

<Scientific Name without Author> <Part>< Dry/Fresh><vehiculum>< dilution method> < dilution>–ref. Pharmacopoeia

Or:

Specified Substance Group 3 Name (Chemical): <Chemical Name, mineral><vehicle><dilution method><dilution>-ref. Pharmacopoeia), see Figure 38.

Element Group: Grade

Grade Type: Pharmacopoeial specification e.g. USP/Ph.Eur.

Grade Name = Name in accordance with the Pharmacopoeia

The Element Group '**Reference Source**' is used to refer to the Pharmacopoeial monograph or to the *In-House monograph*. The Element Group '**Reference Source Document**' is used to capture the monograph or *In-House* specifications as a (pdf) document.

The classes 'Vehicle' and 'Substance Dilution Potentization', as described in the ISO/TS 19844:2016[1] have been replaced by the harmonized general classes 'Constituent' and 'Characteristic Attribute'. The Vehicle is related and mapped to the Substance Role of a constituent. The Substance Dilution Potentization is mapped to the Characteristic Attribute with the name Substance Dilution Potentization Grade and in combination of the Element Group Amount and the attribute unit (e.g. DH, decimal) the homeopathic strength is described.

F.3.8 Nomenclature of Homeopathic Medicines

Regardless the huge variety of substances which are traditionally used for the manufacturing of homeopathic medicinal products, the nomenclature of all these homeopathic stocks is simple: designation by the scientific name, followed by the potency which consists of the number of dilution steps, related to the symbol reflecting the method of diluting and succession.

F.3.9 Nomenclature of Homeopathic Medicines

Homeopathic medicine	*Scientific name of stock*	*Dilution grade*	*Dilution method*
Aurum metallicum 6 X	Aurum metallicum	6	X (decimal)
Arnica montana 30C	Arnica montana L.	30	C (centisimal)

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Figure F.2 — Name: Aurum metallicum; Potentization steps: 6 Dilution method: X (decimal 1:10)



Figure F.3 — Name: Arnica montana; potentization steps: 30: Dilution method: C (centesimal 1:100)

In Figure F.4 an example is given from the registration dictionaries of the FDA. At the substance level, the Substance Ingredient name is provided accompanied with the Identifier UNII. In the column 'Strength,' the dilution and the dilution method are provided.

ACTIVE INGREDIENT/ACTIVE MOIETY		
Ingredient Name	**Basis of Strength**	**Strength**
ACONITUM NAPELLUS (UNII: U0NQ8555JD) (ACONITUM NAPELLUS – UNII: U0NQ8555JD)	ACONITUM NAPELLUS	30 [hp_C] In 30 [hp_C]
ARSENIC ACID (UNII: N7CIZ75ZPN) (ARSENIC ACID – UNII: N7CIZ75ZPN	ARSENIC ACID	30 [hp_C] In 30 [hp_C]
ASARUM CANADENSE ROOT (UNII: E2O4O7TQYK) (ASARUM CANADENSE ROOT – UNII: E2O4O7TQYK	ASARUM CANADENSE ROOT	30 [hp_C] In 30 [hp_C]
CONIUM MACULALATUM FLOWERING TOP (UNII: Q28R5GF371) (CONIUM MACULATUM FLOWERING TOP – UNII: Q28R5GF371	CONIUM MACULALATUM FLOWERING TOP	30 [hp_C] In 30 [hp_C]

Figure F.4 — The Ingredient, basis of strength and the strength are provided for a homeopathic medicinal product in accordance with the current FDA-GSRS

F.3.10 Nomenclature according to homeopathic tradition

In spite of the use of well-defined raw materials for homeopathic use, and chemical and mineral substances which are well characterized, several homeopathic stocks still are named according to the traditional homeopathic names, some of them established in the 19th century. Neither in Europe, nor globally, a fully harmonized and recognized Nomenclature for homeopathic substances exists. The growing number of Monographs in the European Pharmacopoeia of materials and stocks "for homeopathic use" are established under scientific titles (English/French).

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Table F.3

Homeopathic medicine	*Scientific name*	*Traditional name used in homeopathy*	*Dil. Grade*	*Dil. Method*
Arsenicum album 30 C	Arsenic trioxide	Arsenicum album	30	C (centisimal)
Anacardium orientale 200 K	*Semecarpus anacardium* L.f. (syn. Anacardium orientale Steud.)	Anacardium orientale	200	K (Korsakovian)



Figure F.5 — Example of homeopathic medicine/product: Arsenicum album 30 C

F.3.11 Nomenclature according to homeopathic tradition

Table F.4 — Classification homeopathic stock to the origin

Origin:	**Raw material/stock:**	**Nomenclature**
Botanical origin: Plants	Plant material – fresh or dry, whole, fragmented or cut plants, parts of plants including algae, fungi or lichens.	The scientific name – genus, species, variety, author, part.
Biological origin: Animals	Zoological material or pathological material from zoological origin.	The scientific (animal) name – genus, species, tissue(s), fluid(s), organ(s) or parts of organ(s).
Chemical origin: Minerals	Chemical/mineral material	Chemical Name, Systematic name
Chemical origin: Chemicals	Organic compounds Inorganic compounds Pharmacological active substances	International nonproprietary name (INN)
Biological origin: Human tissue	Human material or pathological material from human origin.	The scientific (anatomical) name – tissue(s), fluid(s), organ(s) or parts of organ(s).

The following information should be captured:

— the scientific name of the homeopathic ingredient/homeopathic stock;

— the “traditional homeopathic” name, when mentioned on the label;

— the grade of dilution/potentization steps;

— the method of dilution/potentization, related to the used symbol;

— reference to the (Homeopathic) Pharmacopoeia where the method of manufacturing of the stock, is described;

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— reference to the (Homeopathic) Pharmacopoeia where the method of dilution/potentization, is described;

— name of the manufacturer.

F.4 Examples in tabular format

F.4.1 Structured information of material combining the elements for Arnica montana 6DH, Substance of botanical origin according to the French tradition

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	HOM1234GDA (Artificial ID)	II	
Substance Type	Structurally Diverse	CD	
Element Group: Substance Name			
Substance (fresh) Name	*Arnica montana* L., Whole Plant	ST	1)
Substance Name Type	Other	CD	
Language	en	CD	
Substance Name Domain	Drug, Homeopathic	CD	
Jurisdiction	EU	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	PhF	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Pharmacopée française	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Arnica montana	ST	
Substance Name Type	Homeopathic	CD	
Language	la	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	PhF	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	

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Element Name	Value	Data Format	Note #
Reference Source Type	PhF, Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Pharmacopée française, European Pharmacopoeia	ST	
Element Group: Substance Code			
Code	O80TY208ZW	CD.Code	
Code System	FDA Substance Registration (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Source Material			
Source Material Class	Botanical	CD	
Source Material Type	Plant	CD	
Organism ID	CVFSE6753H (Artificial ID)	II	
Organism Name	*Arnica montana* L.	ST	
Development Stage	Adult	CD	
Element Group: Organism			
Family	*Asteraceae*	CD	
Genus	*Arnica*	CD	
Species	*montana*	CD	
Element Group: Author			
Author Type	Species primary author	CD	
Author Description	L.	ST	
Element Group: Organism General			
Kingdom	Plantae	CD	
Phylum	Tracheophyta	CD	
Class	Magnoliopsida	CD	
Order	Asterales	CD	
Element Group: Part Description			
Part	Whole Plant	CD	2)
Element Group: Specified Substance Group 1			
Specified Substance Group 1 ID	HOMGHFTE67 (Artificial ID)	II	

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Element Name	Value	Data Format	Note #
Element Group: Substance Name			
Substance Name	*Arnica montana*, Whole Plant, Fresh, Ethanol 30 % {v/v}, dil. 6DH	ST	
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Homeopathic	CD	
Jurisdiction	EU	CD	
Element Group: Substance Name (Repeat)			
Substance Name	Arnica montana DH 6	ST	
Substance Name Type	Specified Homeopathic	CD	
Language	la	CD	
Substance Name Domain	Homeopathic	CD	
Jurisdiction	EU	CD	
Element Group: Official Name			
Official Name Type	PhF, Ph.Eur.	CD	
Official Name Status	Current	CD	
Element Group: Constituent			
Constituent Substance ID	HOM1234GDA (Artificial ID)	II	
Constituent Substance Name	*Arnica montana* L., Whole Plant	ST	
Language	en	CD	
Substance Role	Parent Substance	CD	
Is Defining	Yes	BL	
Element Group: Characteristic Attribute			
Attribute Type	Particular Homeopathic	CD	
Attribute Name	Substance Dilution Grade	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Average	6	PQ	
Unit	DH (Decimal)	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	ETHAN98765 (Artificial ID)	II	

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Element Name	Value	Data Format	Note #
Constituent Substance Name	Ethanol	ST	
Language	en	CD	
Substance Role	Vehicle	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Average	30	PQ	
Unit	Volume per cent	CD	
Amount Text	Ethanol 30 % {v/v}	ST	
Element Group: Constituent (Repeat)			
Constituent Substance ID	WATERP67543 (Artificial ID)	II	
Constituent Substance Name	Water	ST	
Language	en	CD	
Substance Role	Vehicle	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	70	PQ	
Unit	% {v/v}	CD	
Amount Text	Ethanol 30 % {v/v}	ST	
Element Group: Specified Substance Group 2			
Specified Substance Group 2 ID	HOMYRT76452	II	
Element Group: Substance Name			
Substance Name	*Arnica montana,* Whole Plant, Fresh, Ethanol 30 %{v/v}, dil. 6DH – COMPANY BB	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	HOMGHFTE67 (Artificial ID)	II	3)
Element Group: Manufacturing			
Manufacturer Type	Manufacturer	CD	
Production Method Type	Extraction and Potentization	CD	
Production Method Description	Mother tinctures prepared according to Ph. Eur. Method 1.1.10 are prepared by	ST	

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Element Name	Value	Data Format	Note #
	maceration using 1 part of Herbal Drug and 10 parts of ethanol of the appropriate concentration. Generally used for Herbal Drugs (fresh or dried).		
Version	HOM-001	ST	
Version Date	20170904	TS.Date	
Element Group: Organization			
Manufacturer ID	LABOY87654 (Artificial ID)	II	
Manufacturer Name	COMPANY BB	ST	
Issuer of ID	EMAOMS	CD	
Manufacturer Role	Substance Manufacturer	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph. Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur., monograph 01/2011: 2371	ST	
Element Group: Reference Source (Repeat)			
Public Domain	Yes	BL	
Reference Source Type	PhF	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Pharmacopée française, Monograph	ST	
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	HOMGHFE674 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Arnica montana*, Whole Plant, Fresh, Ethanol 30 % {v/v}, dil. 6DH, for Homeopathic Preparations–Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	HOMGHFTE67 (Artificial ID)	II	3)
Element Group: Grade			
Grade Type	PhF	CD	
Grade Name	Arnica (plante entire) pour preparations homéopathiques	ST	

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Element Name	Value	Data Format	Note #
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia monograph. 2371 (Methods of preparation of homoeopathic stocks and potentization) method 1.1.10	ST	

NOTE 1 Captured for the Substance (fresh) which is the Parent substance of this Substance (Herbal/Homeopathic drug).

NOTE 2 Plant Part (controlled vocabulary terms used to specify exactly which parts are used): e.g. Flower, Fruit, Leaf, Root, Stem). Whole Plant (Plantae Tota) is a value for homeopathic stock (see F.3.5).

NOTE 3 This (Parent) Substance ID corresponds to The (Specified) Substance (Group 1) Name : *Arnica montana*, Whole Plant, Fresh, Ethanol 30 %{v/v}, dil. 6DH.

F.4.2 Structured information of material, combining the elements for Arnica montana D6, Substance of botanical origin according to the German tradition

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	HOM56432G1 (Artificial ID)	II	
Substance Type	Structurally Diverse	CD	
Element Group: Substance (Homeopathic drug) Name			
Substance Name	*Arnica montana*, Root	ST	1)
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Substance Official Name			
Official Name Type	HAB	CD	2)
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	HAB	CD	2)
Reference Source Class	Official Name Source	CD	

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Element Name	Value	Data Format	Note #
Reference Source Citation	Homöopathisches Arzneibuch	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Arnica montana	ST	
Substance Name Type	Homeopathic	CD	
Language	la	CD	
Substance Name Domain	Drug, Homeopathic	CD	
Jurisdiction	EU, US	CD	
Element Group: Substance Official Name			
Official Name Type	HAB	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	HAB	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Homöopathisches Arzneibuch	ST	
Element Group: Substance Code			
Code	O80TY208ZW	CD.Code	
Code System	FDA Substance Registration (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Source Material			
Source Material Class	Botanical	CD	
Source Material Type	Plant	CD	
Organism ID	CVFSE6753H (Artificial ID)	II	
Organism Name	*Arnica montana* L.	ST	
Parent Substance ID	HOM90867AR (Artificial ID)	II	
Parent Substance Name	*Arnica montana* L., Root	ST	
Development Stage	Mature plant stage	CD	
Element Group: Organism			
Family	*Asteraceae*	CD	

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Element Name	Value	Data Format	Note #
Genus	*Arnica*	CD	
Species	*montana*	CD	
Element Group: Author			
Author Type	Species primary author	CD	
Author Description	L.	ST	
Element Group: Organism General			
Kingdom	Plantae	CD	
Phylum	Tracheophyta	CD	
Class	Magnoliopsida	CD	
Order	Asterales	CD	
Element Group: Part Description			
Part	Root	CD	1)
Element Group: Specified Substance Group 1			
Specified Substance Group 1 ID	HOMHJGT675 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Arnica montana*, Root, Dry, Ethanol 50 %{v/v}, dil. D6	ST	
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU	CD	
Element Group: Substance Name (Repeat)			
Substance Name	Arnica montana DH 6	ST	
Substance Name Type	Specified Homeopathic	CD	
Language	la	CD	
Substance Name Domain	Drug, Homeopathic	CD	
Jurisdiction	EU	CD	
Element Group: Official Name			
Official Name Type	PhF, Ph.Eur.	CD	3), 4)
Official Name Status	Current	CD	
Element Group: Constituent			
Constituent Substance ID	HOM56432G1 (Artificial ID)	II	
Constituent Substance Name	*Arnica montana*, Root	ST	

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Element Name	Value	Data Format	Note #
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Characteristic Attribute			
Attribute Type	Particular Homeopathic	CD	
Attribute Name	Substance Dilution Grade	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	6	PQ	
Unit	DH (Decimal)	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	ETHAN98765 (Artificial ID)	II	
Constituent Substance Name	Ethanol	ST	
Language	en	CD	
Substance Role	Vehicle	CD	
Is Defining	Yes	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	50	PQ	
Unit	% {v/v}	CD	
Amount Text	Ethanol 50 % {v/v}	ST	
Element Group: Constituent (Repeat)			
Constituent Substance ID	WATERP67543 (Artificial ID)	II	
Constituent Substance Name	Water	ST	
Language	en	CD	
Substance Role	Vehicle	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	50	PQ	
Unit	% {v/v}	CD	

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Element Name	Value	Data Format	Note #
Amount Text	Ethanol 50 % {v/v}	ST	
Element Group: Specified Substance Group 2			
Specified Substance Group 2 ID	HOMHJF764P (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Arnica montana*, Root, Dry, Ethanol 50 %{v/v}, dil. D6–COMPANY CC	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	HOMHJGT675 (Artificial ID)	II	5)
Element Group: Manufacturing			
Manufacturer Type	Manufacturer	CD	
Production Method Type	Extraction and Potentization	CD	
Production Method Description	Mother tinctures prepared according to Ph. Eur. method 1.1.8 are prepared by maceration or percolation, using 1 part of dried Herbal Drug and 10 parts of ethanol of the appropriate concentration. Generally used for dried Herbal Drugs.	ST	
Version	ABCD-001	ST	
Version Date	20170901	TS.Date	
Element Group: Organization			
Manufacturer ID	HJD56432VS (Artificial ID)	II	
Manufacturer Name	COMPANY CC	ST	
Issuer ID	EMA OMS	CD	
Manufacturer Role	Substance Manufacturer	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur., monograph 01/2011: 2371	ST	
Element Group: Reference Source (Repeat)			
Public Domain	Yes	BL	
Reference Source Type	HAB	CD	
Reference Source Class	Official Name Source	CD	

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Element Name	Value	Data Format	Note #
Reference Source Citation	Homöopathisches Arzneibuch, Monograph	ST	
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	HOM67432US (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Arnica montana*, Root, Dry, Ethanol 50 %{v/v}, dil. D6, for Homeopathic Preparations–Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	HOMHJGT675 (Artificial ID)	II	5)
Element Group: Grade			
Grade Type	HAB	CD	
Grade Name	Arnica montana	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia monograph 2371 (methods of preparation of homoeopathic stocks and potentization), 1.1.8 (equivalent to HAB 4a: Mother tinctures and liquid dilutions)	ST	

NOTE 1 Plant Part (CV terms used to specify exactly which parts are used): e.g. Flower, Fruit, Leaf, Root, Stem.

NOTE 2 HAB (Homöopathisches Arzneibuch, ambtliche Ausgabe).

NOTE 3 PhF (Pharmacopée française).

NOTE 4 Ph.Eur. (European Farmacopeia), (Pharmacopée European).

NOTE 5 This (Parent) Substance ID corresponds to the (Specified) Substance (Group 1) Name : *Arnica montana*, Root, Dry, Ethanol 50 %{v/v}, dil. D6.

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F.4.3 Structured information of material, combining the elements for Arsenicum album C30 Substance of chemical origin according to the German tradition

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	ASO56432TY (Artificial ID)	II	
Substance Type	Chemical	CD	

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Element Name	Value	Data Format	Note #
Element Group: Substance Name			
Substance Name	Arsenic trioxide	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	Martindale	CD	
Official Name Status	Primary	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Martindale	CD	
Reference Source Class	Official Name Source	CD	
Reference Source URL	https://www.medicinescomplete.com/mc/martindale/current/12396-y.htm?q=Arsenic%20trioxide&t=search&ss=text&p=4#_hit	ST	1)
Element Group: Substance Name (Repeat)			
Substance Name	Arsenicum album	ST	
Substance Name Type	Homeopathic	CD	
Language	la	CD	
Substance Name Domain	Drug, Homeopathic	CD	
Jurisdiction	EU, US	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	HAB	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Homöopathisches Arzneibuch	ST	
Element Group: Substance Code			
Code	1327-53-3	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	

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Element Name	Value	Data Format	Note #
Element Group: Substance Code (Repeat)			
Code	S7V92P67HO	CD.Code	
Code System	FDA Substance Registration System (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	L01XX27	CD.Code	
Substance Classification Type	Other antineoplastic agents, Arsenic trioxide	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source	Web	CD	
Reference Source Class	Literature	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=L01XX27	ST	
Element Group: Structure			
Stereochemistry	Achiral	CD	
Molecular Formula	As_2O_3	ST	
Element Group: Structure Representation			
Structural Representation Type	Full	CD	
Structural Representation	[As] 2 . [O] 3	ST	
Element Group: Structure Representation (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation	InChI=1S/As2O3/c3-1-4-2(3)5-1	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Class	Literature	CD	

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Element Name	Value	Data Format	Note #
Reference Source URL	http://www.chemspider.com/Chemical-Structure.452539.html	ST	
Element Group: Structure			
Structural Representation Type	Full	CD	
Structural Representation	[As] 2 . [O] 3	ST	
Element Group: Structure (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation	InChI=1S/As2O3/c3-1-4-2(3)5-1	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Class	Literature	CD	
Reference Source URL	http://www.chemspider.com/Chemical-Structure.452539.html	ST	
Element Group: Reference Source (Repeat)			
Public Domain	Yes	BL	
Reference Source Type	Martindale	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Martindale, Current edition	ST	
Element Group: Chemical			
Stoichiometric	Yes	BL	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	197,8	PQ	
Unit	g/mol	CD	
Element Group: Specified Substance Group 1			
Specified Substance Group 1 ID	ASG5632TYE (Artificial ID)	II	

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Element Name	Value	Data Format	Note #
Element Group: Substance Name			
Substance Name	Arsenic trioxide dil. C30, ethanol 43% (w/w)	ST	
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU	CD	
Element Group: Substance Name (Repeat)			
Substance Name	Arsenicum album C30	ST	
Substance Name Type	Specified Homeopathic	CD	
Language	la	CD	
Substance Name Domain	Drug, Homeopathic	CD	
Jurisdiction	EU	CD	
Element Group: Official Name			
Official Name Type	HAB	CD	
Official Name Status	Current	CD	
Element Group: Constituent			
Constituent Substance ID	ASO56432TY (Artificial ID)	II	
Constituent Substance Name	Arsenic trioxide	ST	
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Characteristic Attribute			
Attribute Type	Particular Homeopathic	CD	
Attribute Name	Substance Dilution Grade	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	30	PQ	
Unit	C (Centisimal)	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	ETHAN98765 (Artificial ID)	II	

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Element Name	Value	Data Format	Note #
Constituent Substance Name	Ethanol	ST	
Substance Role	Vehicle	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	43	PQ	
Unit	%{w/w}	CD	
Amount Text	Ethanol 43 % (w/w)	ST	
Element Group: Constituent (Repeat)			
Constituent Substance ID	WATERP67543 (Artificial ID)	II	
Constituent Substance Name	Water	ST	
Language	en	CD	
Substance Role	Vehicle	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	57	PQ	
Unit	%{w/w}	CD	
Amount Text	Ethanol 43 % (w/w)	ST	
Element Group: Specified Substance Group 2			
Specified Substance Group 2 ID	ASG45389T (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Arsenic trioxide dil. C30, ethanol 43 % (w/w) – COMPANY DD	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	ASG5632TYE (Artificial ID)	II	2)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Chemical solubility and Potentization	CD	

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Element Name	Value	Data Format	Note #
Production Method Description	Preparation according to HAB monograph Acidum arsenicosum: D2=Ø is prepared by adding 1 part of raw material to 90 parts aqua purificata and heated to boiling until all the material has been dissolved. The solution is filtered, the filtrate filled up with 90 parts aqua purificata. After cooling down 10 parts of ethanol 86 % (w/w) are added. The D3 is prepared with ethanol 15 % (w/w) and the following potencies are prepared with ethanol 43 % (w/w).	ST	
Version	DEFG-001	ST	
Version Date	20170904	TS.Date	
Element Group: Organization			
Manufacturer ID	HJD56432VS (Artificial ID)	II	
Manufacturer Name	COMPANY DD	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer of the specified substance	CD	
Element Group: Reference Source			
Public Doain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur., monograph 01/2011: 2371	ST	
Element Group: Reference Source (Repeat)			
Public Doain	Yes	BL	
Reference Source Type	HAB	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Homöopathisches Arzneibuch, ambtliche Ausgabe, monograph of Acidum arsenicosum	ST	
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	ASGHFRS563 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Arsenic trioxide dil. C30, ethanol 43 % (w/w) for Homeopathic Preparations – Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	

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Element Name	Value	Data Format	Note #
(Parent) Substance ID	ASG5632TYE (Artificial ID)	II	2)
Element Group: Grade			
Grade Type	HAB	CD	
Grade Name	Arsenicum album C30 for homeopathic preparations	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia monograph 1599	ST	
Element Group: Reference Source (Repeat)			
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Homöopathisches Arzneibuch, ambtliche Ausgabe, monograph of Acidum arsenicosum	ST	

NOTE 1 This is a Subscription database.

NOTE 2 This (Parent) Substance ID referrs to the (Specified) Substance (Group 1) Name: Arsenic trioxide dil. C30, ethanol 43 % (w/w).

F.4.4 Structured information of material, combining the elements for Lachesis 200K, Substance of zoological origin according to the Korsakovian dilution method

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	HOM67453LA (Artificial ID)	II	
Substance Type	Structurally Diverse	CD	
Element Group: Substance (Homeopathic drug) Name			
Substance Name	*Lachesis muta*, Venom	ST	1)
Substance Name Type	Other	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Substance (Homeopathic drug) Name (Repeat)			
Substance Name	*Lachesis muta* Linnaeus, 1766	ST	1)
Substance Name Type	Scientific	CD	
Language	la	CD	
Substance Name Domain	Drug	CD	

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Element Name	Value	Data Format	Note #
Jurisdiction	EU, US	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	HPUS	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Homeopathic Pharmacopoeia of the United States	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Lachesis muta	ST	
Substance Name Type	Homeopathic	CD	
Language	la	CD	
Element Group: Official Name			
Official Name Type	HAB	CD	
Official Name Status	Primary	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	HAB	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Homöopathisches Arzneibuch	ST	
Element Group: Substance Code			
Code	VSW71SS07I	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Source Material			
Source Material Class	Organic	CD	
Source Material Type	Animal	CD	
Organism ID	ANJ65348FD (Artificial ID)	II	
Organism Name	*Lachesis muta* Linnaeus, 1766	ST	
Development Stage	Adult	CD	
Element Group: Organism			

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Element Name	Value	Data Format	Note #
Family	*Viperidae*	CD	
Genus	*Lachesis*	CD	
Species	*muta*	CD	
Element Group: Author			
Author Type	Species primary author	CD	
Author Description	Linnaeus, 1766	ST	
Element Group: Organism General			
Kingdom	Animalia	CD	
Phylum	Chordata	CD	
Class	Reptilian	CD	
Order	Squamata	CD	
Element Group: Part Description			
Part	Venom	CD	
Element Group: Specified Substance Group 1			
Specified Substance Group 1 ID	HOM56243DS (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Lachesis muta*, Venom, Dried, Ethanol 43 % (w/w), dil. 200K	ST	
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Element Group: Substance Name (Repeat)			
Substance Name	Lachesis muta K 200	ST	
Substance Name Type	Specified Homeopathic	CD	
Language	la	CD	
Substance Name Domain	Drug, Homeopathic	CD	
Jurisdiction	EU	CD	
Element Group: Constituent			
Constituent Substance ID	HOM67453LA (Artificial ID)	II	
Constituent Substance Name	*Lachesis muta,* Venom	ST	

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Element Name	Value	Data Format	Note #
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Characteristic Attribute			
Attribute Type	Particular Homeopathic	CD	
Attribute Name	Substance Dilution Grade	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	200	PQ	
Unit	K (Kosakovian)	CD	
Element Group: Constituent (Repeat)			
Constituent Substance ID	ETHAN98765 (Artificial ID)	II	
Constituent Substance Name	Ethanol	ST	
Language	en	CD	
Substance Role	Vehicle	CD	
Is defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	43	PQ	
Unit	%{w/w}	CD	
Amount Text	Ethanol 43 % (w/w)	ST	
Element Group: Constituent (Repeat)			
Constituent Substance ID	WATERP67543 (Artificial ID)	II	
Substance Name	Water	ST	
Substance Role	Vehicle	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	57	PQ	
Unit	%{w/w}	CD	
Amount Text	Ethanol 43 % (w/w)	ST	

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Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2			
Specified Substance Group 2 ID	HOMJGH4521 (Artificial ID)	II	
Element Group: Substance Name			
(Specified) Substance (Group 2) Name	*Lachesis muta*, Venom, Dried, Ethanol 43 % (w/w), dil. 200K–COMPANY EE	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	En	CD	
(Parent) Substance ID	HOM56243DS (Artificial ID)	II	2)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Chemical solubility and Potentization	CD	
Production Method Description	The potency is prepared according to method 11b of the HPUS. First the D2 is prepared according to the description in the HAB monograph of Lachesis muta: dissolve 0.3 parts of the substance and 0,7 parts of purified water, add 99 parts of glycerol 85 % and succuss. Subsequent dilutions are prepared according to HAB method 5a, using glycerol 85 % for the 3rd to 6th decimal dilutions and ethanol (43 % w/w) for subsequent dilutions.	ST	
Version	EFGH-003	ST	
Version Date	20170902	TS.Date	
Element Group: Organization			
Manufacturer ID	LABOY87654 (Artificial ID)	II	
Manufacturer Name	COMPANY EE	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Substance Manufacturer	CD	
Version	001	ST	
Versioon Date	201709002	TS.Date	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	HAB	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Homöopathisches Arzneibuch, Monograph	ST	
Element Group: Specified Substance Group 3			

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Element Name	Value	Data Format	Note #
Specified Substance Group 3 ID	HOMHGD6735 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Lachesis muta*, Venom, Dried, Ethanol 43 % (w/w), dil. 200K, for Homeopathic Preparations - HPUS	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	HOM56243DS (Artificial ID)	II	2)
Element Group: Grade			
Grade Type	USHP	CD	
Grade Name	Lachesis mutus	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Homeopathic Pharmacopoeia	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Homoeopathic Pharmacopoeia of the United States; method 11b Korsakovian attenuations-single flask method of preparation	ST	

NOTE 1 In zoological taxonomy the author name is fully written and the year is added.

If the Herbal structure is going to be used for Animals, then this would be the Substance (Herbal/Homeopathic Drug) and the name would not include the author or date, and it would have a parent Substance (fresh) with a name that does include the author and date, see Scientific Name Type in F.4.4 and J.4.2, Substance name and Source Material.

NOTE 2 This (Parent) Substance ID corresponds to the (Specified) Substance (Group 1) Name: *Lachesis muta*, Venom, Dried, Ethanol 43 % (w/w), dil. 200K.

F.4.5 Structured Information of material, combining the elements for Pyrit D2, Substance of mineral origin according to the German tradition.

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	MIUDP7564E (Artificial ID)	II	
Substance Type	Chemical (Mineral, naturally occurring substance)	CD	
Element Group: Substance Name			
Substance Name	Ferrous disulfide	ST	
Substance Name Type	Other	CD	

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Element Name	Value	Data Format	Note #
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Web	CD	
Reference Source URL	http://en.wikipedia.org/wiki/Sulfide_minerals	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Pyrit	ST	
Substance Name Type	Homeopathic	CD	
Language	la	CD	
Substance Name Domain	Mineral, Homeopathic	CD	
Jurisdiction	EU, US	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	HAB	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Homöopathisches Arzneibuch	ST	
Element Group: Substance Code			
Code	12068-85-8	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	132N09W4PR	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	

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Element Name	Value	Data Format	Note #
Element Group: Structure			
Stereochemistry	Octahedral	CD	
Molecular Formula	FeS_2	ST	
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation	$[Fe]^{2+}$. $[S\text{-}S]^{2-}$	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation	InChI=1S/Fe.S2/c;1-2/q 2;-2	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Web	CD	
Reference Source URL	http://www.ebi.ac.uk/chebi/searchId.do;jsessionid=413A85565AA9FFD28D43286D14D7E4AE?chebiId=CHEBI%3A86471	ST	
Element Group Chemical			
Stoichiometric	Yes	BL	
Element Group Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group Amount			
Amount Type	Exact	CD	
Quantity	119,98	PQ	
Unit	g/mol	CD	
Element Group: Specified Substance Group 1			
Specified Substance Group 1 ID	FES76543RS (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Pyrit, trit D2	ST	
Substance Name Type	Specified Homeopathic	CD	

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Element Name	Value	Data Format	Note #
Language	en	CD	
Substance Name Domain	Drug, Homeopathic	CD	
Jurisdiction	EU	CD	
Element Group: Official Name			
Official Name Type	HAB	CD	
Official Name Status	Primary	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Element Group: Constituent			
Constituent Substance ID	MIUDP7564E (Artificial ID)	II	
Constituent Substance Name	Ferrous disulfide	ST	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Characteristic Attribute			
Attribute Type	Particular Homeopathic	CD	
Attribute Name	Substance Dilution Grade	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	2	PQ	
Unit	Decimal, D (trituration)	CD	
Element Group: Constituent			
Constituent Substance ID	LACT8765FS (Artificial ID)	II	
Constituent Substance Name	Lactose monohydrate	ST	
Language	en	CD	
Substance Role	Vehicle	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	100	PQ	
Unit	%{w/w}	ST	

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Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2			
Specified Substance Group 2 ID	HGFT67534W (Artificial ID)	II	
Element Group: Substance Name			
(Specified) Substance (Group 2) Name	Pyrit, trit D2-COMPANY WW	ST	
Substance Name Type	Specified Substance Group 2	CD	
(Parent) Substance ID	FES76543RS (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Chemical mixing and Potentization	CD	
Production Method Description	The trituration is prepared according to method 6 of the HAB. First, a 1st decimal trituration (D1) is produced by triturating one part of the powdered mineral pyrites with triturated with 9 parts lactose monohydrate. The D2 is obtained by triturating one part of the D1 with 9 parts lactose monohydrate.	ST	
Version	WXYZ-005	ST	
Version Date	20170912	TS.Date	
Element Group: Organization			
Manufacturer ID	WEDS6754G (Artificial ID)	II	
Manufacturer Name	COMPANY WW	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Substance Manufacturer	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	HAB	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Homöopathisches Arzneibuch, ambtliche Ausgabe, monograph of Acidum arsenicosum	ST	
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	GHFTS67453 (Artificial ID)	II	

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Element Name	Value	Data Format	Note #
Element Group: Substance Name			
(Specified) Substance (Group 3) Name	Pyrit D2 for Homeopathic Preparations – HAB	ST	
Substance Name Type	Specified Substance Group 3	CD	
(Parent) Substance ID	FES76543RS (Artificial ID)	II	1)
Element Group: Grade			
Grade Type	HAB	CD	
Grade Name	Pyrit (HAB)	ST	
Element Group: Reference Source			
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Homöopathisches Arzneibuch, ambtliche Ausgabe, monograph, method 6	ST	
NOTE This (Parent) Substance ID refers to the (Specified) Substance (Group 1) Name: Pyrit, trit D2.			

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Annex G
(informative)

Structurally Diverse Substance — Plasma-derived substances

G.1 Scope

This Annex provides guidance for the elements that are necessary to define Plasma-derived Substances. The Plasma-derived substances are structurally diverse substances derived from biological matrices.

G.2 General Aspects of Plasma-derived Substances

At the substance level, all plasma-derived substances will primarily be described as protein substances. This includes plasma-derived purified proteins and intermediates in the fractionation process.

Purified plasma proteins are typically derived from a series of fractionation and purification steps that can vary between manufacturers or even between batches depending on the state of the starting materials or the manufacturing site. For these reasons, intermediate or process steps that do not result in known covalent or irreversible changes will not be captured in the description of the product. Plasma-derived purified proteins will simply be described as a fraction of plasma. Polyclonal Immunoglobulins will be discussed in a future iteration of ISO/TS 19844.

G.2.1 Source material

Plasma-derived products consist of proteins or mixtures of proteins that are derived from human plasma via extraction and purification, and formulated into a medicinal product. The human plasma is obtained from healthy, voluntary donors via apheresis or whole blood donation and pooled into a manufacturing plasma pool. Requirements to ensure quality and safety of the plasma used for the manufacture of plasma-derived products are described in legislation and guidelines that may vary according to the jurisdiction. Requirements include, but are not limited to, donor, selection criteria, requirements for processing, freezing and storage of donations, testing requirements for donations and plasma pools, and ensuring traceability. ISBT 128[56] is a widely used international standard that describes the information necessary for labelling and traceability of human tissues including blood and plasma source material. The requirements stated in this annex are to identify substances that are manufactured from plasma.

G.2.2 Manufacturing process

The manufacturing processes of plasma-derived products are often complex and may contain several optional steps, see Figure G.1. The starting point for all products is human plasma for fractionation (frozen). After controlled thawing of the frozen plasma unit's donations are pooled and separated by centrifugation into Cryoprecipitate and Cryopoor plasma. Cryoprecipitate may be directly used in products distinguished by the ABO system or further purified to isolate specific proteins, such as coagulation Factor VIII, VWF or fibrinogen. The Cryopoor plasma can be used in cold-ethanol

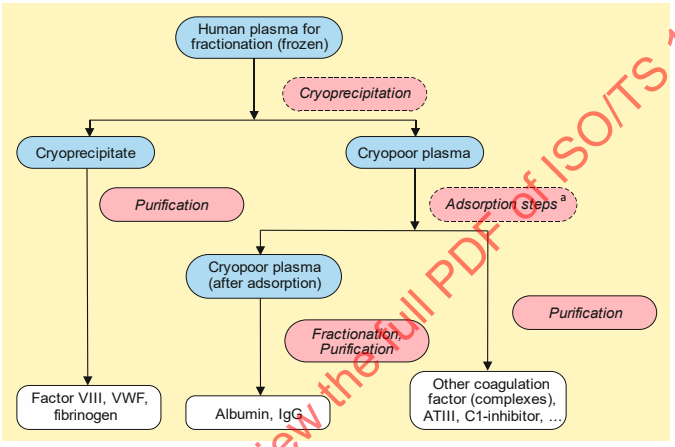
[56] http://www.iccbba.org/

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fractionation to obtain plasma fractions that can be further purified to albumin and IgG. Prior to fractionation often one or more adsorption steps are performed intended for purification of the substance of interest or for the isolation of other substance(s). Adsorption steps intended for the isolation of other substance(s) are often optional steps. Also, the manufacturing processes of products that are obtained via adsorption rather than fractionation may contain optional adsorption steps that are performed for isolation of other substances of interest.

EXAMPLE Cryopoor plasma is the starting material for Human Albumin, plasma-derived, which can be considered as the resultant material. In fact there are several intermediate steps necessary to collect the 'final' purified human albumin which complies to the Ph.Eur. The steps may be variable and therefore each steps has a starting material and a resultant material, which is in fact the starting material for the next step. It is clearly explained by Figure G.1, Figure G.2 and Figure G.5 as well in section G.4.6.



a) Adsorption (chromatography) steps may be mandatory or optional steps in the manufacturing process. Optional adsorption steps are not directly aimed at adsorption or purification of the substance of interest.

Figure G.1 — Simplified schematic representation of the manufacturing processes of different types of plasma-derived products

G.2.3 Adventitious agents

An important aspect of the safety of plasma-derived products is the minimization of the risk of viral contamination. This issue is addressed at three levels, i.e. selection of donors, testing of donations and plasma pools, and inactivation or removal of viruses by the manufacturing process.

Donor selection and plasma testing is covered by legislation. However, besides the legal requirements, manufacturers of plasma-derived products in general perform additional testing for the presence of viruses in donations or plasma pools. In addition, especially where legislation does not cover the required test sensitivity, differences may exist in the sensitivity of the different tests used by manufacturers. These issues directly impact the residual risk of virus contamination of plasma-derived products.

Inactivation or removal of viruses by the manufacturing process can be achieved by fractionation or chromatography steps, or by dedicated virus removing steps such as solvent/detergent (S/D) treatment, nanofiltration, low pH treatment, or heat treatment. Manufacturers of plasma-derived products are obliged to demonstrate that their production process contains effective steps for inactivation/removal of viruses (i.e. log reduction factor ≥4).

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G.2.4 Substance classification for plasma-derived products

G.2.4.1 General Remarks

Plasma-derived products are defined by characteristics of the source material used, the production process, and of the final product. When capturing these characteristics for a given plasma-derived product the following issues should be taken into account, see Figure G.2.

— **First**, plasma-derived products are often manufactured at different manufacturing sites, using slightly different manufacturing processes (e.g. with respect to optional adsorption steps), from source material that may have different characteristics with respect to e.g. country of plasma origin or testing strategy. As these differences, may influence the levels of impurities and residual risk of contamination with adventitious agents such as viruses and prions in the final product, it is considered important to be able to capture this information.

— **Second**, the same 'manufacturing plasma pool' may be used to manufacture a number of different plasma-derived products, see Figure G.1. These products thus share a common intermediate (Cryopoor plasma or Cryoprecipitate, see below), which, at least partly, defines the levels of impurities and residual risk of contamination with adventitious agents. It is a requirement to be able to trace the products back to this intermediate, the pools and donations. This also requires that the intermediate is properly defined.

— **Third** a 'manufacturing plasma pool' only exists in theory as pooling of donations and cryoprecipitation occur simultaneously (see Figure G.1). Nevertheless, it can be important to be able to trace back a product to its 'manufacturing plasma pool' to identify all products produced from both the Cryoprecipitate and the Cryopoor plasma side of this pool's 'manufacturing tree'. The plasma pool sample for testing has to be taken from the first homogeneous pool, which is usually the Cryopoor plasma pool. This means that both Cryopoor plasma and Cryoprecipitate are considered to be covered by the pool test.

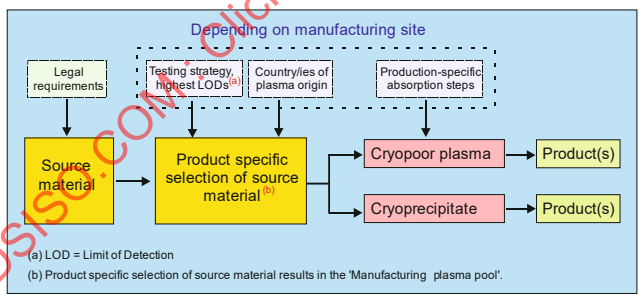


Figure G.2 — Simplified schematic representation of the factors defining the Cryopoor plasma and Cryoprecipitate used for the manufacturing of plasma-derived products[57]

G.2.4.2 Manufacturing plasma pool/Plasma for fractionation (Ph.Eur. monograph 0853)

The 'human plasma for fractionation' is obtained from donors via apheresis or whole blood donation and pooled into a manufacturing plasma pool. Taking into account the definitions in ISO 11238, the source material is considered 'human', and the class from which the fraction 'plasma for fractionation' via

[57] Several manufacturing sites may be manufacturing Cryoprecipitate/Cryopoor plasma used for the manufacturing of a specific plasma-derived product. Depending on the manufacturing site, differences between these factors may exist.

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apheresis or separation of cellular elements from whole blood donations is obtained, is considered part of the source material, see G.3 Terms and definitions.

In Figure E.2, the information model of the Structurally Diverse Substance has been provided and on which human plasma for fractionation is defined as part.

NOTE Country of Origin is mandatory in case of Plasma-derived substances.

G.2.4.3 Cryoprecipitate and Cryopoor plasma

The intermediates Cryoprecipitate and Cryopoor plasma can be defined as fractions of plasma and as substances in their own right derived from source plasma material by fractionation.

A: Cryopoor plasma is a starting material for the production of e.g. albumin and IgG and can also be an active substance in its own right. See information models in Figure E.2 and in Figure 19.

Table G.1 — Tabular information of Cryopoor Plasma

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	CRYOP12345 (Artificial ID)	II	
Substance Type	Structurally Diverse (Plasma-derived)	CD	
Element Group: Substance Name			
Substance Name	Cryopoor plasma	ST	1)
Substance Name Type	Plasma-derived	CD	2)
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	FDA GSRS	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://fdasis.nlm.nih.gov/srs/auto/2zio83gw1v	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Cryosupernatant	ST	
Substance Name Type	Other Name	CD	
Language	en	CD	

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Element Name	Value	Data Format	Note #
Element Group: Reference Source (Repeat)			
Public Domain	Yes	BL	
Reference Source Type	Web page	CD	
Reference Source Class	Web	CD	
Reference Source URL	https://en.wikipedia.org/wiki/Cryosupernatant	ST	
Element Group: Substance Code			
Code	2ZIO83GW1V	CD.Code	
Code System	FDA GSRS (UNII)	CD.Code SystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Source Material			
Source Material Class	Biologic	CD	
Source Material Type	Human	CD	
Source Material State	N/A		
Organism ID	HUMA875601 (Artificial ID)	II	
Organism Name	*Homo sapiens*, Linnaeus 1758	ST	
Parent Substance ID	N/A		
Parent Substance Name	N/A		
Country of Origin	NL, DE, FR, ES, US	CD	3)
Development Stage	N/A		
Element Group: Part Description			
Part	Human plasma for fractionation	CD	
Part Location	N/A		
Element Group: Fraction Description			
Fraction	Cryopoor Plasma	ST	
Material Type	Biological fluid	CD	
Element Group: Modification			
Modification Type	Physical	CD	
Element Group: Physical Modification			
Role	Removal of Cryoprecipitate by Centrifugation	ST	
Number of Parameters	2	INT	

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Element Name	Value	Data Format	Note #
Element Group: Parameters			
Parameter	Thaw temperature	ST	
Element Group: Amount			
Amount Type	Average	CD	
Low Limit	1	PQ	
High Limit	6	PQ	
Unit	Degree Celsius	CD	
Element Group: Parameters (Repeat)			
Parameter	Centrifugation temperature	ST	
Element Group: Amount			
Amount Type	Average	CD	
Low Limit	1	PQ	
High Limit	6	PQ	
Unit	Degree Celsius	CD	
(Capturing of the Plasma Master File documentation, testing and safety document)			
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Plasma Master File	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	01234SQ (Artificial PMF-number)	ST	4)
Reference Source Citation	CBG178600 (Artificial CBG-Case number)	ST	5)
Element Group: Reference Source Document			
Reference Source Document	PDF	ED	6)
Reference Source Document Type	Regulatory specification	CD	
Reference Source Document Classification	Plasma Master File	CD	7)

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Element Name	Value	Data Format	Note #

Capturing of information on virus testing for Cryopoor Plasma

Attachment: Documentation tables of testing strategy linked to the plasma pool:

Test	Donation	Minipool	Plasma pool
HBsAg	Y/N	Y/N	Y/N
HBV DNA			
HCV Antibody			
HCV RNA			
HIV-1 Antibody			
HIV-2 Antibody			
HIV-1 RNA			
HIV-2 RNA			
Parvovirus			

Figure G.3 — Overview of the information that should be provided on test requirements

Test	High LOD per single donation	Highest LOD first Homogeneouspool
HBV DNA	U/ml	U/ml
HCV RNA		
HIV-1 RNA		
HIV-2 RNA		
PB 19 DNA		
HAV RNA		
HEV RNA		
Other [specify]		

Figure G.4 — Overview of the information that should be provided on the test specifics

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Element Name	Value	Data Format	Note #
NOTE 1 Cryopoor plasma: a: Plasma pool; Human Plasma for fractionation is stored frozen in the containers. After thawing plasma is pooled. b: Cryoprecipitation: the plasma is pumped into the separator, where the Cryoprecipitate is separated by centrifugation. c: Cryopoor plasma or Cryoprecipitate-depleted plasma. NOTE 2 Plasma-derived is a Substance Name Type, see 5.3.2. NOTE 3 The Attribute 'Country of Origin' includes the countries used for the manufacturing of the Cryopoor plasma or Cryoprecipitate as mentioned in the plasma master file document or information provided by the manufacturer. This information may be differing between the countries in which the Cryopoor plasma or Cryoprecipitate is prepared. These countries include the subset of countries in which the collection organizations are located from which plasma for manufacturing of a specific plasma-derived product(s) is obtained. These countries are captured in the Characteristic Attribute 'countries of origin' at the Specified Substance Group 1 information level. NOTE 4 Reference Source ID: Plasma Master File Number which is used by the manufacturer to perform the tests and requirements laid down related to the manufacture of Cryopoor plasma intended to manufacture Human Albumin, Plasma-derived. NOTE 5 Reference Source Citation: This is the Case number used by the Regulatory Authority in which the PMF is stored. NOTE 6 Reference Source Document: This is the actual PMF-file of the Company who manufactures Cryopoor plasma intended to manufacture Human Albumin, Plasma-derived. NOTE 7 The Testing Strategy and Country of Origin are directly coupled to the plasma pool and the manufacturer. The manufacturer of this Cryopoor plasma sourced from this plasma pool is captured at the Specified Substance Group 2 information level.			

The manufacturing process is described at the Specified Substance Group 2 Information level up to the information group 'Manufacturing', see Figure 36.

However, the information shown in the green box in Figure 36 will be described by the extended information class manufacturing, see Figure E.7. This model can describe a starting material processed to become a resultant material which will be in turn become a parent (specified) substance to be processed to a second resultant material until the final specifications are met for the substance which is called the resultant substance that may capture the protein substance.

Table G.2 — Tabular information for the manufacturing of Cryopoor plasma Substance — Specified Substance Group 2 Information connection

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2 (Cryopoor Plasma – Company YY)			
Specified Substance Group 2 ID	FDSTE7453A (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Cryopoor Plasma—Company YY	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	CRYOP12345 (Artificial ID)	II	1)

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Element Name	Value	Data Format	Note #
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Fractionation	CD	
Production Method Description	Continuous plasma fractionation from Human Plasma for Fractionation	ST	
Critical Process Version Number	1	INT	2)
Version	008	ST	
Version Date	20170121	TS.Date	
Element Group: Organization			
Manufacturer ID	DUNS64539B (Artificial ID)	II	
Manufacturer Name	Company YY	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	FINAL67543 (Artificial ID)	ST	
Reference Source Citation	CBG564231 (Artificial CBG-Case number)	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	Regulatory submission	ED	
Reference Source Document Type	Release Specification	CD	
Reference Source Document ID	FR1231 (Artificial ID)	ST	
Reference Source Document Classification	In-house/Batch release specification	CD	

NOTE 1 This (Parent) Substance ID refers to the Substance Name: Cryopoor plasma.

NOTE 2 The Critical Process Number Version Number would change if a substantial change in the (synthetic) manufacturing process occurred. These would include a change in the chemistry or, addition or elimination of a purification step. The change in a version number should be tied to the production system type.

B: Cryoprecipitate is both an active substance in its own right, typically distinguished by the ABO system, and a starting material for the production of coagulation factors. Cryoprecipitate that is not distinguished by the ABO system is described below.

Table G.3 — Tabular information of Cryoprecipitate

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Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	PLASMC786542 (Artificial ID)	II	
Substance Type	Structurally Diverse (Plasma-derived)	CD	
Element Group: Substance Name			
Substance Name	Cryoprecipitate	ST	1)
Substance Name Type	Plasma-derived	CD	2)
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	FDA GSRS	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://fdasis.nlm.nih.gov/srs/auto/09j8qnb0l9	ST	
Element Group: Substance Code			
Code	09J8QNB0L9	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Source Material			
Source Material Class	Biologic	CD	
Source Material Type	Human	CD	
Source Material State	N/A		
Organism ID	HUMA875601 (Artificial ID)	II	
Organism Name	Homo sapiens, Linnaeus 1758	ST	
Parent Substance ID	N/A		
Parent Substance Name	N/A		
Country of Origin	NL, DE, FR, ES, US	CD	3)
Development Stage	N/A		
Element Group: Part Description			
Part	Human plasma for fractionation	CD	

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Element Name	Value	Data Format	Note #
Part Location	N/A		
Element Group: Fraction Description			
Fraction	Cryoprecipitate	ST	
Material Type	Protein	CD	
Element Group: Modification			
Modification Type	Physical	CD	
Element Group: Physical Modification			
Role	Isolation of Cryoprecipitate by Centrifugation	ST	
Number of Parameters	2	INT	
Element Group: Parameters			
Parameter	Thaw temperature	ST	
Element Group: Amount			
Amount Type	Average	CD	
Low Limit	–2	PQ	
High Limit	3	PQ	
Unit	Degree Celsius	CD	
Element Group: Parameters (Repeat)			
Parameter	Centrifugation temperature	ST	
Element Group: Amount			
Amount Type	Exact, range	CD	
Low Limit	1	PQ	
High Limit	3	PQ	
Unit	Degree Celsius	CD	
(Capturing of the Plasma Master File documentation, testing and safety document)			

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Element Name	Value	Data Format	Note #
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Plasma Master File	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	01234SQ (Artificial PMF-number)	ST	
Reference Source Citation	CBG178600 (Artificial CBG-Case number)	ST	
Element Group: Reference Source Document			
Reference Source Document	PDF	ED	
Reference Source Document Type	Regulatory specification	CD	
Reference Source Document Classification	Plasma Master File	CD	

Capturing information on virus testing for the Cryoprecipitate

Attachment: Documentation tables of testing strategy linked to the Plasma Pool:

Table G.4 — Overview of the information that should be provided on test requirements

Test	Donation	Minipool	Plasma pool
HBsAg	Y/N	Y/N	Y/N
HBV DNA			
HCV Antibody			
HCV RNA			
HIV-1 Antibody			
HIV-2 Antibody			
HIV-1 RNA			
HIV-2 RNA			
Parvovirus			

Table G.5 — Table Overview of the information that should be provided on the test specifics

Test	High LOD per single donation	Highest LOD first Homogeneous pool
HBV DNA	U/ml	U/ml
HCV RNA		
HIV-1 RNA		
HIV-2 RNA		
PB 19 DNA		
HAV RNA		
HEV RNA		
Other [specify]		

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Element Name	Value	Data Format	Note #
NOTE 1 **Cryoprecipitate.** a: Plasma pool; Human Plasma for fractionation is stored frozen in the containers. After thawing plasma is pooled. b: Cryoprecipitation: the plasma is pumped into the separator, where the Cryoprecipitate is separated by centrifugation c: Cryoprecipitate. NOTE 2 Plasma-derived is a Substance Name Type, see 5.3.2. NOTE 3 The Attribute 'Country of Origin' includes the countries used for manufacturing of the Cryoprecipitate as mentioned in the plasma master file document or information provided by the manufacturer. This information may be different from the countries of which the Cryoprecipitate is prepared. These countries include the subset of countries in which the collection organizations from which the plasma for manufacturing of a specific plasma-derived product(s) is obtained are located. These countries are captured in the Characteristic Attribute 'countries of origin' at the Specified Substance Group 1 information level. The Testing Strategy and Country of Origin are directly coupled to the plasma pool and the manufacturer. The manufacturer of this Cryoprecipitate sourced from this plasma pool is captured at the Specified Substance Group 2 information level.			

Table G.6 — Tabular information for the manufacturing of Cryoprecipitate (Manufacturer YY) Substance-Specified Substance Group 2 information connection

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2 (Cryopoor Plasma (Minipool)– Company YY)			
Specified Substance Group 2 ID	HGTDFE8965 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Cryoprecipitate—Company YY	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	PLASMC786542 (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Fractionation	CD	
Production System Type	Continuous plasma fractionation from Human Plasma for Fractionation	CD	
Critical Process Version Number	1	INT	2)
Version	002	ST	
Version Date	20170218	TS.Date	

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Element Name	Value	Data Format	Note #
Element Group: Organization			
Manufacturer ID	DUNS64539B (Artificial ID)	II	
Manufacturer Name	Company YY	ST	
Issuer of ID	EMA OMS	ST	
Manufacturer Role	Manufacturer	CD	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	FINAL12345 (Artificial ID)	ST	
Reference Source Citation	CBG564231 (Artificial CBG-Case number)	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	Regulatory submission	ED	
Reference Source Document Type	Release Specification	CD	
Reference Source Document ID	FR4563 (Artificial ID)	ST	
Reference Source Document Classification	In-house/Batch release specification	CD	
NOTE 1 This (Parent) Substance ID refers to the Substance Name: Cryoprecipitate. NOTE 2 The Critical Process Number Version Number would change if a substantial change in the (synthetic) manufacturing process occurred. These would include a change in the chemistry or, addition or elimination of a purification step. The change in a version number should be tied to the production system type.			

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G.2.4.4 Plasma-derived substance

The final plasma-derived substance is described as structurally diverse substance with Cryopoor plasma or Cryoprecipitate as the parent substance. The resultant substance from the physical modification process of the Cryopoor plasma/Cryoprecipitate is a constituent e.g. Human Albumin, Plasma-derived', 'human coagulation Factor VIII/von Willebrand Factor, plasma-derived' which can be described as a substance following the protein information model, see Figure C.1.

G.3 Terms and definitions

G.3.1
ICCBBA
International Council for Commonality in Blood Bank Automation (http://www.iccbba.org/)

Note 1 to entry: ICCBBA is to improve patient safety through standardization of the manner in which critical information is carried on labels of Medical Products of Human Origin (MPHO). MPHO comprise all human derived

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donated material used for human application and include blood, organs, bone marrow, cord blood, corneas, tissues, reproductive cells and milk.

G.3.2
ISBT 128
ISBT 128 is the global standard for the terminology, identification, coding and labeling of Medical Products of Human Origin

Note 1 to entry: ISBT 128 is used in more than 70 countries across six continents and disparate health care systems. It is widely endorsed by the professional community. The standard has been designed to ensure the highest levels of accuracy, safety, and efficiency for the benefit of donors and patients worldwide. ISBT 128 provides international consistency to support the transfer, traceability and transfusion/transplantation of blood, cells, tissues and organs.

G.3.3
constituent
substance present within a Specified Substance or parent substance

Note 1 to entry: Constituents can be impurities, degradants, extraction solvents, vehicles, active markers or signature substances, parent substances or single substances mixed together to form a multi-substance material.

Note 2 to entry: Constituents shall have an associated role and amount at the Specified Substance Group 1 information model. Constituent specifications shall be used to describe components as well as limits on impurities or related substances for a given material.

G.3.4
critical process parameter
process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality

Note 1 to entry: A manufacturing parameter is considered “critical” and necessary for production of Substance or Specified Substance e.g. inclusion of chromatographic step for removal or reduction of impurities, viruses etc.

Note 2 to entry: The critical process is tied to the Production Method type.

Note 3 to entry: Critical Process Parameter is defined in accordance with the ICH Q8 Guideline[35] as:
A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

G.3.5
fraction
distinct portion of material derived from complex matrix, the composition of which differs from antecedent material

Note 1 to entry: This concept is used to describe source material and is recursive in that a subsequent fraction can be derived from an antecedent fraction.

EXAMPLE Sera to immunoglobulins to polyclonal IgG is an example of recursive fractionation.

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G.3.6
manufacturing
process of production for a substance or medicinal product from the acquisition of all materials through all processing stages

Note 1 to entry: The critical process, critical process steps, starting and processing materials and critical production parameters are included.

G.3.7
material
any entity that has mass, occupies space and consists of one or more substances

G.3.8
microheterogeneity
substances isolated together that contain minor differences in source material (e.g. sequence heterogeneity) and/or post-translational modification such as glycosylation. Differences in glycosylation will be captured at the Specified Substance Group 1 information level.

Note 1 to entry: Microheterogeneity is not a defining characteristic of substances but can be a defining one at the Specified Substance Group 1 information level.

Note 2 to entry: Microheterogeneity consists of variability in the type of glycosylation (biantennary, triantennary), extent of glycosylation at a given site (site occupancy), sequence heterogeneity due to polymorphism in source material, translation errors or variable proteolytic processing or other.

G.3.9
mixture
type of polydisperse substance that is a combination of single substances isolated together or produced in the same synthetic process

Note 1 to entry: Single substances of diverse origin that are brought together and do not undergo a chemical transformation as result of that combination are defined as multi-substance materials (Specified Substances Group 1) and not as a mixture.

EXAMPLE Gentamicin is defined as a mixture substance of Gentamicin C1, Gentamicin C1A, Gentamicin C2, Gentamicin C2A and Gentamicin C2B. Glyceryl monoesters are defined as mixture substances of two single substances which differ in the position of esterification. Simethicone, which consists of dimethicone and silicon dioxide, is not defined as a mixture substance since these are diverse materials brought together to form a multi-substance material.

Note 2 to entry: Mixture substance could be used for a homologous group of structurally diverse single substances used as starting materials in order to prepare an allergen extract. The extract is further described by using the class source material, element group fraction description (allergen preparation) obtained from the structurally diverse single substances (starting materials) as parent substances. This substance (allergen extract) is the result of the same (synthetic) process and hence the extract is considered as a mixture substance.

G.3.10
part
entity of anatomical origin and location of source material within an organism

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Note 1 to entry: Entity is a thing with distinct and independent existence.

G.3.11
processing material
type of material essential to the manufacturing process that is not incorporated into the resultant material

G.3.12
protein substance
type of substance with a defined sequence of alpha-amino acids connected through peptide bonds

Note 1 to entry: A protein consists of one or more chains with a length of more than 40 amino acids. A peptide is defined as a linear sequence consisting of 2 to 40 amino acid residues.

Note 2 to entry: Synthetic peptides and proteins with defined sequences, recombinant proteins and highly purified proteins extracted from biological matrices are described as protein substances. Sites of glycosylation, disulphide linkages and glycosylation type (e.g. fungal, plant, anthropoid, avian mammalian, human) are defining elements of protein substances, when known. A graphical molecular structure is also included in the definition of all peptides of 40 amino acid residues or less.

Note 3 to entry: The absolute configuration at the a-carbon atom of the a-amino acids is designated by the prefixed small capital letter D or L to indicate a formal relationship to D- or L-serine and thus to D- or L-glyceraldehyde. The prefix 4 (Greek xi) indicates unknown configuration. (Biochem. J. (1984) 219, 345-373).

G.3.13
resultant material
material that is the result of a manufacturing process.

Note 1 to entry: Resultant material may be the starting material of the next process step or the final material or actual specified substance.

G.3.14
source material
material from which a substance is derived, which is defined based on taxonomic and anatomical origins
Note 1 to entry: Source material is used to define structurally diverse, chemical, mixture, polymer and protein substances isolated from biological matrices.

G.3.15
specified substance
group of elements which describe multi-substance materials and specify further information on substances and multi-substance materials relevant to the description of medicinal products

EXAMPLE This could include grade, units of measure, physical form, constituents, manufacturer, critical manufacturing processes (i.e. extraction, synthetic, recombinant processes), specification and the analytical methods used to determine that a substance is in compliance with the specification.

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Note 1 to entry: There are four different groups of elements that can be used to define a given Specified Substance and specific relationships between each group of elements.

G.3.16
starting material
material from which the manufacturing process of the substance starts. This material is a building block which will be (partly) incorporated in the structure of the resultant product

G.3.17
structurally diverse substance
type of polydisperse substance isolated from a single source that is a complex combination which cannot be described as a mixture of a limited number of single substances

Note 1 to entry: Structurally diverse substances are defined based on immutable properties of a given material. Modifications that irreversibly alter the structure of the material, distinctive physical properties of components subsumed into the material, e.g. a gene in gene therapy substances, are defining elements for structurally diverse substances. Fractions derived from source material (oils and juices) are also captured in the definition. Protein mixtures containing a large number of diverse sequences such as polyclonal immunoglobulins are defined as structurally diverse substances.

G.4 Structuring the required information

The plasma-derived substance information is described in accordance with the definitions used in ISO 11238 and this document.

G.4.1 Substance information level

There are five types of single substances in ISO 11238 (see 5.2.1). Structural Diverse Substance is one of these five types. Whole blood or Human Plasma for fractionation, Cryoprecipitate and Cryopoor plasma are defined using the elements for a Structurally Diverse Substance in which Homo sapiens, Linnaeus (1758) is the Source material. Human plasma for fractionation or Whole blood is considered as a <Part> of the Source Material. The information model also accommodates Fraction information at the Substance level, see Figure E.2 and Figure 19. The element 'Fraction' is considered as fractions of the Part 'Human plasma for fractionation', from which two further fractions can be obtained: 'Cryoprecipitate' and 'Cryopoor plasma', each requiring different information as explained in Figure G.1. No 'modifications that result in irreversible changes in the underlying material and/or physical or biological properties related to underlying molecular composition of the material' are identified for these fractions/structurally diverse substances. However, characteristics with respect to testing strategy and country of plasma origin should also be described as they are related to safety and/or are of importance for pharmacovigilance purposes. Human plasma for fractionation or Whole blood is the Parent substance of Cryopoor plasma or Cryoprecipitate.

It is considered important to specify the plasma used for the manufacture of a specific plasma-derived product. This could be achieved by linking the required information on testing strategy and countries of plasma origin to specific manufacturing site(s) of Cryoprecipitate and Cryopoor plasma. Linking the information directly to a plasma-derived substance is not preferred for several reasons.

— Linking the Country of Origin and testing strategy to the manufacturing site at the Substance information level:

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One Cryoprecipitate or Cryopoor plasma pool can be used for the manufacturing of a number of different plasma-derived substances and products. If the information on country of plasma origin and testing strategy are linked to the manufacturing site rather than the substance/product, there is no need to define the same Cryoprecipitate or Cryopoor plasma pool for each substance/product separately. The information on the Cryoprecipitate or the Cryopoor plasma pool has been captured at the Substance information level/Source Material domain with the attribute: 'Country of Origin'. The Testing Strategy is captured by the element group Reference Source, see Table G.1, Table G.2, Table G.3 and Table G.6 respectively.

— Linking the Country of Origin and testing strategy to a specific process flow used for the manufacturing of a specific Substance/Product captured at the Specified Substance Group 1 information level, see Figure 35:

  Cryoprecipitate or Cryopoor plasma can be used for the manufacturing of a specific plasma-derived substance/product that may be produced at different manufacturing sites. If the information on country of plasma origin and testing strategy are linked to the substance/product rather than the manufacturing site, potentially relevant differences between manufacturing sites would be lost.

There may be substantial differences between the characteristics of Cryopoor plasma or Cryoprecipitate produced by the same manufacturer, but intended for the production of different plasma-derived substances/products, e.g. in case of manufacturing using plasma from a different country of origin. As a consequence, it may be required to include additional levels of specification for Cryoprecipitate and Cryopoor plasma from a given manufacturer, depending on the process flows (e.g. additional adsorption/purification steps). The Cryopoor plasma or Cryoprecipitate of a certain flow may contain the subset of collection and testing organizations from which plasma for the manufacturing of specific substances/product(s) may be obtained. This additional information is captured at the Specified Substance Group 1 information level. This should be reflected in the name used, e.g. 'Cryoprecipitate from process flow 'N' at manufacturing site X', where 'process flow' at the Specified Substance level is used to differentiate between Cryoprecipitates or Cryopoor plasmas with different characteristics with respect to country of plasma origin and testing strategy. This information as provided in G.2.4 can be enclosed as a Reference Document.

It is noted that, if applicable, reference to a Plasma Master File (PMF) is considered insufficient to capture the required information. For each plasma-derived product mentioned in a PMF it is likely only a subset of the plasma described in this PMF will be used. Given the diversity of plasma described in a PMF with respect to countries of plasma origin, testing strategy, and test kits used, reference to a PMF therefore does not provide a sufficient level of detail although the PMF can additionally be used as a reference source.

The information starts with a Specified Substance Group 1 ID, a Substance Name Type 'Specified Substance Group 1' and the (Specified) Substance (Group 1) Name 'Cryopoor plasma, process flow 'N''. The Element Group 'Constituent' contains the Constituent Substance ID and the Constituent Substance Name Cryopoor plasma, resp. Cryoprecipitate' with the Substance Role of Parent Substance. The Amount Type of the class 'Amount' is not used where the Substance Role has the value 'Parent substance'.

In addition, the Constituent Group contains the resultant substance Human Albumin, Plasma-derived obtained from the starting material Cryopoor plasma process flow 'N'.

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The specific information of the country of plasma origin is described by the Element Group 'Characteristic Attribute' at the Specified Substance Group 1 information level and is envisioned to also capture testing and safety information, see Figure 35. The manufacturing of the fraction steps at a particular manufacturing site is captured at the Specified Substance Group 2 information level, with the Specified Substance Group 2 ID, the Substance Name Type 'Specified Substance Group 2' and the Substance Name: 'Cryopoor plasma, process flow 'N'-Manufacturer ZZ', resp. 'Cryoprecipitate, process flow 'N'-Manufacturer ZZ', see Figure 36.

G.4.2 Country of plasma origin

Information on the country of plasma origin is considered important as it would enable the identification of products involved in case there are relevant issues with respect to infectious diseases in certain countries or regions. The information should include all possible countries of origin of plasma used for the manufacturing of Cryoprecipitate or Cryopoor plasma, taken into account process flows (e.g. the subset of collection and testing organization from which plasma for the manufacturing of a specific plasma-derived product(s) may be obtained) for specific plasma-derived product(s). The attribute 'Country of Origin' is captured as a subset of country (ies) at the Specified Substance Group 1 Information level with respect to the Plasma manufacturing pool, where the Element Group 'Source Material' at the Substance level captures the countries with respect to the Plasma Master File. If the country of origin as a specific subset of countries is captured at the Specified Substance Group 1 information level in the Element Group 'Characteristic Attribute', it should be coupled to testing strategy and each individual country (set of countries) would be generating a different Specified Substance Group 1 ID, see Figure 35, Figure 36 and Figure E.7. This will be the case when a Cryopoor plasma or a Cryoprecipitate is described at the Specified Substance Group 1 level and is related in particular to a specific process flow 'N' intended for the manufacturing of a particular plasma-derived substance/product.

G.4.3 Reference Source and Reference Source Document

The definition of every plasma-derived product should refer to both a reference source and a document. Oftentimes these are regulatory documents.

G.4.4 Testing strategy

Given the differences in e.g. testing strategy and test kits used for plasma, it is considered important to provide further detail for Cryoprecipitate or Cryopoor plasma used for the manufacturing of a specific plasma-derived product. A document providing the following information should be included for a defined Cryoprecipitate or Cryopoor plasma at the Reference Source document information level, which is confidential information:

— Viruses for which serology testing is performed on all single donations;

— Viruses for which serology testing is performed on the first homogenous pool;

— Viruses for which NAT[58] testing is performed on all donations (single or mini-pools);

— Viruses for which NAT testing is performed on the first homogenous pool.

For each virus tested with NAT the highest limit of detection (LOD) of the test kits used, if relevant per single donation; see Table G.7 and Table G.8.

[58] NAT Testing: 'NAT for the testing of viral DNA or RNA'. (NAT: Nucleic acid Amplification Technology).

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Table G.7 — Overview of the information that should be provided on test requirements

Test	Donation	Minipool	Plasma Pool
HbsAg	Y/N	Y/N	Y/N
HBV DNA			
HCV Antibody			
HCV RNA			
HIV-1 Antibody			
HIV-2 Antibody			
HIV-1 RNA			
HIV-2 RNA			
Parvovirus B19 DNA			
HAV RNA			
HEV RNA			
Other [specify]			

Table G.8 — Overview of the information that should be provided on the test specifics

Test	Highest LOD per single donation	Highest LOD first homogeneous pool
HBV DNA	U/ml	U/ml
HCV RNA		
HIV-1 RNA		
HIV-2 RNA		
PB19 DNA		
HAV RNA		
HEV RNA		
Other [specify]		

In some cases, additional testing may be performed, e.g. on donor populations from specific regions, or only by certain blood/plasma collection organizations. However, adding this as product identifier may be misleading if testing is not performed on all donations in a manufacturing plasma pool.

G.4.5 Summary of the information regarding Cryoprecipitate and Cryopoor plasma

Cryopoor plasma and Cryoprecipitate can be defined by the source material, the manufacturing site, and the testing strategy and origin of the plasma used at this manufacturing site, see Table G.7. It may be required to include additional levels of specifications depending on the process flows (e.g. the subset of collection and testing organizations from which plasma specific product(s) will be manufactured).

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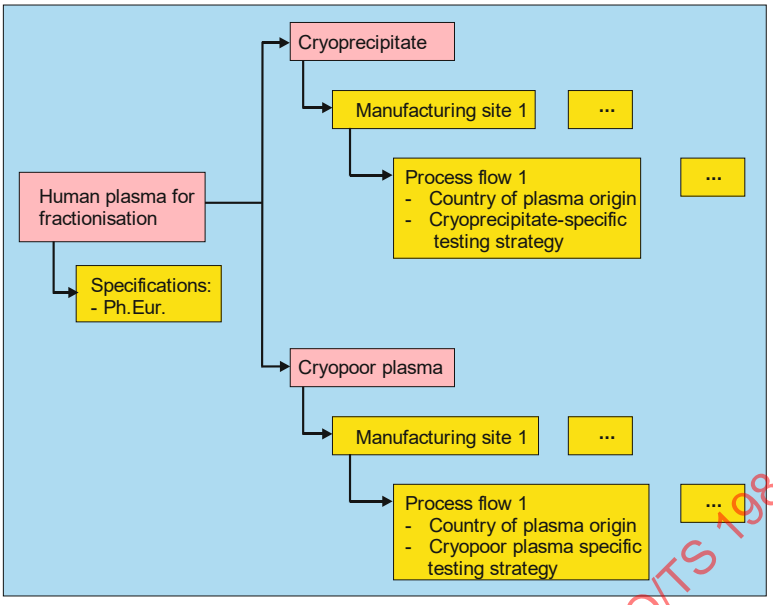


Figure G.5 — Simplified schematic representation of the process flow at a specific manufacturing site

The simplified schematic representation of the information that can define Cryoprecipitate and Cryopoor plasma in which the characteristics of the Cryoprecipitate/Cryopoor plasma are described for each manufacturing site is described in Figure 19 and Figure E.2. Where relevant, a manufacturer should define different process flows. The testing strategy should be described taking into account the tests used by the test labs responsible for testing plasma from the defined countries of origin and the plasma pool.

G.4.6 Substance information example for a plasma-derived Substance/product 'Human Albumin, Plasma-derived', Part 1: Cryopoor plasma

At the substance information level, the information regarding 'human plasma for fractionation' used for the manufacturing is captured as illustrated in Figure G.5 and Figure G.6. The fraction 'Cryopoor plasma' obtained from 'Human plasma for fractionation/Fresh Frozen Plasma' can be further described at the Specified Substance Group 1 information level as illustrated under the name 'Process flow '1'' in which 'Cryopoor plasma' is the Parent Substance. The constituent substance 'Human Albumin, plasma-derived' is considered as the resultant material obtained from the physical modification of 'Cryopoor plasma'. The formulation of Human Albumin into solution for injection 40 mg/ml and Albumin concentrate solution for injection 200 mg/ml is considered a medicinal product and is discussed in the ISO/TS 20443 Medicinal Product Implementation Guidance. Note that the manufacturer of the Cryopoor plasma or Cryopoor plasma process flow 'N=1'' and the Substance Albumin, Plasma-derived could be manufactured by different manufacturers. The constituent substance 'Human Albumin, plasma-derived' is considered as the resultant material obtained from the physical modification of 'Cryopoor plasma'.

The parent substance for albumin is Cryopoor plasma which is the common starting material for the preparation of Human Albumin, Plasma-derived. As mentioned above all plasma-derived proteins will be captured as structurally diverse substances. Two possibilities are provided.

A) Human Albumin, Plasma-derived manufactured directly from Cryopoor plasma based on minimal information with Cryopoor plasma as the parent Substance. This includes provision of information on Testing (see Table G.7, Table G.8) and Manufacturing (see Figure E.7 and Figure G.5).

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B) Human Albumin, Plasma-derived manufactured in a simplified two-step process. The first step is the manufacture of an intermediate 'Cryopoor plasma process flow 'N=1'' which is captured as a Specified Substance at the Group 1 information level with Cryopoor plasma as the parent substance. The second step is the manufacture of the constituent substance Human Albumin, Plasma-derived using the 'Cryopoor plasma process flow 'N=1'' as the starting material, see Figure 35, Figure 36 and, the extended element class Manufacturing provided in Figure E.7. The The two steps may be performed by different manufacturers. Manufacturers of Cryopoor plasma may also perform (part of) the fractionation/purification process. However, the manufacturing details of this part of the process are captured at the level of the Human Albumin, Plasma-derived rather than at the level of Cryopoor plasma because this enables the definition of the Cryopoor plasma in such a way that it can be considered the starting material for Albumin but also for other products derived from the same Cryopoor plasma e.g. human normal IgG and blood coagulation Factor IX (FIX) (not further defined in this example) Table G.8. he albumin is defined by its manufacturing sites, production process, product characteristics and specifications, and virus safety.

NOTE The albumin product can be manufactured from Cryopoor plasma produced at different manufacturing sites.

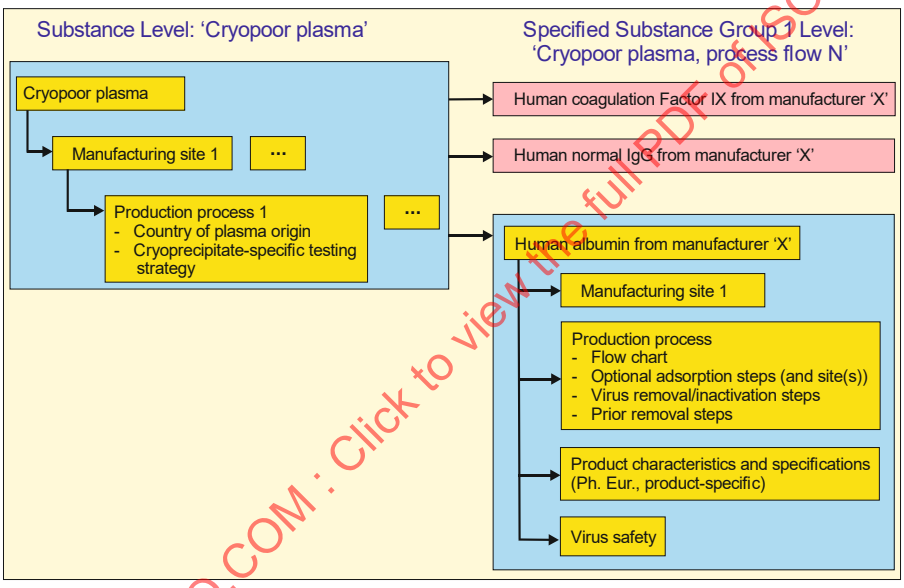


Figure G.6 — Simplified schematic representation of the downstream parameters of the Cryopoor plasma for albumin from manufacturer 'X'

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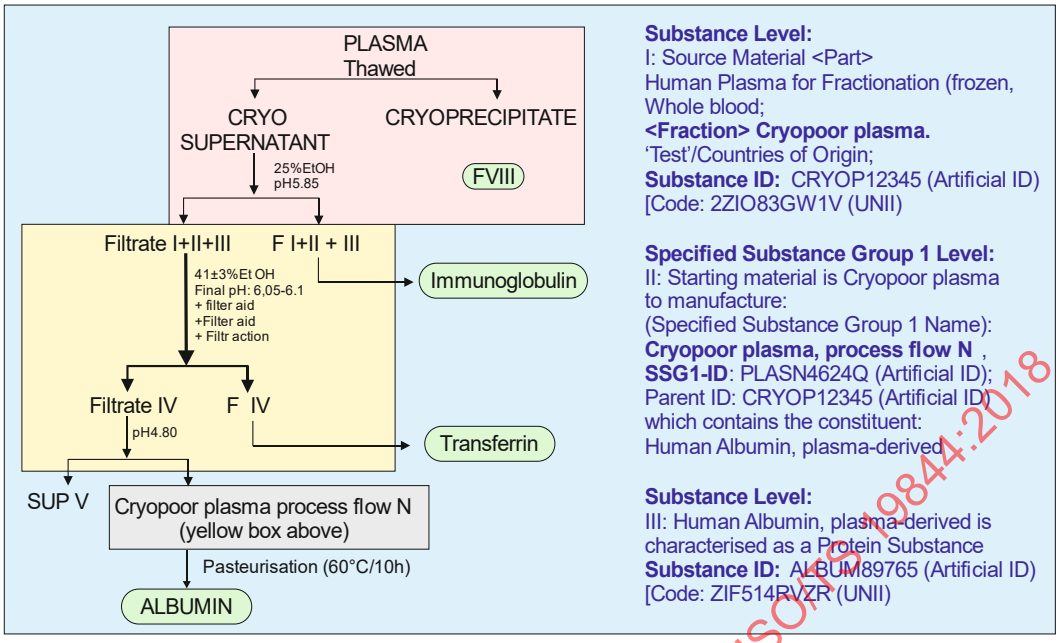


Figure G.7 — Simplified two step manufacturing of Human Albumin, Plasma-derived

Table G.9 — Tabular information for Human Albumin, Plasma-derived sourced from a Cryopoor plasma with minimal information captured at the Substance information level

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	ALBUM89765 (Artificial ID)	II	
Substance Type	Structurally Diverse (Plasma-derived)	CD	
Element Group: Substance Name			
Substance Name	Human Albumin, Plasma-derived	ST	
Substance Name Type	Official Name	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia, monograph 01/2013 corrected 8.0	ST	

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Element Name	Value	Data Format	Note #
Element Group: Substance Name (Repeat)			
Substance Name	Human Serum Albumin	ST	
Substance Name Type	Plasma-derived	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Journal	CD	
Reference Source Class	Literature	CD	
Reference Source Citation	Gabriella Fanali *et al.*, Molecular Aspects of Medicines 33(2012) 209 -290 'Human Serum Albumin'	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Albumins, blood serum	ST	
Substance Name Type	Other Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	
Element Group: Substance Code			
Code	9006-53-5	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	ZIF514RVZR	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Classification			

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Element Name	Value	Data Format	Note #
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	B05AA01	CD.Code	
Substance Classification Type	Blood substitutes and plasma protein fractions, Albumin	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=B05AA01	ST	
Element Group: Source Material			
Source Material Class	Biologic	CD	
Source Material Type	Human	CD	
Source Material State	N/A		
Organism ID	HUMA875601 (Artificial ID)	II	
Organism Name	*Homo sapiens*, Linnaeus 1758	ST	
Parent Substance ID	CRYOP12345 (Artificial ID)	II	
Parent Substance Name	Cryopoor Plasma	ST	
Country of Origin	NL, DE, FR, ES, US	CD	1)
Development Stage	N/A		
Element Group: Part Description			
Part	Human plasma for fractionation	CD	
Part Location	N/A		
Element Group: Fraction Description			
Fraction	Human Albumin, Plasma-derived	ST	2)
Material Type	Protein	CD	

NOTE 1 Country of Origin with reference to the Cryopoor plasma mentioned in the Plasma Master File.

NOTE 2 Human Albumin, Plasma-derived is further described as a protein substance in Table G.17.

Table G.10 — Tabular information for the manufacturing of Human Albumin, Plasma-derived from Cryopoor plasma (See Figure 36)

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Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2 (Cryopoor plasma pool — Manufacturer 1)			
Specified Substance Group 2 ID	HUMA12345S (Artificial ID)	II	
Element Group: Substance			
Substance Name	Human Albumin, Plasma-derived-Company ZZ	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	CRYOP12345 (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Fractionation	CD	
Production Method Description	Fractionation, absorption, virus inactivation and depth filtration	ST	
Critical Process Version Number	1	INT	2)
Version	01	ST	
Version Date	20170125	TS.Date	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	FINAL34521 (Artificial ID)	ST	
Reference Source Citation	CBG564231 (Artificial CBG-Case number)	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	PDF	ED	
Reference Source Document Type	Release Specification	CD	
Reference Source Document ID	FR1232 (Artificial ID)	ST	
Reference Source Document Classification	In-house/Batch release specification	CD	
Element Group: Organization			
Manufacturer ID	DUNS78645 (Artificial ID)	II	
Manufacturer Name	Company ZZ	ST	
Issuer of ID	EMA OMS	CD	

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Element Name	Value	Data Format	Note #
Manufacturer Role	Manufacturer	CD	
NOTE 1 This (Parent) Substance ID refers to the Substance Name: Cryopoor plasma. NOTE 2 The Critical Process Number Version Number would change if a substantial change in the (synthetic) manufacturing process occurred. These would include a change in the chemistry, addition of elimination of a purification step. The change in a version number should be tied to the production system type.			

G.4.7 Specified Substance Group 1 Information level

Specified Substances include additional information for substances and multi-substance materials (multiple Substances and/or Specified Substances of diverse origin used as a component in the formulation of a medicinal product).

Specified Substance Group 1 (SSG1), see subclause G.4.6, captures the Cryopoor plasma used in process flow 'N' with the constituents (such as ranges of marker or signature substance(s), other substances (e.g. Human Albumin, Plasma-derived) that may have biological activity and extraction solvent(s)), physical form and any properties essential to the description of the material.

NOTE The characteristic attribute "Country of Origin" is mandatory for Plasma-derived substance captured at the Specified Substance Group 1. This attribute has been repeated at the Specified Substance Group 1 information level because this information is tied to the Specified Substance Group 1 ID and Specified Substance Group 1 Name and may have a different value from what is captured at the Substance level for the Parent Cryopoor plasma pool, since for Cryopoor plasma, process flow 'N' several batches Cryopoor plasma could be used, with different countries or origin. For example, the Substance Human Albumin, Plasma-derived can be considered to be produced by a two-step process as described above.

Table G.11 — Tabular information captured at the Specified Substance Group 1 information level for Cryopoor plasma process flow 'N' (intended for Human Albumin solution for injection (Ph.Eur.)

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 1			
Specified Substance Group 1 ID	PLASN4624Q (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Cryopoor plasma process flow 'N'	ST	
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Constituent			
Constituent Substance ID	HPFF12345O (artificial ID)	II	
Constituent Substance Name	Human Plasma for Fractionation	ST	

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Element Name	Value	Data Format	Note #
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Constituent (Repeat)			
Constituent Substance ID	PROT3456TP (Artificial ID)	II	
Constituent Substance Name	Total Protein of Human Plasma	ST	
Language	en	CD	
Substance Role	Ingredient	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	NLT	CD	
Quantity	200	PQ	
Unit	g/kg	CD	
Amount Text	NLT 200 g/kg	ST	
Element Group: Constituent (Repeat)			
Constituent Substance ID	ALBUM89765 (Artificial ID)	II	
Constituent Substance Name	Human Albumin, Plasma-derived	ST	
Language	en	CD	
Substance Role	Ingredient	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	95	PQ	
Unit	%{w/w}	CD	
Amount Text	Number Average of Total Protein		
Element Group: Fraction Description			
Fraction	Process Flow 'N'	ST	
Material Type	Protein	CD	
Element Group: Modification			
Modification Type	Physical	CD	
Element Group: Physical Modification			

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Element Name	Value	Data Format	Note #
Role	Isolation of Cryopoor plasma process flow 'N' by Precipitation and absorption steps by the modified Cohn fractionation process.	ST	
Element Group: Characteristic Attribute			
Attribute Type	Cryopoor Plasma Process Flow	CD	
Attribute Name	Country of Origin	ST	1)
Is Defining	Yes	BL	
Element Group: Amount			
Non Numeric Value	NL, DE, FR	ST	1)
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Cryopoor Plasma Process Flow	CD	
Attribute Name	Pathogen test, testing strategy	ST	2)
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	NLT	CD	
Quantity	8,4	PQ	
Unit	^{10}logarithmic virus reduction factors	CD	
Element Group: Characteristic Attribute (Viral reduction capacity validation) (Repeat)			
Attribute Type	Cryopoor Plasma Process Flow	CD	
Attribute Name	Pathogen test, testing strategy	ST	3)
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	NLT	CD	
Quantity	4,7	PQ	
Unit	^{10}logarithmic virus reduction factors	CD	

NOTE 1 Country of Origin with reference to the Cryopoor plasma (see Table G.9, Table G.7, Note 2).

Country of Origin used in manufacturing of Cryopoor plasma process flow intended to manufacture Human Albumin, Plasma-derived (Subset of countries as defined in the plasma master file).

NOTE 2 See Table G.5 Enveloped viruses e.g. Bovine Viral Diarrhoea Virus (BVDV).

NOTE 3 See Table G.2, Non-enveloped viruses (Teiler's virus, CPV, HAV)

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G.4.8 Summary

The manufacturing starts at the substance level with the starting material Human plasma for fractionation with the resultant material Cryopoor plasma. In special occasions, a specific process flow 'N' will be used to obtain the plasma-derived product.

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Cryopoor plasma, process flow 'N' manufactured from Human Plasma for Fractionation as Parent Substance is captured in this case at Specified Substance Group 1 and its manufacturing process at Specified Substance Group 2. The Substance Human Albumin, Plasma-derived captured as a constituent from Cryopoor plasma, process flow 'N' is described at the substance information level using the Substance Type Protein information model.

G.4.9 Specified Substance Group 2 Information level

The manufacturing process of plasma-derived products is an important product identifier, as it directly affects quality, e.g. with respect to impurities, product integrity, stability, virus safety etc. However, flow-charts of the manufacturing process and brief narrative overviews do not allow swift evaluation of the presence or absence of relevant process steps. Specifically, this includes steps that are relevant for removal of viruses, prions, pro-coagulant activity (for certain immunoglobulin products), or other impurities.

Plasma-derived products are often manufactured at different manufacturing sites using slightly different manufacturing processes (e.g. with respect to optional adsorption steps). This may unexpectedly turn out to be relevant for product quality or safety, as has been observed for instance for impurities in immunoglobulin products causing thrombogenicity. It is therefore considered important to capture this information. This specifically concerns the adsorption steps that are often performed prior to fractionation or further purification of Cryopoor plasma. These steps are intended for purification of the substance of interest (mandatory steps) or for isolation of other substances of interest (often optional steps) and may directly influence the levels of impurities in the final product.

Therefore, in addition to a flow chart providing an overview of the manufacturing process, specific information should be provided on the following steps.

Adsorption steps

A list of all optional adsorption steps performed prior to fractionation or further purification of Cryopoor plasma should be provided. The optional adsorption steps are considered important to identify a given plasma-derived product but should also be linked to specific manufacturing site(s) of this product. Thus, in the overview of optional adsorption steps, for each optional step it should be indicated at which site(s) it is performed.

Virus removal

A list of all virus inactivation/removal steps should be provided separated in dedicated virus removal steps and other virus removal steps. Other virus removal steps are steps that have been demonstrated to have virus reduction capacity (i.e. log reduction factor ≥1,0), but are not included in the manufacturing process with the sole intention of virus reduction. Examples are partitioning steps in fractionation or chromatography steps. Dedicated virus removal steps include S/D treatment, virus filtration, pasteurization, heat treatment, and low pH treatment. If present in the production of plasma-derived products, these steps should be identified as such and the relevant process parameters should be described.

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For each of the virus inactivation/removal steps, it should be indicated whether its reduction capacity can be considered effective for enveloped and for non-enveloped viruses i.e. log reduction factor ≥4, see: 'Note for Guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses'[36]. Specific log reduction factors demonstrated for the different steps are not captured at this level, as these will be dependent on the specific virus(es) tested. This information can be included when defining the virus safety of the plasma-derived product.

The information that should be provided on virus removal/inactivation steps included in the production process of plasma-derived products is summarized in Table G.12, Table G.13.

Table G.12 — Overview of the information that should be provided on dedicated virus removal/inactivation steps

Dedicated virus removal/inactivation step	Present	Characteristics (if applicable)	Efficacy demonstrated against: Enveloped viruses	Non-enveloped viruses
Nanofiltration	Y/N	Pore size: Manufacturer: Maximum filtration pressure: Minimum filtration pressure:	Y/N	Y/N
S/D treatment	Y/N	Type of S/D chemicals: Concentration of S/D chemicals: Temperature: Duration:	Y/N	Y/N
Heat treatment	Y/N	Temperature: Duration:	Y/N	Y/N
Low pH treatment	Y/N	pH: Temperature: Duration:	Y/N	Y/N

Table G.13 — Overview of the information that should be provided on other virus removal/inactivation steps

Other virus removal/inactivation step	Efficacy demonstrated against	
	Enveloped viruses	Non-enveloped viruses
[Specify]	Y/N	Y/N
…		

Prion removal

The potential of specific manufacturing processes to reduce prion infectivity should be estimated. This should follow a step-wise approach, first taking into account published literature and if necessary

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performing investigational studies and/or considering the addition of a step that may increase reduction capacity. The following information should be provided with respect to prion removal:

— estimated prion reduction capacity of the manufacturing process;

— manufacturing process step(s) expected to contribute to prion reduction;

— for each process step that is expected to contribute to prion reduction, whether this assumption is based on literature data or on investigational studies of the manufacturing process step itself.

The information that should be provided on prion removal steps included in the production process of plasma-derived products is summarized in Table G.14.

Table G.14 — Overview of the information that should be provided on prion removal steps

Manufacturing steps expected to contribute to prion reduction	Estimated prion reduction capacity	Data
[specify]	LRF	Literature/experimental
…		
NOTE LRF: Log_{10} Reduction Factor		

Removal of pro-coagulant activity

For immunoglobulin products intended for intravenous or subcutaneous administration, the process step(s) demonstrated to be capable of removing pro-coagulant activity should be indicated.

The manufacturing process is described at the Specified Substance Group 2 Information level, class 'Manufacturing' (see Figure 36). However, the information shown in Figure E.7 is used for describing the extended information class Manufacturing.

NOTE
Cycle 1: Resultant material Cryopoor plasma, selected by Cryopoor plasma, process flow 'N' from the starting material Human Plasma for Fractionation.

Cycle 2: Starting material Cryopoor plasma, process flow 'N', resultant material Human Albumin, Plasma-derived.

Table G.15 — Tabular information for the manufacturing of Cryopoor plasma Process flow 'N' (Manufacturer AA): Cycle 1

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2 (Cryopoor plasma Process Flow 'N' – Manufacturer AA)			
Specified Substance Group 2 ID	FEPM78654F (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Cryopoor plasma Process Flow 'N'-Company AA	ST	
Substance Name Type	Specified Substance Group 2	CD	

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Element Name	Value	Data Format	Note #
Language	en	CD	
(Parent) Substance ID	CRYOP12345 (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Fractionation	CD	
Production Method Description	Fractionation, absorption, virus inactivation and depth filtration	ST	
Production System Type	Continuous plasma fractionation from Cryopoor plasma	CD	
Critical Process Version Number	1	INT	2)
Version	007	ST	
Version Date	20161124	TS.Date	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	FINAL34521 (Artificial ID)	ST	
Reference Source Citation	CBG564231 (Artificial CBG-Case number)	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	PDF	ED	
Reference Source Document Type	Release Specification	CD	
Reference Source Document ID	FR1232 (Artificial ID)	ST	
Reference Source Document Classification	In-house/Batch release specification	CD	
Element Group: Organization			
Manufacturer ID	DUNS78645 (Artificial ID)	II	
Manufacturer Name	Company AA	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	

NOTE 1 This (Parent) Substance ID refers to the Substance Name: Cryopoor plasma.

NOTE 2 The Critical Process Number Version Number would change if a substantial change in the (synthetic) manufacturing process occurred. These would include a change in the chemistry, addition of elimination of a purification step. The change in a version number should be tied to the production system type.

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Table G.16 — Tabular information for the manufacturing of the constituent Human Albumin, Plasma-derived from Cryopoor plasma Process flow 'N' (Manufacturer BB): Cycle 2

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2 (Human Albumin, Plasma-derived–Manufacturer 3)			
Specified Substance Group 2 ID	FALBU67543 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Human Albumin, Plasma-derived-Company BB	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	PLASN4624Q (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Fractionation	CD	
Production System Description	Fractionation, absorption, virus inactivation and depth filtration	ST	
Production System Type	Human Albumin by Continuous plasma fractionation from Cryopoor plasma process flow 'N'	CD	
Critical Process Version Number	1	INT	2)
Version	009	ST	
Version Date	20170419	TS.Date	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	MAA	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	FINALBUM87 (Artificial ID)	ST	
Reference Source Citation	CBG564231 (Artificial CBG-Case number)	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	PDF	ED	
Reference Source Document Type	Release Specification	CD	
Reference Source Document ID	FR1233 (Artificial ID)	ST	
Reference Source Document Classification	In-house/Batch release specification	CD	

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Element Name	Value	Data Format	Note #
Element Group: Organization			
Manufacturer ID	DUNS12345 (Artificial ID)	II	
Manufacturer Name	Company BB	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	

NOTE 1 This (Parent) Substance ID refers to the (Specified) Substance (Group 1) Name: Cryopoor plasma process flow 'N'.

NOTE 2 The Critical Process Number Version Number would change if a substantial change in the (synthetic) manufacturing process occurred. These would include a change in the chemistry, addition of elimination of a purification step. The change in a version number should be tied to the production system type.

G.4.10 Structuring of the plasma-derived substance information

The plasma-derived substance information is described in accordance with the definitions used in the ISO 11238 and ISO/TS 19844.

G.4.10.1 Substance Information level

The final plasma-derived substance is defined as a structurally diverse substance. An alternative definition would be to describe a purified plasma protein as a protein. The Substance Type 'Protein' following the requirements as described in Annex C, e.g. Albumin, antithrombin III, human coagulation Factor XI or fibrinogen. For other products, such as polyvalent immunoglobulin (IgG) products or mixtures of coagulation factors such as pro-thrombin complex, are described following the Mixture information model, see Figure 34.

The product characteristics that should be described for plasma-derived products in addition to the source material and certain aspects of their production process (see above) include the active substance(s), product specifications and virus safety.

The characteristics of the proteins in relatively simple plasma-derived products containing a single protein such as albumin, antithrombin III, human coagulation Factor XI or fibrinogen can be described in a similar manner as non-plasma-derived/recombinant proteins. Elements to be captured include structure, molecular formula, molecular weight, amino-acid composition, disulfide bonds and post-translational modifications as is described for the class Substance Type Protein, see Figure C.1 and Figure C.1. It is noted that plasma-derived products are often not specifically characterized with respect to these elements, due to practical constraints and/or because the available public data are considered generally applicable. These characteristics can therefore be described at substance information level.

Table G.17 — Tabular information of preregistration at the Substance information level for Human Albumin, Plasma-derived (Limited information)

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	ALBUM12345 (Artificial ID)	II	1)
Substance Type	Protein (Plasma-derived)	CD	

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Element Name	Value	Data Format	Note #
Element Group: Substance Name			
Substance Name	Human Albumin	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP38-NF33 Page 2067	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Human Serum Albumin	ST	
Substance Name Type	Plasma-derived	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Journal	CD	
Reference Source Class	Literature	CD	
Reference Source Citation	Gabriella Fanali *et al.*, Molecular Aspects of Medicines 33(2012) 209 -290 'Human serum Albumin'	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Albumins, blood serum	ST	
Substance Name Type	Other Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	

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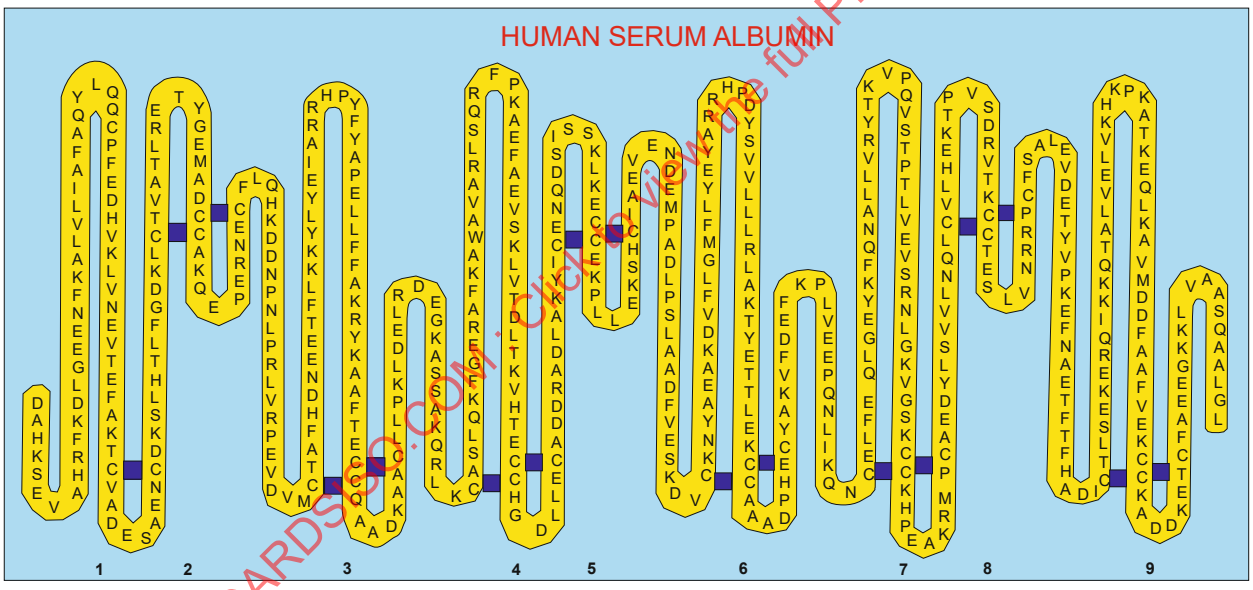
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Element Name	Value	Data Format	Note #
Element Group: Substance Code			
Code	9006-53-5	CD.Code	
Code System	CAS Registry	CD.CodeSystem Name	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	ZIF514RVZR	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystem Name	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	B05AA01	CD.Code	
Substance Classification Type	Blood substitutes and plasma protein fractions, Albumin	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=B05AA01	ST	
Element Group: Source Material			
Source Material Class	Biologic	CD	
Source Material Type	Human	CD	
Source Material State	N/A		
Organism ID	HUMA875601 (Artificial ID)	II	
Organism Name	Homo sapiens, Linnaeus 1758	ST	
Parent Substance ID	PLASN4624Q (Artificial ID)	II	
Parent Substance Name	Cryopoor plasma process flow 'N'	ST	
Country of Origin	NL, DE, FR, ES, US	CD	2)
Development Stage	N/A		

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Element Name	Value	Data Format	Note #
Element Group: Part Description			
Part	Human Plasma for Fractionation	CD	
Part Location	N/A		
Element Group: Fraction Description			
Fraction	Human Albumin, Plasma-derived	ST	
Material Type	Protein	CD	
Element Group: Structure			**3)**
Molecular Formula	$C_{2936}H_{4624}N_{786}O_{889}S_{41}$	ST	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	See image below	ED	



NOTE Figure adapted from Peters Theodore Jr., [37], from Figure Human Serum Albumin.

Figure G.8 — Structural representation of Human Serum Albumin

Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	UniProt	CD	
Reference Source Class	Public database	CD	
Reference Source URL	http://www.uniprot.org/uniprot/Q56G89	ST	
Element Group: Molecular Weight			

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Element Name	Value	Data Format	Note #
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	66,437	PQ	4), 5)
Unit	g/mol	CD	
Element Group: Gene			
Gene Sequence Origin	Human	CD	
Gene ID	PRO0883	CD	
Gene Name	ALB	ST	6)
Element Group: Protein			
Sequence Type	Complete	CD	
Number of Subunits	1	INT	
Element Group: Protein Subunit			
Subunit	1	INT	
Sequence	See below	ST	
*MKWVTFISLL FLFSSAYSRG VFRR*DAHKSE VAHRFKDLGE ENFKALVLIA FAQYLQQCPF EDHVKLVNEV TEFAKTCVAD ESAENCDKSL HTLFGDKLCT VATLRETYGE MADCCAKQEP ERNECFLQHK DDNPNLPRLV RPEVDVMCTA FHDNEETFLK KYLYEIARRH PYFYAPELLF FAKRYKAAFT ECCQAADKAA CLLPKLDELR DEGKASSAKQ RLKCASLQKF GERAFKAWAV ARLSQRFPKA EFAEVSKLVT DLTKVHTECC HGDLLECADD RADLAKYICE NQDSISSKLK ECCEKPLLEK SHCIAEVEND EMPADLPSLA ADFVESKDVC KNYAEAKDVF LGMFLYEYAR RHPDYSVVLL LRLAKTYETT LEKCCAAADP HECYAKVFDE FKPLVEEPQN LIKQNCELFE QLGEYKFQNA LLVRYTKKVP QVSTPTLVEV SRNLGKVGSK CCKHPEAKRM PCAEDYLSVV LNQLCVLHEK TPVSDRVTKC CTESLVNRRP CFSALEVDET YVPKEFNAET FTFHADICTL SEKERQIKKQ TALVELVKHK PKATKEQLKA VMDDFAAFVE KCCKADDKET CFAEEGKKLV AASQAALGL			
Length	609	INT	7)
Element Group: Protein (Part of Group)			
Disulfide Linkage	Residue 34: -SH; 17 intra chain disulfide bonds (positions indicated in the Figure above).	ST	
Element Group: Glycosylation (Not applicable)			
NOTE Human serum albumin (HAS) is a monomeric, single-chain molecule, with no prosthetic group or carbohydrates attached. HSA is normally unglycosylated since its primary structure lacks the canonical Asn-X-Thr/Ser tripeptide acceptor sequence required for N-glycosylation. To date, three HSA N-glycosylated genetic variants have been identified, with glycosylation sites at Asn63, Asn318 and at Asn494. (Source lit. Note 7).			
Element Group: Protein Subunit (Part of Group); modification of Albumin shall be captured as a modification within the Structural Modification group. For further information, see Note 5)			
Element Group: Property			

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Element Name	Value	Data Format	Note #
Property Type	Physical	CD	
Property Name	pH	CD	
Property Parameters	Measured at 20 °C in water 40 mg/ml	ST	
Property Substance ID	ALBUM89765 (Artificial ID)	II	
Property Substance Name	Human Albumin, Plasma-derived	ST	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	7,0	PQ	
Low Limit	6,7	PQ	
High Limit	7,3	PQ	
Unit	N/A (dimensionless quantity)		
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Molecular Size Distribution	CD	
Property Parameters	N/A		
Property Substance ID	ALBUM89765 (Artificial ID)	II	
Property Substance Name	Human Albumin, Plasma-derived	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	95,5	PQ	
Unit	%{w/w}	CD	
Amount Text	Average Weight per cent of Monomers-Dimers	ST	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Molecular Size Distribution	CD	
Property Parameters	N/A		
Property Substance ID	ALBUM89765 (Artificial ID)	II	
Property Substance Name	Human Albumin, Plasma-derived	ST	
Element Group: Amount			
Amount Type	Exact	CD	

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Element Name	Value	Data Format	Note #
Quantity	4,5	PQ	
Unit	%{w/w}	CD	
Amount Text	Average weight distribution, Polymers	ST	

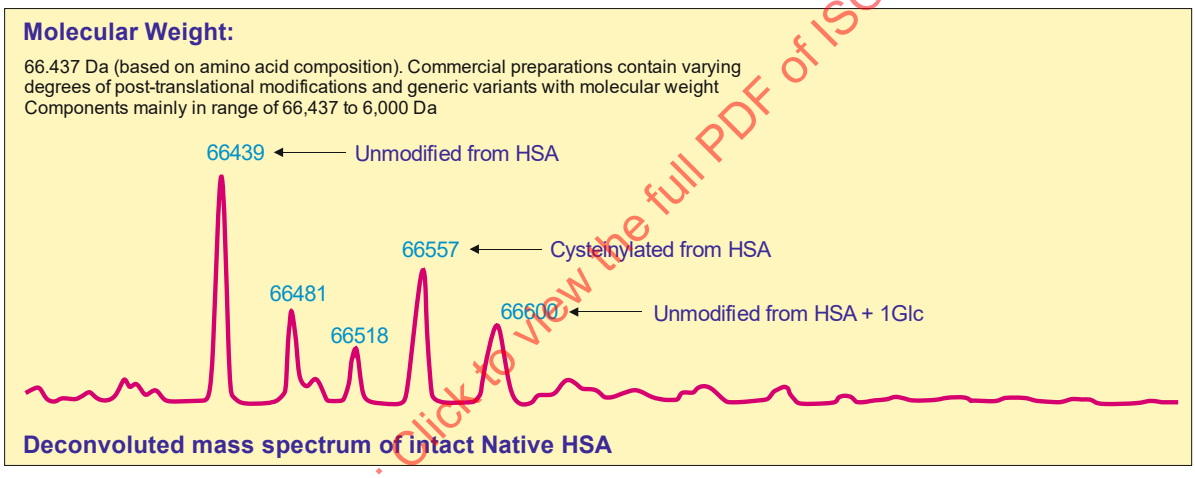
NOTE 1 Substance ID corresponds to the Human Albumin, Plasma-derived as a constituent manufactured from the Cryopoor plasma flow 'N'. See Table G.16.

NOTE 2 Country of Origin related and specified in the Plasma Master File.

NOTE 3 From the Element Group 'Structure' to the end of the table, the Protein model is followed.

NOTE 4 Molecular weight distribution, see Note 5 below.

NOTE 5 Mass spectroscopy Analysis of various preparations indicates the presence of several post-translational modifications. Native human serum albumin is not a glycoprotein in the traditional sense. However, several genetic variants exist that may undergo enzymatic N-& O-glycosylation. Upon circulation in plasma, albumin often becomes glycosylated on ε amine groups of lysine and possibly arginine residues. This is the result of the non-enzymatic spontaneous Maillard Reaction between the carbonyl group of the open ring form of glucose, present in small amounts in plasma, forming a Schiff base with the exposed primary amines of circulating proteins such as albumin, insulin and haemoglobin.



NOTE Figure adapted from Sigma-Aldrich[38].

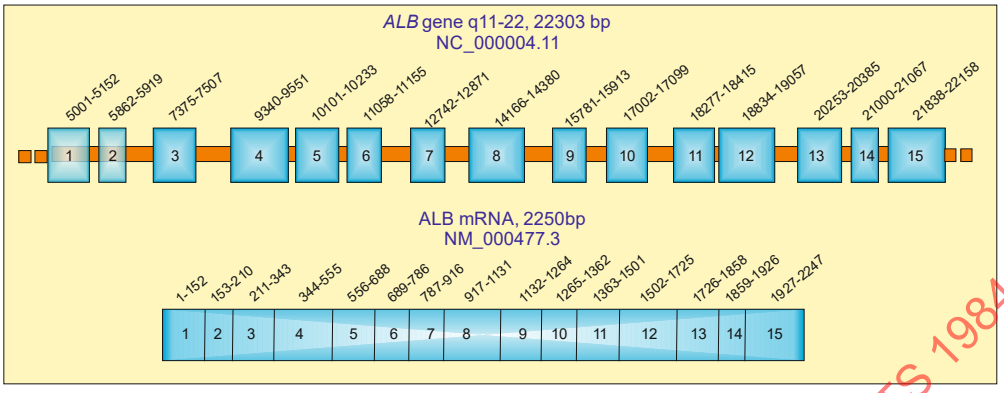
Figure G.9 — Deconvoluted mass spectrum of intact Native HAS

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Element Name	Value	Data Format	Note #

[6] HSA synthesis is governed by a single copy gene (ALB; GenBank reference sequence NC_000004.11) lying on the long arm of chromosome 4, near the centromere at position q11–22, where the genes of the other members of the SA family are located.



NOTE Figure adapted from Fanali G. *et al.* [39], from Fig. 1, page 213.

Figure G.10 — ALB gene and mRNA organization

ALB gene and mRNA organization. The ALB gene lies on the long arm of chromosome 4, near the centromere at position q11-22, and is composed of 22306 base pair (bp) subdivided in 15 exons and 14 introns. The exons and introns numbering is based on the GenBank reference sequence NC_000004.11.

The ALB transcript is composed of 2250 bp; the exons bp numbering is based on the GenBank reference sequence NM_000477.3 [39].

[7] Of the 609 amino acids in this sequence, encoded by the ALB gene [11] and translated to form the precursor protein, only 585 amino acids are observed in the final product present in the blood; the first 24 amino acids of the sequence (here italicized), including the signal peptide (1–18) and propeptide (19–22, or 19–24) portions, are cleaved after translation. The three-dimensional structure of human serum Albumin has been determined crystallographically to a resolution of 2.8Å. It comprises three homologous domains that assemble to form a heart-shaped molecule. Each domain is a combination of two subdomains that possess common structural motifs. The principal regions of ligand binding to human serum albumin are located in the hydrophobic cavities in subdomains IIA and IIIA, which exhibit similar chemistry. For further documentation see Xiao Min He & Daniel C. Carter [40].

G.4.10.2 Specified Substance Group 2 Information level

For some single-protein plasma-derived products, protein characteristics may be dependent on the production process. This is for instance the case for human α-1-proteinase inhibitor, which is a glycoprotein existing in isoforms with different isoelectric points. The isoform composition may vary depending on the production process and should be captured at the manufacturing level.

A number of coagulation factors are in practice always co-purified to some extent with other proteins, see Figure G.13. As the extent of co-purification depends on the production process, the level of these co-purified proteins should be captured related to the manufacturing process coupled to the manufacturer e.g. captured at the Specified Substance Group 2 information level. In the specific case of Factor VIII (FVIII) and Von Willebrand Factor (VWF), these proteins are co-purified and exist in complexes and manufacturer specific information on the proportions of VWF and FVIII should be provided. VWF is assembled in multimers, which may vary in molecular size depending on the production process. Given the influence on multimer size on VWF potency, this information should also be captured at the Specified Substance Group 2 information level when this information is available.

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Polyvalent immunoglobulin (IgG) products consist of a mixture of IgGs against a variety of antigens. These mixtures of proteins can be characterized by the general characteristics of IgG proteins, but not by specific characteristics such as antigen binding capacity or effector function of each subset of IgGs that is present, as this may also be highly dependent on the characteristics of the blood/plasma donors. Subclass distribution in IgG products may be influenced by the production process, and should be captured at the Specified Substance Group 2 information level.

Table G.18 — Overview of coagulation factors that contain co-purified proteins

Product	Co-purified proteins
Human coagulation Factor VII (FVII)	FVIIa, FII, FIX, FX, protein C, and protein S
Human coagulation Factor (FVIII)	VWF
Human coagulation Factor IX (FIX)	FII, FVII, and FX (levels should be <5%)
Human von Willebrand Factor	FVIII

G.4.10.3 Specified Substance Group 3 Information level: specifications

This information is provided for information only. It should be captured as part of the Medicinal Product as defined by the ISO/TS 20443.

The captured information on specifications should include reference to relevant Pharmacopoeia monographs, which the product complies with. In addition, product-specific release specifications should be provided. For some products, it may be necessary to include additional information, e.g. regarding specific activity, impurities or potency. The latter is for instance the case for FVIII and FIX products for which it is known that the results of potency determination may be dependent on the assay used. This information is captured at the Specified Substance Group 3 information level with reference to the pharmaceutical grade, see Figure 38. Additional specification can be laid down in the Element Group Reference Source with the Reference Source Document Type 'In-house specification' the actual document itself will be stored in the Reference Source Document Classification attribute '(Release) Specification document'.

Table G.19 — Tabular information captured at the Specified Substance Group 3 information level for Human Albumin solution for injection (Ph.Eur.)

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	QRTD97854A3 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Human Albumin solution - Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	FALBU67543 (Artificial ID)	II	1)

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Element Name	Value	Data Format	Note #
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name	Human albumin solution-Ph.Eur.	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia, monograph 0255	ST	
Element Group: Substance Name (Repeat)			
Substance Name	ALUBUSOL (Artificial grade name used by Manufacturer BB)	ST	
Substance Name Type	Other Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	Kljuf67543 (Artificial ID)	ST	
Reference Source Citation	CBG231675 (Artificial CBG-Case number)	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	PDF	ED	
Reference Source Document Type	In-house specification	CD	
Reference Source Document ID	5643 (Artificial ID)	ST	
Reference Source Document Classification	In-house/Batch release specification	CD	
NOTE This (Parent) Substance ID refers to the (Specified) Substance (Group 2) Name: Human Albumin, Plasma-derived – Company BB, which connect the Grade specification to the manufacturing process based on Cryopoor plasma, process flow 'N'.			

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G.4.11 Virus Risk Assessment

Virus safety of plasma-derived products is evaluated by estimating the potential virus load in a vial of finished product taken into account the estimated worst-case viral load in the volume of plasma needed

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to produce this vial and the virus reduction/removal capacity of the production process. To allow comparison of the results, a standardized format for presentation of the results should be aimed at.

G.5 Example Plasma-derived Factor VIII + VWF

G.5.1 Introduction/background information for FVIII example

Plasma-derived Factor VIII (FVIII) is a glycoprotein that is present in plasma in a non-covalently bound complex with the glycoprotein von Willebrand Factor (VWF). The proteins can be co-purified from human plasma via precipitation and chromatographic techniques. Depending on the manufacturing process the ratio between FVIII and VWF in plasma-derived products may vary. In addition, the manufacturing process could affect the VWF multimer distribution, which may influence VWF potency and FVIII binding capacity. Information on these product characteristics should be provided.

With regard to the production process of FVIII/VWF of a given manufacturer, the main effect of the use of different manufacturing sites would be related to potential differences in the country of plasma origin and the testing strategy applied to the source material 'human plasma for fractionation'. This can be captured at the Cryoprecipitate level. As the parent substance for FVIII/VWF is Cryoprecipitate, discussion of optional adsorption steps (see Figure G.5) is not relevant. Information on virus and prion reduction capacity of the production process should be provided. As no major differences are allowed in these steps when performed at different manufacturing sites, this information can be captured at the substance level. Note that, in the process of fractionation and/or adsorption the use of heparin or heparin-antithrombin III complexes of antithrombin III as reagents is not unusual. Because heparin is an animal-derived reagent and caused problems in the past, information on this substance shall be provided. The required information on heparin should be submitted and the information of the manufacturer should be provided. Excipients of human albumin are captured at the product level.

In Figure G.1, the process flow of the manufacturing of human coagulation Factor VIII together with varying amounts of human von Willebrand Factor is described with Cryoprecipitate as Parent substance.

In accordance with the Pharmacopoeial monographs (e.g. Ph. Eur. Monograph 07/2013:0275 Human Coagulation Factor VIII) consistency of the method of production for products stated to have human von Willebrand factor activity (products intended for treatment of von Willebrand' s disease) is required. It shall be demonstrated by suitable analytical procedures determined during process development, that the manufacturing process yields a product with a constant composition with respect to human von Willebrand factor activity. This composition can be characterized in a number of ways. For example, the distribution of the different human von Willebrand factor multimers may be determined by sodium dodecyl sulfate (SDS) agarose gel electrophoresis with or without Western blot analysis, using a normal plasma pool as reference. Visualization of the multimeric pattern may be performed using, for example, an immunoenzymatic technique and quantitative evaluation may be carried out by densitometric analysis.

G.5.2 General discussion of the structure of FVIII

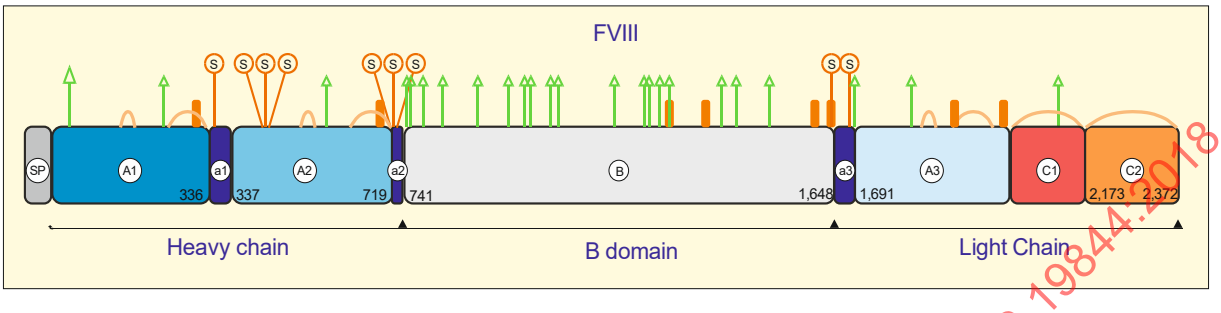
G.5.2.1 Molecular characterization of FVIII

Protein structure:

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The human *F8* gene is localized on the long arm of the X chromosome and consists of 26 exons and introns, for a total length of 9 kbp in coding sequence. Sinusoidal endothelial and Kupffer cells in the liver are the major site of FVIII expression. The gene encodes a large precursor glycoprotein of 2,332 amino acid residues (the maximum length), consisting of six structural domains and three acidic subdomains, organized in a heavy chain [A1(a1)A2(a2)B] and light chain [(a3)A3C1C2], as shown in Figure G.11.



NOTE Figure adapted from Santagostino Elena[41] from figure 1, p. 2509.

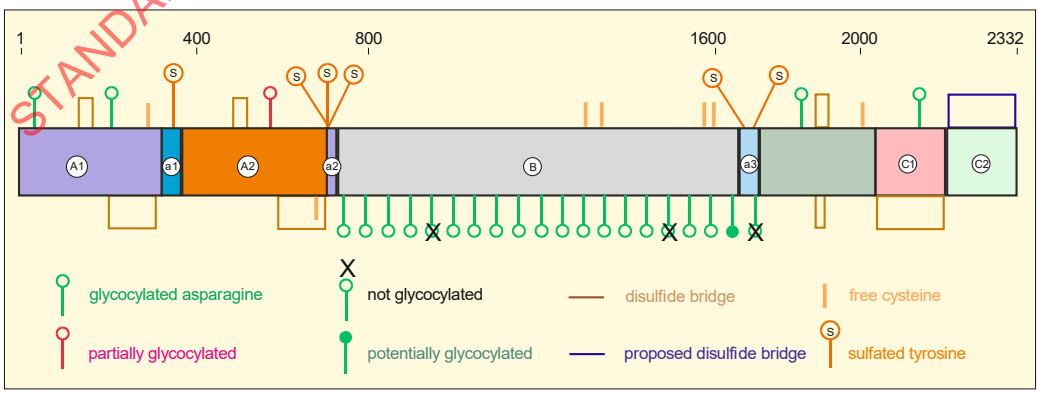
Figure G.11 — Representative structure of precursor human Factor VIII.

NOTE Domains are indicated with capital letters and subdomains with lower case letters. Glycosylation sites are denoted by triangles, disulfide bonds are denoted by arches, reduced cysteine residues are denoted by orange vertical lines, and "S" inside a circle indicates sulfated tyrosine residues. SP denotes Signal Peptide.

The *F8* gene comprises 26 exons, which encode a polypeptide chain for a signal peptide of 19 amino acids and a mature protein of 2332 amino acids. FVIII is synthesized as an inactive single chain with the discrete domain structure of A1-a1-A2-a2-B-a3-A3-C1-C2. The full single chain protein consisting of 2,351 amino acids has a molecular weight of 267,039 Da [42].

Domains a1, a2 and a3 are acidic amino acid rich regions between the major structural domains and contain sulfated tyrosine residues. The A domains of FVIII share approx. 40 % amino acid identity with each other and to the A domains of FV. The FVIII C domains in turn also exhibit approximately 40 % amino acid identity to each other and to the C domains of FV and proteins that bind negatively charged phospholipids, suggesting a role in phospholipid interaction. Encoded by exon 14, the B domain spans the sequence from amino acids 741–1648. Several characteristics distinguish the B domain.

According to Lenting P.J. at al., 1998 [43], the mature FVIII is represented by Figure G.12.



NOTE Figure adapted from Lenting P.J. *et al.* [43] from page 3986.

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Figure G.12 — Representative structure of mature human FVIII

Amino acid sequence:

The Factor VIII protein. Mature Factor VIII consists of 2332 amino acids, which are arranged in a discrete domain structure: A1 (residues 1-336), A2 (373-710), B (741-1648), A3 (1690-2019), C1 (2020-2172), and C2 (2173-2332). See for the full sequence including the signal peptide Table G.22 (http://www.nextprot.org/db/entry/NX_P00451/sequence ; >sp|P00451|FA8_HUMAN Coagulation Factor VIII OS=Homo sapiens GN=F8 PE=1 SV=1; Isoform: Iso 1, 2351 aa, Mass: 267,009 Da.)

The A domains are bordered by acidic regions a1 (337-372), a2 (711-740), and a3 (1649-1689).

Disulfide Bridges:

Using B-domainless Factor VIII, seven disulfide bonds have been identified: residues 153-179; 248-329 (A1 domain); 528-554; 630-711; (A2 domain), 1832-1858; 1899-1903 (A3 domain); 2021-2169 (C1 domain). Within the C2 domain, residues 2174-2326 most likely also form a disulfide bridge.

Free cysteine-residues have been identified at positions 310, 692, and 2000. Cys528 and Cys1858 may be present as free cysteines, because these residues are reactive toward a sulfhydryl-specific agent. With regard to the Cys-residues in the B-domain it is unknown whether they are free or linked.

N-Linked Glycosylation:

Factor VIII contains 25 consensus sequences (Asn-Xxx-Thr/Ser) that allow N-linked glycosylation. Using either full-length or B-domainless Factor VIII the majority of these sites have been shown to be glycosylated: residues 42 and 239 (A1 domain), residues 757, 784, 828, 900, 963, 1001, 1005, 1055, 1066, 1185, 1255, 1259, 1282, 1300, 1412, and 1442 (B domain), residue 1810 (A3 domain), and residue 2118 (C2 domain). Non-glycosylated residues are present at positions 943 and 1384 (B domain) and at position 1685 (a3 acidic region). Residue 582 (A2 domain) has been reported to be non-glycosylated or to be partially glycosylated.

Finally, it remains to be investigated whether residue 1512 (B domain) is glycosylated.

Tyrosine Sulfation:

The acidic regions contain consensus sequences that allow sulfation of Tyr-residues at positions 346 (a1 region), 718, 719, 723 (a2 region), 1664, and 1680 (a3 region).

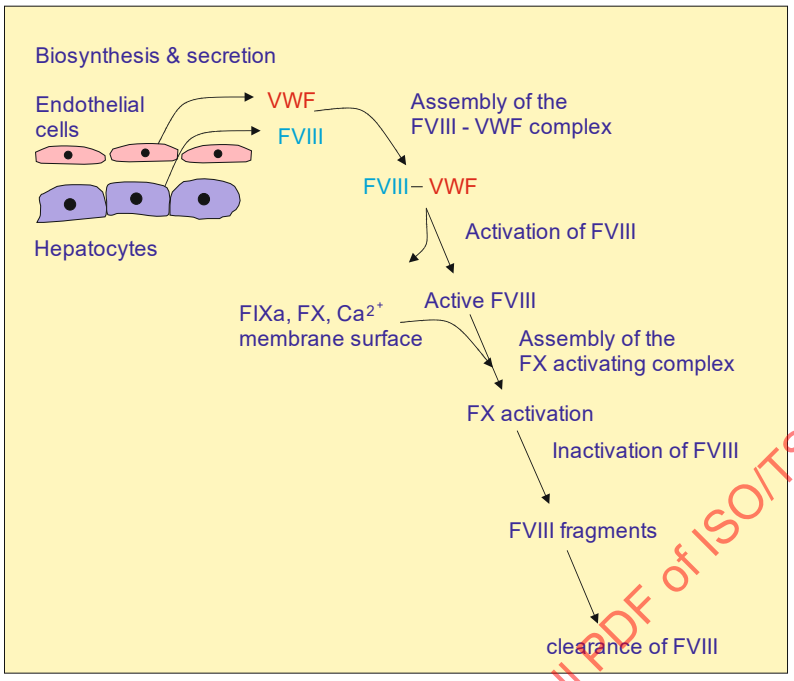
The lifespan of Factor VIII:

Factor VIII is synthesized by various tissues, including liver, kidney, and spleen, as an inactive single-chain protein. After extensive posttranslational processing, Factor VIII is released into the circulation as a set of heterodimeric proteins, see Figure G.13 and Figure G.14. This heterogenous population of Factor VIII molecules readily interacts with VWF, which is produced and secreted by vascular endothelial cells. Upon triggering of the coagulation cascade and subsequent generation of serine proteases, Factor VIII is subject to multiple proteolytic cleavages. These cleavages are associated with dramatic changes of the molecular properties of Factor VIII, including dissociation of VWF and development of biological activity. After conversion into its active conformation, and participation in the Factor X activating complex,

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activated Factor VIII rapidly loses its activity. This process is governed by both enzymatic degradation and subunit dissociation and illustrated in Figure G.13.



NOTE Figure adapted from Lenting P.J. *et al.* [43] from page 3984.

Figure G.13 — Biosynthesis & secretion of FVIII

The mature protein has an apparent molecular weight of 280 kDa composed of a light chain and a heavy chain. The light chain has a molecular weight of 80 kDa and is made up of domains A3-C1-C2.

The heavy chain is composed of domains A1-A2-B and has a more heterogeneous composition with molecular weights varying from 90 – 200 kDa depending on additional cleavage in the B-chain: The smallest is composed of the A1-A2 domains only.

The protein is formed and cleaved and undergoes intracellular proteolysis as is shown in Figure G.14.

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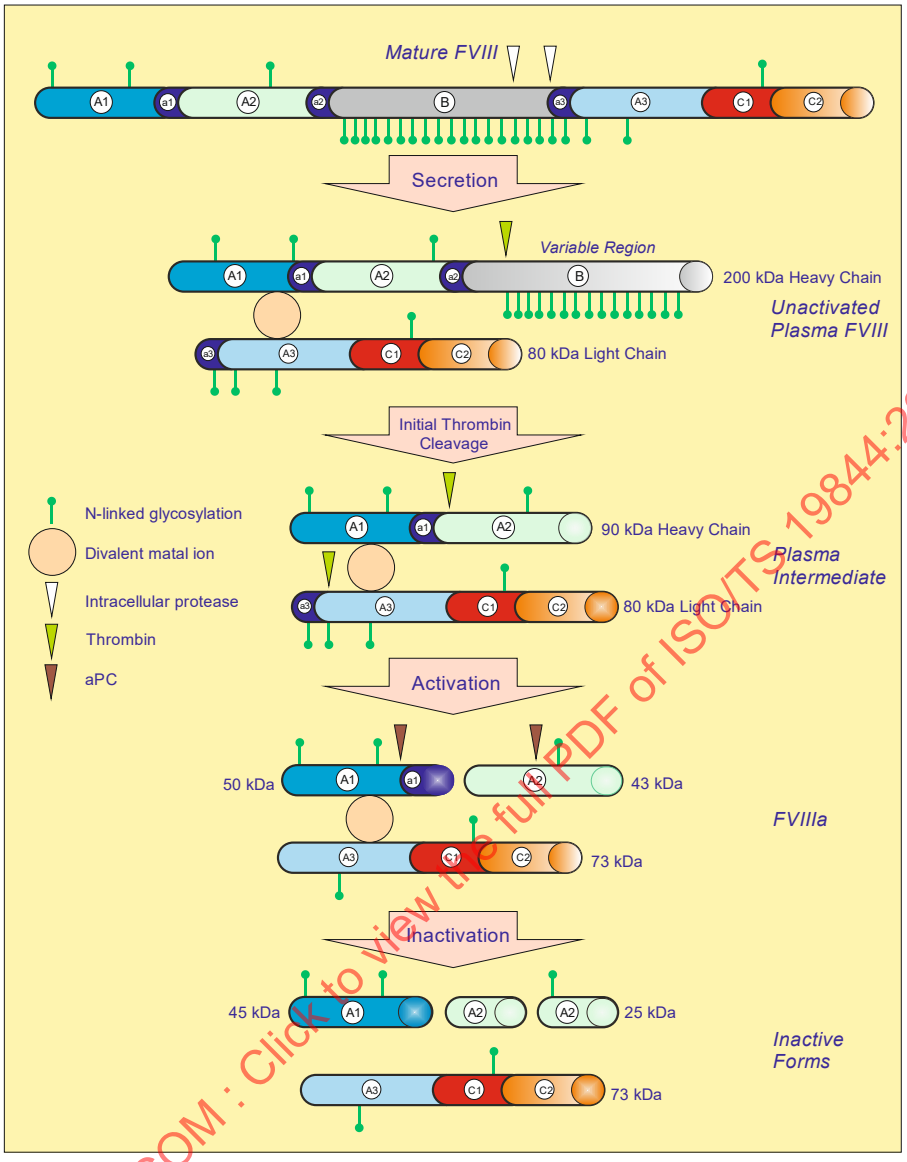


Figure G.14 — Representative structure of Mature FVIII and Representation after secretion: unactivated plasma FVIII

(Figure adopted from Pipe S.W. [44], From Fig.1, page 1188)

Depended on the proteolysis of Factor VIII the major part of Factor VIII circulates as a set of heterogenous dimers consisting of a heavy chain (A1-a1-A2-a2-B) and the light chain (a3-A3-C1-C2). The dimer is held together by a divalent Metal ion (Cu2+) shown as a ball in Figure G.15 bridging domains A1 and A3. The possible variable sizes of the heavy chain are illustrated in Figure G.15.

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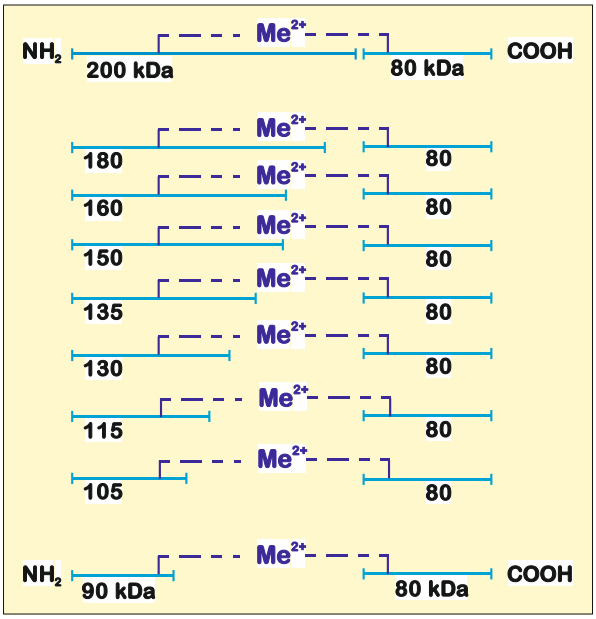


Figure G.15 — Variable sizes of heterogenous dimers of FVIII after limited proteolysis within the B domain

Every domain plays a physiological role throughout the life cycle of FVIII, from biosynthesis to clearance. A particular case is the 908 amino acid residue B-domain, which does not seem to be required for FVIII clotting activity but is important for processing, intracellular transport, and secretion of FVIII protein. At present, it is not possible to definitely exclude potential post-secretion B-domain role during FVIII activation, platelet binding, and inactivation. The B-domain is partially removed from mature FVIII, so that several truncated B-domain variants of FVIII circulate in the bloodstream, see Figure G.16.. Complete or partial deletions of the B-domain are not associated with significant differences in procoagulant properties of these FVIII variants.

Secretory proteins follow a path through the cell that leads through the endoplasmic reticulum (ER) to an endoplasmic reticulum-Golgi intermediate compartment (ERGIC) and finally to the Golgi before release into the plasma. After synthesis the FVIII protein, directed by the signal peptide, is translocated into the lumen of the ER, which serves as the major site for the folding and assembly of secretory proteins as well as integral membrane proteins. Facilitated by enzymes and molecular chaperones, newly synthesized proteins fold and assemble into tertiary structures within the ER. The molecular chaperones also serve as an essential part of the ER quality control (QC) system ensuring export of only properly folded proteins. The QC system recognizes general structural differences between native and non-native proteins and prevents the secretion of non-native proteins that could be non-functional and antigenic.

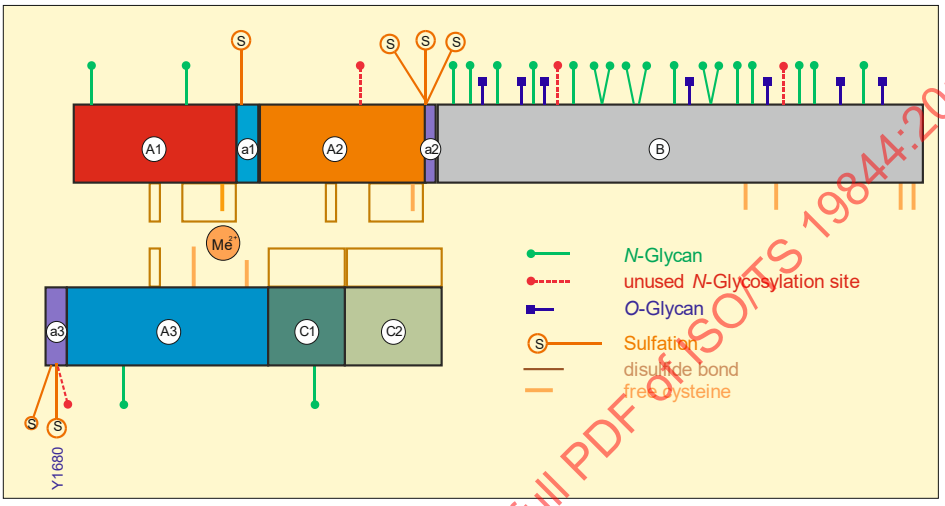
Once in the Golgi compartment, FVIII is among the many proteins to undergo intracellular proteolysis. The tertiary structure of FVIII confers on the B domain region a particular susceptibility to proteolysis. The heavy- and light-chain portions of FVIII form a globular domain, while the connecting B domain region forms an exposed extended rod-like structure. Moreover, the middle part and the carboxy-terminal region of the B domain comprise a motif (Arg-X-X-Arg) similar to that recognized by intracellular proteases of the subtilisin-like family. Consequently, the FVIII polypeptide is cleaved in the B domain after residues 1313 and 1648 to generate the heavy chain of 200 kDa (A1-a1-A2-a2-B) in a metal ion complex with the light chain of 80 kDa (a3-A3-C1-C2). Within the Golgi apparatus, FVIII also undergoes

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modification of the N-linked oligosaccharides to complex-type structures, O-linked glycosylation, and sulfation of specific tyrosine residues.

Glycosylation sites: The FVIII protein contains 25 sites for N-glycosylation: 2 in domain A1, 1 in A2 and 19 in the B-domain (heavy chain) plus 1 in a3, 1 in A3 and 1 in C1 (light chain). Not all are occupied – the sites in A2 and a3 plus 2–3 in the B domain are unoccupied, resulting in 21 N-glycosylations in native full-length FVIII, see Figure G.16.



NOTE Figure adapted from Kannicht Christoph *et al.* [45], from Fig. 3, Page 83.

Figure G.16 — Graphical representation of Glycosylation and sulfation sites

The most important N-linked glycosylations and sulfation sites are captured in Table G.20.

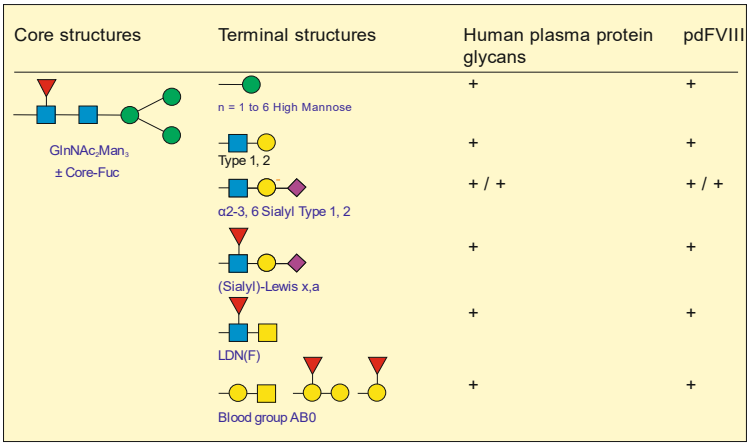
Table G.20 — Principle N-linked Glycosylation sites of human FVIII

PTM	aa	Isolated peptide*	Plasma-derived FVIII	
			Mass range of detected glycopeptides (Da)	Structure
N-linked glycosyl-	N41	HC 37-47	3314–3971	Core- fucosylated biantennary complex structures
	N239	HC 231-240	2407–3104	High-mannose, hybrid and complex structures
	N1810	LC 1804-1813	2899–3614	Core fucosylated biantennary complex structures
	N2118	LC 2117-2136	3247–3896	High-mannose structures (Man 5-9)

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Common features of glycans of plasma-derived human FVIII are:



NOTE Figure adapted from Kannicht Christoph *et al.* [45] from Table 3, Page 84.

Figure G.17 — Core- and Terminal structures present in Human plasma protein glycans

Physiological sulfation of FVIII: Sulfation is required for full activity of FVIII. When recombinant FVIII is expressed in the presence of chlorate, a potent inhibitor of protein sulfation, or when tyrosine residues are replaced by other amino acids, the functional activity of secreted FVIII is reduced five-fold.

Post-translational cellular processing of the FVIII precursor enables sulfation of tyrosine residues in the Golgi apparatus, mediated by a sulfotransferase. There are six potential tyrosine sulfation sites on the FVIII molecule, four on the heavy chain (at amino acid residues 346, 718, 719, and 723) and two on the light chain (residues 1664 and 1680). All the six sulfation sites are required to modulate FVIII activity, see G.21. Sulfation of key tyrosine residues is crucial not only for the function of FVIII, but also for its stability and binding to von Willebrand Factor (VWF) by residue 1680.

Table G.21 — Function specificity of sulfated tyrosine residues in Factor VIII

Tyrosine residues	Significance and activity for FVIII
346 and 1664	Increase of affinity for thrombin interaction and thereby the rate of FVIII activation by thrombin
718, 719, and 723	Increase of specific procoagulant activity of FVIIIa in the complex with FIXa and FX bound to the phospholipid membrane
1680	Prerequisite for complex formation with VWF, influencing half-life of FVIII in the circulation

High affinity VWF-binding appears to be dependent on full post-translational sulfation of the crucial Tyrosine (Y)1680 residue in the N-terminus of the FVIII light (80 kDa) chain. Post-translational tyrosine sulfation is absolutely required for certain functions of FVIII. Interaction with endogenous VWF is thought to protect circulating FVIII molecules from endocytosis by dendritic cells, reducing effector cell presentation and lowering immunogenic potential.

When therapeutic FVIII concentrate (not containing VWF) is infused into patients, complex formation between FVIII and VWF occurs within seconds. In the circulating complex, VWF serves as a chaperone,

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protecting FVIII from premature inactivation (cleavage by FXa and activated protein C), thereby helping to maintain a constant level of circulating FVIII.

Binding sites for von Willebrand Factor (VWF):

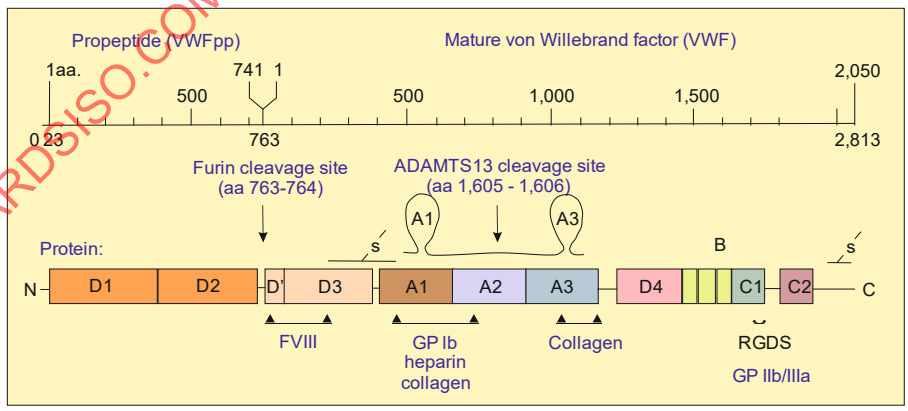
Immediately after its release into the circulation, the Factor VIII heterodimer interacts with its carrier protein VWF to form a tight, noncovalent complex. Each monomer of the multimeric VWF protein is able to bind one Factor VIII molecule with high affinity (K_d, 0,5 nmol/L). In vivo, however, the stoichiometry is limited by the number of Factor VIII molecules present, resulting in approximately a 1:50 ratio, see Figure G.19.

Mature VWF:

Mature VWF is a multimeric protein composed of covalently linked dimeric subunits of about 500 kDa. Each dimer consists of two identical protein chains of 2050 amino acids each (about 255 kDa) covalently linked. The mature VWF chain is post-translationally modified by glycosylation and sulfation. Whereas the VWF monomers are linked by C-terminal Cysteine residues to form the dimeric subunit, the multimers are assembled by N-terminal disulfide bonds. The molecular weight of VWF multimers ranges from 500 kDa to about 20 000 kDa.

The mature VWF monomer can be subdivided into different domains (D', D3, Al, A2, A3, D4, B, C1, C2), see Figure G.18. Several of these domains contain cryptic binding sites in the non-activated molecule that become accessible upon activation. These conformational changes triggered by increased shear stress, vascular damage or binding of agonists for example, are essential for supporting primary haemostasis (adhesion to platelets). A proteolytic cleavage site in domain A2 of ultra-large VWF multimers also becomes accessible under high shear stress conditions. As a consequence, a cleavage at position Tyr842/Met843 by ADAMTS-13 is facilitated. This process leads to degradation of ultra-large VWF multimers yielding corresponding cleavage products that can be detected as satellite bands in SDS-Agarose multimer electrophoresis.

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NOTE Figure adapted from Haberichter, Sandra L. *et al.* [46] from Figure 13.2, Page 199.

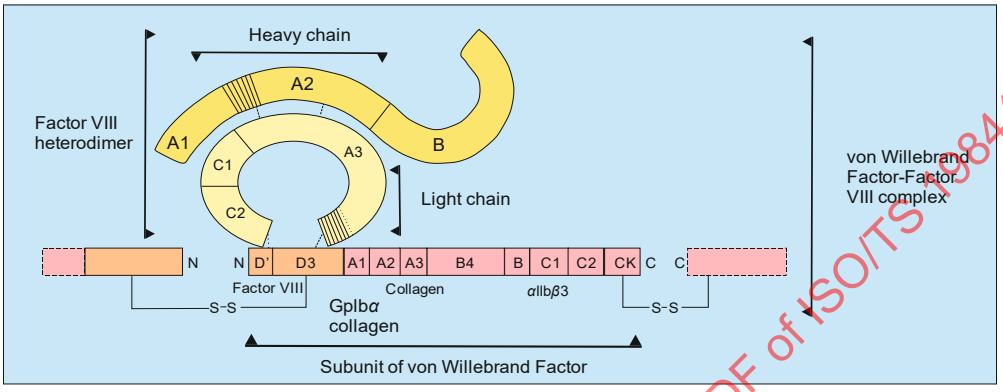
Figure G.18 — Graphical representation of the structure of VWF monomer

The von Willebrand Factor (VWF) protein is initially synthesized as a 2 813-amino acid pro-VWF molecule whose synthesis is directed by an 87-kb mRNA. The pre-pro-VWF is composed of a 22-amino acid signal peptide, a 74I-amino acid propeptide (VWFpp), and a 2 050-amino acid mature VWF monomer. The pro-VWF is composed of A, B, C, and D repeats. Various functional domains have been

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identified and contain the sites of interaction with Factor VIII, platelet glycoprotein GP lb, GP IIb/IIIa, collagen, and heparin [46].

Although in plasma the VWF component is in large excess of the FVIII component on a molar level of the monomer units, it has been described that even equimolar complexes of FVIII and VWF may be obtained in vitro by combination of both components in corresponding ratios. The complex formation of FVIII and VWF is mediated by the A3 region and C2 domain of FVIII and D'/D3 domains of VWF as shown in Figure G.19.



NOTE Figure adapted from Mannucci P. M. [47], from Figure 2, Page 685.

Figure G.19 — Graphical Representation of FVIII/VWF complex

NOTE von Willebrand Factor circulates as a complex with Factor VIII, thereby protecting Factor VIII from degradation by the naturally occurring anticoagulant-activated protein C and localising Factor VIII at the site of vascular injury. Each mature von Willebrand Factor subunit (domains D', D3, A1, A2, A3, D4, B, C1, C2, CK) dimerizes through disulfide bonds (shown as S–S) near the carboxy terminus (C). Each dimer further multimerizes through disulfide bonds near the amino terminus (N). Factor VIII is cleaved before secretion and binds to von Willebrand Factor as a heterodimer.

The acidic region (cross-hatching) of the A3 domain of Factor VIII and the carboxy-terminal region on the C2 domain bind (noncovalent bonds are shown as dotted lines) in the amino-terminal region of the von Willebrand Factor subunit (domain D'–D3). The A1 and A2 domains of the heavy chain of Factor VIII are non-covalently bonded to the A3 domain of the light chain (dotted lines). At the bottom of the Figure, areas of the von Willebrand Factor subunit involved in the interaction with collagen and platelet glycoproteins Ibα (GpIbα) and αIIbβ3 are shown.

G.5.2.2 Tabular information of the FVIII example at the Substance information level

Depending on the parent substance Cryoprecipitate pool, Substance ID PLASMC786542 (Artificial ID), or according to the FDA GSRS Code: 09J8QNB0L9 (UNII), see Table G.3 and the documentation provided in the tables of testing strategy linked to the plasma pool results shall be provided for the test requirements. In addition, the information of the manufacturing of the Cryoprecipitate should be provided as is described in Table G.6 Specified Substance Group 2 Information in connection to the Cryoprecipitate pool, in this example HGTDFE8965 (Artificial ID). Information shall be provided in tabular example for Plasma-derived human coagulation Factor VIII as is described in accordance with the format described in Table G.17 with the information provided in subclause G.5.2.1.

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Table G.22 — Tabular information at the Substance Information level for Human Coagulation Factor VIII

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	FACT8YUR (Artificial ID)	II	1)
Substance Type	Structurally Diverse (Plasma-derived)	CD	
Element Group: Substance Name			
Substance Name	Human coagulation Factor VIII, Plasma-derived	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia 8.6, monograph 07/2013:0275	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Antihaemophilic Factor VIII and von Willebrand Factor	ST	
Substance Name Type	Plasma-derived	CD	
Language	En	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Journal	CD	2)
Reference Source Class	Literature	CD	
Reference Source Citation	Harvey J. Weiss *et al.*, J. of Clinical Investigation, Vol. 60, August 1977, 390 – 404. 'Stabilization of Factor VII in Plasma by the von Willebrand Factor'.	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Blood-coagulation Factor VIII, complex	ST	
Substance Name Type	Other Name	CD	

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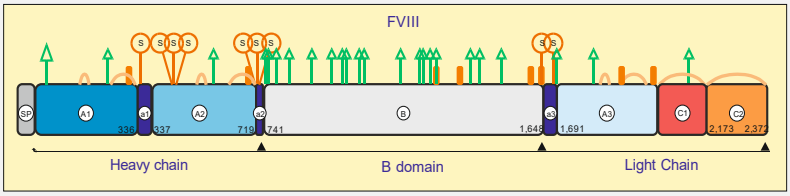
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Element Name	Value	Data Format	Note #
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Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	
Element Group: Substance Code			
Code	9001-27-8	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.Codesystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	5T6B772R4Q	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.Codesystem	
Code System Status	Active	CD	
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	B02BD06	CD.Code	
Substance Classification Type	Antihaemorrhagics: Blood coagulation Factor, von Willebrand Factor and coagulation Factor VIII in combination	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=B02BD06	ST	

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Element Name	Value	Data Format	Note #
Element Group: Source Material			
Source Material Class	Biologic	CD	
Source Material Type	Human	CD	
Source Material State	N/A		
Organism ID	HUMA875601 (Artificial ID)	II	
Organism Name	Homo sapiens, Linnaeus 1758	ST	
Parent Substance ID	PLASMC786542 (Artificial ID)	II	
Parent Substance Name	Cryoprecipitate	ST	
Country of Origin	NL, DE, FR, ES, US	CD	3)
Development Stage	N/A		
Element Group: Part Description			
Part	Human plasma for fractionation	CD	
Part Location	N/A		
Element Group: Fraction Description			
Fraction	Cryoprecipitate	CD	
Material Type	Protein	CD	
Element Group: Structure			**4)**
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	PDF NOTE The Figure G.20 below, represents the full length of 19 amino acid signal peptide and a mature protein of 2332 amino acids. The gene encodes a large precursor glycoprotein (the maximum length), consisting of six structural domains and three acidic subdomains, organized in a heavy chain [A1(α1)A2(α2)B] and light chain [(α3)A3C1C2], as shown in Figure G.21. Variable sizes of heterogenous dimers of FVIII after limited proteolysis within the B domain are shown in Figure G.15.	ED	



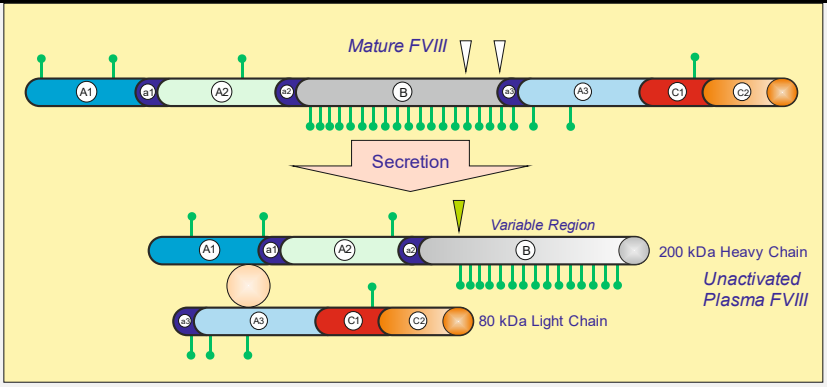
NOTE Figure adapted from Santagostino E. 2014 [41] from Figure I, Page 2509.

Figure G.20 — Full mature glycoprotein having a maximum length of 19 + 2332 = 2.351 amino acids (see sequence below, http://www.nextprot.org/db/entry/NX_P00451/sequence)

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Element Name	Value	Data Format	Note #



NOTE Figure adapted from Pipe S.W. [44], from Fig.1, Page 1188.

Figure G.21 — Depending on the proteolysis of Factor VIII the major part of Factor VIII circulates as a set of heterogenous dimers consisting of a heavy chain (A1-a1-A2-a2-B) and the light chain (a3-A3-C1-C2)(the dimer is held together by a divalent metal ion (Cu2+) shown as a ball bridging domains A1 and A3)

The mature glycoprotein part of Factor VIII consists of 2 332 amino acids, which are arranged in a discrete domain structure: A1 (residues 1-336), A2 (373-710), B (741-1648), A3 (1690-2019), C1 (2020-2172), and C2 (2173-2332). The A domains are bordered by acidic regions a1 (337-372), a2 (711-740), and a3 (1649-1689).

The possible variable sizes of the heavy chain are illustrated in Figure G.15.

The B-domain is partially removed from mature FVIII, so that several truncated B-domain variants of FVIII circulate in the bloodstream, see Figure G.15. Complete or partial deletions of the B-domain are not associated with significant differences in procoagulant properties of these FVIII variants.

Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Web	CD	
Reference Source Citation	Figure 1: E. Santagostino, Drug design, Development and Therapy, Vol.8 (2014), 2507 – 2515. Figure 2: P.J. Lenting at al., Blood Vol.92. no 11 'The life cycle of Coagulation Factor VIII in view of its structure and function', December 1998; Pipe, S.W (2009): Haemophilia 15, 1187-1196	ST	
Element Group: Protein (Natural occurring FVIII)			
Sequence Type	Complete	CD	
Number of Subunits	2	INT	
Element Group: Protein Subunit			
Subunit (Heavy Chain)	1	INT	
Element Group: Molecular Weight			

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Element Name	Value	Data Format	Note #
Molecular Weight Method	SDS-polyacrylamide gel electrophoresis	CD	4)
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Average	CD	
Low Limit	90 000	PQ	
High Limit	210 000	PQ	
Unit	g/mol	CD	
Element Group: Protein Subunit (Repeat)			
Subunit (Light Chain)	2	INT	
Element Group: Molecular Weight (Repeat)			
Molecular Weight Method	SDS-polyacrylamide gel electrophoresis	CD	4)
Molecular Weight Type	Number average	CD	
Element Group: Amount (Repeat)			
Amount Type	Exact	CD	
Quantity	80 000	PQ	10)
Unit	g/mol	CD	
Element Group: Reference Information			
Element Group: Gene			
Gene Sequence Origin	Human	CD	
Gene ID	P00451	CD	5)
Gene Name	*F8C*	ST	
Element Group: Protein (Precursor FVIII)			
Sequence Type	Complete	CD	
Number of Subunits	1	INT	6)
Element Group: Protein Subunit			
Subunit	1	ST	
Sequence	See below: http://www.nextprot.org/db/entry/NX_P00451/sequence; >sp|P00451|FA8_HUMAN Coagulation Factor VIII OS=Homo sapiens GN=F8 PE=1 SV=1 >nxp|NX_P00451-1|F8|Coagulation Factor VIII |Iso 1: Isoform Iso 1 2351 aa, Mass: 267 009 Da.	ST	

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Element Name	Value	Data Format	Note #
	MQIELSTCFFLCLLRFCFSATRRYYLGAVELSWDYMQSDLGELPVDARFPPRVPKSFPFN TSVVYKKTLFVEFTDHLFNIAKPRPPWMGLLGPTIQAEVYDTVVITLKNMASHPVSLHAV GVSYWKASEGAEYDDQTSQREKEDDKVFPGGSHTYVWQVLKENGPMASDPLCLTYSYLSH VDLVKDLNSGLIGALLVCREGSLAKEKTQTLHKFILLFAVFDEGKSWHSETKNSLMQDRD AASARAWPKMHTVNGYVNRSLPGLIGCHRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNH RQASLEISPITFLTAQTLLMDLGQFLLFCHISSHQHDGMEAYVKVDSCPEEPQLRMKNNE EAEDYDDDLTDSEMDVVRFDDDNSPSFIQIRSVAKKHPKTWVHYIAAEEEDWDYAPLVLA PDDRSYKSQYLNNGPQRIGRKYKKVRFMAYTDETFKTREAIQHESGILGPLLYGEVGDTL LIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDFPILPGEIFKYKWTVTVEDGP TKSDPRCLTRYYSSFVNMERDLASGLIGPLLICYKESVDQRGNQIMSDKRNVILFSVFDE NRSWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEVAYWYILS IGAQTDFLSVFFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFRNRG MTALLKVSSCDKNTGDYYEDSYEDISAYLLSKNNAIEPRSFSQNSRHPSTRQKQFNATTI PENDIEKTDPWFAHRTPMPKIQNVSSSDLLMLLRQSPTPHGLSLSDLQEAKYETFSDDPS PGAIDSNNSLSEMTHFRPQLHHSGDMVFTPESGLQLRLNEKLGTTAATELKKLDFKVSST SNNLISTIPSDNLAAGTDNTSSLGPPSMPVHYDSQLDTTLFGKKSSPLTESGGPLSLSEE NNDSKLLESGLMNSQESSWGKNVSSTESGRLFKGKRAHGPALLTKDNALFKVSISLLKTN KTSNNSATNRKTHIDGPSLLIENSPSVWQNILESDTEFKKVTPLIHDRMLMDKNATALRL NHMSNKTTSSKNMEMVQQKKEGPIPPDAQNPDMSFFKMLFLPESARWIQRTHGKNSLNSG QGPSPKQLVSLGPEKSVEGQNFLSEKNKVVVGKGEFTKDVGLKEMVFPSSRNLFLTNLDN LHENNTHNQEKKIQEEIEKKETLIQENVVLPQIHTVTGTKNFMKNLFLLSTRQNVEGSYD GAYAPVLQDFRSLNDSTNRTKKHTAHFSKKGEEENLEGLGNQTKQIVEKYACTTRISPNT SQQNFVTQRSKRALKQFRLPLEETELEKRIIVDDTSTQWSKNMKHLTPSTLTQIDYNEKE KGAITQSPLSDCLTRSHSIPQANRSPLPIAKVSSFPSIRPIYLTRVLFQDNSSHLPAASY RKKDSGVQESSHFLQGAKKNNLSLAILTLEMTGDQREVGSLGTSATNSVTYKKVENTVLP KPDLPKTSGKVELLPKVHIYQKDLFPTETSNGSPGHLDLVEGSLLQGTEGAIKWNEANRP GKVPFLRVATESSAKTPSKLLDPLAWDNHYGTQIPKEEWKSQEKSPEKTAFKKKDTILSL NACESNHAIAAINEGQNKPEIEVTWAKQGRTERLCSQNPPVLKRHQREITRTTLQSDQEE IDYDDTISVEMKKEDFDIYDEDENQSPRSFQKKTRHYFIAAVERLWDYGMSSSPHVLRNR AQSGSVPQFKKVVFQEFTDGSFTQPLYRGELNEHLGLLGPYIRAEVEDNIMVTFRNQASR PYSFYSSLISYEEDQRQGAEPRKNFVKPNETKTYFWKVQHHMAPTKDEFDCKAWAYFSDV DLEKDVHSGLIGPLLVCHTNTLNPAHGRQVTVQEFALFFTIFDETKSWYFTENMERNCRA PCNIQMEDPTFKENYRFHAINGYIMDTLPGLVMAQDQRIRWYLLSMGSNENIHSIHFSGH VFTVRKKEEYKMALYNLYPGVFETVEMLPSKAGIWRVECLIGEHLHAGMSTLFLVYSNKC QTPLGMASGHIRDFQITASGQYGQWAPKLARLHYSGSINAWSTKEPFSWIKVDLLAPMII HGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGNVDSSGIKHNIFN PPIIARYIRLHPTHYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSYFTNMFA TWSPSKARLHLQGRSNAWRPQVNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTSMYVKEFL ISSSQDGHQWTLFFQNGKVKVFQGNQDSFTPVVNSLDPPLLTRYLRIHPQSWVHQIALRM EVLGCEAQDLY		

Figure G.22 — Sequence representation of Human FVIII

Length	2351	INT	5)
Element Group: Protein (Part of Group)			
Disulfide linkage	1_153-1_179; 1_248-1_329 (A1 domain); 1_528-1_554; 1_630-1_711; (A2 domain), 2_1832-2_1858; 2_1899-2_1903 (A3 domain); 2_2021-2_2169 (C1 domain), 2_2174-2_2326 (C2 domain)	ST	7)

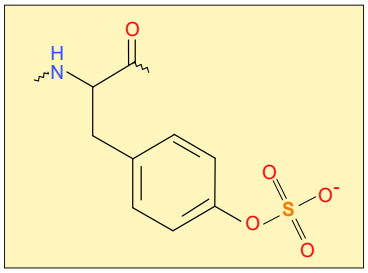
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Element Name	Value	Data Format	Note #
Element Group: Glycosylation			
Glycosylation Type	Human	CD	
N-Glycosylation Site (Principle N-linked Glycosylation sites in human Factor VIII)	1_41; 1_239 (A1 domain); 2_1810 (A3 domain); 2_2118 (C1 domain)	ST	8)
Element Group: Modification (O-tyrosine modification)			
Modification Type	Structural Modification	CD	
Residue Modified	Tyrosine	CD	
Residue Sites	1_346; 1_1664; 1_718; 1_719; 1_723; 2_1680 (A3 domain)	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Sulfation	CD	
Element Group: Molecular Fragment			
Role	Post Translational Modification	CD	
Molecular Fragment ID	29166358BF (UNII)	II	
Molecular Fragment Name	Tyrosine O-sulfate	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Non Numeric Value	Incomplete	CD	
Element Group: Modification (Repeat), (O-tyrosine modification)			
Modification Type	Structural Modification	CD	
Residue Modified	Tyrosine	CD	
Residue Sites	2_1680 (A3 domain)	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Sulfation	CD	
Element Group: Molecular Fragment			
Role	Post Translational Modification	CD	
Molecular Fragment ID	29166358BF (UNII)	II	
Molecular Fragment Name	Tyrosine O-sulfate	ST	
Element Group: Amount			
Amount Type	Exact	PQ	

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Element Name	Value	Data Format	Note #
Non Numeric Value	Complete	CD	9)
Element Group: Structure (Part of group)			
Structural Representation	Full	CD	10)
Structural Representation Attachment	See image below.  **Figure G.23 — Structural representattion of the Tyrosine O-sulfate molecular fragment**	ED	
Element Group: Property			
Property Type	Physical	CD	
Property Name	pH	CD	
Property Parameters	Measured at 20 °C in water /ml	ST	
Property Substance ID	FACT8YUR (Artificial ID)	II	
Property Substance Name	Human coagulation Factor VIII, Plasma-derived	ST	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	7,0	PQ	
Low Limit	6,5	PQ	
High Limit	7,5	PQ	
Unit	N/A (dimensionless quantity)		

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Element Name	Value	Data Format	Note #

NOTE 1 Substance ID corresponds to the Human Coagulation Factor VIII, Plasma-derived as a constituent manufactured from the Cryoprecipitate (see Table G.3).

NOTE 2 See Harvey J. Weiss *et al.* [59].

NOTE 3 Country of Origin related and specified in the Plasma Master File.

NOTE 4 From the class 'Structure' to the end of the table, the Protein model is followed.

Molecular weight distribution analysed by SDS-polyacrylamide gel electrophoresis, see Gordon A. Vehar *et al.* [53].

NOTE 5 The F8C gene comprises 26 exons, which encode a polypeptide chain for a signal peptide of 19 amino acids and a mature protein of 2 332 amino acids. These total of 2 351 amino acids have a relative mass of 267 039 Da.

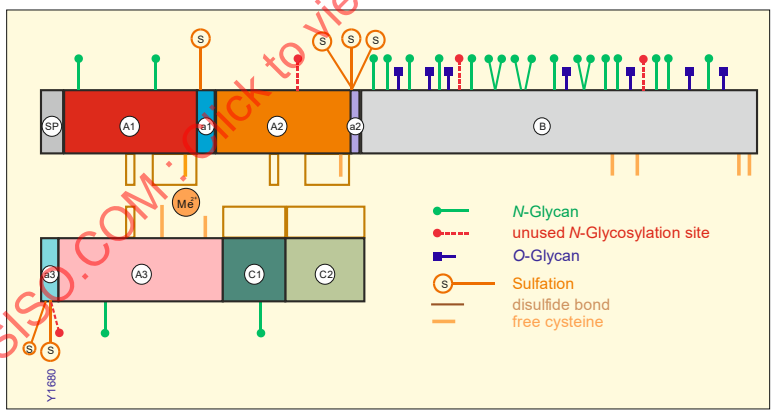
NOTE 6 For the Protein subunit, the value is provided representing the precursor glycoprotein after cleavage of the signal peptide and the formation of the mature Factor VIII glycoprotein dimer.

NOTE 7 Seven disulfide bonds have been identified: residues 153-179; 248-329 (A1 domain); 528-554; 630-711; (A2 domain), 1832-1858; 1899-1903 (A3 domain); 2021-2169 (C1 domain). Within the C2 domain, residues 2174-2326 most likely also form a disulfide bridge. Note that the heavy chain is indicated as subunit 1 and the light chain is indicated as subunit 2.

Free cysteine-residues have been identified at positions 310, 692, and 2000. Cys528 and Cys1858 may be present as free cysteines, because these residues are reactive toward a sulfhydryl-specific agent. With regard to the Cys- residues in the B-domain it is unknown whether they are free or linked. See P.J. Lenting *et al.* [54].

Confirmation of the disulfide bridges can be obtained in B.A. McMullen *et al.* [60].

NOTE 8 The FVIII protein contains 25 sites for N-glycosylation: 2 in domain A1, 1 in A2 and 19 in the B-domain (heavy chain) plus 1 in a3, 1 in A3 and 1 in C1 (light chain). Not all are occupied – the sites in A2 and a3 plus 2–3 in the B domain are unoccupied, resulting in 21 N-glycosylations in native full-length FVIII, see Figure G.24. Only 4 principle N-Glycosylation sites in human Factor VIII are listed in the table [see Christoph Kannicht *et al.* [56]].



NOTE Figure adapted from Kannicht Christoph *et al.* [45], Fig. 3, Page 83.

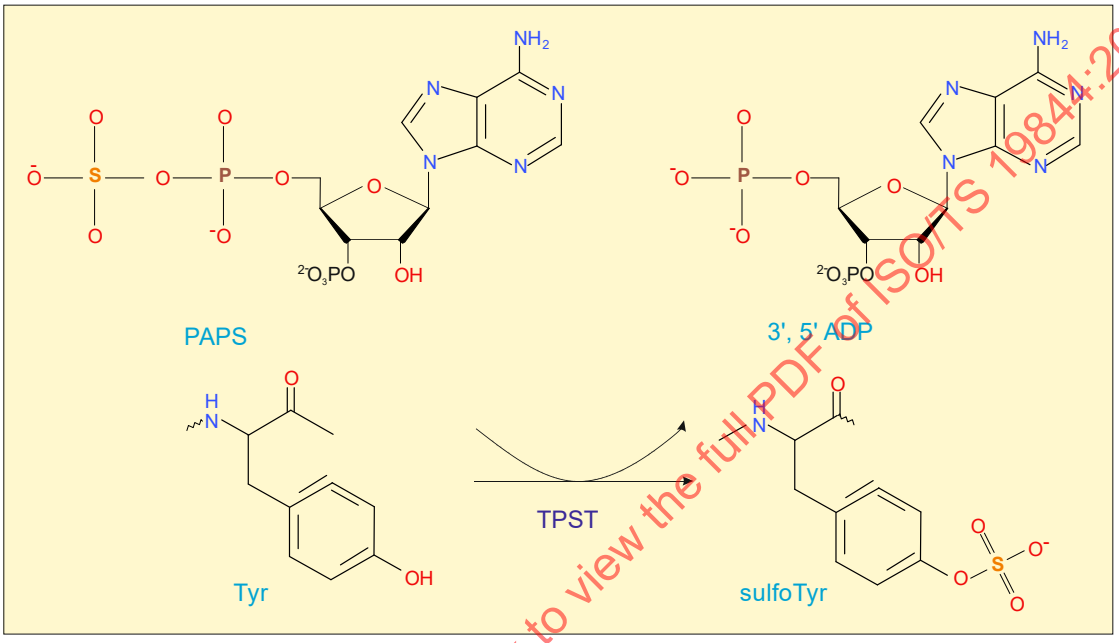
Figure G.24 — Glycosylation sites of FVIII

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Element Name	Value	Data Format	Note #

NOTE 9 The post-translational sulfation of tyrosine residues occurs in numerous secreted and integral membrane proteins and, in many cases, plays a crucial role in controlling the interactions of these proteins with physiological binding partners as well as invading pathogens. The reaction catalysed by tyrosylprotein sulfotransferase TPSTs is shown below, see Figure G.25. TPSTs employ 3′-phosphoadenosine 5′-phosphosulfate (PAPS) as the sulfate donor. The sulfate is transferred from the 5′-phosphosulfate group of PAPS to the phenol of a tyrosine residue of a peptide or protein to form an O-sulfated tyrosine and adenosine 3′,5′-diphosphate (3′,5′-ADP). Both TPST-1 and TPST-2 are optimally active at slightly acidic pH (6,5 and 6,0, respectively) and both are strongly stimulated by Mn2+ and inhibited by Ca2+; curiously, TPST-2 is also stimulated by Mg2+ whereas TPST-1 is not.



NOTE Figure adapted from Martin J. Stone *et al.* [50].

Figure G.25 — Formation of Sulfo-tyrosine catalysed by tyrosylprotein sulfotransferases (TPSTs)

NOTE 10 Structural Representation [Molecular Fragment].

G.5.2.3 Information of the FVIII example at the Specified Substance Group 2 information level

Table G.23 — Tabular information for the manufacturing of Human Coagulation Factor VIII, Plasma-derived Substance from Cryoprecipitate pool used

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2 (Cryopoor Plasma (Minipool)– Company CBA)			
Specified Substance Group 2 ID	DFSRA9786M (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Human Coagulation Factor VIII, Plasma-derived-Company CBA	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	

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Element Name	Value	Data Format	Note #
(Parent) Substance ID	FACT8YUR (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Fractionation	CD	
Production System Type	Continuous plasma fractionation from Human Plasma for Fractionation	CD	
Critical Process Version Number	1	INT	2)
Version	01	ST	
Version Date	20170303	TS.Date	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	12345 (Artificial ID)	ST	
Reference Source Citation	CBG123456 (Artificial CBG-Case number)	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	PDF	ED	
Reference Source Document Type	Release Specification	CD	
Reference Source Document ID	FR4563 (Artificial ID)	ST	
Reference Source Document Classification	In-house/Batch release specification	CD	
Element Group: Manufacturing			
Manufacturer ID	DUNS564321 (Artificial ID)	II	
Manufacturer Name	Company CBA	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	

NOTE 1 This (Parent) Substance ID refers to the Substance Name: Human Coagulation Factor VIII, Plasma-derived which has a parent ID: PLASMC786542 (Artificial ID) with the corresponding Cryoprecipitate used as starting material.

NOTE 2 The Critical Process Number Version Number would change if a substantial change in the (synthetic) manufacturing process occurred. These would include a change in the chemistry or, addition or elimination of a purification step. The change in a version number should be tied to the production system type.

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Annex H
(normative)

Polymer substance

H.1 Introduction

Polymers are one of the five types of single substances described in ISO 11238.

The essential elements for defining polymers are:

— **Polymer Class**: Homopolymer or Copolymer.

— **Polymer Geometry**: Linear, Branched, Cross-linked, Network or Dendritic.

— **Copolymer connectivity**: Random, Statistical, Alternating, Periodic, Block, Graft, Cross or Mixed

— **Structural Repeat Units (SRU)**: The number and amounts of each structural repeat unit and the orientation of polymerization. A structural representation of the polymer that indicates the connectivity within and between the structural repeat units and end-groups.

— **Degree of Polymerization**: The average number of monomers or repeat units in a polymeric block or chain.

— **Monomers**: Monomers are the starting materials or building blocks of polymers. The number of monomers and the amount or relative amount of each monomer should be given. Each monomer will be a substance in its own right and identified with a Substance ID.

— **Molecular Weight**: Molecular weight or mass of the polymer and the type of molecular weight and ranges or dispersity of molecular weights should be given. Molecular weights are often distinguishing characteristics of structurally related polymers.

— **Property**: Physical properties are often necessary to distinguish polymeric material. Viscosity is often given and can be required if the molecular weight is not given or known. Other physical properties such as density, glass transition temperature, interfacial or rheological properties should also be given, if relevant.

— **Modification**: Any modification that results in changes in the covalent structure of the polymer should be captured.

— **Source Material**: For biosynthetic polymers, the biological source of the polymers should also be indicated.

Although all of the elements listed above should be submitted if known, polymers are often defined using a partial set of the elements listed above.

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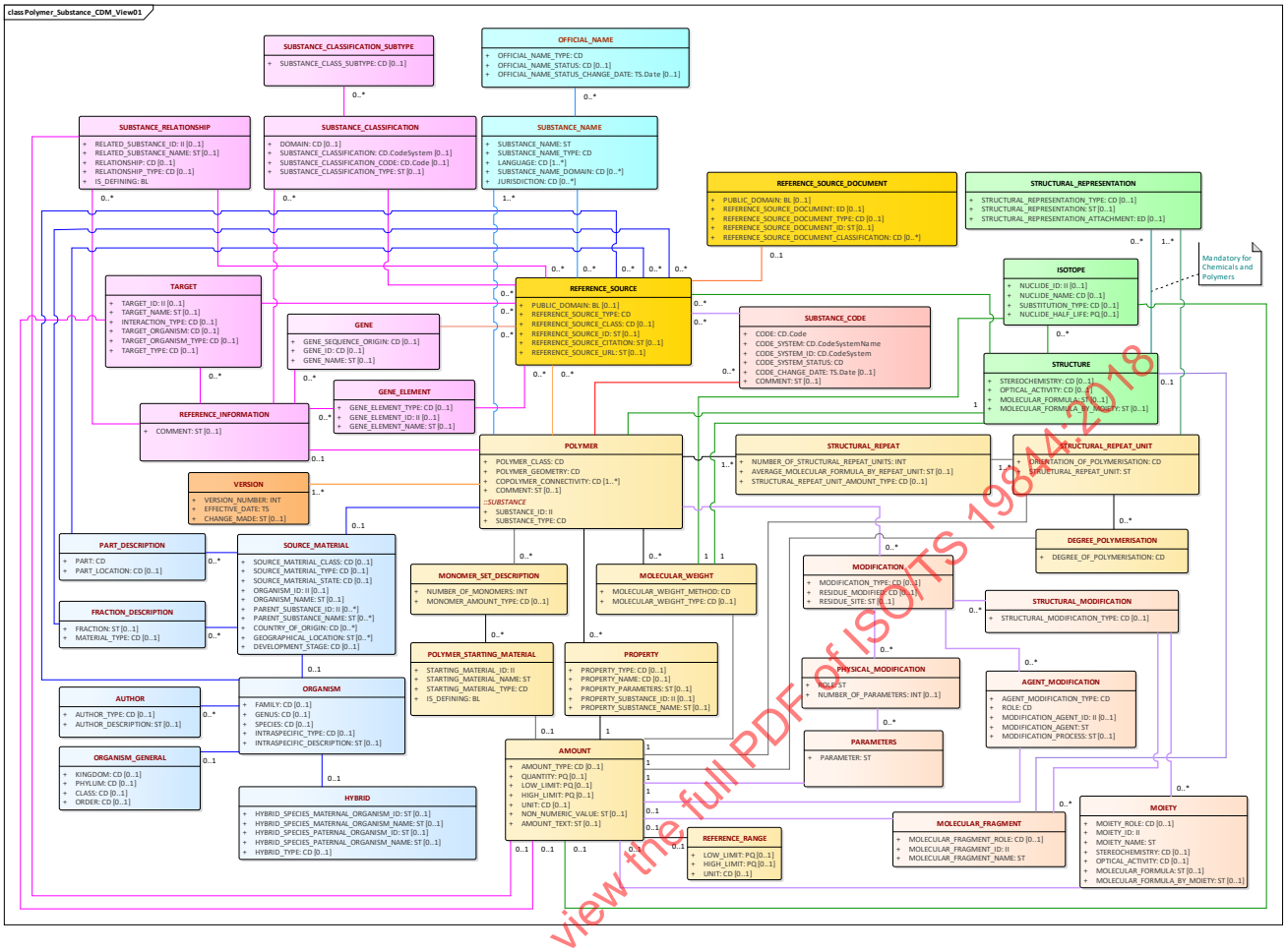


Figure H.1 — Conceptual Data Model View for Polymer Substance

H.2 Scope

Polymers are one of the five types of single substances described in ISO 11238. This Annex provides guidance to describe the elements that are necessary to define polymers. Polymers can be chemically synthesized or isolated from biological matrices. Polymers do not include either proteins or nucleic acids of defined sequences. Polymers are defined by a combination of a structural representation and descriptive elements.

H.3 Terms and definitions

H.3.1
copolymer
polymer with more than one type of structural repeat unit linked through covalent bonds

Note 1 to entry: Copolymers are obtained by copolymerization or sequential polymerization of two or more different monomers. Copolymers can be random, statistical, alternating, periodic, block, cross, graft or mixed.

H.3.2
degree of polymerization
average number of monomers or repeat units in a polymeric block or chain

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Note 1 to entry: Applies to both homopolymers and block copolymers where it refers to the degree of polymerization within a block.

H.3.3
homopolymer
polymer containing a single structural repeat unit

H.3.4
polydisperse substance
single substance containing multiple related entities

Note 1 to entry: Polydisperse substances include polymers, mixture and structurally diverse material isolated from a single source. Chemical substances, proteins and nucleic acids with defined sequences are not described as polydisperse substances.

H.3.5
polydispersity
measure of the range of molecular masses in polymer substance

Note 1 to entry: The dispersity of polymers is typically calculated by the ratio of weight average molecular weight to number average molecular weight.

H.3.6
polymer substance
type of polydisperse substance that contains structural repeat units linked by covalent bonds

Note 1 to entry: Monodisperse proteins and nucleic acids with defined sequences shall not be defined using the polymer substance elements.

H.3.7
structural repeat unit
a fundamental descriptor of a polymer typically derived from a monomer that is used to synthesize the polymer

H.4 Data elements

H.4.1 Polymer Class

Polymers are classified as either a homopolymer or a copolymer. Copolymers typically consist of multiple SRUs. Many polymers may be made from multiple monomers but if the resultant polymer has a single structural repeat unit it will be classified as a homopolymer. Example: Nylon 66 is made from adipic acid and hexamethylenediamine but is a single SRU and therefore would be classified as a homopolymer (see Figure H.2).

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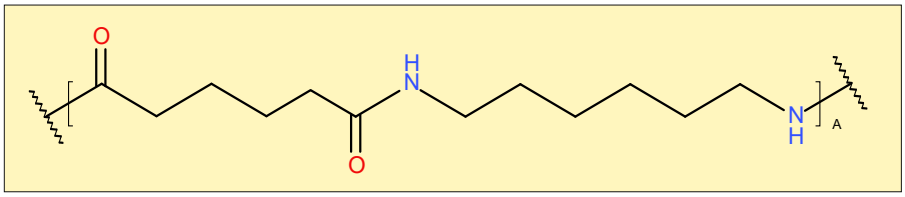


Figure H.2 — SRU of Nylon 66

Additional sub-classes could be developed to further classify polymers.

H.4.2 Polymer Geometry

The values for this field are linear, branched, cross-linked, network or dendritic.

Examples of linear polymers include polyethylene, polyethylene glycol, and cellulose.

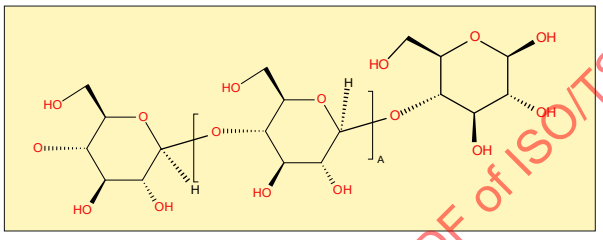


Figure H.3 — SRU and structure of Cellulose

Branched polymers are typically made of the same monomers and these monomers typically have more than two connection points. Usually there is a predominant chain and predominant type of connectivity. Branches of the polymer also have the same connectivity of the main chain. An example of a branched polymer would be amylopectin.

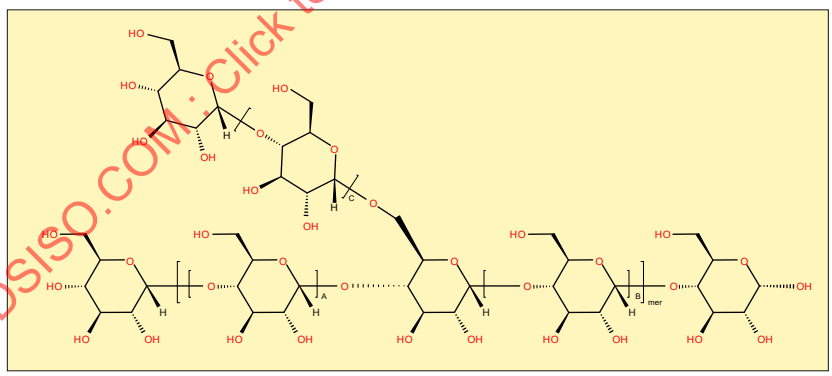


Figure H.4 — Representative presentation of SRU and structure of Amylopectin

Network polymers typically have more than two connection points on one of the monomers and form multidimensional structural representations. Although network polymers could be considered to be homopolymer it is often not possible to have a single representative SRU and they will be typically defined by the ratio of monomers used to synthesize the polymers. Phenol formaldehyde resins, particularly when the molar ratio of formaldehyde to phenol is greater than one, are examples of network polymers, see Figure H.5.

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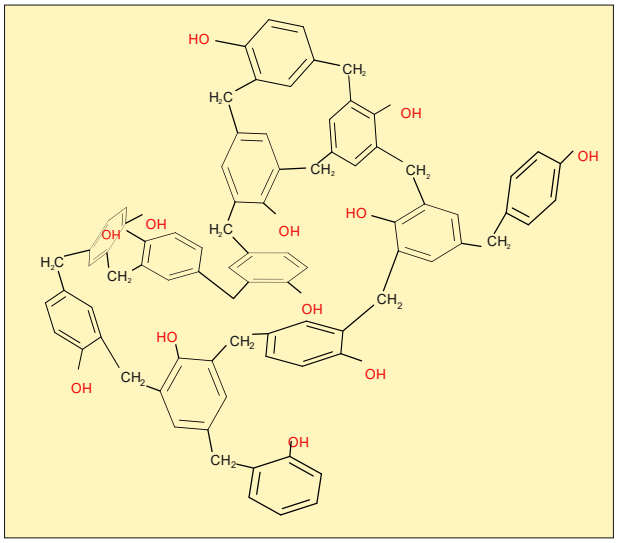


Figure H.5 — Representative stucture of a phenol formaldehyde resin.

NOTE Phenol reacts with formaldehyde at the ortho and para sites (sites 2, 4 and 6) allowing up to 3 units of formaldehyde to attach to the ring. The initial reaction in all cases involves the formation of a hydroxymethyl phenol: $HOC_6H_5 + CH_2O \rightarrow HOC_6H_4CH_2OH$. The hydroxymethyl group is capable of reacting with either another free ortho or para site, or with another hydroxymethyl group. The first reaction gives a methylene bridge and the second forms an ether bridge: $HOC_6H_4CH_2OH + HOC_6H_5 \rightarrow (HOC_6H_4)_2CH_2 + H_2O$; $(HOC_6H_4CH_2OH)_2 \rightarrow (HOC_6H_4CH_2)_2O + H_2O$. Only the representation of the structure with the methylene bridge is shown.

Cross-linked polymers also form networks of linear chains but the distinguishing factor is that a cross-linked polymer typically contains one monomer that forms a long linear chain and a second monomer or cross-linking agent that will connect the linear chains, see Figure H.6. A cross-linking monomer or agent is typically present in amounts of less than 5 %. Commercial grade polystyrene typically consists of 95 % to 99 % styrene and 1 % to 5 % divinyl benzene.

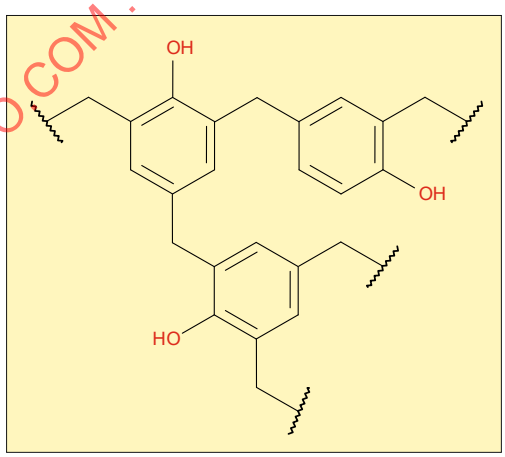


Figure H.6 — Structure of Poly (4-hydroxystyrene)

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H.4.3 Copolymer connectivity

Copolymer sequence type[59] (Copolymer connectivity) can either be random, statistical, alternating, periodic, block, graft, cross or mixed. Mixed copolymers are polymers that contain a region of block copolymers and a region that contains random copolymers.

Alternating copolymers are with regular alternating A and B units, e.g. $(–A-B-A-B-A-)_n$.

Periodic copolymers are polymers with A and B units arranged in a repeating sequence, e.g. $(A-B-A-B-B-A-A-A-A-B-B-B)_n$.

Statistical copolymers are copolymers in which the sequence of monomer residues follows a statistical rule. If the probability of finding a given monomer residue at a particular point in the chain is equal to the mole fraction of that monomer residue in the chain, then the polymer may be referred to as a truly random copolymer, e.g. $(-A-B-B-B-A-B-A-B-A-A-)_n$.

Block copolymers comprise two or more homopolymer subunits linked by covalent bonds. The union of the homopolymer subunits may require an intermediate non-repeating subunit, known as a junction block. Block copolymers with two or three distinct blocks are called diblock copolymers and triblock copolymers, respectively, e.g. $(B-B-B-B-A-A-A-A-B-B-B-B-A-A-A-A)_n$.

Graft polymers are similar to branched polymers with the main difference being that the branches of the graft are made from a different monomer. There are a number of dimethicone-peg polymers that would be considered to be graft polymers, e.g. A-B diblock copolymer with A-B alternating copolymer side chains is properly called a graft copolymer. Cross polymers are also network polymers similar to cross-linked polymers with the main difference being that the cross-linking is done by another polymer or oligomer. There are a number of silicate-methicone or methicone-dimethicone polymers that would be considered cross polymers.

Random copolymers of ethene and various polar olefins can be prepared by means of Pd(II) catalysts bearing Phosphine-sulfonate ligands by using an in situ generated catalytic system to prepare a nonalternating copolymerization of ethene and carbon monoxide. The result is a random incorporation of circa 10% alkyl acrylate units into a linear polyethene backbone [60].

H.4.4 Structural Repeat Unit (SRU)

The SRU is a fundamental descriptor of most polymers. SRUs always contain two or more connection points and the repeating unit of the polymer is enclosed within brackets.

The SRU is usually not the smallest nor the largest repeating unit within a polymer. Rather it is typically derived from the actual monomers that were used to construct the polymer.

For example, the SRU for polyethylene is:

[59] For further clarification, definition and examples see Herk Alex van [135].

[60] See Lena, F.D., Bomfim, J. A. S. [136]

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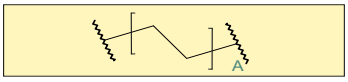


Figure H.7 — Ethylene SRU

and neither

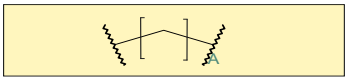


Figure H.8 — Methylene SRU

nor

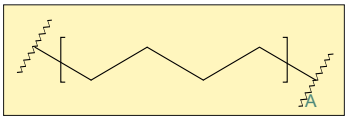


Figure H.9 — Butylene SRU

Each SRU is typically derived from the monomer that is used to synthesize the polymer.

All descriptions of polymers should contain at least one structural representation and the representation should attempt to represent the SRU and the overall structure of the polymer. The structural representation of the SRU should include brackets that enclose the SRU and also include the end-groups of the polymer outside of the bracket if the end-groups are known and the polymer is a homopolymer or a defined block copolymer.

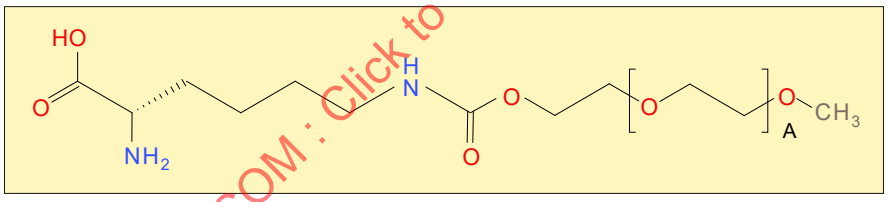


Figure H.10 — Representation of end-groups and SRU: N6-[MPEG-12000]-Lysine

For some polymers the actual end-groups may vary or be a mixture. For random copolymers the actual SRU that the end-group attaches to may also vary. In these cases, the end-group should be drawn independent of the polymeric chain and connection points should be indicated.

Although an actual structural representation of a polymer should be provided, the actual definition of the polymer SRU may be captured in a tabular format where connectivity, connection points and the relative amounts of the SRUs and end-groups are captured.

H.4.5 Degree of Polymerization

The degree of polymerization is the average number of times the SRU repeats in the polymeric material. The degree of polymerization is tied to the bracket that encloses the SRU for a homopolymer and the bracket that encloses a block copolymer.

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H.4.6 Monomers, Polymer starting material

Monomers are the building blocks for every polymer. They can be considered as polymer starting materials. Monomers will typically be chemical substances and their Starting Material ID and Starting Material Name should be provided. It should be noted that many polymers could be made from different monomers or sets of monomers. For example, the same silicate polymer could be made from the controlled reaction of water with silicon tetrachloride, tetramethyl silicate or tetraethyl silicate. In this and most cases the monomers and amount of monomers would not be defining elements. However, as mentioned above for some network polymers e.g. phenol formaldehyde monomers and the ratio of monomers will be defining elements. The ratio of end-group or capping agents to monomers could also be a defining property for certain types of polymers.

H.4.7 Molecular Weight

Polymers are inherently polydisperse and accordingly have a range of molecular entities that vary in molecular weight. Therefore, they are described by their average molecular weight. Average molecular weights or masses and ranges of molecular weight are elements that are essential to distinguish structurally related polymers. For polymers, there are basically five types of average molecular weight:

— Number-average molecular weight which is defined as the number average molecular mass as arithmetic mean or average of molecular masses of individual macromolecules

— Weight-average molecular weight which is defined as the mass average of the molecular mass of a polymer

— Z-average molecular weight which is the third moment or third power average molar mass

— Z+1-average molecular weight

— Viscosity molecular weight

The number-average weight is defined as:

$$M_n = \frac{\sum_i n_i M_i}{\sum_i n_i} = W/N$$

where

n is the number or fraction of molecules having, a given molecular mass;

M is the molar mass of the molecules;

W is the total weight of all the molecules;

N is the total number of molecules.

Number-average molecular weights are typically determined through end-group analysis or the measurement of colligative properties, e.g. vapour pressure osmometry and by gel permeation chromatography, proton NMR.

The weight-average molecular weight is defined as:

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$$M_w = \frac{\sum_i n_i M_i^2}{\sum_i n_i M_i} = \frac{\sum_i n_i M_i^2}{W}$$

Weight-average molecular weights are typically determined from light scattering or sedimentation measurements.

The Z-average molecular weight is defined as:

$$M_Z = \frac{\sum_i n_i M_i^3}{\sum_i n_i M_i^2}$$

Z-average molecular weights are typically determined from sedimentation measurements.

The Z+1-average molecular weight is defined as:

$$M_{Z+1} = \frac{\sum_i n_i M_i^4}{\sum_i n_i M_i^3}$$

Z+1-average molecular weights are typically determined from sedimentation measurements.

The viscosity-average molecular weight is derived from the Mark-Houwink equation, also known as Kuhn-Mark-Houwink-Sakurada:

$$M_v = \left[\frac{\sum_i n_i M_i^{(1+a)}}{\sum_i n_i M_i} \right]^{\frac{1}{a}}$$

where a is related to the intrinsic viscosity. The value of the viscosity-average molecular weight is often very close to the weight-average molecular weight.

To fully characterize most polymers at least two of the above molecular weights should be provided. The ratio between the weight-average molecular weight and the number-average molecular weight (M_w/M_n) is defined as dispersity and structurally related polymers with significantly different dispersity would be considered different polymers.

In addition to average molecular weight, the total molecular weight or mass distribution obtained from a gel permeation chromatogram or field flow fractionation techniques should also be provided, if available. Material having chromatograms that differ significantly from one another may also be considered to be different polymers.

H.4.8 Property

Properties, particularly physical properties, are often essential for distinguishing polymeric material. Viscosity, density and glass transition temperature are properties frequently used to define and distinguish polymers. For all properties, values should be captured, along with the units and parameters where relevant.

Viscosity is one of the most important properties for distinguishing structurally related polymers. Viscosity is a term that refers to the resistance of a fluid to stress or flow. In measuring viscosity fluids are usually assumed to be “Newtonian” and it is necessary to capture the solvent, concentration of the

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polymer, and the temperature at which the viscosity was measured. In some cases, the actual apparatus used to measure the viscosity may also be relevant. The unit for dynamic viscosity are pascal-second (Pa.s) which conforms to the International System of Units.

Other physical properties should be described in a manner similar to viscosity. In addition to physical properties, biological/enzymatic properties may also be necessary to distinguish related materials. For example, low-molecular weight heparins are often distinguished by the Factor IIa to Factor Xa inhibition ratio, since the effect on inhibition of Factor Xa is two to three times higher and the effect on Factor IIa is weaker compared to heparin.

H.4.9 Modification

Modifications that alter the molecular structure of a polymer should also be captured and are essential for defining polymers. Modifications should be captured in a manner that is consistent with proteins, nucleic acids and structurally diverse materials.

For polymers the predominant modifications will be agent and structural modifications. For agent modification the actual chemical agent is captured as well as the amount of the agent. Agent modifications are typically captured when the actual structural modification cannot be defined.

When treatment with a given agent results in well-defined structural modification the polymer is defined by describing that structural modification. Many of the structural modifications will be described by fragments. Fragments will be used when the actual positions of substitution are variable and incomplete. For polymers that are acylated the fragments from the resultant esters or amides will be broken such that the alcohol oxygen or nitrogen is retained by the polymer.

EXAMPLE CELLABURATE (MW 70000, 37 % BUTYRYL, 14 % ACETYL).

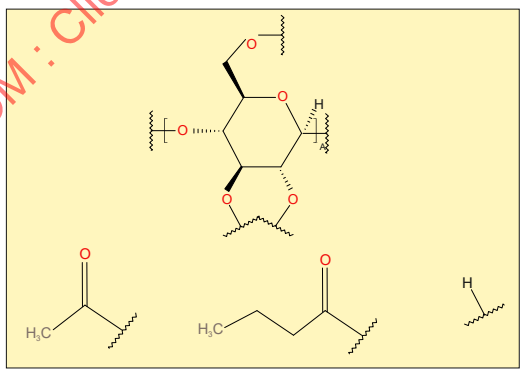


Figure H.11 — Structural representation of Cellaburate fragments

Each of the fragments should be registered and assigned a Substance ID. A connection point table may be necessary to completely define these polymers.

H.4.10 Source Material

The biological source would be a defining element for polymers isolated from biological matrices. This element is an important element to distinguish polymers that may differ consistently because of the source from which the material was isolated. It will also indicate that potential residual allergenic substances related to the source may be present. The source material should be captured.

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Examples: potato starch, corn starch, wheat starch and tapioca starch should all be described as mixtures of amylose and amylopectin and distinguished based on the material source.

H.5 Linear Synthetic Polymers

Linear Homopolymers.

H.5.1 Example1: Polyethylene Glycol 3350

Polyethylene glycol 3350 in solution is an osmotic laxative that increases the amount of water in the intestinal tract to stimulate bowel movements.

Table H.1 — Polyethylene Glycol 3350

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	POLGL12345 (Artificial ID)	II	
Substance Type	Polymer	CD	
Element Group: Substance Name			
Substance Name	Polyethylene glycol 3350	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	USAN	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USAN	CD	
Reference Source Class	Public Database	CD	
Reference Source Citation	USP Dictionary	ST	
Reference Source URL	http://www.uspnf.com	ST	1)
Element Group: Substance Name (Repeat)			
Substance Name	Macrogol 3350	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	

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Element Name	Value	Data Format	Note #
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Recommended INN List	CD	
Reference Source Class	Public Database	CD	
Reference Source Citation	INN Recommended List 17	ST	
Reference Source URL	http://mednet.who.int/inn/db/media/docs/r-innlist17.pdf	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Macrogol 3350	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur., monograph: 04/2013 :1444	ST	
Reference Source URL	http://online6.edqm.eu/ep806/	ST	1)
Element Group: Substance Name (Repeat)			
Substance Name	PEG-75	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Cosmetic	CD	
Jurisdiction	US	CD	
Element Group: Official Name			

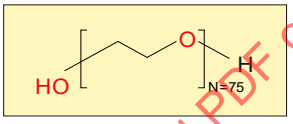
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Element Name	Value	Data Format	Note #
Official Name Type	INCI	CD	4)
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Personal Care Products Council	CD	
Reference Source Class	Official Name Source	CD	
Reference Source URL	http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp	ST	1), 5)
Element Group: Substance Code			
Code	25322-68-3 (generic code for the whole family)	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	G2M7P15E5P	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	A06AD15	CD.Code	
Substance Classification Type	macrogol	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Public Database	CD	

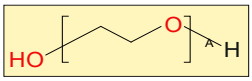
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Element Name	Value	Data Format	Note #
Reference Source URL	https://www.whocc.no/atc_ddd_index/?code=A06AD15&showdescription=yes	ST	
Element Group: Polymer			
Polymer Class	Homopolymer	CD	
Polymer Geometry	Linear	CD	
Copolymer Connectivity	N/A	CD	
Element Group: Structure			
Stereochemistry	Achiral	CD	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	 **Figure H.12 — Structural representation of Macrogol 3350**	ED	
Element Group: Monomer Set Description			
Number of Monomers	1	INT	
Monomer Amount Type	Monomer/Polymer Ratio	CD	2)
Element Group: Polymer Starting Material			
Starting Material ID	ETHYL87654 (Artificial ID); [JJH7GNN18P (UNII)]	II	
Starting Material Name	Ethylene Oxide	ST	
Starting Material Type	Chemical substance	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	75	PQ	
Element Group: Structural Repeat			
Number of Structural Repeat Units	1	INT	
Average Molecular Formula by Repeat Unit	$HO(CH_2CH_2O)H$	ST	
Structural Repeat Unit Amount Type	Exact	CD	
Element Group: Structural Repeat Unit			

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Element Name	Value	Data Format	Note #
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	A (in Structural Representation Attachment)	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	1	PQ	
Element Group: Structural Representation			3)
Structural Representation Type	Representative	CD	
Structural Representation Attachment	 **Figure H.13 — Representation of Structural Repeat Unit A of Macrogol 3350**	ED	
Element Group: Degree Polymerization			
Degree of Polymerization	A (in Structural Representation Attachment)	CD	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	75	PQ	
Low Limit	71	PQ	
High Limit	79	PQ	
Amount Type	SRU/Polymer Ratio	ST	
Element Group: Molecular Weight			
Molecular Weight Method	End-group titration	CD	
Molecular Weight Type	Number Average	CD	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	3 350	PQ	
Low Limit	3 200	PQ	
High Limit	3 500	PQ	
Unit	g/mol	CD	
Element Group: Property			
Property Type	Physical	CD	
Property Name	Viscosity	CD	

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Element Name	Value	Data Format	Note #
Property Parameters	Capillary viscometer giving a flow time of NLT 200 s; 98,9 C in liquid bath	ST	
Property Substance ID	POLGL12345 (Artificial ID)	II	
Property Substance Name	Macrogol 3350	ST	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	93	PQ	
Low Limit	76	PQ	
High Limit	100	PQ	
Unit	cSt	CD	

NOTE 1 This reference is subject to subscription.

NOTE 2 Monomer amount type is used (one type of monomer used in the (homo) polymer) to distinct from the average amount of ethylene oxide units.

NOTE 3 A structural representation of the structural repeat unit is provided; this is important when you have several SRUs and one overall structural representation of all SRUs together.

NOTE 4 International Nomenclature of Cosmetic Ingredient.

NOTE 5 Personal Care Products Council Database.

H.6 Modified Linear Polymers

H.6.1 Example 2: Hypromellose 2910 (4000 mPa.s)

Hypromelloses are semisynthetic polymers derived from cellulose used as active drug substance in artificial tears. They are also used as excipients in drug products and as food additives. They have variable levels of substitution with methoxy and hydroxypropoxy groups and differ in molecular weight as indicated by viscosity.

Table H.2 — HYPROMELLOSE 2910 (4000 MPA.S)

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	HYPRE87654 (Artificial ID)	II	
Substance Type	Polymer	CD	
Element Group: Substance Name			
Substance Name	Hypromellose 2910	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	

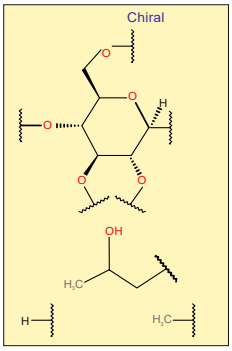
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Element Name	Value	Data Format	Note #
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph. Eur. Monograph 01/2016:0348	ST	
Reference Source URL	http://online6.edqm.eu/ep806/	ST	1)
Element Group: Official Name (Repeat)			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP/NF	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP 39-NF34, second supplement, page 8679	ST	
Reference Source URL	http://www.uspnf.com	ST	
Element Group: Substance Code			
Code	9004-65-3 (generic code for the whole family)	CD.Code	
Code System	CAS Registry	CD.COde SystemName	
Code System ID	0049	CD.Code System	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	RN3152OP35	CD.Code	
Code System	FDA GSRS (UNII)	CD.COde SystemName	
Code System ID	0050	CD.Code System	

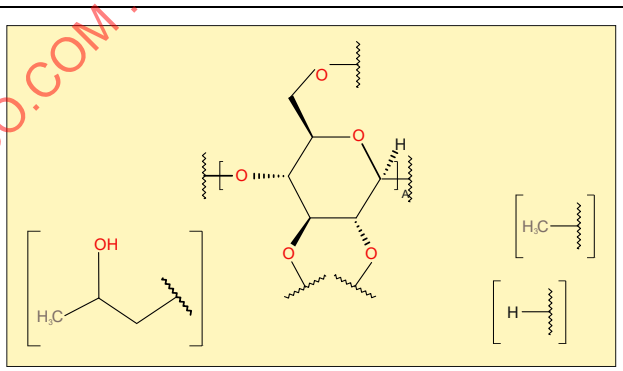
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Element Name	Value	Data Format	Note #
Code System Status	Active	CD	
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.Code System	
Substance Classification Code	S01KA02	CD.Code	
Substance Classification Type	hypromellose	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=S01KA02	ST	
Element Group: Structure			
Stereochemistry	Chiral	CD	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	 **Figure H.14 — Structural representation of Hypromellose 2910**	ED	
Element Group: Polymer			
Polymer Class	Homopolymer (Substituted)	CD	
Polymer Geometry	Linear	CD	
Element Group: Monomer Set Description			
Number of Monomers	1	INT	
Monomer Amount Type	Monomer/Polymer Ratio	CD	

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Element Name	Value	Data Format	Note #
Element Group: Polymer Starting Material			
Starting Material ID	J4R00M814D	II	
Starting Material Name	.BETA.-D-Glucopyranose	ST	
Starting Material Type	Chemical Substance	CD	
Is Defining	Yes	BL	
Element Group: Structural Repeat			
Number of Structural Repeat Units	1	INT	
Average Molecular Formula by Repeat Unit	N/A		
Structural Repeat Unit Amount Type	Exact	CD	
Element Group: Structural Repeat Unit			
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	A (in Structural Representation Attachment)	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	1	PQ	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	 **Figure H.15 — Representation of Structural Repeat Unit A and possible substitution fragments of Hypromellose 2910**	ED	3)
Element Subgroup: Degree Polymerization			
Degree of Polymerization	A (in Structural Representation Attachment)	CD	
Element Group: Amount			
Amount Type	Exact	CD	

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Element Name	Value	Data Format	Note #
Quantity	460	PQ	
Amount Text	SRU/Polymer Ratio	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Size-exclusion chromatography	CD	
Molecular Weight Type	Number Average	CD	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	86 000	PQ	
Unit	g/mol	CD	
Element Group: Property			
Property Type	Physical	CD	
Property Name	Kinematic Viscosity	CD	
Property Parameters	Single-cylinder type rotational viscometer (Brookfield type LV Model, or equivalent), at 20 °C ± 0,1 °C	ST	
Property Substance ID	HYPRE87654 (Artificial ID)	II	
Property Substance Name	Hypromellose 2910 4000 mPa.s	ST	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	93	PQ	
Low Limit	76	PQ	
High Limit	100	PQ	
Unit	cSt	CD	
Element Group: Modification			
Modification Type	Structural modification	CD	
Element Group: Structural Modification			
Structural Modification Type	Chemical Substitution	CD	
Element Group: Molecular Fragment			
Molecular Fragment Role	Substituent	CD	
Molecular Fragment ID	1Q34N83D9I	II	
Molecular Fragment Name	Hydroxypropoxy Fragment	ST	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	10	PQ	
Low Limit	7	PQ	

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Element Name	Value	Data Format	Note #
High Limit	12	PQ	
Unit	%mass fraction	CD	2)
Element Group: Molecular Fragment			
Molecular Fragment Role	Substituent	CD	
Molecular Fragment ID	26CH8P1JAS	II	
Molecular Fragment Name	Methoxy Fragment	ST	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	29	PQ	
Low	28	PQ	
High	30	PQ	
Unit	% mass fraction	CD	2)
NOTE 1 This is a Subscription database. NOTE 2 Per cent mass fraction to Hypromellose. NOTE 3 Structural Representation Attachment (of the SRU).			

H.7 Linear Block Copolymers

H.7.1 Example 3: Poloxamer 338

Poloxamers are non-ionic copolymers composed of a central hydrophobic chain of polypropylene glycol flanked by two hydrophilic chains of polyethylene glycol. Poloxamers are primarily used as excipients in medicinal products. For block copolymers the blocks should be drawn connected in the structural representations.

Table H.3 — Poloxamer 338

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	GHYR78654S (Artificial ID)	II	
Substance Type	Polymer	CD	
Element Group: Substance Name			
Substance Name	Poloxamer 338	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug, Cosmetic	CD	

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Element Name	Value	Data Format	Note #
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	INCI	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Personal Care Products Council	CD	
Reference Source Class	Official Name Source	CD	
Reference Source URL	http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp	ST	6), 7)
Element Group: Official Name (Repeat)			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP 39-NF34, Page 7445	ST	
Reference Source URL	http://www.uspnf.com	ST	
Element Group: Substance Name (Repeat)			
Substance Name	α-Hydro-ω-hydroxypoly(oxyethylene)141-poly(oxypropylene)44-poly(oxyethylene)141, block copolymer	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP 39-NF34, Page 7445	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Kolliphor P 388	ST	1)
Substance Name Type	Brand Name	CD	

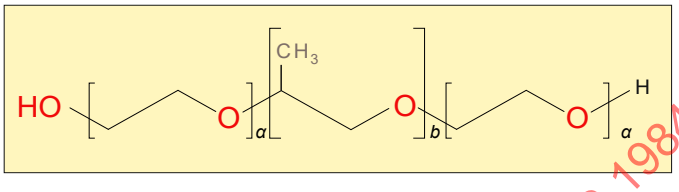
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Element Name	Value	Data Format	Note #
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Web	CD	
Reference Source URL	https://pharmaceutical.basf.com/en/Drug-Formulation/Kolliphor-P188.html	ST	
Element Group: Substance Code			
Code	106392-12-5 (generic code for the whole family)	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	691397-13-4 (generic code for the whole family)	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	F75JV2T505	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Polymer			
Polymer Class	Copolymer	CD	
Polymer Geometry	Linear	CD	
Copolymer Connectivity	Block	CD	

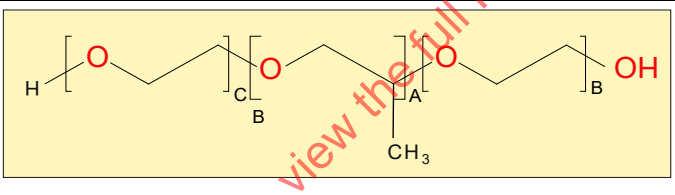
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Element Name	Value	Data Format	Note #
Element Group: Structure			
Stereochemistry	Mixed	CD	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	 **Figure H.16 — Structural representation of Poloxamer 338**	ED	
Element Group: Monomer Set Description			
Number of Monomers	2	INT	
Monomer Amount Type	Monomer/Polymer Ratio	CD	
Element Subgroup: Polymer Starting Material			
Starting Material ID	PROPY98765 (Artificial ID); [F75JV2T505 (UNII)]	II	
Starting Material Name	Propylene Oxide	ST	
Starting Material Type	Chemical Substance	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	8)
Quantity	44	PQ	
Element Subgroup: Polymer Starting Material (Repeat)			
Starting Material ID	ETHYL87654 (Artificial ID); [JJH7GNN18P (UNII)]	II	
Starting Material Name	Ethylene Oxide	ST	
Starting Material Type	Chemical Substance	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	282	PQ	
Element Group: Structural Repeat			
Number of Structural Repeat Units	3	INT	

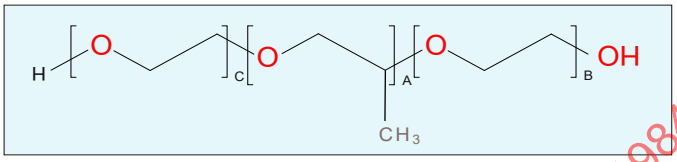
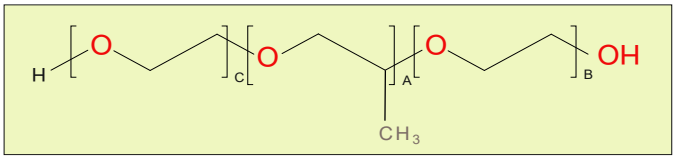
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Element Name	Value	Data Format	Note #
Average Molecular Formula by Repeat Unit	$HO(C_2H_4O)_{141}(C_3H_6O)_{44}(C_2H_4O)_{141}H$	ST	
Structural Repeat Unit Amount Type	Average	CD	
Element Group: Structural Repeat Unit			
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	A (shown in the Structural Representation Attachment)	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	1	PQ	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	 **Figure H.17 — Representation of Structural Repeat Units A, B and C of Poloxamer 338**	ED	2)
Element Group: Degree Polymerization			
Degree of Polymerization	A (shown in the Structural Representation Attachment)	CD	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	44	PQ	
Low Limit	42	PQ	
High Limit	47	PQ	
Amount Text	SRU/Polymer Ratio	ST	
Element Group: Structural Repeat Unit (Repeat)			
Orientation of Polymerization	Head-tail	CD	
Structural Repeating Unit	B (shown in the Structural Representation Attachment)	ST	
Element Group: Amount			
Amount Type	Exact	CD	

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Element Name	Value	Data Format	Note #
Quantity	1	PQ	
Element Group: Structure			
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	 **Figure H.18 — Representation of Structural Repeat Units A, B and C of Poloxamer 338**	ED	3)
Element Subgroup: Degree Polymerization			
Degree of Polymerization	B (shown in the Structural Representation Attachment)	CD	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	141	PQ	
Low Limit	137	PQ	
High Limit	146	PQ	
Amount Text	SRU/Polymer Ratio	ST	
Element Group: Structural Repeat Unit (Repeat)			
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	C (shown in the Structural Representation Attachment)	ST	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	1	PQ	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	 **Figure H.19 — Representation of Structural Repeat Units A, B and C of Poloxamer 338**	ED	4)

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Element Name	Value	Data Format	Note #
Element Subgroup: Degree Polymerization			
Degree of Polymerization	C (shown in the Structural Representation Attachment)	CD	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	141	PQ	
Low Limit	137	PQ	
High Limit	146	PQ	
Amount Text	SRU/Polymer Ratio	ST	
Element Group: Molecular Weight			
Molecular Weight Method	End-group titration	CD	
Molecular Weight Type	Number Average	CD	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	14 600	PQ	
Low Limit	12 700	PQ	
High Limit	17 400	PQ	
Unit	g/mol	CD	
Element Group: Modification			
Modification Type	Agent modification	CD	
Element Group: Agent Modification			
Agent Modification Type	Chemical	CD	
Role	End-cap polymerization	CD	
Modification Agent ID	NAHYH12345 (Artificial ID); [55X04QC32I (UNII)]	II	
Modification Agent	Sodium Hydroxide	ST	
Modification Process	Basic hydrolysis	CD	5)

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Element Name	Value	Data Format	Note #
Element Group: Amount			
Amount Type	Exact	CD	
Amount Text	Partial Hydrolysis to 17000	ST	

NOTE 1 Kolliphor P 338 is a prilled grade of Poloxamer 338 with a particle size around 1 000 µm. Microprilled Substances like Poloxamer 188 and 407 Grades are manufactured with a particular defined particle size. When this is the case the particle size information shall be provided at the Specified Substance Group 1 information level.

NOTE 2 Structural Representation of part A of the three SRUs.

NOTE 3 Structural Representation of part B of the three SRUs.

NOTE 4 Structural Representation of part C of the three SRUs.

NOTE 5 0.1 N Sodium Hydroxide at 75 °C.

NOTE 6 This reference is subject to subscription.

NOTE 7 Personal Care Products Council Database.

NOTE 8 Monomer Amount Type.

H.7.2 Poloxamer 338 Specified Substance Group 2 information Level

The ID of Specified Substance Group 2 has been appointed uniquely to the Specified Substance Group 2 Name, which couples the (Specified) Substance Name to the Manufacturer, see Figure 36.

Table H.4 — Poloxamer 338 SSG2

Element Group: Specified Substance Group 2			
Specified Substance Group 2 ID	POLO89765G (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Poloxamer 338—Company BB	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	GHYR78654S (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Synthetic	CD	
Production Method Description	Condensation polymerization of non-ionic ethylene oxide and propylene oxide	ST	
Production System Type	Condensation Chemistry	CD	
Critical process version number	1	INT	2)
Version	POLO338-1	ST	
Version Date	20170213	TS.Date	

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Element Group: Organization			
Manufacturer ID	DUNS897564 (Artificial ID)	II	
Manufacturer Name	Company BB	ST	
Issue of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	
(See Specified Substance Group 3 for further information below)			

NOTE 1 This (Parent) Substance ID corresponds to the Substance Name: Poloxamer 338.

NOTE 2 The version number would change if a substantial change in the (synthetic) manufacturing process occurred. These would include a change in the chemistry, addition or elimination of a purification step. A substantial change is a purification or processing step (i.e. changing a chromatographic matrix, changes in deprotection reagents etc.). The initial Critical Process Version Number shall be one and each subsequent number shall be increased sequentially.

H.7.3 Poloxamer Specified Substance Group 3

For Poloxamer there are two monographs one in the USP and one in the Ph.Eur. The limit tests are comparable but the monographs have slightly different tests. When reference is made to two different Pharmacopoeias two Specified Substance Group 3 should be created each with reference to the particular Pharmacopoeia. The Information model for Specified Substance Group 3 is provided in Figure 38.

Table H.5 — POLOXAMER 338 SSG3

Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	YUTR75643U (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Poloxamer 338 – USP	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	GHYR78654S (Artificial ID)	II	1)
Element Group: Grade			
Grade Type	USP	CD	
Grade Name	Poloxamer, type 338	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP 39-NF34, Page 7445	ST	
Reference Source URL	http://www.uspnf.com	ST	2)

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Element Group: Specified Substance Group 3 (Repeat)			
Specified Substance Group 3 ID	EURO78563E (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Poloxamer, type 338 – Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	GHYR78654S (Artificial ID)	II	1)
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name	Poloxamer, type 338	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Resource Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia 8.6 p. 5012-5013 Monograph number: 01/2008:1464, corrected 8.5	ST	
Reference Source URL	http://online6.edqm.eu/ep806/#	ST	2)

NOTE 1 This (Parent) Substnace ID corresponds to the Substnace Name: Poloxamer 338.

NOTE 2 This reference is subject to subscription.

H.8 Linear Biologically Sourced Polymers

H.8.1 Glycosaminoglycans

Glycosaminoglycans (GAGs) are one of the most abundant classes of polysaccharides in mammalian organisms. They consist of highly heterogenous mixtures of linear polysaccharides having a disaccharide structural repeat unit (SRU). The SRU typically consists of a uronic acid saccharide linked to an amino-sugar. GAGs vary in types of linkage within the disaccharide, monosaccharides in the disaccharide and the presence and degree of sulfation. GAGs are typically highly negatively charged, attract water, are essential components of extracellular matrices and have a variety of functions. In addition to heparins listed below, hyaluronic acid, dermatan sulfate, keratan sulfate and chondroitin sulfate are found in large amounts in all mammalian systems.

H.8.2 Heparins

Heparin is a naturally derived heterogeneous polymer composed of sulfated glycosaminoglycans of varying chain lengths. Commercial heparins are unfractionated, fractionated by molecular weight or reacted with chemicals or enzymes to reduce the chain length and thereby the molecular weight. Unfractionated heparin is typically derived from porcine intestinal mucosa or beef lungs.

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Heparin is primarily used to inhibit blood clotting. It accomplishes this through two distinct mechanisms. One mechanism involves binding and activating antithrombin III which then directly inhibits blood coagulation Factor Xa. Heparin can also inhibit thrombin (Factor IIa) by formation a ternary complex consisting of heparin, antithrombin III and thrombin. The ratio of Factor Xa inhibition to Factor IIa inhibition can be a defining characteristic that distinguishes low molecular weight heparins from one another. Antithrombin III binds to a five residue fragment within heparin while the formation of a ternary complex requires at least a 16 residue polysaccharide. The identification of the high affinity binding sequence of heparin led to the development of fondaparinux, a pentasaccharide that directly binds and activates antithrombin III. As noted below fondaparinux contains a 3-O-sulfated glucosamine [GlcNS(3S,6S)] residue which is essential for activity but rarely present within heparin or heparin sulfate. Only one-third of the heparin polysaccharide chains contain a sequence capable of high-affinity binding to antithrombin III.

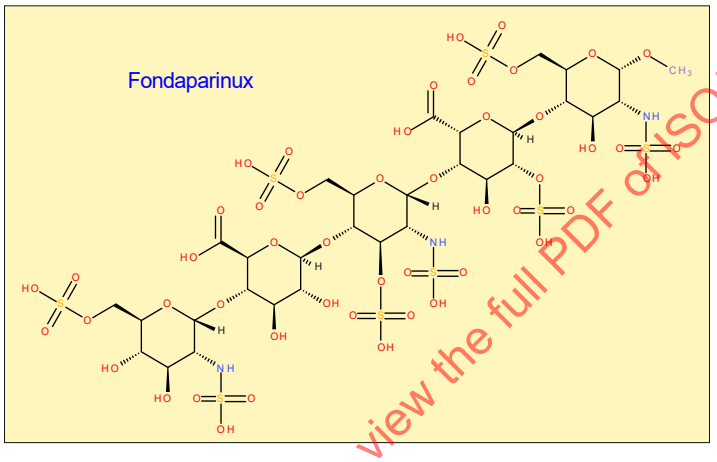


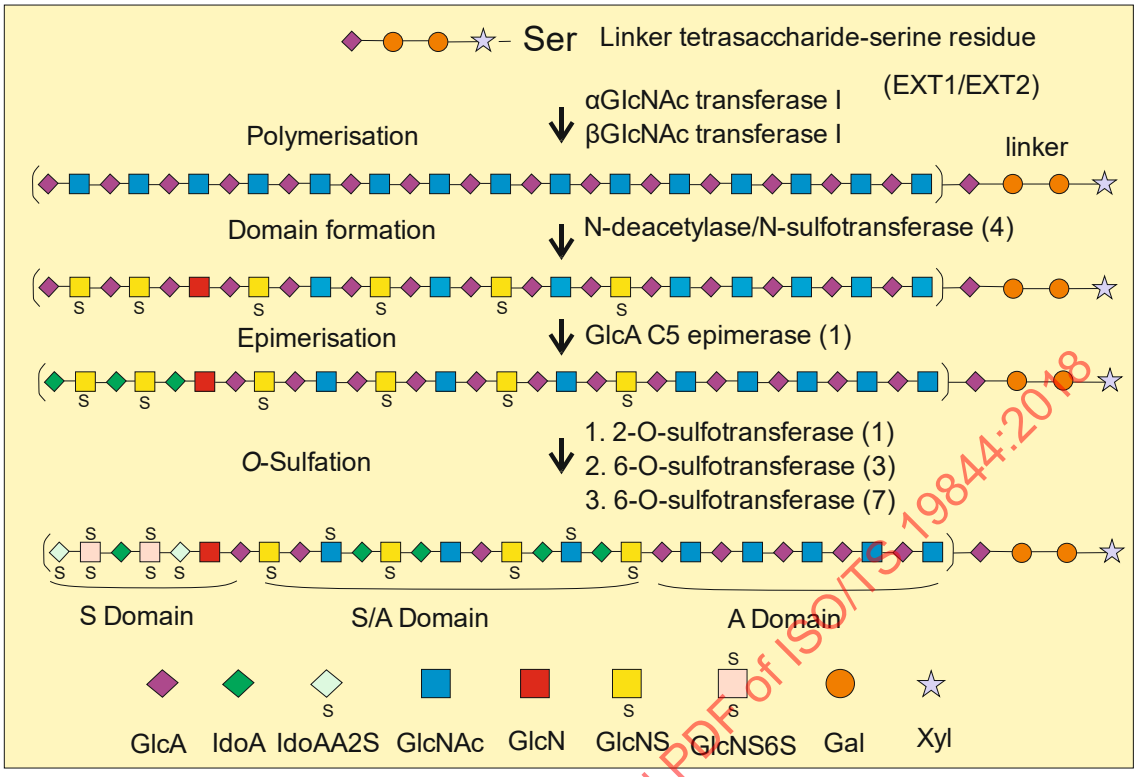
Figure H.20 — Fondaparinux

Heparins are typically described with a disaccharide SRU containing iduronic acid or glucuronic acid linked through a 1->4 bond with variable sulfation. There are six common disaccharides found in heparin each one will be represented as a Structural Repeat Unit. Heparins are synthesized as proteoglycans connected to hydroxyl groups on serine through a tetrasaccharide linker, see Figure H.21[61]. The chain is then elongated and modified.

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[61] http://protein.bio.msu.ru/biokhimiya/contents/v78/full/78070938.html

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NOTE Figure adapted from Nugent M.A. *et al.* [51], from Fig.1, Page 727.

Figure H.21 — Biosynthesis of Heparin and Heparan Sulfate

H.8.3 Example 4: Heparin Sodium

Table H.6 — Heparin Sodium

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	HEPAR12345 (Artificial ID)	II	
Substance Type	Polymer	CD	
Element Group: Substance Name			
Substance Name	Heparin Sodium	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	

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Element Name	Value	Data Format	Note #
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph.Eur. 8.6, monograph 01/2015:0333	ST	
Reference Source URL	http://online6.edqm.eu/ep806/	ST	1)
Element Group: Official Name (Repeat)			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP 39-NF34, Page 4188	ST	
Reference Source URL	http://www.uspnf.com	ST	1)
Element Group: Substance Name (Repeat)			
Substance Name	Unfractionated Heparin	ST	
Substance Name Type	Common Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Web	CD	
Reference Source URL	http://www.webmd.com/dvt/unfractionated-heparin-for-deep-vein-thrombosis	ST	
Element Group: Substance Code			
Code	9041-08-1 (generic code for the whole family)	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	

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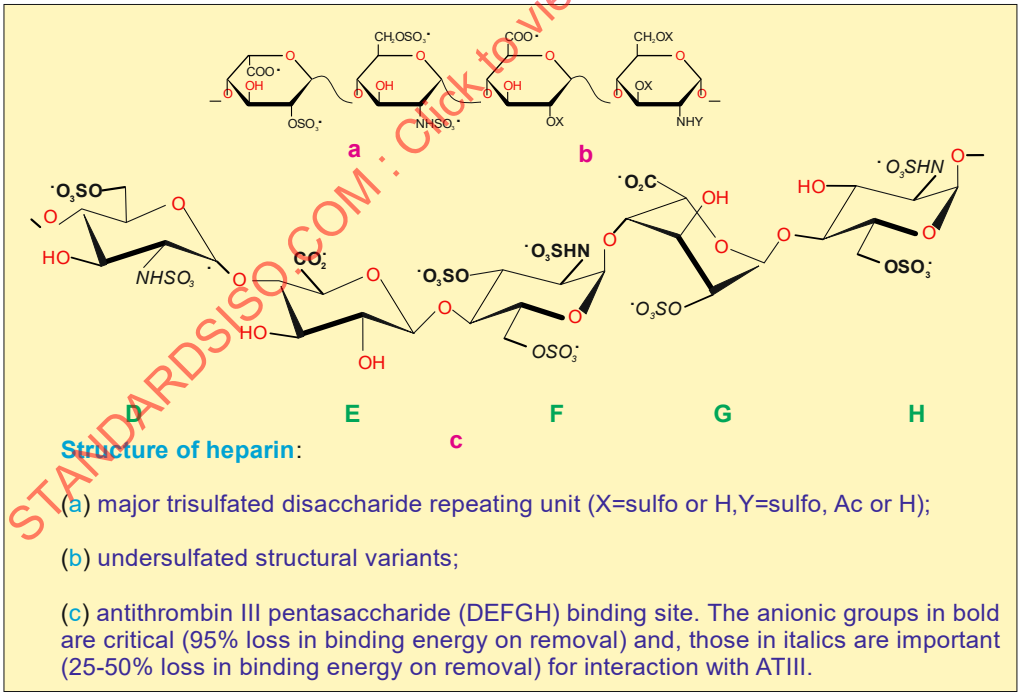
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Element Name	Value	Data Format	Note #
Element Group: Substance Code (Repeat)			
Code	ZZ45AB24CA	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Polymer			
Polymer Class	Copolymer	CD	
Polymer Geometry	Linear	CD	
Copolymer Connectivity	Random	CD	
Element Group: Monomer Set Description			
Number of Monomers	3	INT	
Monomer Amount Type	Monomer Percentage	CD	
Element Subgroup: Polymer Starting Material			
Starting Material ID	GLUCOR7654 (Artificial ID); [M7Y086VB5G (UNII)]	II	
Starting Material Name	.ALPHA.-D-Glucuronic acid	ST	
Starting Material Type	Biological Substance	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	10	PQ	
Element Subgroup: Polymer Starting Material (Repeat)			
Starting Material ID	LIDURO1234 (Artificial ID); [60Q5S101ID (UNII)]	II	
Starting Material Name	.BETA.-L-Iduronic acid, Pyranose form	ST	
Starting Material Type	Biological Substance	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	40	PQ	
Element Subgroup: Polymer Starting Material (Repeat)			
Starting Material ID	GLUCOSA5643 (Artificial ID0; [58L064K8RR (UNII)]	II	

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Element Name	Value	Data Format	Note #
Starting Material Name	.BETA.-D-Glucosamine	ST	
Starting Material Type	Biological Substance	CD	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	50	PQ	
Element Group: Structural Repeat			
Number of Structural Repeat Units	6	INT	
Average Molecular Formula by Repeat Unit	N/A		
Element Group: Structure			
Stereochemistry	Chiral	CD	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	See below next row	ED	



NOTE Figure adapted from Linhardt R.J. [52], Figure 2, Page 2552.

Figure H.22 — Structural representation of Heparin

Element Group: Reference Source

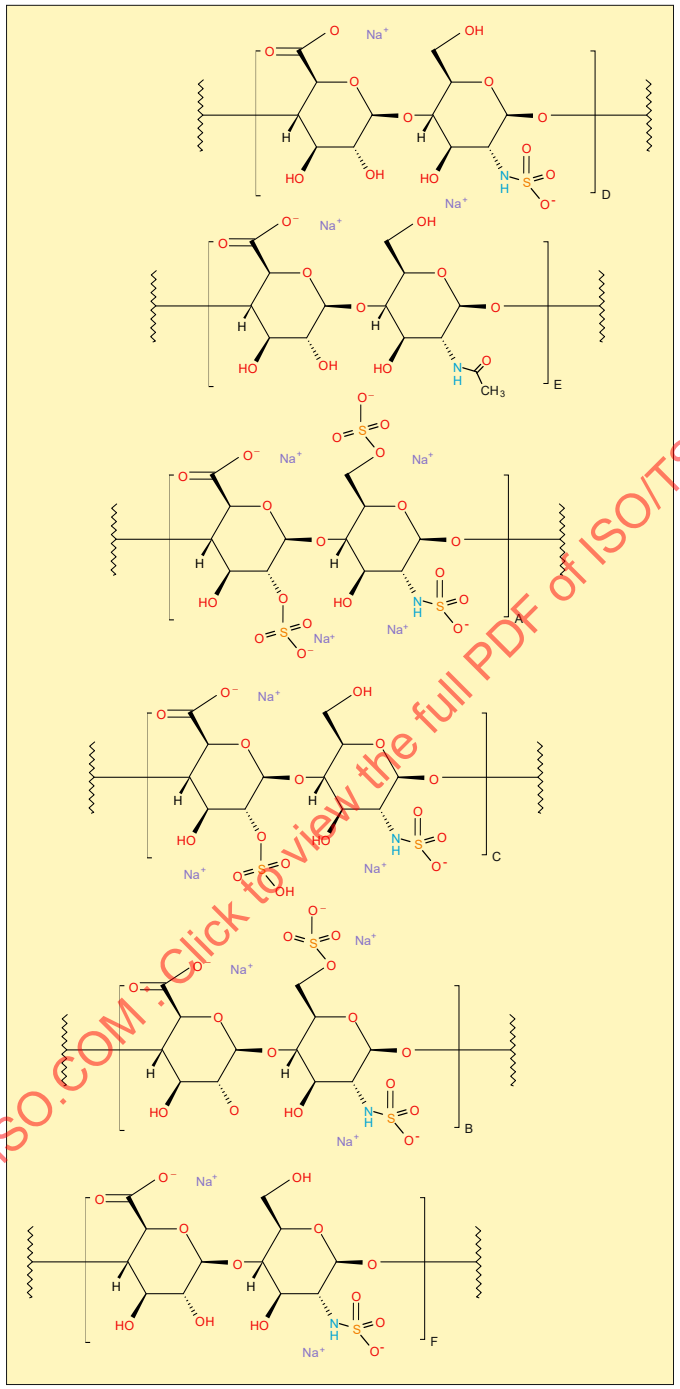
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Element Name	Value	Data Format	Note #
Public Domain	Yes	BL	
Reference Source URL	http://www-heparin.rpi.edu/main/app/webroot/files/papers/306.pdf	ST	
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Journal	CD	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	Representative	CD	

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Element Name	Value	Data Format	Note #
Structural Representation	 **Figure H.23 — Representation of Structural Repeat Units A, B, C, D, E and F of Heparin**	ED	
Element Group: Structural Repeat Unit			
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	A (shown in the Structural Representation Attachment)	ST	

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Element Name	Value	Data Format	Note #
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	75	PQ	
Amount Text	SRU Per cent	ST	
Element Group: Structural Repeat Unit (Repeat)			
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	B (shown in the Structural Representation Attachment)	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	5	PQ	
Amount Text	5-C-F (Average) SRU Per cent	ST	
Element Group: Structural Repeat Unit (Repeat)			
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	C (shown in the Structural Representation Attachment)	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	5	PQ	
Amount Text	5-B-F (Average) SRU Per cent	ST	
Element Group: Structural Repeat Unit (Repeat)			
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	D (shown in the Structural Representation Attachment)	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	20	PQ	
Amount Text	20-E (Average) SRU Per cent	ST	
Element Group: Structural Repeat Unit (Repeat)			
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	E (shown in the Structural Representation Attachment)	ST	
Element Group: Amount			
Amount Type	Exact	CD	

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Element Name	Value	Data Format	Note #
Quantity	20	PQ	
Amount Text	20-D (Average) SRU Per cent	ST	
Element Group: Structural Repeat Unit (Repeat)			
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	F (shown in the Structural Representation Attachment)	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	5	PQ	
Amount Text	5-B-C (Average) SRU Per cent	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Gel permeation chromatography	CD	
Molecular Weight Type	Number Average	CD	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	12 000	PQ	
Low Limit	3 000	PQ	
High Limit	30 000	PQ	
Unit	g/mol	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Journal	CD	
Reference Source Class	Literature	CD	
Reference Source Citation	2003 Claude S. Hudson Award Address in Carbohydrate Chemistry Heparin: Structure and Activity, Linhardt RJ, J. Med. Chem., 2003, 46 (13), pp 2551–2564	ST	
Reference Source URL	http://www-heparin.rpi.edu/main/app/webroot/files/papers/306.pdf	ST	
Element Group: Source Material			
Source Material Class	Biologic	CD	
Source Material Type	Porcine	CD	
Source Material State	N/A		
Organism ID	PORC67564 (Artificial ID); [659O12FKBL (UNII)]	II	

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Element Name	Value	Data Format	Note #
Organism Name	SUS SCROFA WHOLE	ST	
Parent Substance ID	S61JFZ33Z1 (UNII)	II	
Parent Substance Name	SUS SCROFA INTESTINAL MUCOSA	ST	
Country of Origin	CN	CD	
Element Group: Part Description			
Part	Intestinal Mucosa	CD	
Part Location	N/A		
Element Group: Fraction Description			
Fraction	Heparin	ST	
Material Type	Polysaccharide	CD	
NOTE This is a Subscription service.			

H.9 Nucleic Acids

Although nucleic acid with a limited number of strands with defined sequences are their own class of substances, nucleic acids that consist of a mixture of strands with varied sequences will be defined as a polymer. These substances are typically generated from the random cleavage of genomic DNA or total cellular RNA.

H.9.1 Defibrotide (Porcine)

Defibrotide (porcine) is the sodium salt of a polydisperse mixture of oligonucleotides produced by random, chemical cleavage (depolymerization) of porcine DNA. It is predominantly single stranded, of variable sequence length. The mean oligonucleotide length is 50 bases with a mean molecular weight of 17 ± 4 kDa. It is prepared by controlled chemical hydrolysis.

Table H.7 — Defibrotide (Porcine)

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance Type	Polymer	CD	
Substance ID	BROTI12345 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Defibrotide (Porcine)	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	

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Element Name	Value	Data Format	Note #
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Recommended INN List	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	INN Recommended List 27	ST	
Reference Source URL	https://mednet-communities.net/inn/db/media/docs/rinnlist27.pdf	ST	
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Journal article	CD	
Element Group: Substance Code			
Code	83712-60-1	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	L7CHH2B2J0	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	

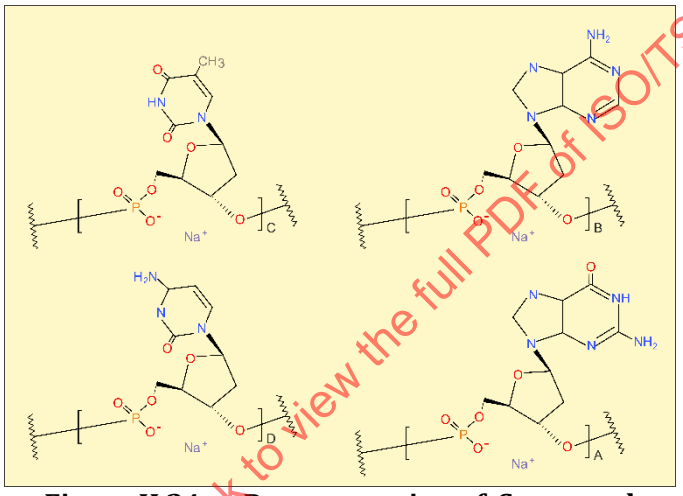
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Element Name	Value	Data Format	Note #
Substance Classification Code	B01AX01	CD.Code	
Substance Classification Type	difibrotide	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Public database	CD	
Reference Source URL	http://www.whocc.no/atc_ddd_index/?code=B01AX01	ST	
Element Group: Polymer			
Polymer Class	Copolymer	CD	
Polymer Geometry	Linear	CD	
Copolymer Connectivity	Random	CD	
Element Group: Monomer Set Description			
Number of Monomers	4	INT	
Monomer Amount Type	Monomer percentage	CD	
Element Subgroup: Polymer Starting Material			
Starting Material ID	DEOXYG8765 (Artificial IS); [7EAM4TG712 (UNII)]	II	
Starting Material Name	Deoxyguanosine 5'-Monophosphate	ST	
Starting Material Type	Biological Substance	CD	
Is Defining	Yes	BL	
Element Subgroup: Polymer Starting Material (Repeat)			
Starting Material ID	DEOXYT1234 (artificial ID); [43W3021X6C (UNII)]	II	
Starting Material Name	Deoxythymidine 5'-Monophosphate	ST	
Starting Material Type	Biological Substance	CD	
Is Defining	Yes	BL	
Element Subgroup: Polymer Starting Material (Repeat)			
Starting Material ID	VFR8I97ORM	II	
Starting Material Name	Deoxyadenosine 5'-Monophosphate	ST	
Starting Material Type	Biological Substance	CD	
Is Defining	Yes	BL	
Element Subgroup: Polymer Starting Material (Repeat)			
Starting Material ID	W7A9174XQL	II	
Starting Material Name	Deoxycytidine 5'-Monophosphate	ST	

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Element Name	Value	Data Format	Note #
Starting Material Type	Biological Substance	CD	
Is Defining	Yes	BL	
Element Group: Structural Repeat			
Number of Structural Repeat Units	4	INT	
Element Group: Structure			
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	 **Figure H.24 — Representation of Structural Repeat Units A, B, C and D of Defibrotide Sodium**	ED	
Element Group: Structural Repeat Unit			
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	A (shown in the Structural Representation Attachment)	ST	
Element Group: Structural Repeat Unit (Repeat)			
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	B (shown in the Structural Representation Attachment)	ST	
Element Group: Structural Repeat Unit (Repeat)			
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	C (shown in the Structural Representation Attachment)	ST	
Element Group: Structural Repeat Unit (Repeat)			

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Element Name	Value	Data Format	Note #
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	D (shown in the Structural Representation Attachment)	ST	
Element Group: Degree Polymerization			
Degree of Polymerization	A+B+C+D	CD	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	50	PQ	
Low Limit	9	PQ	
High Limit	80	PQ	
Amount Text	SRU/Polymer Ratio	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Gel electrophoresis	CD	
Molecular Weight Type	Number Average	CD	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	17 000	PQ	
Low Limit	13 000	PQ	
High Limit	21 000	PQ	
Unit	g/mol	CD	
Element Group: Source Material			
Source Material Class	Biologic	CD	
Source Material Type	Porcine	CD	
Parent Substance ID	659O12FKBL	II	
Parent Substance Name	SUS SCROFA WHOLE	CD	
Element Group: Part Description			
Part	Intestinal Mucosa	CD	
Part Location	N/A		
Element Group: Fraction Description			
Fraction	DNA Partially Depolymerized	ST	
Material Type	Nucleic Acid	CD	

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Annex I
(informative)

Structurally diverse vaccines

I.1 Scope

This Annex provides guidance to describe the elements that are necessary to define substances in human and veterinary vaccine products. Vaccine products typically consist of antigens, adjuvants and excipients. Individual antigens in polyvalent vaccines shall be identified as separate substances. Antigens can be proteins, nucleic acids, polymers or structurally diverse substances. Adjuvants can fall into all five substance types and Specified Substance Group 1. This document addresses the essential elements needed to define antigens and adjuvants for prophylactic vaccines. Therapeutic vaccines may be covered in future, in another annex.

Vaccines for human use are preparations containing antigens capable of inducing a specific and active immunity in man against an infectious agent or the toxin or antigen produced by it. Immune responses include the induction of the innate and the adaptive (cellular, humoral) parts of the immune system. A vaccine typically contains an agent that resembles a disease-causing micro-organism and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. Although most vaccines are used to prevent disease, vaccines are also being used to treat diseases.

I.2 Introduction

I.2.1 Introduction

Vaccines are the most cost-effective tools to prevent the spread of infectious disease. It is estimated vaccines save over 2 million lives every year and significantly reduce morbidity. Vaccines when effective prime the immune system to rapidly respond to a specific infectious agent and prevent its spread throughout the host and eventually society through herd immunity. Vaccine antigens typically contain either structural elements of infectious agents (proteins or polysaccharides) or live, live attenuated or inactivated infectious agents whose pathogenicity has been reduced. In addition to antigens most vaccines will also contain adjuvants. Adjuvants are often essential for the development of adaptive immune responses. The mechanism of action of many adjuvants is beginning to be understood and many act through multiple mechanisms. Adjuvants can provide sustained release of the antigen at the site of injection; upregulate the production of chemokines and/or recruit immune cells to the site of injection; and an increase uptake and presentation of antigens. The most widely used adjuvant is alum (Aluminium hydroxide, Aluminium phosphate, or Aluminium sulfate) but several others have been licensed and interactions between an adjuvant and the antigen will be captured at the substance information level or Specified Substance Group 1 information level.

NOTE Adsorption of Aluminium salt can be considered as an ion-bonding complex, thus this can be captured as a structural modification. The combination between a vaccine and a separate formulated adjuvant like AS03 (squalene/tocopherol/polysorbate 80) is considered as a Specified Substance Group 1. The combination will be

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considered as a product. The same protein complexed either to Aluminium phosphate or Aluminium hydroxide is considerd to be another substance and shall have a separate Substance ID.

I.2.2 Types of Vaccines Antigens

Antigens are generally defined as a substance or molecule that is capable of generating a specific immune response in a host. These responses are typically antibodies that bind to the antigen and/or T-cells that are activated to provide help to produce antibodies or to eliminate cells or pathogens that express the antigen or a processed form of the antigen. Vaccine antigens are meant to generate an immune response against an infectious agent to clear the infectious agent or reduce the spread or pathogenicity of the infectious agent.Vaccine antigens can be recombinant or purified proteins, polysaccharides, polysaccharides or hapte ns conjugated to proteins; inactivated or killed viruses or bacteria; live and attenuated viruses or bacteria; live viruses, bacteria or other cells engineered to express an antigen from an infectious agent and DNA that it contains. Antigens may induce broad immunity against all strains of a given infectious agent, more limited immunity against a series of strains or against single strain of an infectious agents (often referred to as serotypes).

In designing vaccines, the goal is to use an antigen to which all or nearly individuals will develop lasting protective immunity but this goal is often not possible. Lasting immunity requires generation of memory B and T cells and to accomplish this it is often necessary to have multiple injections of a given antigen or related antigen. This document will address the variety of antigens used in vaccine products.

I.2.3 Strategy for Defining Vaccines

Individual antigens will always be defined as substances. Substances that are isolated together from a biological matrix such as the two proteins haemagglutinin and neuraminidase found in influenza virus vaccines will be defined as a mixture of two proteins or a split virion. Antigens will be defined to a level necessary to distinguish related antigens. For many vaccines, this will require taxonomic definitions to the strain and even isolate levels. Serotypes may also be captured but emphasis will be placed on the actual strain or isolate from which the antigen was isolated. Recombinant proteins will be defined by their amino acid sequence, type of glycosylation and any permanent post-translational modifications that occur either *in vivo* or *in vitro*.

The oldest vaccines are structurally diverse mixtures of lysed cells or partially purified cellular components. Their identity is associated with the source organism typically including serotype/serogroup. Their immunogenicity and toxicity can be modulated by chemical and/or physical inactivation agents typically involving protein crosslinking. Another common approach is to use a less virulent (attenuated) organism.

Vaccines for human use may contain:

— Whole micro-organisms (bacteria, viruses or parasites), inactivated by chemical or physical means that maintain adequate immunogenic properties.

— Whole live micro-organisms that are either naturally avirulent or that have been passaged or treated to attenuate their virulence whilst retaining adequate immunogenic properties.

EXAMPLES [53] Live attenuated vaccines such as measles, mumps, rubella, oral polio, smallpox, varicella and yellow fever are a weakened form of the ‘wild’ viruses. These attenuated virus vaccines rely on limited replication of the virus in the host following vaccination. Immune responses induced are similar to those from

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natural infections and often these vaccines are effective after a single dose. However, such vaccines may cause severe reactions in some patients, which are often the result of the limited replication of the attenuated virus following vaccination. In contrast to attenuated live virus vaccines, inactivated (or killed) vaccines can not replicate, as their genetic material or overall structure are purposefully destroyed.

— Antigens extracted from the micro-organisms or produced by genetic engineering or chemical synthesis. The antigens may be used in their native state, or detoxified by chemical or physical means. They often aggregated, polymerized, conjugated to a carrier protein or adsorbed on an adjuvant to increase their immunogenicity.

Influenza vaccines are formulations of an inactivated influenza virus grown in fertilized hens' eggs or in cell cultures. Influenza virus seed to be used in the production of vaccine is propagated in fertilized eggs from chicken flocks free from specified pathogens (SPF) or in suitable cell cultures, such as chick-embryo fibroblasts or chick kidney cells obtained from SPF chicken flocks. For production, the virus of each strain is grown in the allantoic cavity of fertilized hens' eggs from healthy flocks or in cell cultures e.g. MDCK (Madin Darby canine kidney) or Vero (kidney epithelial cells extracted from an African green monkey) cells.

The vaccines are formulated as whole inactivated virus particles, virosomal vaccine particles (virus particles from which the genetic material has been removed) and split vaccine (split virus) or subunit vaccine suspensions containing purified surface proteins (haemagglutinin and neuraminidase).

Vaccine substances for which the source of the organism is predominantly the defining element can be captured by the Structurally diverse information model, see Figure E.2.

I.2.4 Recombinant Proteins

The development of recombinant DNA techniques to produce large amount of specific proteins has revolutionized the development of vaccines. Licensed hepatitis B and human papillomavirus vaccine antigens are recombinant proteins typically made in yeast or insect cells that typically form virus-like particles (VLPs) that are very effective immunogens. A major advantage in subunit immunogen production has been the assembly of proteins as VLPs using protein expression technology in yeast, insect or mammalian cells. VLPs are a highly effective type of subunit vaccines that mimic the overall structure of virus particles without the requirement that they contain infectious genetic material. Indeed, many VLPs lack the DNA or RNA genome of the virus altogether, but have the authentic conformation of viral capsid proteins seen with attenuated virus vaccines, without any risks associated with virus replication or inactivation. VLP preparations are all based on the observation that expression of the capsid proteins of many viruses leads to the spontaneous assembly of particles that are structurally similar to authentic virus. In addition to their ability to stimulate B cell mediated responses, VLPs have been demonstrated to be highly effective in stimulating CD4 proliferation and cytotoxic T lymphocyte responses. These rDNA protein substances as VLPs can be captured by the Protein information model and making use of the Source Material element group, see Figure C.1.

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I.3 Terms and definitions

For the purposes of this Annex I, both the terms and definitions given in ISO 11238 and the following apply.

Terms related to Vaccine Substances:

I.3.1
attenuation
alteration of an infectious agent and alters it so that it becomes harmless or less virulent but remains replication competent. Attenuated vaccines contrast to inactivated vaccines which are produced by "killing" the virus

I.3.2
passage number
number of times a cell culture has been subcultured

I.3.3
subculturing
removal of the medium and transfer of cells from a previous culture into fresh growth medium, a procedure that enables the further propagation of the cell line or cell strain. It is also called passaging

I.3.4
vaccine
biological preparation that provides active acquired immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing micro-organism and is often made from weakened or killed forms of the microbe, its toxins, one of its surface proteins or polysaccharides

I.4 Example: Hepatitis B vaccines

Safe and effective hepatitis B vaccines have been licensed since 1982. The initial vaccine consisted of the hepatitis B surface antigen (HBsAg) that was isolated from the plasma of patients that were chronically infected with hepatitis B. The initial vaccine consisted of highly purified HBsAg antigens harvested as 22 nm particles in this example.

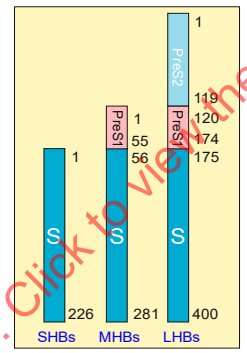
All currently licensed hepatitis B vaccines are produced using recombinant DNA techniques. The antigen consists of a 226 amino acid protein that is predominantly produced in yeast cells. The antigen aggregates into a 20-22 nm particle similar to the particle isolated from chronically infected patients. The substance is the 226 amino-S-protein, the 22 nm VLP will be described as a characteristic attribute of the Substance at the Specified Substance Group 1 information level. The virus-like particle adsorbed on the aluminium-based adjuvant will also be described at the Substance information level.

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I.4.1 Background information of Hepatitis B S protein

The human hepatitis B virus (HBV) and the related hepatotropic viruses discovered in woodchucks (WHV), ground squirrels (GSHV), ducks (DHBV), and herons (HHBV) are classified as the family of Hepadnaviridae. The virion structures, genome sizes, and modes of replication of these viruses are similar. The prototype, HBV, has a diameter of approximately 42 nm with a 27 nm core enclosing a 3.2kb DNA genome. The lipid-containing envelope carries three closely related protein components, large, middle and small envelope proteins respectively. The C-terminal 226 amino acids corresponding to the small S protein contains the major antigenic determinant, hepatitis B surface antigen (HbsAg), which is exposed on the surface of the viral particles. The S protein is initially synthesized as a membrane protein spanning the membrane of the endoplasmic reticulum (ER) at least twice and is partially glycosylated at Asn (N) 146. Secreted 22 nm particles contain both unglycosylated P24 protein and its glycosylated GP27 derivate. The S proteins in the secreted viral and subviral particles are extremely cross-linked by disulfide bridges. Covalent cross-linking occurs concomitantly with assembly and budding of lipoprotein particles. The small, middle, and large HBV envelope proteins contain Cysteine residues exclusively in the 226-amino acid sequence common to all three polypeptides, see Figure I.1. Of the 14 Cysteines, 8 are located in the hydrophilic region carrying the surface antigen. Only three of the remaining Cysteine residues are conserved among all hepadnaviruses, see Figure I.2. Cysteines 48, 65, and 69 (and histidine 60) in the HBV-S protein are essential for secretion of the 22 nm particles.



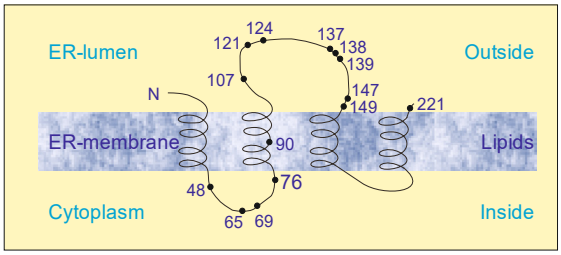
NOTE Figure adapted from HBVdb [54], from Figure 1.

Figure I.1 — HBV surface membrane proteins

NOTE HBV virions and VLPs contain variable proportions of the three co-carboxyterminal surface (glyco)-proteins: the large (LHBs), middle (MHBs) and small (SHBs) surface proteins. HBV surface proteins are products of a single open reading frame and distinguished by three domains. HBV comprises: preS1 (108 or 119 aa depending on the genotype) only in LHBs, preS2 (55 aa) in LHBs and MHBs, and S (226 aa) common to all three HBs proteins [53][55]. Further description of the organization of the hepadnaviral envelope is described by Dieter Glebe and Stefan Urban [56] and 'The Hepatitis B Virus data base' (HBVdb) [54].

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NOTE Figure adapted from Mangold Constance M.T. [55], from Fig.9, Page 4596.

Figure I.2 — Secondary structure model for the HBV proteins

NOTE A secondary structure model divides the HBV S protein into hydrophobic regions that interact with lipids (shaded area) and more hydrophylic regions. The numbers indicate the positions of the Cysteine residues in the protein. Cysteines in the first hydrophylic loop are initially located in the cytoplasma, whereas Cysteines in the second hydrophylic loop (100 – 170) carrying the major antigenic determinant. The S-domain contains 8 Cysteine residues within the antigenic loop that form inter- and intramolecular disulfide bonds, resulting in high molecular weight multiprotein complexes, while the preS-domain does not contain Cysteine and forms linear epitopes.

The double-layered mature infectious particle, known as the Dane particle, is a structure comprising an inner core formed from 180 or 240 copies of the HB core antigen (HBcAg) arranged with an outer proteolipid HB surface Ag (HBsAg) layer. About 80 % of HBsAg is in the S form, which assembles with M and L forms into both the outer surface of the Dane particle and smaller VLPs. These HBsAg subviral particles, known as 22-nm particles because of their diameter, are stabilized by disulfide bonds. HBsAg particles greatly outnumber mature virus particles and presumably act as decoys for the immune system. Because HBV subviral particles share important immunological determinants with the mature virus, they can be used as effective immunogens. Indeed, expression of SHBsAg particles in yeast in the 1980s led to the development of the first recombinant human vaccine. This HBsAg can also be produced in mammalian cells [Chinese hamster ovary (CHO)] cells or other suitable cell lines.

According to Roldão *et al*., (2010) [58] the current existing recombinant HB vaccines are produced in yeast (S. cerevisiae, P. pastoris and H. polymorpha) or in mammalian cells (CHO cell line). The choice of the host cell has consequences both in terms of the structure of the resulting VLPs and of the production process. HBsAg produced in CHO cells have significant differences in molecular weight (4,9 kDa) and a size of 22,1 nm having an average of 155 monomers on average, while the yeast-derived VLPs are smaller (3,0 kDa) and a size of 18,1 nm and contain about 86 monomers on average. CHO-derived VLPs contain glycosylated and non-glycosylated HBsAg proteins similar to the antigens found in infected sera, whereas yeast-derived have been reported as being non-glycosylated. The yeast based process has to have a disruption step to carry out the release of the VLPs, where mammalian cells are able to secrete the HBsAg as 22-nm subviral paricles. Process-related parameters, such as the mutiplicity of infection (number of viruses per cell), time of harvest and cell concentration at infection, and dissolved oxygen concentration are key elements for optimal protein expression and consequently VLP assembly. These factors will not be captured as a Specified Substance Groups 1, 2 or 3 but are elements to be captured at Specified Substance Group 4 information level which will not be included in this version of the ISO/TS 19844.

I.4.2 Development of hepatitis B vaccine from transformed yeast cells

The production in yeast cells of the recombinant DNA Hepatitis B vaccine involves an optimized fermentation process followed by cell disruption and extraction, together with other soluble yeast components of the surface antigen of the HBV subsequently followed by a purification process including

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precipitation steps, ion exchange and gel permeation chromatography, and Cesium chloride ultracentrifugation. The yeast-derived antigen occurs as spherical particles containing non-glycosylated HBsAg polypeptide, lipid and Tween 20. The purity of the polypeptide is above 95 % and confirmed by the absence of an immune response to yeast-derived contaminants in vaccines. The purified yeast-derived HBsAg was obtained from fermentor-grown transformed Y194 yeast cells. As a host for production the common baker's yeast *Saccharomyces cerevisiae* was used[62]. N-terminal modification is reported[63] and the N-terminal sequence of the recombinant product was analysed by 15 cycles of Edman degradation and FAB-MS in which evidence was found that partial acetylation occurs for the N-terminal Methionine.

Other examples are described by Z.A. Janowicz *et al*. [59]. The article described an expression system for the methyloptrophic yeast *Hansenula polymorpha* and used to co-express both the L (preS1-S2-S) and SHBsAg under the control of strong methanol inducible promoters derived from Methanol oxidase and Formate dehydrogenase genes. The gene coding for the major surface antigen is inserted in the DNA of the yeast *H. polymorpha* by a plasmid vector making up a recombinant DNA. The gene coding for HBsAg is isolated from the serum of a patient chronically infected with the HB virus by Polymerase Chain Reaction and inserted via EcoRI/BamHI fragment into the plasmid vector. The gene coding for the HBsAg contains about 678 bp and the HBsAg is a 226 amino acid antigen S. The surface antigen (HBsAg) exists as a particle composed of proteins and lipids, mainly phospholipids, essentially phosphatidylcholine, phosphatidylserine, phosphatidylinositol and phosphatidylethanolamine, triglycerides and free fatty acids.

Table I.1 — Tabular Substance information level for Hepatitis B Surface Antigen (Limited information)

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	HBSAG98765 (Artificial ID)	II	
Substance Type	Protein	CD	
Element Group: Substance Name			
Substance Name	Hepatitis B Surface antigen rDNA, adsorbed on aluminium hydroxide.	ST	1)
Substance Name Type	Preferred Name	CD	
Language	en	CD	
Substance Name Domain	Biologic	CD	
Jurisdiction	EU, US	CD	
Element Group: Substance Name (Repeat)			
Substance Name	Hepatitis B Surface antigen rDNA, adsorbed	ST	1)

[62] See Petre J. et al. [71]

[63] See Petre J. et al. [71]

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Element Name	Value	Data Format	Note #
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Biologic	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	Ph. Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph. Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia, Monograph 07/2011:1056	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Hepatitis B virus HBsAg Surface Protein Antigen (recombinant)	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	EDA GSRS	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	N/A		
Element Group: Substance Name (Repeat)			
Substance Name	Hepatitis B surface antigen (Hepatitis B virus gene S)	ST	
Substance Name Type	Other Name	CD	
Language	en	CD	

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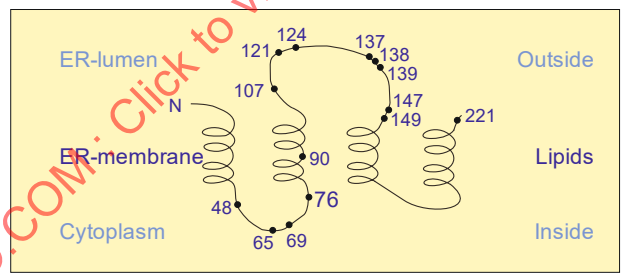
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Element Name	Value	Data Format	Note #
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	
Element Group: Substance Code			
Code	811352-97-3	CD.Code	
Code System	CAS Registry	CD.CodeSystem Name	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	IFJ010MNE4	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystem Name	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Reference Information			
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	J07BC01	CD.Code	
Substance Classification Type	hepatitis B, purified antigen	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	https://www.whocc.no/atc_ddd_index/?code=J07BC&showdescription=no	ST	

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Element Name	Value	Data Format	Note #
Element Group: Reference Information			
Element Group: Gene			
Gene Sequence Origin	Hepatitis B virus	CD	
Gene ID	AAB88102.1	CD	2)
Gene Name	HBsAg gene, subtype adw2	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	European Nucleotide Archive (ENA)	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	http://www.ebi.ac.uk/ena/data/view/AAB88102	ST	
Element Group: Structure			
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	See image below	ED	



NOTE Figure adapted from Mangold Constance M.T. [55], from Fig.9, Page 4596.

Figure I.3 — Representation of the structure of Hepatitis B Surface Antigen

Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Journal	CD	
Reference Source Class	Literature	CD	
Reference Source Citation	C.M.T. Mangold and R.E. Streeck, J. of Virology, Aug. 1993, 4588-4597	ST	

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Element Name	Value	Data Format	Note #
Element Group: Protein			
Sequence Type	Complete	CD	
Number of Subunits	1	INT	
Disulfide Linkage	Residue 1_48; 1_65; 1_69; 1_76; 1_90; 1_107;1_121; 1_124; 1_137; 1_138; 1:139; 1_147; 1_149; 1_221 intra and inter chain disulfide bonds including 3 free sulfhydryl groups (positions indicated in Figure above).	ST	2)
Element Group: Protein Subunit			
Subunit	1	INT	
Sequence	MENITSGFLGPLLVLQAGFFLLTRILTIPQSLDSWWTSLN FLGGSPVCLGQNSQSPTSNHSPTSCPPICP GYRWMCLRRF IIFLFILLLCLIFLLVLLDYQGMLPVCPLIPGSTTTSTGPCKT CTTPAQGNSMFPSCCCTKPTDGNCTCIPIPSSWAFAKYW EWASVRFSWLSLLVPFVQWFVGLSPTVWLSAIWMMWY WGPSLYSIVS PFIPLLPIFFCLWVYI	ST	
Sequence Attachment	See below	ED	

```
        10         20         30         40         50
MENITSGFLG PLLVLQAGFF LLTRILTIPQ SLDSWWTSLN FLGGSPVCLG
        60         70         80         90        100
QNSQSPTSNH SPTSCPPICP GYRWMCLRRF IIFLFILLLC LIFLLVLLDY
       110        120        130        140        150
QGMLPVCPLI PGSTTTSTGP CKTCTTPAQG NSMFPSCCCT KPTDGNCTCI
       160        170        180        190        200
PIPSSWAFAK YLWEWASVRF SWLSLLVPFV QWFVGLSPTV WLSAIWMMWY
       210        220
WGPSLYSIVS PFIPLLPIFF CLWVYI
```

Figure I.4 — Representation of the sequence of Hepatitis B Surface Antigen

N-Terminal Modification ID	AE28F7PNPL (UNII)	II	
N-Terminal Modification	N-Acetylmethionine	ST	
C-Terminal Modification	N/A		
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Journal	CD	
Reference Source Class	Literature	CD	
Reference Source Citation	http://www.uniprot.org/uniprot/Q773S4 selection 'Sequence'	ST	3)

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Element Name	Value	Data Format	Note #
Element Group: Molecular Weight			
Molecular Weight Method	SDS-PAGE	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	24 000	PQ	
Unit	g/mol	CD	
Element Group: Glycosylation			
Glycosylation Type	Yeast	CD	4), 5)
N-Glycosylation Site	N/A		
O-Glycosylation Site	N/A		
Element Group: Modification (N-Terminal Modification)			
Modification Type	Structural modification	CD	
Residue Modified	Methionine	CD	
Residue Site	1_1	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Molecular Fragment Role	N-Terminal Methionine acetylation	CD	
Molecular Fragment ID	ACETYLMET1 (Artificial ID); [9J12WX5B6A (UNII)]	II	
Molecular Fragment Name	N-Acetylmethionine	ST	6)
Element Group: Modification (Adjuvant adsorption) (Repeat)			
Modification Type	Agent modification	CD	
Residue Modified	Primary and secondary aminogroups	CD	
Residue Site	Random	ST	
Element Group: Agent Modification			
Agent Modification Type	Chemical	CD	
Role	Adsorption of Aluminium to antigens	CD	
Modification Agent ID	JKHYR98765 (Artificial ID)	II	
Modification Agent	Aluminium hydroxide	ST	

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Element Name	Value	Data Format	Note #
Modification Process	Adsorption of adjuvant	ST	
Element Group: Property			
Property Type	Physical	CD	
Property Name	S-Protein Monomer impurity	CD	
Property Substance ID	HbsAg98765 (Artificial ID)	II	
Property Substance Name	S-Protein	ST	
Element Group: Amount			
Amount Type	NMT	CD	
Quanity	3,0	PQ	
Unit	% {w/w}	CD	
Amount Text	Average weight distribution of Dimers-Trimers	ST	

NOTE 1 Hepatitis B Surface antigen is adsorbed on Aluminium Phosphate in the product 'Ambirix' Suspension for injection. It is adsorbed on Aluminium hydroxide in the multivalent vaccine 'Hexacima' and in ''ENGERIX-B' Vaccine. In this example the substance is adsorbed on Aluminium hydroxide corresponding to 0,6 mg Aluminium (Al3+) in 'Hexacima' and for 'Ambirix' adsorbed on Aluminium phosphate corresponding to 0,4 mg Aluminium (Al3+).

NOTE 2 European Nucleotide Archive: AAB88102.1 code for the HbsAg gene, subtype adw2

NOTE 3 UniProtKB - Q773S4 (Q773S4_HBV), Sequence Protein S.

NOTE 4 See Janowicz Zbigniwe A. *et al*. 1991, [59], *Hansenula polymorpha*, strain RB10 HBS is NOT Asn_146 (N)-glycosylated.

NOTE 5 Dvorah Diminsky. Reinhold Schirmbeck, Jorg Reimann and Yechezkel Barenholz 'Comparison between Hepatitis B surface antigen particles derived from mammalian cells (CHO) and yeast cells (*Hansenula polymorpha*): composition, structure and immunogenicity' Vaccine, Vol. 15 nl. 6/7, 637-647, 1997: In CHO-cells the S,M,L peptides are in each of the two forms S (P24, GP27), M (GP33, GP36) and L (P39, GP42); in *H. Polymorpha* HBsAg only the S non-glycosylated peptide (P24) was observed.

NOTE 6 See Petre J. *et al*. 1987, [60]

I.4.3 Capturing information for Hepatitis B Surface Antigen Virus-like particles produced in yeast cells

VLPs are described at the Specified Substance Group 1 information model using the element groups Constituent and Characteristic Attributes in combination with the element group Amount, see Figure 35.

Table I.2 — Tabular information level for Hepatitis B Surface Antigen Virus-Like Particles captured at the Specified Substance Group 1 information level

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 1			
Specified Substance Group 1 ID	HBSVLP1234 (Artificial ID)	II	
Element Group: Substance Name			

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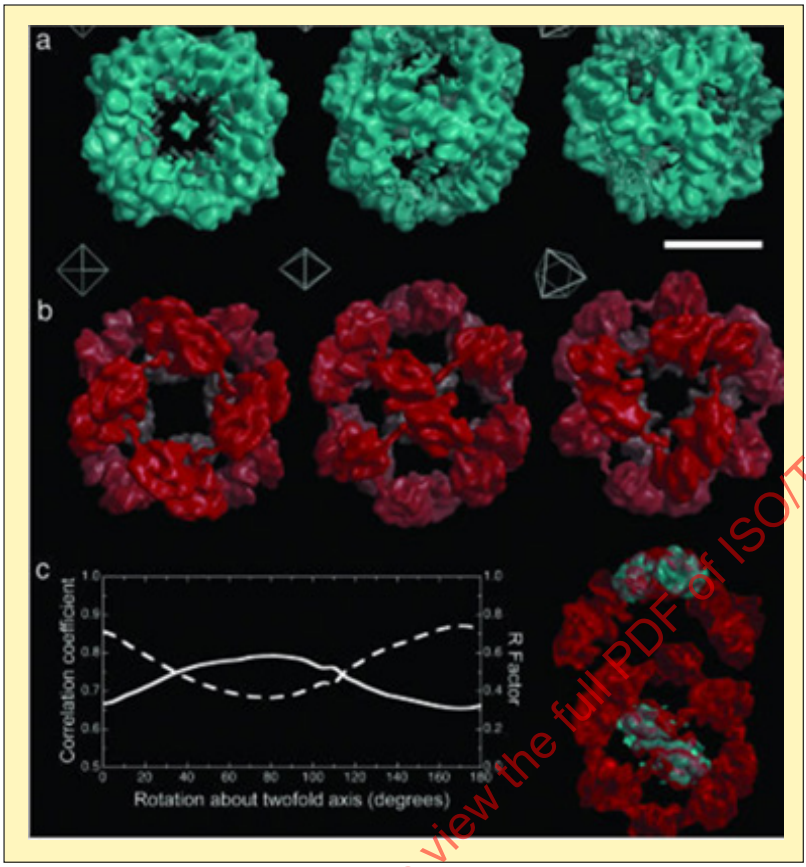
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Element Name	Value	Data Format	Note #
Substance Name	Hepatitis B Surface antigen rDNA, adsorbed on aluminium hydroxide, yeast VLP	ST	1)
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Constituent			
Constituent Substance ID	HBSAG98765 (Artificial ID)	II	
Constituent Substance Name	Hepatitis B Surface antigen rDNA, adsorbed on aluminium hydroxide	ST	1)
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Physical Form			
Physical State	Virus Like Particle	CD	
Physical Form Type	Particle composed of proteins and lipids	CD	2), 3)
Element Group: Characteristic Attribute			
Attribute Type	Physical	CD	
Attribute Name	Particle Size	ST	
Attribute Substance ID	HBSVLP1234 (Artificial ID)	II	
Attribute Substance Name	Hepatitis B Surface antigen rDNA, adsorbed on aluminium hydroxide, yeast VLP	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	20	PQ	
Unit	nm	CD	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	2), 3)
Structural Representation Attachment	See image below, spherical HbsAg particles of about 20-22 nm.	ED	

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Element Name	Value	Data Format	Note #



NOTE (Figure reproduced from Reference [61] (Fig.1, Page 14785).

Figure I.5 — Spherical HbsAg particles of about 20-22 nm

Public Domain	Yes	BL	
Reference Source Type	Journal	CD	
Reference Source Class	Literature	CD	
Reference Source Citation	Gilbert RJ *et al*., Proc Natl Acad Sci USA. 2005: 102, 14783-14788	ST	

NOTE 1 The (Specified) Substance (Group 1) name is composed out of the (Parent) Substance name extended with the virus like particle of the host.

NOTE 2 mHBsAg particle reconstructions. (*a*) Surface-rendered views (threshold 2,5 σ) of the small mHBsAg particle reconstruction at 12-Å resolution. *Insets* show the orientation of each image with respect to the octahedral symmetry of the particle. (Scale bar, 100 Å.) (*b*) As *a* for the large mHBsAg particle. (*c*) A plot of the real-space correlation coefficient (dashed line) and *R* factor (solid line) between the twofold blocks of the large and small reconstructions as they are rotated with respect to one another. The peak in correlation coefficient and trough in *R* factor indicate a rotation of ≈10°. On the right the twofold block from the small reconstruction (cyan) is shown fitted in this manner to that from the large reconstruction.

NOTE 3 The hepatitis B virus (HBV) is an enveloped DNA virus with an icosahedral capsid replicating via reverse transcription. The crystal structure of the capsid is known. It has a diameter of 36 nm and is formed by one protein species

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Element Name	Value	Data Format	Note #
(C protein). The viral envelope contains three different co-terminal proteins (S, M, and L proteins) spanning the membrane several times. These proteins are not only released from infected cells as components of the viral envelope but in 10 000-fold excess as subviral lipoprotein particles with a diameter of 22 nm containing no capsid. Assembly of the capsid occurs in the cytosol and results in packaging of a 3,5 kb RNA molecule together with viral and cellular factors. This newly formed capsid cannot be enveloped. Rather, synthesis of the viral DNA genome in the lumen of the capsid by reverse transcription is required to induce a budding competent state. Envelopment then takes place at an intracellular membrane of the pre-Golgi compartment. The S and the L protein, but not the M protein, is required for this process. The L protein forms two different transmembrane topologies. The isoform exposing the N-terminal part at the cytosolic side of the membrane is essential for budding. In this domain, a 22 amino acid (aa) long linear stretch has been mapped genetically to play a vital role in the morphogenetic process. This domain probably mediates the contact to the capsid. A second matrix domain was mapped to the cytosolic loop of the S protein. A similar genetic approach identified two small areas on the capsid surface, which might interact with the envelope proteins during envelopment [62].			

I.4.4 Capturing manufacturing information for Hepatitis B Surface Antigen Virus-like particles produced in yeast cells

The manufacturing process is described at the Specified Substance Group 2 Information level up to the information group 'Manufacturing', see Figure 36.

However, the manufacturing information shown in the green box in Figure 36 may be described by the extended information class 'Manufacturing', see Figure 37, if applicable. This model is part of the overall manufacturing information model as captured in Specified Substance Group 4 information (ISO 11238). In this model, detailed manufacturing information can be described.

Table I.3 — Tabular information for the manufacturing of HBsAg—Specified Substance Group 2 Information

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2 (HbsAg-Manufacturing information)			
Specified Substance Group 2 ID	FDSTE7453A (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Hepatitis B Surface antigen rDNA, adsorbed on aluminium hydroxide, yeast VLP — Company YY	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	HBSVLP1234 (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Recombinant Protein Production	CD	
Production Method Description	See attached document from Regulatory submission	ST	
Production System Type	Yeast, Cell line	CD	
Production System	*Hansenula polymorpha*, strain RB10	CD	
Critical Process Version Number	1	INT	
Version	HBS-001	ST	2)

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Element Name	Value	Data Format	Note #
Version Date	20170501	TS.Date	
Element Group: Organization			
Manufacturer ID	DUNS8564320 (Artificial ID)	II	
Manufacturer Name	Company YY	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	FINAL67543 (Artificial ID)	ST	
Reference Source Citation	CBG564231 (Artificial CBG-Case number)	ST	

NOTE 1 This (Parent) Substance ID refers to the (Specified) Substance (Group 1) Name: Hepatitis B Surface antigen rDNA, adsorbed on aluminium hydroxide, yeast VLP.

NOTE 2 The Critical Process Number Version Number would change if a substantial change in the (biological) manufacturing process occurred. These would include a change in the chemistry or host cell line, addition or elimination of a purification step. The change in a version number should be tied to the production system type.

I.4.5 Capturing manufacturing information for Hepatitis B Surface Antigen Virus-like particles produced in yeast cells

The captured information on specifications and Pharmacopoeial grades should include reference to relevant Pharmacopoeia monographs, which the product complies with. In addition, product-specific release specifications should be provided as 'In-House specification'. Information on specifications is captured at the Specified Substance Group 3 information level with reference to the pharmaceutical grade, see Figure 38. Additional specification can be laid down in the Element Group Reference Source with the Reference Source Document Type 'In-house specification'. The actual document itself will be stored in the Reference Source Document classification attribute '(Release) Specification document'.

Table I.4 — Tabular information captured at the Specified Substance Group 3 information level for Hepatitis B Surface antigen rDNA, adsorbed on aluminium hydroxide, yeast VLP

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	KHGTR12345 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Hepatitis B Surface antigen rDNA, adsorbed on aluminium hydroxide, yeast VLP - Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	HBSVLP1234 (Artificial ID)	II	1)

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Element Name	Value	Data Format	Note #
Element Group: Grade			
Grade Type	Ph.Eur.	CD	2)
Grade Name	Hepatitis B vaccine (rDNA)-Ph.Eur.	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia, monograph 1056	ST	
Element Group: Grade (Repeat)			
Grade Type	In-house	CD	2)
Grade Name	Hepatitis B vaccine (rDNA), adsorbed-In-house	ST	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	HBVS001 (Artificial ID)	ST	
Reference Source Citation	CBG231675 (Artificial CBG-Case number)	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	PDF	ED	
Reference Source Document Type	In-house specification	CD	
Reference Source Document ID	5643 (Artificial ID)	ST	
Reference Source Document Classification	In-house/Batch release specification	CD	

NOTE 1 This (Parent) Substance ID refers to the (Specified) Substance (Group 1) Name: Hepatitis B Surface antigen rDNA, adsorbed on aluminium hydroxide, yeast VLP.

NOTE 2 The hepatitis B surface antigen specifications are described in the 'In-house specifications' as laid down in the dossier. They are in compliance with the bulk hepatitis B surface antigen part of the Ph. Eur. Monograph 1056 "Hepatitis B vaccine (rDNA)", and with the WHO Recommendations to assure the quality, safety and efficacy of recombinant hepatitis B vaccines, adopted by ECBS in October 2010 (revised TRS 786).

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I.5 Example: Live attenuated Vaccines, BCG vaccine, Freeze-dried and BCG for immunotherapy

BCG vaccines are described in Pharmacopoeial monographs e.g. Ph. Eur. monograph 01/2012:0163, 'BCG Vaccine, freeze-dried' and Ph. Eur. monograph 01/2009:1929 'BCG for Immunotherapy'. In addition, the vaccines have to comply with the Ph. Eur. monograph 01/2013:0153 'Vaccines for Human use' or the Ph. Eur. monograph 01/2008:0062 'Vaccines for Veterinary use' when the live attenuated vaccine concerns a veterinary product. Although therapeutic vaccines may be covered in future in another annex of this document (Advanced Therapy Medicinal Products), the BCG for immunotherapy is discussed here because it is the same substance. This is justified following the definition of a substance as described in ISO 11238, a structurally diverse substance is defined as 'a type of polydisperse substance isolated from

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a single source that is a complex combination which cannot be described as a mixture of a limited number of single substances'.

Both the European Pharmacopoeial BCG monographs will be briefly discussed in order to capture the necessary requirements for structuring the information at the Substance information level and the Specified Substance Group 1 information level.

NOTE Reference to the USP BCG monographs, USP 40 page 2954 and 2955 will not be made for the following reasons: In the USP Pharmacopeial Forum 43(1) published in 2017 it was proposed to remove both the BCG Live and BCG vaccine monographs, see: http://www.usppf.com/pf/pub/index.html

Table I.5 — Capturing Pharmacopoeial requirements for BCG

BCG Vaccine, Freeze-dried	BCG For Immunotherapy
Definition: Freeze-dried BCG vaccine is a preparation of live bacteria derived from a culture of the bacillus of Calmette and Guérin (*Mycobacterium bovis* BCG) **whose capacity to protect against tuberculosis has been established.**	**Definition**: **BCG for immunotherapy is a freeze-dried preparation of live bacteria derived from a culture of the bacillus of Calmette and Guérin (Mycobacterium bovis BCG)** whose capacity for treatment has been established. **It complies with the monograph vaccines for human use 0153**.
Bacterial seed lots: The strain used to establish the master seed lot is chosen for and maintained to preserve its characteristics, its capacity to sensitize man to tuberculin and to protect animals against tuberculosis, and its relative absence of pathogenicity for man and laboratory animals. The strain used shall be identified by historical records that include information on its origin and subsequent manipulation. A suitable batch of vaccine is prepared from the first working seed lot and is reserved for use as the comparison vaccine. When a new working seed lot is established, a suitable test for delayed hypersensitivity in guinea-pigs is carried out on a batch of vaccine prepared from the new working seed lot; the vaccine is shown to be not significantly different in activity from the comparison vaccine. Antimicrobial agent sensitivity testing is also carried out.	**Seed Lots**: The strain used to establish the master seed lot is chosen for and maintained to preserve its characteristics, its capacity to treat and prevent superficial bladder cancer, and its relative absence of pathogenicity for man and laboratory animals. The strain used shall be identified by historical records that include information on its origin and subsequent manipulation. Before establishment of a working seed lot a batch is prepared and reserved for use as the comparison product. When a new working seed lot is established, a suitable test for delayed hypersensitivity in guinea-pigs is carried out on a batch of product prepared from the new working seed lot; the product is shown to be not significantly different in activity from the comparison product. Antimicrobial agent sensitivity testing is also carried out.

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Only a working seed lot that complies with the following requirements may be used for propagation: — Identification; Bacterial and fungal contamination and virulent mycobacteria as described under TESTS using 10 guinea-pigs, each weighing 250 g to 400 g and **having received a quantity of vaccine equivalent to at least 50 human doses.** At the end of this period, euthanize the guinea-pigs and examine by autopsy for signs of infection with tuberculosis, ignoring any minor reactions at the site of injection. Animals that die during the observation period are also examined for signs of tuberculosis. The vaccine complies with the test if none of the guinea-pigs shows signs of tuberculosis and if not more than 1 animal dies during the observation period. If 2 animals die during this period and autopsy does not reveal signs of tuberculosis repeat the test on 6 other guinea-pigs. The vaccine complies with the test if not more than 1 animal dies during the 42 days following the injection and autopsy does not reveal any sign of tuberculosis. **In addition, the final lot has to comply with the test on Excessive dermal reactivity.**	**Only a working seed lot that complies with the following requirements may be used for propagation:** — Identification; Bacterial and fungal contamination and virulent mycobacteria as described under TESTS using 10 guinea-pigs, each weighing 250 g to 400 g and **having received a quantity of the product to be examined equivalent to at least 1/25 of 1 human dose**. Observe the animals for at least 42 days. At the end of this period, euthanize the guinea-pigs and examine by autopsy for signs of infection with tuberculosis, ignoring any minor reactions at the site of injection. Animals that die during the observation period are also examined for signs of tuberculosis. The product complies with the test if none of the guinea-pigs shows signs of tuberculosis and if not more than 1 animal dies during the observation period. If 2 animals die during this period and autopsy does not reveal signs of tuberculosis, repeat the test on 6 other guinea-pigs. The product complies with the test if not more than 1 animal dies during the 42 days following the injection and autopsy does not reveal any sign of tuberculosis.

I.5.1 General information about the BCG strain

The original *Mycobacterium bovis* Bacillus Calmette Guérin vaccine strain has developed into several different substrains which have been used for production of BCG vaccines throughout the world since 1921. Based on the latest genetic and antigenic knowledge, as well as the early literature reports on BCG vaccination, Oettinger *et al*., 1999 [63] were able to fit the different pieces of the BCG puzzle together and outline the origin of the different substrains of *M. bovis BCG*. The BCG vaccine substrains analysed demonstrate two distinct patterns, with an abrupt change consisting of a loss of several genes and altered biochemical characteristics in strains originating from Institut Pasteur after 1927. Further evidence from the literature is provided that a change occurred in virulence of the BCG parent strain at Institut Pasteur in the late 1920s.

Development of the Mycobacterium bovis BCG vaccine

At the turn of the 20th century, Nocard isolated a virulent Mycobacterium bovis strain from the milk of a heifer with tuberculosis mastitis. This strain, 'lait Nocard', was transferred in 1901 to Institut Pasteur at Lille and was destined to be the source of the many differing BCG sub-strains which developed during the 1920s and in the years following. After the reports of successful BCG vaccination in 1921 cultures of BCG were delivered for propagation in laboratories all over the world. In the period from 1924 to the early 1950s, the sub-strains of BCG were propagated in the various countries in different ways, in particular by sub-culturing on potato or Sauton media and harvesting after a varying number of passages. It is therefore not surprising that different variants have emerged during the production of BCG vaccine, as has been described elsewhere in both animal and human studies.

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Today, the most widely used BCG vaccine sub-strains include **Connaught, Danish, Glaxo, Moreau, Pasteur**, and **Tokyo** – all of which show morphological, biochemical and immunological differences. Markedly different levels of vaccine efficacy ranging from 0 to 94% have been recorded in different human studies with some of these sub-strains.

Based on the latest knowledge concerning the sub-strains of BCG in use today, Oettinger *et al*., 1999 have attempted to trace the development of BCG from the original strain 'Nocard' until the present time.

Immunological properties

Based on literature studies [63] one would expect that BCG strains derived from the 'early' BCG substrains would be more virulent and the most immunogenic, thus protecting more efficiently than the 'late' BCG substrains. However, studying the literature no clear picture emerges. Most of the 'early' substrains now in use, including BCG Moreau and Tokyo, have been shown only to belong to the 'moderately' immunogenic BCG substrains in animal studies. In addition, some of the 'late' substrains, like BCG Danish and Pasteur belong to the strongly immunogenic end of the BCG family and it has never been possible to relate the varying efficacy of BCG in different field trials to the substrains used. As a consequence, WHO has stated that the major internationally used BCG substrains tested in 1989, Danish, Glaxo, Pasteur and Tokyo, all are equally suitable for immunization against tuberculosis.

It is clear, therefore, that differences may exist. In particular, the methods of cultivation, preparation and propagation of the BCG substrains have differed quite substantially since 1924. In the period from 1924 to the early 1950s, the substrains of BCG were propagated in the various laboratories in different ways, and harvested after a varying number of passages. It is, therefore, not unexpected that different variants have emerged during the production of the BCG vaccine, as has been described in both animal and human studies. The BCG vaccine substrains Danish, Glaxo (Merieux), Gothenburg, Montréal (Connaught), Moreau, Pasteur, Tice and Tokyo, all show morphological, biochemical and immunological differences.

It is evident that changes have occurred among the BCG substrains up until the establishment of the seed lots, which may have been intended to minimize adverse reactions by vaccination. The authors suggest the number of passages is conversional to vaccine efficacy. Although this still has to be proven it is interesting that these researchers recently found a number of additional mutations between BCG substrains. A complete genomic sequencing of certain substrains, for example BCG Tokyo 172 (WHO standard BCG) and BCG Danish 1331, may be needed to give an overview among the substrains [64][63].

BCG on Sauton's medium [65]

When in 1921 Calmette and Guérin obtained the final strain of attenuated bovine bacilli, which they called BCG, by means of serial subcultures on bile potato, the question arose as to what medium would best maintain the valuable properties of this strain. As Sauton's liquid medium was particularly favourable for the growth of eugenic cultures of the tubercle bacillus, these two workers carried out tests with this medium, but soon found that after several serial subcultures the cultures grew more slowly and took on an abnormal appearance. This medium was accordingly abandoned and replaced by glycerinated potato which was in its turn replaced by Sauton potato. It is on this latter medium, by fortnightly subculture, that the BCG strain is maintained at the Institut Pasteur. Sauton's medium is now used only for the production of thick films for the preparation of BCG vaccine. For this purpose, two passages and never more-on Sauton's medium are carried out.

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Pasteur BCG strain (77)

At the Pasteur Institute in Lille, France, the virulent bovine strain originally obtained from Nocard was subcultured on potato bile medium 230 times over a period of 13 years between 1908 and 1921. Between 1921 and 1932 it appears that 3 separate lines of transfer of the attenuated BCG were maintained, on potato bile, potato with glycerinated beef broth and potato Sauton medium respectively. Guérin discontinued the transfers on potato with glycerinated beef broth in 1932, and from then on, until 1947 a single line on potato Sauton medium was maintained, with regular substitutions after every 2-3 passages on this medium by 2-3 transfers on potato bile medium. From 1947 onwards continuous passages on potato Sauton medium were introduced, interrupted only once or twice each year by 2-3 subcultures on potato bile medium. This line was discontinued in 1961, but a particularly relevant occurrence in the present context was the preparation in 1961 of freeze-dried seed-lots for the production of vaccine.

Danish BCG daughter strain10 (T.W. Osborn 1983) [66]

In 1931 seed culture was supplied from the 423rd transfer at the Pasteur Institute to initiate a culture line in Copenhagen. At first, and in distinction from the procedure adopted at other centres, series of transfer on potato bile medium were alternated with series of transfer as a surface pellicle on Sauton medium. Furthermore, from 1949 onwards subcultures were made exclusively on Sauton medium until 1966, when the line was discontinued. In 1958 seed culture was sent from Copenhagen to the BCG laboratory in Tokyo where a freeze-dried seed-lot was prepared; this was shipped to the Copenhagen laboratory and since 1966 has supplied seed for the routine production of Danish BCG vaccine. The Statens Serum Institut, Copenhagen, has in its turn supplied seed culture to centres in other countries including those in Great Britain and Czechoslovakia.

I.5.2 Capturing information for a live attenuated vaccine following the Structurally diverse content data model

Live attenuated vaccine like BCG-vaccine shall be captured as a structurally diverse substance. The parent organism will be described following the Source Material content data model. Source Material shall capture information on the taxonomic and anatomic origins as well as the fraction of a material that can result in or can be modified to form a substance, see Figure 19.

I.5.3 Substance Name of the Source Material

A Substance (fresh) is referred to the scientific genus/binomial/trinomial with author, plus the part, e.g. *Ginkgo biloba* L, Leaf; *Lachesis muta* Linnaeus, 1766, Venom; *Dermatophagoides pteronyssinus* Trouessart, 1897, Whole Animal; and is always a single species, or intraspecies, or is occasionally a single genus. It will have a name which is composed of:

[<Scientific genus/binomial/trinomial with Author>,<Part(s)>]

The scientific element of the name is usually a binomial, but may be a trinomial or a genus, as appropriate, together with the author of the name, which is equal to the organism name e.g. *Ginkgo biloba* L, *Dermatophagoides pteronyssinus* Trouessart, 1897. For botanical material, the author is written as an abbreviation (Linnaeus = L.), for zoological material the author is referred by its complete name and the year (Linnaeus, 1766). The Part element of the name should be chosen from a controlled vocabulary

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consisting of a restricted number of terms with broad definitions, e.g. Pollen, Whole Animal, Faeces, Body, Hair. The substance can be further described at the Specified Substance Group 1 information level by the Element Group 'Characteristic Attributes', see Figure 35.

For live attenuated vaccine, the Name of the Parent organism is composed of:

[<Scientific genus/binomial/trinomial with Author>,<Part(s)> and the Part and the Part

e.g. *Mycobacterium bovis*, Karson and Lessel, 1970, whole since it is by default the whole bacteria or virus.

The substance name will be composed of:

[<Scientific genus/binomial/trinomial without Author>, <Intraspecific type (strain, serotype, subspecies)>,<Intraspecific description>, <Organism state>]

e.g. *Mycobacterium bovis*, Bacillus Calmette and Guérin, whole, strain, derived from Pasteur 1173 P2, Live (attenuated) bacteria.

e.g. *Mycobacterium bovis*, Bacillus Calmette and Guérin, whole, Danish strain 1331, Live (attenuated) bacteria.

Taxonomic lineage: see 'Interagency Taxonomic Information' (ITIS) database.

The database is sponsored by the White House Subcommittee on Biodiversity and Ecosystem Dynamics.

http://www.itis.gov/servlet/SingleRpt/SingleRpt?search_topic=TSN&search_value=963813

Kingdom: Bacteria (Cavalier-Smith, 2002)
Phylum: Actinobacteria (Cavalier-Smith, 2002)
Class: Actinobacteridae (Stackebrandt *et al*, 1997)
Order: Actinomycetales (Buchanan, 1917)
Family: ***Mycobacteriaceae*** (Chester, 1897)
Genus: ***Mycobacterium*** (Lehmann and Neumann, 1896)
Species: ***Mycobacterium bovis*** (Karson and Lessel, 1970)
[**Synonym: Mycobacterium tuberculosis var. bovis BCG (USP definition)]**
Intraspecific description: **Bacillus Calmette and Guérin**, derived from Pasteur 1173 P2, resp. Danish strain 1331.

I.5.4 Strain history and population doublings, general information

For vaccines, the antigen identity shall include organism strain or serotype. The strain origin and history should be fully documented. The master seed lot or cell bank is identified by historical records that include information on its origin and subsequent manipulation. The number of passages of a virus, or the number of subcultures of a bacterium, from the master seed lot to harvest of the final vaccine should be documented. When genetically engineered micro-organisms are used the genetic construct should be described.

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In case of the virulence being attenuated by culturing in specific substrates (e.g. culture in fertilized eggs) or under specific conditions, the method of attenuation should be described, including the number of passages and population doublings.

In case of chemical or physical inactivation of the micro-organism the method of inactivation should be fully described.

I.5.5 Specified Substance Group 1 Information

At the Specified Substance Group 1 information level further information shall be described regarding the History of the strain, Master seed, passage and medium used as well as for Working seed. The History of the strain can be captured as a Reference Source Document. The historic information on the strain can be captured in the element group 'Characteristic Attribute'. The Attribute Name to be captured by the Attribute Type 'Particular Vaccine' is 'History of the strain' or 'Passage' information in combination of the element group 'Amount', in which the number of passages are described. In the element group 'Attribute Parameter' the Attribute parameter name has the value 'Passage condition' and the Attribute parameter value describes how the Passage is performed e.g. protected from light at 37°C or a description of the medium may be provided. The composition of the medium itself is captured as a multi-substance material which is captured as a separate Specified Substance Group 1 substance or the composition could be submitted as a Reference Source Document.

I.5.6 Information of the BCG-strain: Danish 1331 strain MS and Working seed.

Master Seed lot/Primary seed lot:

Calmette and Guérin developed the BCG strain from 1908-1921 by 230 passages of a M. bovis strain over glycerinated bile potato medium. In November 1931, Statens Serum Institut in Copenhagen received a BCG culture from Institut Pasteur, Paris. The BCG culture was labelled **423** (passage number). Over the following years several lines were propagated for varying periods of time on either liquid Sauton medium or on bile-potato medium. To prevent mutation of the strain it was decided to make a freeze-dried seed lot from it. In 1958 an ampoule of liquid vaccine from Copenhagen (routine batch number 1331) was freeze-dried. This was done in the Japan BCG laboratory in Tokyo, which at that time was the most experienced in freeze-drying of BCG. In 1960, it was transferred back to Sauton via one passage on Sauton-potato medium. The second passage on Sauton medium was freeze-dried with 1% sodium glutamate as one batch comprising of five freeze-drying lots. The batch is referred to as Japanese batch, Danish strain 1331. BCG Danish 1331 has retained very similar characteristics to the liquid BCG which had been cultured continuously since 1931.

NOTE Passage/attenuation steps are performed to make the strain less virulent and suitable for vaccine production. Proof of the effect of attenuation [67]:

For over 80 years, BCG has been used as a live vaccine against tuberculosis, although the genetic basis of its attenuation has never been defined. A.S. Pym *et al.* [67] demonstrate that the loss of chromosomal region of difference 1(RD1) was one genetic event that contributed to the attenuation of BCG, as a significant increase in virulence was obtained after its reintroduction. BCG was obtained after 230 serial passages of a virulent isolate of *M. bovis* in a medium containing bile salts, glycerol and potato extract over a 14-year period from 1908 to 1921. As early as the 15th passage, Calmette reported a decrease in virulence in guinea pigs (Calmette and Guérin, 1911). Without access to the serial isolates obtained by Calmette and Guérin, it is impossible to determine whether the loss of chromosomal RD1 was the primary attenuating mutation or if it occurred during the subsequent passaging of BCG. Thus, the attempts to elucidate the key events that led to attenuation are restricted to comparison of extant BCG

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isolates with virulent members of the *M. tuberculosis* complex. It was demonstrated that reintroduction of RD1 into BCG does indeed result in a significant increase in virulence. However, complementation of neither BCG Pasteur nor the least passaged strain, BCG Russia, with RD1 resulted in the restoration of virulence to levels characteristic of *M. tuberculosis* or *M. bovis*. This probably indicates that multiple attenuating mutations accrued during the initial isolation of BCG and also possibly during the period 1928–33 when loss of residual virulence for animals was documented (reviewed by Oettinger *et al.* [63]).

In this study, A.S. Pym *et al.* [67], have systematically examined the effects of knocking-in selected RD regions that have been lost since the divergence of *M. bovis* from the last common ancestor of the *M. tuberculosis* complex or that may have been deleted as part of the attenuation process that gave rise to *M. bovis* BCG. Several of these regions are predicted to code for a variety of putative virulence factors. However, the experiments presented demonstrate that, among the RD regions tested, only the absence of RD1 from *M. bovis* BCG and *M. microti* contributes to their avirulence.

Working Seed lot/Second seed lot:

The secundary seed lot batch XXX is used routinely as a working seed lot for BCG vaccine production and a single vial of this lot is used for manufacturing of the batch. The secondary seed lot is removed three passages from the primary seed lot. The BCG vaccine is normally produced from the third Sauton passage, i.e. six total passages from the master seed lot. The passages are carried out in Sauton liquid medium.

NOTE Sauton liquid medium contains Magnesium sulfate heptahydrate, Zinc sulfate heptahydrate, Citric acid, monohydrate, Dipotassium phosphate, L-asparagine monohydrate, Ferric ammonium citrate, Glycerol 85 %, Tap water and Ammonia solution, concentrated q.s. to maintain a pH = 6,7 – 6,8. The solution is sterilized by 121 °C for 30 min.

The culture is harvested and diluted to the final bulk, stabilized with Sodium glutamate, filled into vials and freeze-dried giving to Final Lot.

The Final lot is tested for Identity, Absence of virulent mycobacteria, Sterility, Dermal reactivity, Count of viable units and Bacterial concentration. Specific tests on Delayed hypersensitivity in guinea pigs, Antimicrobial agent sensitivity and Excessive dermal reactivity as is described in the Ph. Eur. monograph 01/2012:0163.

Table I.6 — Tabular Substance Information of the BCG Vaccine, Freeze-dried, Danish strain 1331

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	BCGDA98765 (Artificial ID)	II	
Substance Type	Structurally Diverse	CD	
Element Group: Substance Name			
Substance Name	*Mycobacterium bovis*, Bacillus Calmette and Guérin, whole, Danish strain 1331, Live attenuated bacteria.	ST	1)
Substance Name Type	Preferred Name	CD	2)
Language	en	CD	
Substance Name Domain	Drug	CD	

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Element Name	Value	Data Format	Note #
Jurisdiction	EU, US	CD	
Element Group: Substance Name (Repeat)			
Substance Name	BCG Vaccine, Freeze-dried	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Biologic, Bacteria	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	Ph. Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph. Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia, Monograph 01/2012:0163	ST	
Element Group: Substance Name (Repeat)			
Substance Name	BACILLUS CALMETTE-GUERIN SUBSTRAIN TICE LIVE ANTIGEN	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	FDA GSRS	CD	
Reference Source Class	Public Database	CD	
Element Group: Substance Code			
Code	4CGF0IDN3W	CD.Code	4)
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Reference Information			
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	

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Element Name	Value	Data Format	Note #
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	J07AN01	CD.Code	
Substance Classification Type	Tuberculosis, Live attenuated)	ST	
Element Group: Reference Source 5)			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	https://www.whocc.no/atc_ddd_index/?code=J07AN	ST	
Element Group: Source Material 5)			
Source Material Class	Biologic	CD	
Source Material Type	Bacteria	CD	
Source Material State	Live, attenuated	CD	
Organism ID	MYCOB12345 (Artificial ID)	II	
Organism Name	*Mycobacterium tuberculosis* var. *bovis*, Bacillus Calmette and Guérin, Danish strain 1331	ST	
Parent Substance ID	GHFDR89756 (Artificial ID)	II	
Parent Substance Name	*Mycobacterium bovis*, Karson and Lessel, 1970	ST	
Country of Origin	N/A		
Development Stage	N/A		
Element Group: Organism			
Family	*Mycobacteriaceae*	CD	
Genus	*Mycobacterium*	CD	
Species	*Mycobacterium tuberculosis*	CD	
Intraspecific Type	Var. *bovis*	CD	
Intraspecific Description	Bacillus Calmette and Guérin whole, Danish strain 1331	ST	
Element Group: Author			
Author Type	Species Primary Author	CD	
Author Description	Calmette and Guérin, 1921	ST	
Element Group: Organism General			
Kingdom	Bacteria	CD	
Phylum	Actinobacteria	CD	
Class	Actinobacteridae	CD	
Order	Actinomycetales	CD	

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Element Name	Value	Data Format	Note #
Element Group: Part			
Part	Whole	CD	5)
Part Location	N/A		

NOTE 1 Preferred term, including the specified strain.

NOTE 2 Human vaccine, Veterinary vaccine are examples of Substance Name Type, see 4.3.2.

NOTE 3 Definition of the USP-Monograph: BCG Vaccine conforms to the regulations of the FDA concerning biologics. It is a dried, living culture of the bacillus Calmette-Guérin strain of *Mycobacterium tuberculosis* var. *bovis*, grown in a suitable medium from a seed strain of known history that has been maintained to preserve its capacity for conferring immunity. It contains an amount of viable bacteria such that inoculation, in the recommended dose, of tuberculin-negative persons results in an acceptable tuberculin conversion rate. It is free from other organisms, and contains a suitable stabilizer. It contains no antimicrobial agent.

NOTE 4 This UNII Code Refers to the specified strain.

NOTE 5 For Live attenuated bacterial of viral vaccines the Part description shall be included.

Table I.7 — Tabular information for Bacillus Calmette and Guérin Live attenuated vaccine at the Specified Substance information levels (Passage information)

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 1			
Specified Substance Group 1 ID	DA1331UTEW (Artificial ID)	II	
Element Group: Substance Name			
(Specified) Substance (Group 1) Name	*Mycobacterium bovis*, Bacillus Calmette and Guérin, whole Danish strain 1331, Live attenuated, histo-passage-info	ST	1)
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Constituent			
Constituent Substance ID	BCGDA98765 (Artificial ID)	II	
Constituent Substance Name	*Mycobacterium bovis*, Bacillus Calmette and Guérin, whole, Danish strain 1331, Live attenuated bacteria	ST	1)
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Characteristic Attribute			
Attribute Type	Particular vaccine	CD	
Attribute Name	History of the strain	ST	

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Element Name	Value	Data Format	Note #
Attribute Substance ID	BCGDA98765 (Artificial ID)	II	
Attribute Substance Name	*Mycobacterium bovis*, Bacillus Calmette and Guérin, whole Danish strain 1331, Live attenuated bacteria	ST	
Is Defining	Yes	BL	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	HISTDA1331V (Artificial ID)	ST	
Reference Source Citation	CBG87654 (Artificial CBG-Case number)	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	Regulatory Submission, see below	ED	
History of the Master Seed Lot, Danish Strain 1331 Calmette and Guérin developed the BCG strain from 1908-1921 by 230 passages of a *M. bovis* strain over glycerinated bile potato medium. All BCG sub strains originate from this BCG strain. In November 1931, Statens Serum Institut in Copenhagen received a BCG culture from Institut Pasteur, Paris. The BCG culture was labelled **423** (passage number). Over the following years several lines were propagated for varying periods of time on either liquid Sauton medium or on bile-potato medium. In 1949, a line that had been kept exclusively on bile potato for the previous five years was transferred to Sauton. The transfer was done via one passage on Sauton potato medium. To prevent mutation of the strain it was decided to make a freeze-dried seed lot from it. In October 1958, an ampoule of liquid vaccine from Copenhagen (routine batch number 1331) was transferred to glycerol bile-potato medium. This was done in the Japan BCG laboratory in Tokyo. The line was kept on this medium with a total of 45 serial transfers until September 1960. At this time, it was transferred back to Sauton via one passage on Sauton-potato medium. The second passage on Sauton medium was freeze-dried with 1% sodium glutamate as one batch comprising of five freeze-drying lots. The batch was kept in ampoules and sealed under vacuum and was later transferred to Copenhagen and was examined extensively both as a vaccine and as seed material. **The batch is referred to as Japanese batch, Danish strain 1331.**			
Reference Source Document Type	Text file (pdf)	CD	
Reference Source Document ID	COMPDO (Artificial ID)	ST	
Reference Source Document Classification	Historic overview strain description	CD	
Element Group: Characteristic Attribute (Repeat)			

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Element Name	Value	Data Format	Note #
Attribute Type	Particular vaccine	CD	
Attribute Name	Passage of the Master seed lot of Danish strain 1331	ST	
Attribute Substance ID	BCGDM98765 (Artificial ID)	II	
Attribute Substance Name	*Mycobacterium bovis*, Bacillus Calmette and Guérin, whole, Danish strain 1331, Live attenuated bacteria	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	3	PQ	
Amount Text	Number of Passages	ST	
Element Group: Attribute Parameter			
Attribute Parameter Name	Passage condition	ST	
Attribute Parameter Value	Passage is performed on Sauton medium at pH 6.6-6.7	ST	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular vaccine	CD	
Attribute Name	Passage of the Working seed lot	ST	
Attribute Substance ID	BCGDW89765 (Artificial ID)	II	
Attribute Substance Name	*Mycobacterium bovis*, Bacillus Calmette and Guérin, Danish strain 1331, Live attenuated bacteria	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	3	PQ	
Amount Text	Number of Passages	ST	
Element Group: Attribute Parameter			
Attribute Parameter Name	Passage condition	ST	
Attribute Parameter Value	Passage is performed from the master seed lot on Sauton medium at pH 6,6-6,7	ST	2)

NOTE 1 DA1331UTEW (Artificial ID) corresponds to the (Specified) Substance Name *Mycobacterium bovis*, Bacillus Calmette and Guérin, Danish strain 1331, Live attenuated, histo-passage-info with BCGDA98765 (Artificial ID) as (Parent) ID and *Mycobacterium bovis*, Bacillus Calmette and Guérin, whole, Danish strain 1331, Live attenuated bacteria as (Parent) Substance Name.

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Element Name	Value	Data Format	Note #
NOTE 2 Sauton liquid medium contains Magnesium sulfate heptahydrate, Zinc sulfate heptahydrate, Citric acid, monohydrate, Dipotassium phosphate, L-asparagine monohydrate, Ferric ammonium citrate, Glycerol 85 %, Tap water and Ammonia solution, concentrated q.s. to maintain a pH = 6,7 – 6,8. The solution is sterilized by 121 °C for 30 min.			

Table I.8 — Tabular information for the manufacturing of BCG-Vaccine, Danish strain 3113. Specified Substance Group 2 information

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2– Company ABC			
Specified Substance Group 2 ID	QGHDS98765M (Artificial ID)	II	
Element Group: Substance Name			
(Specified) Substance (Group 2) Name	*Mycobacterium bovis*, Bacillus Calmette and Guérin, whole, Danish strain 1331, Live (attenuated) bacteria—Company ABC	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	BCGDA98765 (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Vaccine production	CD	
Production Method Description	Cultivation of a bacterial strain from a master seed/working seed lot, harvesting and final bulk/final lot preparation as a freeze-dried substance	ST	
Production System Type	Fermentation Harvesting and Purification	CD	
Production System	Bacteria	CD	
Critical Process Version Number	1	INT	2)
Version	ManBCG002	ST	
Version Date	20170405	TS.Date	
Element Group: Organization			
Manufacturer ID	DUNSU4532D (Artificial ID)	II	
Manufacturer Name	Company ABC	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	

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Element Name	Value	Data Format	Note #
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory submission	CD	
Reference Source ID	FINAL12345 (Artificial ID)	ST	
Reference Source Citation	CBG87654 (Artificial CBG-Case number)	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	Regulatory submission, see below	ED	

Capturing information on Final Lot testing for the BCG-Vaccine, freeze-dried

Attachment: Documentation tables of testing strategy linked to the production.

Table I.9 — Overview of the information that should be provided on test requirements (Ph. Eur. Requirements) Specified Substance Group 2 information

1: Identity
2: Absence of virulent mycobacteria
3: Sterility
4: Dermal reactivity
5: Count of viable units
6: Bacterial concentration
7: Delayed hypersensitivity in guinea pigs
8: Antimicrobial agent sensitivity
9: Excessive dermal reactivity

Reference Source Document Type	Release Specification and test of the final lot	CD	
Reference Source Document ID	BCGD4563 (Artificial ID)	ST	
Reference Source Document Classification	In-house/Final lot release specification	CD	

NOTE 1 This (Parent) Substance ID refers to the Substance Name *Mycobacterium bovis*, Bacillus Calmette and Guérin, whole, Danish strain 1331, Live (attenuated) bacteria.

NOTE 2 The Critical Process Number Version Number would change if a substantial change in the (biological) manufacturing process occurred. These would include a change in the chemistry or biological production steps by means

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Element Name	Value	Data Format	Note #
of additional passages, addition or elimination of a purification step. The change in a version number is tied to the production system type.			

Table I.10 — Tabular information captured at the Specified Substance Group 3 information level for BCG-Vaccine, Danish strain 1331

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	HJGHD87765 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Mycobacterium bovis*, Bacillus Calmette and Guérin, whole, Danish strain 1331, Live (attenuated) bacteria-Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	BCGDA98765 (Artificial ID)	II	1)
Element Group: Grade			
Grade Type	Ph.Eur.	CD	2), 3)
Grade Name	BCG Vaccine, Freeze-dried	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia, monograph 01/2012:0163	ST	

NOTE 1 This (Parent) Substance ID refers to the Substance Name *Mycobacterium bovis*, Bacillus Calmette and Guérin, whole, Danish strain 1331, Live (attenuated) bacteria.

NOTE 2 When reference is made to more than one Pharmacopoeia, each Pharmacopoeial Grade shall have a separate Specified Substance Group 3 ID.

NOTE 3 The USP Pharmacopeial Forum 43(1) published in 2017 it was proposed to remove both the BCG Live and BCG vaccine monographs.

Table I.11 — Tabular Substance Information of the BCG for Immunotherapy, strain derived from Pasteur 1173 P2

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	BCGPA86573 (Artificial ID)	II	

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Element Name	Value	Data Format	Note #
Substance Type	Structurally Diverse	CD	
Element Group: Substance Name			
Substance Name	*Mycobacterium bovis*, Bacillus Calmette and Guérin, whole strain derived from Pasteur 1173 P2	ST	1)
Substance Name Type	Preferred Name	CD	2)
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	
Element Group: Substance Name (Repeat)			
Substance Name	BCG for Immunotherapy	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Biologic, Bacteria	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	Ph. Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph. Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia, Monograph 01/2009:1929	ST	
Element Group: Substance Name (Repeat)			
Substance Name	BACILLUS CALMETTE-GUERIN SUBSTRAIN TICE LIVE ANTIGEN	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	FDA GSRS	CD	
Reference Source Class	Public Database	CD	
Element Group: Substance Code			

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Element Name	Value	Data Format	Note #
Code	2XQ558L16Z	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Reference Information			
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	L03AX03	CD.Code	
Substance Classification Type	BCG Vaccine	ST	
Element Group: Reference Source 5)			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	https://www.whocc.no/atc_ddd_index/?code=L03AX03	ST	
Element Group: Source Material 4)			
Source Material Class	Biologic	CD	
Source Material Type	Bacteria	CD	
Source Material State	Live, attenuated		
Organism ID	MYCOB12345 (Artificial ID)	II	
Organism Name	*Mycobacterium tuberculosis* var. *bovis*, Bacillus Calmette and Guérin, whole, strain Pasteur 1173 P2	ST	
Parent Substance ID	GHFDR89756 (Artificial ID)	II	
Parent Substance Name	*Mycobacterium bovis*, Karson and Lessel, 1970	ST	
Country of Origin	N/A		
Development Stage	N/A		
Element Group: Organism			
Family	*Mycobacteriaceae*	CD	
Genus	*Mycobacterium*	CD	

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Element Name	Value	Data Format	Note #
Species	*Mycobacterium tuberculosis*	CD	
Intraspecific Type	Var. *bovis*	CD	
Intraspecific Description	Bacillus Calmette and Guérin strain Pasteur 1173 P2	ST	
Element Group: Author			
Author Type	Species Primary Author	CD	
Author Description	Calmette and Guérin, 1921	ST	
Element Group: Organism General			
Kingdom	Bacteria	CD	
Phylum	Actinobacteria	CD	
Class	Actinobacteridae	CD	
Order	Actinomycetales	CD	
Element Group: Part			
Part	Whole	CD	4)
Part Location	N/A		

NOTE 1 Preferred Name, including the specified strain

NOTE 2 The vaccine name *Mycobacterium bovis*, Bacillus Calmette and Guérin, whole, strain derived from Pasteur 1173 P2) is an example of Substance Preferred Name. The Substance Name Type has the value 'Preferred Name', see 5.3.2.

NOTE 3 The USP Pharmacopeial Forum 43(1) published in 2017 it was proposed to remove both the BCG Live and BCG vaccine monographs.

NOTE 4 For Live attenuated bacterial of viral vaccines the Part description is included.

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Table I.12 — Tabular information for Bacillus Calmette and Guérin Live attenuated vaccin at the Specified Substance information (Passage information)

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 1			
Specified Substance Group 1 ID	PAHJGT7865 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Mycobacterium bovis,* Bacillus Calmette and Guérin, whole strain derived from Pasteur 1173 P2, histo-passage-info	ST	1)
Substance Name Type	Specified Substance Group 1	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU, US	CD	

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Element Name	Value	Data Format	Note #
Element Group: Constituent			
Constituent Substance ID	BCGPA86573 (Artificial ID)	II	
Constituent Substance Name	*Mycobacterium bovis*, Bacillus Calmette and Guérin, whole strain derived from Pasteur 1173 P2	ST	1)
Language	en	CD	
Substance Role	Parent substance	CD	
Is Defining	Yes	BL	
Element Group: Characteristic Attribute			
Attribute Type	Particular vaccine	CD	
Attribute Name	History of the strain	ST	
Attribute Substance ID	BCGPA86573 (Artificial ID)	II	
Attribute Substance Name	*Mycobacterium bovis*, Bacillus Calmette and Guérin, whole strain derived from Pasteur 1173 P2	ST	
Is Defining	Yes	BL	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	PHFD7865ED (Artificial ID)	ST	
Reference Source Citation	CBG13245 (Artificial CBG-Case number)	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	Regulatory submission, see below	ED	

History of the Master Seed Lot, Pasteur 1173 P2

At the Pasteur Institute in Lille, France, the virulent bovine strain originally obtained from Nocard was subcultured on potato bile medium 230 times over a period of 13 years between 1908 and 1921. Between 1921 and 1932 it appears that 3 separate lines of transfer of the attenuated BCG were maintained, on potato bile, potato with glycerinated beef broth and potato Sauton medium respectively. Guérin discontinued the transfers on potato with glycerinated beef broth in 1932, and from then on, until 1947 a single line on potato Sauton medium was maintained, with regular substitutions after every 2-3 passages on this medium by 2-3 transfers on potato bile medium. From 1947 onwards continuous passages on potato Sauton medium were introduced, interrupted only once or twice each year by 2-3 subcultures on potato bile medium. This line was discontinued in 1961, but a particularly relevant occurrence in the present context was the preparation in

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Element Name	Value	Data Format	Note #
1961 of freeze-dried seed-lots for the production of vaccine. **The master seed lot used for the production is called Master seed lot P3 December 21th 1964.**			
Reference Source Document Type	Text file (pdf)	CD	
Reference Source Document ID	COMPDO (Artificial ID)	ST	
Reference Source Document Classification	Historic overview strain description	CD	
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular vaccine	CD	
Attribute Name	Passage of the Master seed lot PX	ST	
Attribute Substance ID	BCGPA86573 (Artificial ID)	II	
Attribute Substance Name	*Mycobacterium bovis*, Bacillus Calmette and Guérin strain derived from Pasteur 1173 P2	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	7	PQ	
Amount Text	Number of Passages	ST	

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Element Name	Value	Data Format	Note #
Element Group: Attribute Parameter			
Attribute Parameter Name	Passage condition	ST	
Attribute Parameter Value	Passage is performed on 3 solid Löwenstein medium, followed by 2 successive passages in Dubois medium and finally one passage in liquid Ungar medium	ST	2)
Element Group: Characteristic Attribute (Repeat)			
Attribute Type	Particular vaccine	CD	
Attribute Name	Passage of the Working seed lot	ST	
Attribute Substance ID	BCGPA86573 (Artificial ID)	II	
Attribute Substance Name	*Mycobacterium bovis*, Bacillus Calmette and Guérin strain derived from Pasteur 1173 P2	ST	
Is Defining	Yes	BL	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	3	PQ	
Amount Text	Number of Passages	ST	
Element Group: Attribute Parameter			
Attribute Parameter Name	Passage condition	ST	
Attribute Parameter Value	Passage is performed from the master seed lot P3 on one passage on solid Löwenstein medium, followed by 2 successive passages in liquid Dubos medium with Polysorbate 80 and one passage in liquid Ungar medium with Polysorbate 80	ST	2)

NOTE 1 PAHJGT7865 (Artificial ID) corresponds to the (Specified) Substance (Group 1) Name *Mycobacterium bovis*, Bacillus Calmette and Guérin, strain Pasteur 1173 P2, histo-passage-info with BCGDA98765 (Artificial ID) as Parent ID and *Mycobacterium bovis*, Bacillus Calmette and Guérin, Danish strain 1331, Live (attenuated) bacteria as Parent substance.

NOTE 2 Löwenstein medium contains potato starch and glycerol.

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Table I.13 — Tabular information for the manufacturing of BCG-Vaccine, Danish strain 3113. Specified Substance Group 2 information

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Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2 – Company ABC			
Specified Substance Group 2 ID	QGHDS98765M (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Mycobacterium bovis,* Bacillus Calmette and Guérin strain derived from Pasteur 1173 P2—Company DEF	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	BCGPA86573 (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Vaccine production	CD	
Production System Type	Cultivation of a bacterial strain from a master seed/working seed lot, harvesting and final bulk/final lot preparation as a freeze-dried substance	CD	
Critical Process Version Number	1	INT	2)
Version	Man001	ST	
Version Date	21070410	TS.Date	
Element Group: Organization			
Manufacturer ID	DUNSU4532D (Artificial ID)	II	
Manufacturer Name	Company ABC	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	FINAL12345 (Artificial ID)	ST	
Reference Source Citation	CBG87654 (Artificial CBG-Case number)	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	Regulatory Submission, see below	ED	

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Element Name	Value	Data Format	Note #
Capturing information on Final Lot testing for the BCG-Vaccine, freeze-dried Attachment: Documentation tables of testing strategy linked to the production.			

Table I.14 — Overview of the information that should be provided on test requirements (Ph. Eur. Requirements)

1: Identity (Ziehl Neelsen smears technique)	
2: Absence of virulent mycobacteria	
3: Sterility	
4: Dermal reactivity	
5: Count of viable units	
6: Bacterial concentration	
7: Delayed hypersensitivity in guinea pigs	
8: Antimicrobial agent sensitivity	
9: Excessive dermal reactivity	

Reference Source Document Type	Release Specification and test of the final lot	CD	
Reference Source Document ID	BCGD4563 (Artificial ID)	ST	
Reference Source Document Classification	In-house/Final lot release specification	CD	

NOTE 1 This (Parent) Substance ID refers to the Substance Name *Mycobacterium bovis*, Bacillus Calmette and Guérin strain derived from Pasteur 1173 P2.

NOTE 2 The Critical Process Number Version Number would change if a substantial change in the (biological) manufacturing process occurred. These would include a change in the chemistry or biological production steps by means of additional passages, addition or elimination of a purification step. The change in a version number is tied to the production system type.

Table I.15 — Tabular information captured at the Specified Substance Group 3 information level for BCG-for Immunotherapy, strain Pasteur 1173 P2

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	HJGHD87765 (Artificial ID)	II	
Element Group: Substance Name			

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Element Name	Value	Data Format	Note #
(Specified) Substance (Group 3) Name	*Mycobacterium bovis,* Bacillus Calmette and Guérin strain derived from Pasteur 1173 P2- Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	BCGPA86573 (Artificial ID)	II	1)
Element Group: Grade			
Grade Type	Ph.Eur.	CD	2), 3)
Grade Name	BCG for Immunotherapy	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia, monograph 01/2009:1929	ST	

NOTE 1 This (Parent) Substance ID refers to the Substance Name Mycobacterium bovis, Bacillus Calmette and Guérin strain Pasteur 1173 P2.

NOTE 2 When reference is made to more than one Pharmacopoeia, each Pharmacopoeial Grade has a separate Specified Substance Group 3 ID.

NOTE 3 The USP Pharmacopeial Forum 43(1) published in 2017 was proposed to remove both the BCG Live and BCG vaccine monographs.

I.6 Bacterial vaccine, inactivated antigen and conjugated to a carrier protein

Meningococcal disease is a serious illness caused by a type of bacteria called *Neisseria meningitidis*. It can lead to meningitis (infection of the lining of the brain and spinal cord) and infections of the blood. Meningococcal disease can spread from person to person through close contact (coughing or kissing) or lengthy contact. Even when it is treated, meningococcal disease kills 10 to 15 people out of 100 infected. Of those who survive, about 10 to 20 out of every 100 will suffer disabilities[64]. There are at least 13 types of *N. meningitidis*, called "serogroups."

NOTE *N. meningitidis*, also called Meningococcus is an aerobic, fastidious, Gram-negative diplococcus that is found only in humans. Its cell wall has a cytoplasmic membrane, a peptidoglycan layer, and an outer membrane. Meningococci isolated from the bloodstream or the spinal fluid are almost always encapsulated. The capsules are polysaccharides, which consist of repeating sugar units. The capsular polysaccharide can be isolated, purified, and chemically and physically defined. Based on the chemical and immunological specificity of its capsular polysaccharides, N. meningitidis has been classified serologically into groups A, B, C, 29E, H, I, K, L, W135, X, Y and Z (2). Of these, groups A, B, and C are responsible for approx 90% of meningococcal meningitis, and group B meningococcus is responsible for the majority of meningococcal disease in industrialized countries [68].

64 U.S. Department of Health and Human Services, Centers for Disease Control and Prevention

https://www.cdc.gov/vaccines/hcp/vis/vis-statements/mening.html

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There are two kinds of meningococcal vaccines licensed by the Food and Drug Administration (FDA) for protection against serogroups A, C, W, and Y: a meningococcal vaccine containing conjugated polysaccharides and a meningococcal vaccine containing non-conjugated polysaccharides.

In this example, the conjugated MenACWY-CRM_{197} vaccine is further discussed.

Pharmacodynamic effect

The Meningococcal and other polysaccharides have been classified as T cell independent type 2 (TI-2) antigens based on their inability to stimulate an immune response in animals that carry an X-linked immune B-cell defect (xid). TI-2 antigens tend to be characterized by high molecular weight, multiple repeat epitopes, slow degradation in vivo, and a failure to stimulate major histocompatibility complex (MHC) type II mediated T-cell help. TI-2 antigens generally are incapable of stimulating an immune response in neonatal humans under 18 months of age. This has spurred attempts to modify the capsular polysaccharides such that vaccines will result that are protective for all at-risk groups. To date, the most successful approach has been to covalently bind carrier proteins to the polysaccharides, thus creating a vaccine capable of invoking a T-dependent response.

I.6.1 Definition as described in the Ph. Eur Meningococcal group ACWY Vaccine monograph 01/2008:0250

Meningococcal ACWY conjugate vaccine is a tetravalent conjugated meningococcal vaccine that contains sized oligosaccharides from *Neisseria meningitidis* serogroup A, C W-135 and Y conjugated to CRM_{197} protein. CRM_{197} is a non-toxic mutant of *Corynebacterium diphtheriae* toxin, termed Cross Reacting Material 197.

The requirements for the vaccine are described in the Ph. Eur. monograph 01/2010:0250 Meningococcal Polysaccharide vaccine and in its Ph.Eur. general chapter 5.2.11 Carrier proteins for the production of conjugated polysaccharide vaccines for human use.

The requirements of the Ph. Eur. are based on the definition of the source material and the production method; see also USP monograph[65].

Monograph Definition

Meningococcal polysaccharide vaccine is a freeze-dried preparation of one or more purified capsular polysaccharides obtained from one or more suitable strains of *Neisseria meningitidis* group A, group C, group Y and group W135 that are capable of consistently producing polysaccharides.

The substance *N. meningitidis* group A polysaccharide consists of partly *O*-acetylated repeating units of *N*-acetylmannosamine, linked with 1α→6 phosphodiester bonds.

The substance *N. meningitidis* group C polysaccharide consists of partly *O*-acetylated repeating units of sialic acid, linked with 2α→9 glycosidic bonds.

[65] USP 40 <1234> Vaccines for Human Use- Polysaccharide and Glycoconjugate vaccines, p. 1888 – 1905.

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The substance *N. meningitidis* group Y polysaccharide consists of partly *O*-acetylated alternating units of sialic acid and D-glucose, linked with 2α→6 and 1α→4 glycosidic bonds.

The substance *N. meningitidis* group W135 polysaccharide consists of partly *O*-acetylated alternating units of sialic acid and D-galactose, linked with 2α→6 and 1α→4 glycosidic bonds.

The polysaccharide component or components stated on the label together with calcium ions and residual moisture account for over 90 per cent of the mass of the preparation

NOTE Description and Nomenclature of Neisseria meningitidis Capsule Locus [69].

Pathogenic *Neisseria meningitidis* isolates contain a polysaccharide capsule that is the main virulence determinant for this bacterium. Thirteen capsular polysaccharides have been described, and nuclear magnetic resonance spectroscopy has enabled determination of the structure of capsular polysaccharides responsible for serogroup specificity. Molecular mechanisms involved in *N. meningitidis* capsule biosynthesis have also been identified, and genes involved in this process and in cell surface translocation are clustered at a single chromosomal locus termed cps. The use of multiple names for some of the genes involved in capsule synthesis, combined with the need for rapid diagnosis of serogroups commonly associated with invasive meningococcal disease, prompted a requirement for a consistent approach to the nomenclature of capsule genes. A comprehensive description of all *N. meningitidis* serogroups along with a proposed nomenclature, which was presented at the 2012 XVIIIth International Pathogenic Neisseria Conference in Würzburg, Germany, see Table I.16.

Table I.16 — Gene Nomenclature of Neisseria meningitidis Capsule Locus

Region, sero-group	Proposed nomencla-ture (NEIS	Previous nomencla-ture	Protein function	Size, bp
A	*csaA* (NEIS2157)	*mynA/sacA*	UDP-*N*-acetyl-D-glucosamine 2-epimerase	1,119
	csaB (NEIS2158)	*mynB/sacB*	Polymerase linking *N*-acetyl-D-mannosamine-1-phosphate monomers [a]	1,638
	csaC (NEIS2159)	*mynC/sacC*	*O*-acetyltransferase	1,638
	csaD (NEIS2160)	*mynD/sacD*	Capsule transport	864
B, C, W, Y	*cssA* (NEIS0054)	*siaA/synX/synA/neuC*	*N*-acetylglucosamine-6-P 2-epimerase	1,134
	cssB (NEIS0053)	*siaB/synB/neuA*	CMP-*N*-acetylneuraminic acid synthase	687
	cssC (NEIS0052)	*siaC/synC/neuB*	*N*-acetylneuraminic acid synthetase	1,050
	csb (NEIS2161)	$siaD_B$/*synD*	Polysialyltransferase	1,488
	csc (NEIS0051)	$siaD_C$/*synE*	Polysialyltransferase	1,479
	csy (NEIS2163)	$siaD_Y$/*synF*	Polymerase linking glucose and *N*-acetylneuraminic acid	3,114
	cssE (NEIS0050)	*oatC*	*O*-acetyltransferase	1,383
	cssF (NEIS2164)	*oatWY*	*O*-acetyltransferase	636
	ctrG (NEIS0049)	*ctrG/NMB0065*	Putative role in surface expression of sialic capsules	957

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Region, sero-group	Proposed nomencla-ture (NEIS	Previous nomencla-ture	Protein function	Size, bp
[a] According to Liu T.Y. *et al.* [70]: Serogroup A polysaccharide consist of a homopolymer of partially acetylated 2.acetamido-2.deoxymannosyl phosphate. In this article is stated that the experimental data obtained, together with the formation of glycoaldehyde phosphate as a product of periodate oxidation, could result only if the monomer structure is N-acetyl-mannosamine 6-phosphate. The principal bond in the Group A polysaccharide seems to be α l-6 phosphodiester bond. The phosphorus as noted before is all linked to D-mannosamine. Apparently, the phosphorus forms a diester linkage because the polysaccharide is resistant to the action of phosphomonoesterases such as potato acid phosphatase and an E. coli alkaline phosphatase and is also not hydrolysed by snake venom phosphodiesterase.				

I.6.2 Description of the substances comprised in Men(ACWY)

I.6.2.1 MenA Polysaccharide and Oligosaccharide Description

The meningococcal polysaccharide serogroup A (MenA) is a polymer whose repeating unit is composed of N-acetyl Mannosamine-6-phosphate. Meningococcal A polysaccharide is produced from fermentation and purification of Neisseria meningitidis serogroup A. Purified polysaccharide MenA is a process intermediate, which is subsequently hydrolysed, sized, activated and conjugated to the carrier protein CRM_{197} to give the drug substance MenA-CRM. The structural representation of Meningococcal A polysaccharide is provided in Figure I.6.

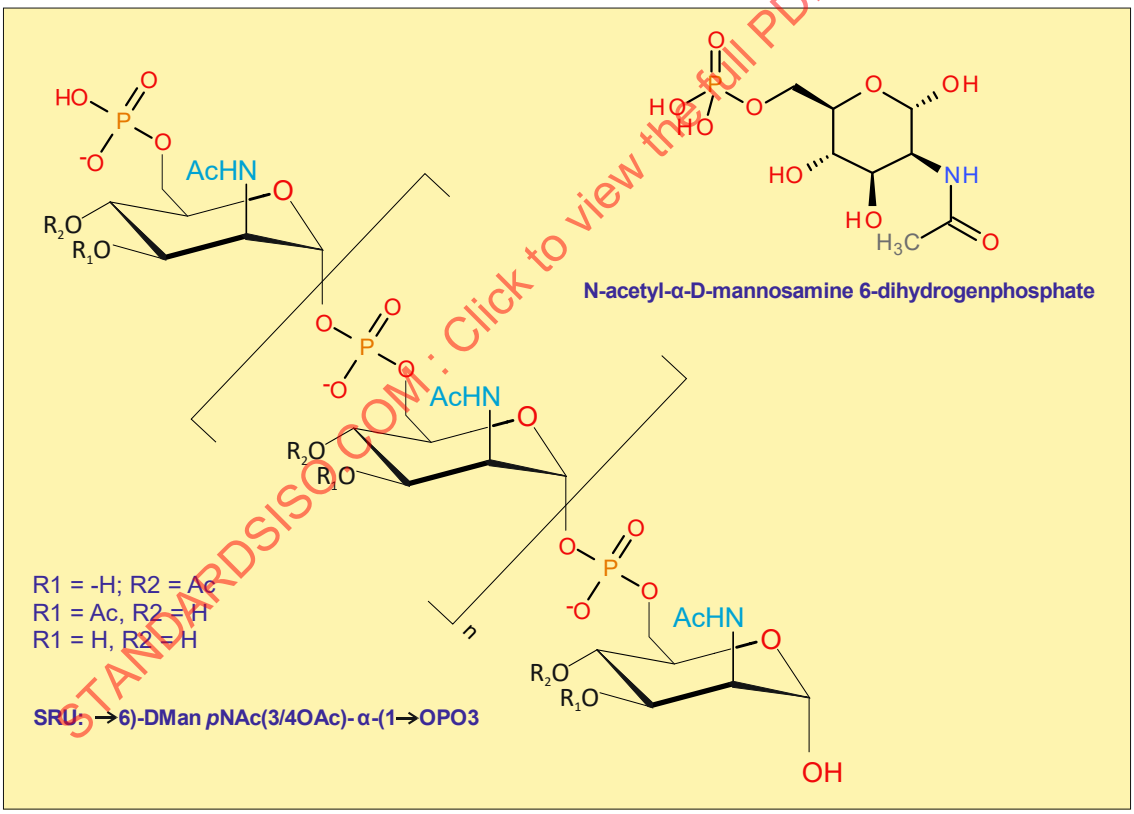


Figure I.6 — Structural representation of the MenA polysaccharide and the Structural repeat unit partly *O*–acetylated N-acetyl-α-D-mannosamine 6-dihydrogenphosphate[66]

[66] Systematic Name: IUPAC: 2-acetamido-2-deoxy-6-O-phosphono-α-D-mannopyranose, see http://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:62165

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I.6.2.2 MenC Polysaccharide and Oligosaccharide Description

The meningococcal polysaccharide serogroup C (MenC) is a homopolymer of N-acetylneuraminic acid. Meningococcal C polysaccharide is produced from fermentation and purification of *Neisseria meningitidis* serogroup C. Purified polysaccharide MenC is a process intermediate, which is subsequently hydrolysed, sized, activated and conjugated to the carrier protein CRM_{197} to give the drug substance MenC-CRM. The structural representation of Meningococcal C polysaccharide is provided in Figure I.7.

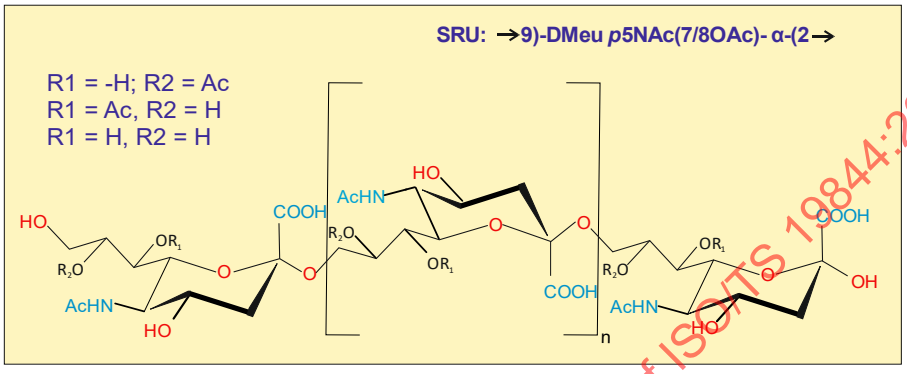
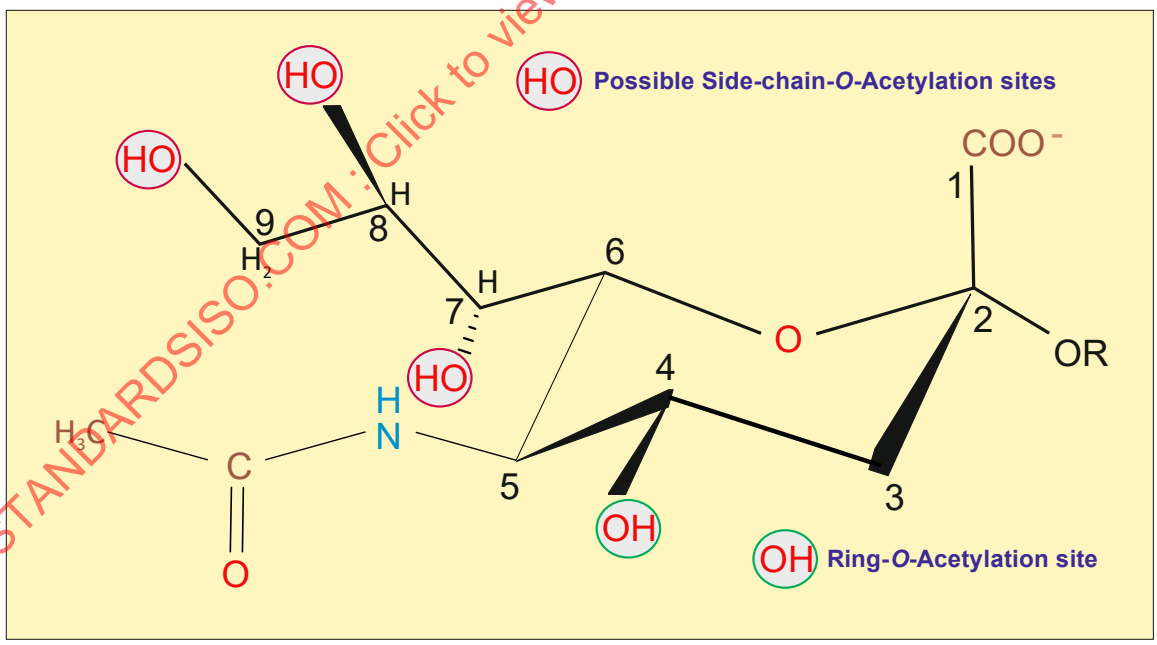


Figure I.7 — Structural representation of the MenC polysaccharide

NOTE Serogroup C polysacharide is a homopolymer of sialic acid containing 1.16 mol of *O*-acetyl per sialic acid residue, all the *O*-acetyl substituents being located on **C-7** or **C-8** of the individual residues. The polysaccharide contains un-acetylated residues (24 %), di-O-acetylated residues (C-7 and C-8), and at least 1 mono-*O*-acetylated residue at C-7 or C-8 [71]. A representation of the *O*-acetylation sites of sialic acid is provided in Figure I.8.



NOTE Figure adapted from Schauer, Roland *et al.* [72], from Figure 1, Page 325.

Figure I.8 — Representation of *O*-Acetylation sites of natural occurring sialic acid

NOTE Sialic acid *O*-acetylation can take place at the positions C4, C7, C8 and C9. They can be mono-*O*-acetylated or oligo-*O*-acetylated, e.g. a combination at C7 and C9 leads to the di-O-acetylated Neu5,7,9Ac3 [72].

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I.6.2.3 MenW Polysaccharide and Oligosaccharide Description

The meningococcal polysaccharide serogroup W (MenW) is a polymer of N-acetylneuraminic acid and galactose. Meningococcal W polysaccharide is produced from fermentation and purification of *Neisseria meningitidis* serogroup W. Purified polysaccharide MenW is a process intermediate, which is subsequently hydrolysed, sized, activated and conjugated to the carrier protein CRM_{197} to give the drug substance MenW-CRM. The structural representation of Meningococcal W polysaccharide is provided in Figure I.9.

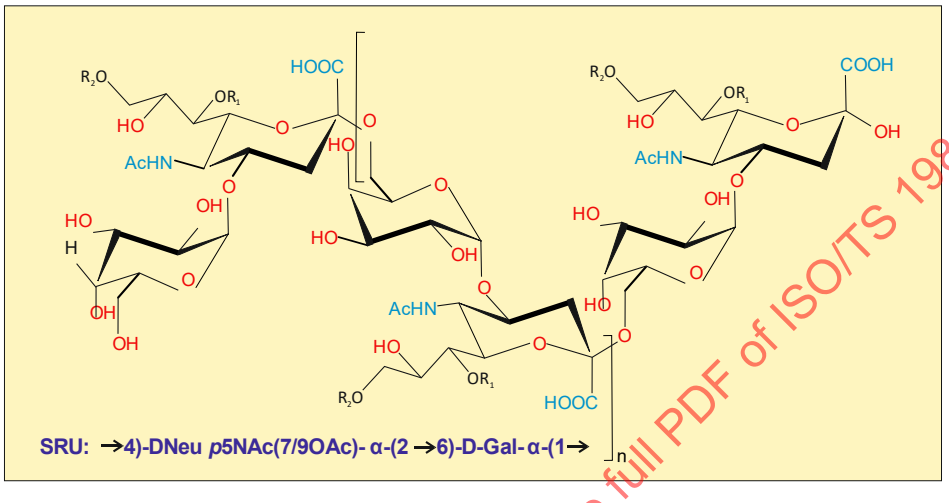


Figure I.9 — Structural representation of the MenW polysaccharide

NOTE MenW-135 polysaccharide, the 7-OAc to 9-OAc ratio was initially 1:1 and reaches an equilibrium value of 1:2 after three days, although this rate is probably sensitive to pH. No evidence of *0*-acetylation of the Gal residue or 8-*0*-acetylation of the NeuNAc was obtained, although the 8-*0*-acetyl NeuNAc may be an intermediate in the acetyl migration [73].

I.6.2.4 MenY Polysaccharide and Oligosaccharide Description

The meningococcal polysaccharide serogroup Y (MenY) is a polymer whose repeating unit is composed of N-acetylneuraminic acid and glucose. Meningococcal Y polysaccharide is produced from fermentation and purification of *Neisseria meningitidis* serogroup Y. Purified polysaccharide MenY is a process intermediate, which is subsequently hydrolysed, sized, activated and conjugated to the carrier protein CRM_{197} to give the drug substance MenY-CRM. The structural representation of Meningococcal Y polysaccharide is provided in Figure I.10.

I.6.2.5 Requirements as described in the Ph. Eur Meningococcal group ACWY Vaccine monograph 01/2008:0250

I.6.2.5.1 Production

Production of the meningococcal polysaccharides is based on a seed-lot system. The production method shall have been shown to yield consistently meningococcal polysaccharide vaccines of satisfactory immunogenicity and safety in man.

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The production method is validated to demonstrate that the product, if tested, would comply with the test for abnormal toxicity for immunosera and vaccines for human use.

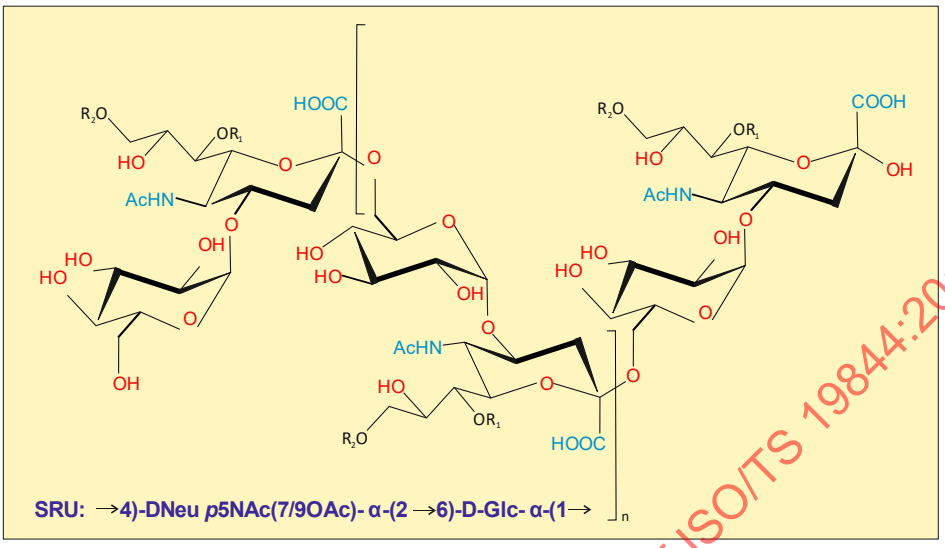


Figure I.10 — Structural representation of the MenY polysaccharide

NOTE For MenY polysaccharide, two lowfield resonances at 4,19 ppm and 4,41 ppm were attributed to H-9 and H-9' of 9-*O*-acetylated NeuNAc. In the more highly acetylated sample, a minor resonance at 5,15 ppm indicated the presence of *7-O*-acetylated NeuNAc. No evidence was found to suggest *O*-acetylation of the glucose residues, or migration of *O*-acetyl groups from the O-9 position. The 500 MHz proton NMR spectrum of MenY polysaccharide is provided, with important resonances labelled[67].

I.6.2.5.2 Seed Lots

The strains of *N. meningitidis* used for the master seed lots shall be identified by historical records that include information on their origin and by their biochemical and serological characteristics. Cultures from each working seed lot shall have the same characteristics as the strain that was used to prepare the master seed lot. The strains have the following characteristics:

— colonies obtained from a culture are rounded, uniform in shape and smooth with a mucous, opalescent, greyish appearance;

— Gram staining reveals characteristic Gram-negative diplococci in "coffee-bean" arrangement;

— the oxidase test is positive;

— the culture utilizes glucose and maltose;

— suspensions of the culture agglutinate with suitable specific antisera.

Purity of bacterial strains used for the seed lots is verified by methods of suitable sensitivity. These may include inoculation into suitable media, examination of colony morphology, microscopic examination of Gram-stained smears and culture agglutination with suitable specific antisera.

[67] This is formation is considered confidential and therefore the example is artificial information.

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I.6.2.5.3 Propagation and Harvest

The working seed lots are cultured on solid media that do not contain blood-group substances or ingredients of mammalian origin. The inoculum may undergo 1 or more subcultures in liquid medium before being used for inoculating the final medium. The liquid media used and the final medium are semisynthetic and free from substances precipitated by cetrimonium bromide (hexadecyltrimethylammonium bromide) and do not contain blood-group substances or high-molecular-mass polysaccharides.

The bacterial purity of the culture is verified by methods of suitable sensitivity. These may include inoculation into suitable media, examination of colony morphology, microscopic examination of Gram-stained smears and culture agglutination with suitable specific antisera.

The cultures are centrifuged and the polysaccharides precipitated from the supernatant by addition of cetrimonium bromide.

I.6.3 History of the strain

I.6.3.1 Taxonomic information

Taxonomic lineage: see 'Interagency Taxonomic Information' (ITIS) database.
The database is sponsored by the White House Subcommittee on Biodiversity and Ecosystem Dynamics. (https://www.itis.gov/servlet/SingleRpt/SingleRpt?search_topic=TSN&search_value=964013#null)

Kingdom: Bacteria (Cavalier-Smith, 2002)
Phylum: Proteobacteria (Garrity *et al*., 2005)
Class: Betaproteobacteria (Garrity *et al*., 2006)
Order: Neisseriales (Tønjum, 2006)
Family: ***Neisseriaceae*** (Prévot, 1933)
Genus: ***Neisseria*** (Trevisan, 1885)
Species: ***Neisseria meningitidis*** (Albrecht and Ghon, 1901), Murray, 1929
[**Synonym:** **Micrococcus meningitidis cerebrospinalis** (Albrecht and Ghon, 1901)]
Intraspecific description: Serogroup A, resp. Serogroup C, resp. Serogroup W, resp. Serogroup Y.

I.6.3.2 Master Seed[68]

The parent seed was obtained from the 'Bureau of Biologics' which is the precursor organization of CBER FDA in the US. This parent seed undergo X Passages on solid growth medium and is incubated. One colony was sub-cultured and stored in vials under Nitrogen. The master seed was designated as *Neisseria meningitidis* no X.

[68] This is formation is considered confidential and therefore the example is artificial information.

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I.6.3.3 Working Seed[69]

The parent seed for the production of the working seed is the master seed *Neisseria meningitidis* no X. The culture was incubated on a Y-medium and the vials constitute the working seed were stored under Nitrogen and designated as S12345 (artificial Code).

I.6.3.4 Propagation and Harvesting

The fermentation process shall follow the pharmacopoeial requirements as described above in I.6.2.5 and after formaldehyde treatment to kill the *Neisseria meningitidis* cells the cultures are centrifuged and the polysaccharides are precipitated from the supernatant by addition of Cetrimonium bromide. The precipitate may be stored at –20 °C awaiting downstream further purification.

I.6.3.5 Downstream Purification of the Crude Polysaccharides

The downstream procedure for purification of the crude polysaccharides is following the procedures as described in the Pharmacopoeial monograph. The polysaccharides are purified, after dissociation of the complex of polysaccharide and cetrimonium bromide, using suitable procedures to remove successively nucleic acids, proteins and lipopolysaccharides.

The final purification step consists of ethanol precipitation of the polysaccharides which are then dried and stored at −20 °C. If Calcium chloride is used during the purification a test for Calcium shall be included. The loss on drying is determined by thermogravimetry and the value is used to calculate the results of the other chemical tests with reference to the dried substance. Only purified polysaccharides that comply with the following requirements specified by the tests below may be used in the preparation of the final bulk vaccine. The final bulk shall comply to the following tests for: Protein; Nucleic acids; O-Acetyl groups; Phosphorus; Sialic acid; Calcium and Distribution of the molecular size.

I.6.4 Coupling to a Carrier Protein

Bacterial polysaccharides are not able to induce a T-cell-dependent B-cell immune response, which is needed to obtain an immunological memory response, and are generally poorly immunogenic in children under 2 years of age. The limitations are overcome by conjugating polysaccharides to carrier proteins. Carrier proteins are highly immunogenic and, when conjugated to bacterial polysaccharides, increase the capacity of polysaccharides to induce a protective response in infants.

Requirements for the carrier proteins are described in the Ph. Eur. monograph 01/2015:50211 ‘CARRIER PROTEINS FOR THE PRODUCTION OF CONJUGATED POLYSACCHARIDE VACCINES FOR HUMAN USE’. Carrier proteins currently used in polysaccharide vaccines for human use are toxoids, non-toxic mutated toxins, surface or outer membrane proteins extracted from micro-organisms. Micro-organisms used for the production of the protein may be of genetically modified origin.

The production method used for a carrier protein shall have been shown to yield consistently batches suitable for conjugation of the carrier protein to a polysaccharide antigen. The production of carrier proteins is based on a seed-lot system. The seed lots are shown to be free from contamination using suitable methods of appropriate sensitivity. The culture may be inactivated and the carrier protein is

[69] This is formation is considered confidential and therefore the example is artificial information.

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purified by a suitable method. Only a carrier protein that complies with the tests described in the pharmacopoeial monograph may be used in the preparation of the conjugate of which the requirements for CRM 197 diphtheria protein are described.

CRM_{197} diphtheria protein

CRM_{197} diphtheria protein may be prepared from the growth of genetically modified (C7/β197) or non-genetically modified (mCRM) *Corynebacterium diphtheriae* or prepared by recombinant DNA technology in organisms such as *Escherichia coli*. The culture supernatant may be concentrated by ultrafiltration and purified by successive precipitation, filtration, and chromatography steps. When it is produced on the same premises as diphtheria toxin, CRM_{197} diphtheria protein should be distinguished from the active toxin by a suitable method. The purity is not less than 90 per cent of diphtheria protein. The carrier protein CRM_{197} should be pre-registered. The description of the requirements for carrier protein CRM_{197} will be described in I.7.

I.6.5 CRM_{197} Coupling mechanism to polysaccharides

For coupling of polysaccharides to a protein, chemical activation of the polysaccharide and sometimes activation of both the polysaccharide and the protein compound is necessary. The procedure to activate the carbohydrate depends on the structure e.g.:

— Reactive aldehyde groups can be created from vicinal hydroxyl groups by periodate oxidation;

— Carboxyl groups can be activated with carbodiimide followed by appropriate conversion which is the case with coupling to CRM_{197};

— N-acetylamino functions can be (partially) de-N-acetylated followed by activation with nitrous acid;

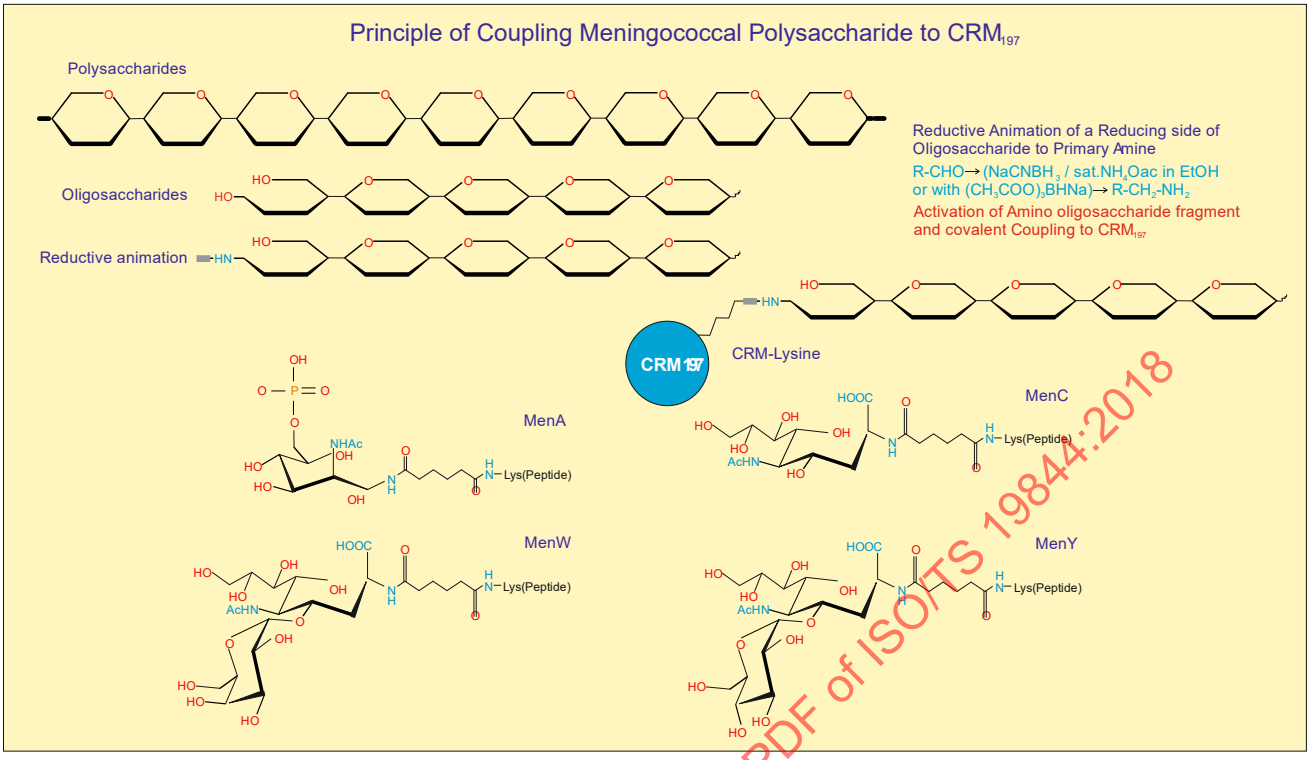
— Reductive amination, to introduce an amino group at the reducing end of the oligosaccharide followed by activation, to react with the free amino group of the oligosaccharide with a carbodiimide which is one of the possibilities with coupling to CRM_{197} [74].

Most of these reactions give rise to a random creation of reactive centres in the polysaccharide. Main reactive groups in proteins are the terminal amino group and the e-amino functions of lysine. Random activation of the reaction partners will allow the formation of conjugates; however, the structure of the reaction product may be rather undefined.

The steps to generate the glycoconjugate vaccine are shown in Figure I.11.

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NOTE Figure adapted from Bardotti Angela *et al.* [75], from (Fig.3, Page 2293) and (Fig.4, Page 2294).

Figure I.11 — Principle of Coupling Sized Oligosaccharides to CRM_{197}

The isolated and purified polysaccharides are hydrolysed and sized to oligosaccharides with a desired degree of polymerization followed by reductive amination of the reducing site of the oligosaccharide[75]. The oligosaccharides are generated through mild acid hydrolysis followed by sizing via tangential flow ultrafiltration and/or ionic exchange chromatography aimed at restricting the polydispersion. Subsequently they are activated via reductive amination followed by active ester derivatization. The terminal reducing end of the oligosaccharide reacts with the ammonium ion and the Schiff base obtained is reduced by Sodium Cyanoboronhydride ($NaCNBH_3$) or Sodium triacetoxyborohydride [$NaBH(OAc)_3$] (see Reference [76] and reductive amination reaction mechanism overview [77]). In the final step, the activated oligosaccharides react with available amino groups on the surface of the protein, ε-amino groups of lysine and the N-terminal amino groups, to form the conjugate vaccine, which consists of a population of glycoforms for which the average properties can be measured. The representation of the covalent bonding of reduced end of the sized oligosaccharide of MenA, MenC, Men W and MenY are provided in the lower part of Figure I.12 coupled to the lysine of CRM_{197}.

I.6.6 Requirements of the Degree of Polymerization [78]

The requirements for the degree of polymerization are laid down in the technical report series of the WHO regarding Meningococcal polysaccharides (90). With respect to the molecular size the requirements are described by their distribution constant K_D.

WHO, Annex 2, section 3 .4. 6 *Molecular size*

The molecular size of each lot of purified polysaccharide shall be estimated by gel filtration using Sepharose 4B. Chromatography shall be carried out in a solvent having a concentration of 0.2 ionic

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strength. The molecular weight shall be determined by measuring the distribution constant K_D of the polysaccharide at the main peak of the elution curve. The K_D value must be no greater than 0,40.

NOTE There are clinical data indicating that vaccines with a K_D value as high as 0,45 are immunogenic for man. As there is a general relationship between immunogenicity and molecular weight, however, material with the lower K_D value of 0,40 is considered preferable. Attempts can be made to produce material with still lower K_D values, and when such vaccines are being produced regularly these regulations can be amended to require a reduction in K_D value below the currently specified upper limit of 0,40.

I.6.7 New strategies concerning type coupling and type of glycan structure conjugates

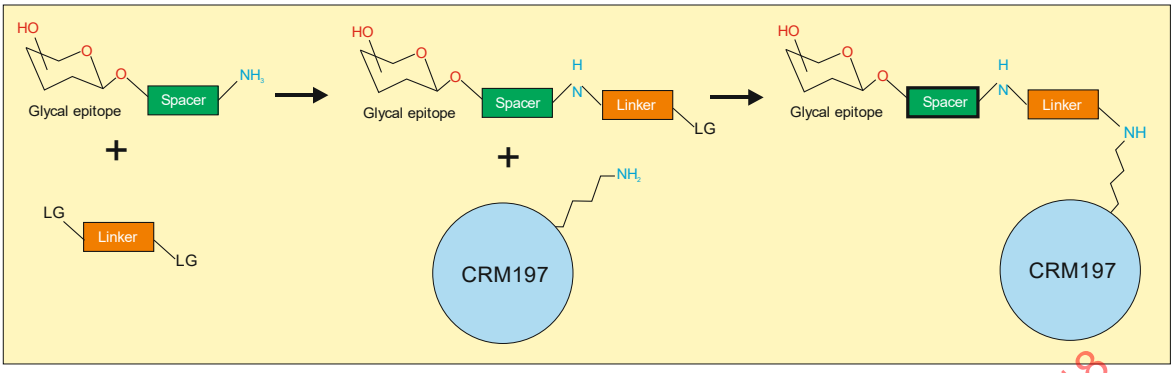
There may be different spacer and binding procedures involved to couple glycan structures to CRM_{197}. It may be that vaccines will be developed which make use of synthetic glycoforms coupled to CRM_{197} in different form. These types of binding will be captured at the Specified Substance Group 1 information level, where as the general coupling of the isolated purified naturally occurring sized oligosaccharides will be captured as a structural modification at the Substance information level.

An example of glycoform coupling to CRM_{197} strategies is illustrated in Figure I.12. Instead of using glycans from natural sources recent vaccine development has been focusing on the use of synthetically defined minimal epitopes. While the glycan is structurally defined, the attachment sites on the protein are not [79].

NOTE Typically, glycans are coupled to the primary amine side chains of lysine residues and to the protein N-terminus via a linker molecule. Alternatively, sulfhydryl groups in cysteine or carboxyl side chains can serve as sites for attachment. Prior to coupling, non-synthetic glycans need to be activated either arbitrarily on hydroxyl or carboxyl groups, leading to attachment at various points or via a single amine group, introduced by reductive amination, at the reducing end. The choice of the linker is crucial since it influences vaccine properties and may be immunogenic itself. In addition, coupling efficiencies have to be considered. Conjugation of a synthetic glyco-epitope to a carrier protein such as CRM_{197} that contains 40 primary amine side chains will result in heterogeneous glycoconjugates since some amino acid side chains more readily engage in conjugation reactions than others. Since variations in epitope loading influence the effectiveness of vaccines understanding which side chains preferentially react with glycans represents an important step towards producing better defined, more effective and safer conjugate vaccines. Glycan attachment to the carrier protein is typically monitored by SDS-PAGE and MALDI-TOF-MS. These methods provide information about average loading and cannot detect any side reactions or alterations occurring on the glycan epitopes. New methods are necessary for quality assurance of conjugate vaccines and to define conjugation sites on the protein. An integrated new middle-down LC-MALDI-TOF-MS approach simplified batch-to-batch comparison, and enabled relative quantification of regional conjugation efficacy. The influence of glycan size and amino acid microenvironment on conjugation efficiencies, determined which amino acid sites were preferably conjugated. Two regions close to the N- and C-termini of the protein engage primarily in the chemical conjugation process and exhibited the highest loading ratios. In addition to accessibility, the local amino acid environment significantly influences which lysine residues will be modified.

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NOTE Figure adapted from Moginger Uwe *et al.* [79], from Figure 1, Page 2.

Figure I.12 — Coupling strategies for glycoform conjugates to CRM_{197}

I.6.8 Registration of CRM_{197}

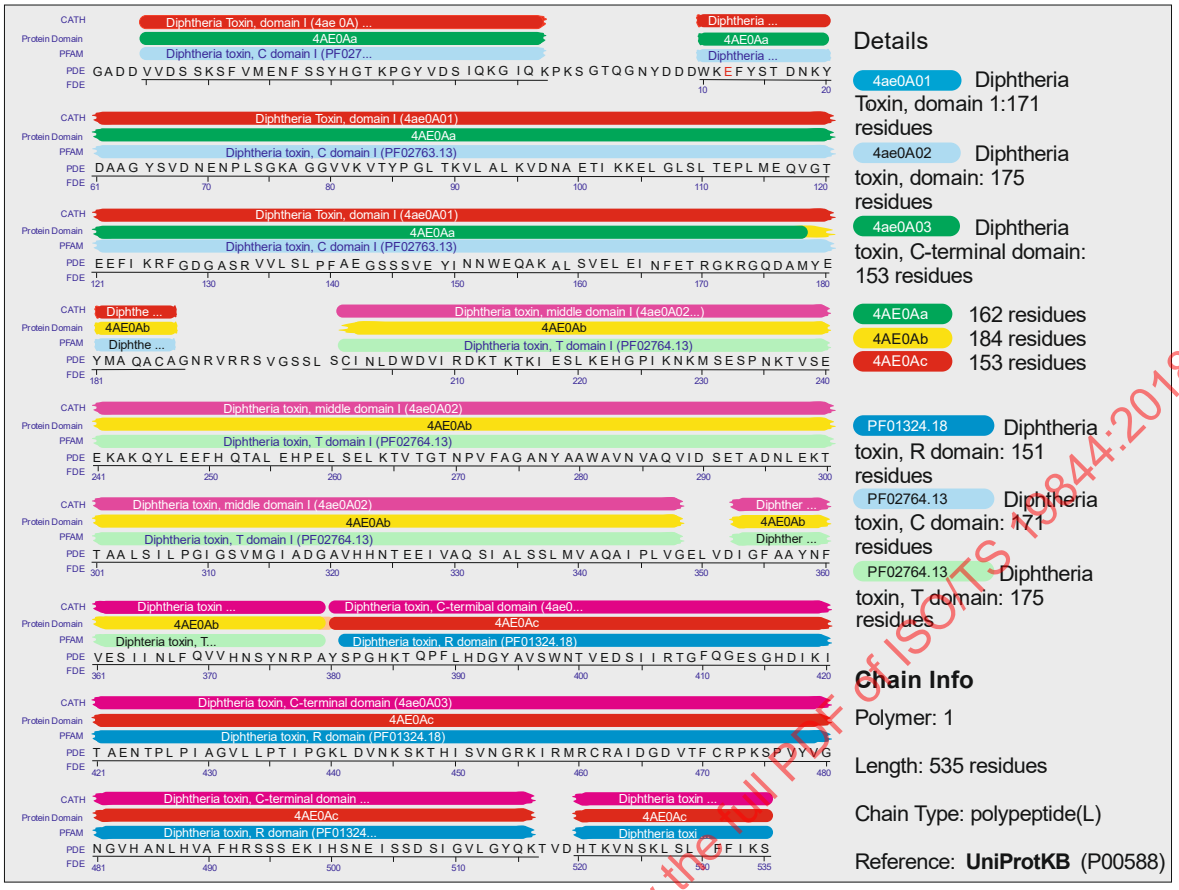
Corynebacterium diphtheriae is a Gram-positive, non-spore forming, non-motile, pleomorphic rod belonging to the genus Corynebacterium and the actinomycete group of organisms. The organism produces a potent bacteriophage-encoded protein exotoxin, diphtheria toxin, which causes the symptoms of diphtheria.

Diphtheria toxin can be proteolytically cleaved into two fragments: N-terminal fragment A (catalytic domain), and fragment B (transmembrane and receptor binding domain). Fragment A catalyses the NAD+-dependent ADP-ribosylation of elongation factor 2, thereby inhibiting protein synthesis in eukaryotic cells. Fragment B binds to the cell surface receptor and facilitates the delivery of fragment A to the cytosol (91).

CRM_{197} is a non-toxic, immunologically cross-reactive mutant protein of diphtheria toxin which is produced as a 58 kDa protein. CRM_{197} contains a Glycine (G) to Glutamic acid (E) substitution at position 52 in the catalytic domain as a result from a mutation in strain tox197 where the wild type codon "GGG" for Glycine is mutated into "GAG" for Glutamic acid. CRM_{197} was shown to possess an enzymatically inactive fragment A. This change drastically reduces the toxicity of the protein while retaining the majority of the toxin's structure and immunochemistry. The parent strain of CRM_{197} is the monolysogen Corynebacterium diphtheriae strain C7(β197). In Figure I.13 the sequence of CRM_{197} is provided according to Malito Enrico *et al.* [81] and Protein Databank, see:
http://www.rcsb.org/pdb/explore.do?structureId=4ae0

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NOTE Figure adapted from Protein Data Bank, [82][83], Reference: UniProtKB (P00588) and Malito Enrico *et al.* [81], from Fig.1, Page 5 230.

Figure I.13 — Amino acid sequence of CRM_{197} and Domains

I.6.9 Capturing the information of Meningococcal conjugated vaccine according to ISO/TS 19844

a) Pre-registration of CRM_{197} protein following the Protein CMD, see Table I.17. The strain information shall be documented by the element group Source Material.

b) Since at the substance level the description of the MenA, MenC, MenW and MenY polysaccharides are the most important parts of the Substance the description of these Oligosaccharides shall follow the Polymer CMD and the strain information shall be captured by the element group Source Material, see Figure I.7. The Polymer CMD is provided in Figure H.1. Additional information regarding the history of the strain, Master seed and Working seed information is considered being confidential information and will be described at the Specified Substance Group 1 information.

c) Taken into account the general information provided in the USP 40 <1234> pre-registration should be laid down of each monovalent polysaccharide e.g. MenA, MenC, MenW and Men Y polysaccharide.

d) Conjugation of the polysaccharide is considered as a modification and will be addressed at the Substance information level as high-level information. Detailed information about the formation of the reductive amination and the type of spacer will be described at the Specified Substance Group 1 information level. Where appropriate information about the degree of polymerization and/or distribution constant can be laid down at the Substance information level or at the Specified

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Substance Group 1 information level, since both information levels have the possibility to capture specific information. At the Specified Substance Group 1 information level degree of polymerization can be captured as a Characteristic Attribute. The degree of glycosylation expressed as saccharide to protein ratio (w/w) can also be captured in the same way.

I.7 Tabular information for CRM_{197}

Table I.17 — Tabular information for Corynebacterium diphtheriae CRM_{197} protein at the Substance information level (as a pre-registration)

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance ID	CRM19798S0 (Artificial ID)	II	
Substance Type	Protein (Naturally-derived)	CD	
Element Group: Substance Name			
Substance Name	*Corynebacterium diphtheriae* CRM_{197} protein	ST	1)
Substance Name Type	Preferred Name	CD	
Language	en	CD	
Substance Name Domain	Biologic	CD	
Jurisdiction	EU, US	CD	
Element Group: Substance Name (Repeat)			
Substance Name	Cross Reactive Material 197 Diphtheria protein	ST	1)
Substance Name Type	Official	CD	
Language	en	CD	
Substance Name Domain	Biologic	CD	
Jurisdiction	EU, US	CD	
Element Group: Official Name			
Official Name Type	Ph. Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph. Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia, Monograph 01/2015:50211	ST	

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Element Name	Value	Data Format	Note #
Element Group: Substance Name (Repeat)			
Substance Name	CORYNEBACTERIUM DIPHTHERIAE CRM_{197} PROTEIN	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	FDA GSRS	CD	
Reference Source Class	Public Database	CD	
Element Group: Substance Code 6)			
Code	08VC9WC084	CD.Code	
Code System	FDA GSRS (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Reference Information			
Element Group: Substance Classification (N/A) 7)			
Element Group: Gene			
Gene Sequence Origin	Tox^{197} gene of corynephage DNA	CD	
Gene ID	MUTA197CRM (Artificial ID)	CD	
Gene Name	Mutant tox 197^{tox}	ST	2)
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Web	CD	
Reference Source Citation	G. Giannini, R. Rappuoli, and G. Ratti, Nucleic Acids Res. 1984 May 25; 12(10): 4063–4069	ST	
Reference Source URL	https://www.ncbi.nlm.nih.gov/pubmed/6427753	ST	
Element Group: Structure			
Molecular formula	$C_{2585}H_{4061}N_{705}O_{813}S_{12}$	ST	

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Element Name	Value	Data Format	Note #
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	See image below	ED	

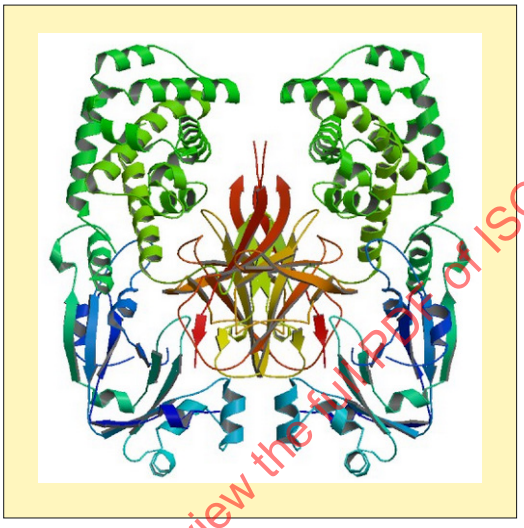


Figure I.14 — Structural representation of *Corynebacterium diphtheriae* CRM_{197} protein

(Figure adopted from Protein Data Bank [82][83] and Malito Enrico *et al.* [81], from Fig.1, Page 5230)

Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Journal	CD	
Reference Source Class	Literature	CD	
Reference Source Citation	Malito Enrico *et al.*, (2012) Proc. Natl. Acad. Sci. USA **109**: 5229-5234	ST	
Reference Source URL	http://www.rcsb.org/pdb/explore.do?structureId=4ae0	ST	
Element Group: Protein			
Sequence Type	Complete	CD	
Number of Subunits	1	INT	
Disulfide Linkage	Residue 1_186-1_201; 1_461_1_471	ST	3)

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Element Name	Value	Data Format	Note #
Element Group: Protein Subunit			
Subunit	1	INT	
Sequence	GADDVVDSSK SFVMENFSSY HGTKPGYVDS IQKGIQKPKS GTQGNYDDDW KEFYSTDNKY DAAGYSVDNE NPLSGKAGGV VKVTYPGLTK VLALKVDNAE TIKKELGLSL TEPLMEQVGT EEFIKRFGDG ASRVVLSLPF AEGSSSVEYI NNWEQAKALS VELEINFETR GKRGQDAMYE YMAQACAGNR VRRSVGSSLS CINLDWDVIR DKTKTKIESL KEHGPIKNKM SESPNKTVSE EKAKQYLEEF HQTALEHPEL SELKTVTGTN PVFAGANYAA WAVNVAQVID SETADNLEKT TAALSILPGI GSVMGIADGA VHHNTEEIVA QSIALSSLMV AQAIPLVGEL VDIGFAAYNF VESIINLFQV VHNSYNRPAY SPGHKTQPFL HDGYAVSWNT VEDSIIRTGF QGESGHDIKI TAENTPLPIA GVLLPTIPGK LDVNKSKTHI SVNGRKIRMR CRAIDGDVTF CRPKSPVYVG NGVHANLHVA FHRSSSEKIH SNEISSDSIG VLGYQKTVDH TKVNSKLSLF FEIKS	ST	11)
Length	535	INT	
Sequence Attachment	See Figure I.15	ED	

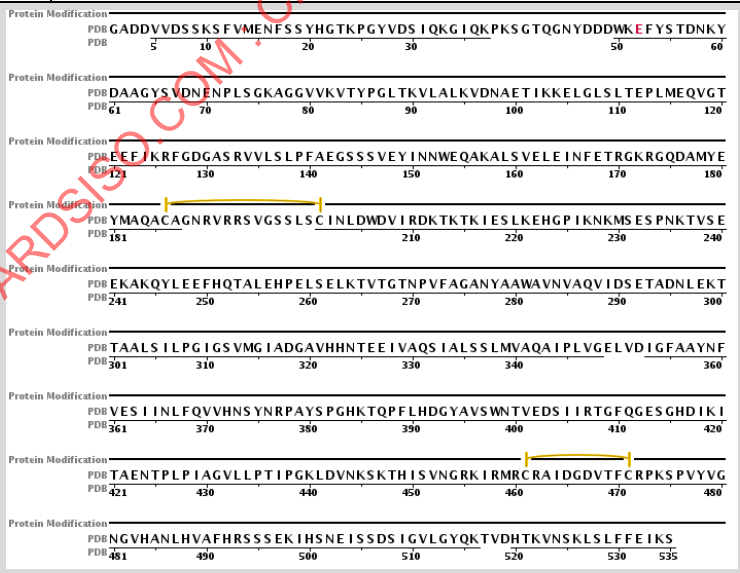


Figure I.15 — Representation of the Sequence of *Corynebacterium diphtheriae* CRM$_{197}$ protein

N-Terminal Modification	N/A		

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Element Name	Value	Data Format	Note #
C-Terminal Modification	N/A		
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Journal	CD	
Reference Source Class	Literature	CD	
Reference Source URL	http://www.uniprot.org/blast/?about=Q6NK15[26-560]&key=Chain&id=PRO_5004279123	ST	9)
Element Group: Reference Source (Repeat)			
Public Domain	Yes	BL	
Reference Source Type	Journal	CD	
Reference Source Class	Literature	CD	
Reference Source URL	http://www.ebi.ac.uk/pdbe/entry/pdb/4ae0	ST	10)
Element Group: Molecular Weight			
Molecular Weight Method	SDS-PAGE	CD	
Molecular Weight Type	Number average	CD	
Element Group: Amount			
Amount Type	Average	CD	
Quantity	58 400	PQ	4)
Unit	g/mol	CD	
Element Group: Glycosylation (N/A)			
Element Group: Property			
Property Type	Physical	CD	
Property Name	pH	CD	
Property Substance ID	CRM19798S0 (Artificial ID)	II	
Property Substance Name	*Corynebacterium diphtheriae* CRM_{197} protein	ST	
Element Group: Amount			
Amount Type	Average	CD	
High Limit	As approved for the substance in the dossier	PQ	8)
Low Limit	As approved for the substance in the dossier	PQ	8)
Unit	N/A		

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Element Name	Value	Data Format	Note #
Element Group: Source Material			
Source Material Class	Biologic	CD	
Source Material Type	Bacteria	CD	
Source Material State	N/A		
Organism ID	CORYC7B197(Artificial ID)	II	
Organism Name	*Corynebacterium diphtheriae* C7(β197)$^{tox-}$	ST	5)
Parent Substance ID	GHFDR89756 (Artificial ID) [ITIS Taxonomic Serial No.: 960918]	II	
Parent Substance Name	*Corynebacterium diphtheriae* C7(β)	ST	
Country of Origin	N/A		
Development Stage	N/A		
Element Group: Organism			
Family	*Corynebacteriaceae* Lehmann and Neumann, 1907	CD	
Genus	*Corynebacterium* Lehmann and Neumann, 1896 emend. Bernard *et al.*, 2010	CD	
Species	*Corynebacterium diphtheriae* (Kruse, 1886) Lehmann and Neumann, 1896	CD	
Intraspecific Type	Mutant Strain	CD	
Intraspecific Description	C7(β)	ST	
Element Group: Author			
Author Type	N/A		
Author Description	N/A		
Element Group: Organism General			
Kingdom	Bacteria	CD	
Phylum	Actinobacteria	CD	
Class	Actinobacteridae	CD	
Order	Actinomycetales	CD	

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Element Name	Value	Data Format	Note #
NOTE 1 The term '*Corynebacterium diphtheriae* CRM_{197} protein' is the authorized term used in the SmPC. CRM_{197} = Cross Reactive Material referring to the de-toxificated *C. diphtheriae* C7(β, phage197)^{tox} strain. NOTE 2 The gene for CRM_{197} is carried by the mutant phage β197^{tox}. The mutants were generated by treatment with nitrosoguanidine during the lytic phase of phage production, induced by ultraviolet treatment of the parent C. diphtheriae strain C7(β). The resulting phage population was used to infect phage-free C. diphtheriae C7(-) and the resulting lysogens were screened for the ability to produce mutant proteins that cross-reacted immunologically with diphtheria toxin but showed no toxicity [84]. NOTE 3 One disulfide bridge joins Cys186 to Cys201 linking fragment A to fragment B; a second bridge joins Cys461 to Cys471 within fragment B. NOTE 4 Molecular weight measured by MS is provided in the dossier. Molecular weight measured by SDS-PAGE is taken from the Literature [84]. NOTE 5 CRM_{197} protein is produced by fermentation of the *C. diphtheriae* C7(β197)$^{tox-}$ strain. The protein is secreted into the supernatant, which is recovered by centrifugation, filtration, and concentration. Subsequently purification is achieved by chromatography steps, followed by concentration (see footnote corresponding to Note 4 above. NOTE 6 There is no CAS Registration Code and Name available in the STN*Easy* database. NOTE 7 There is no ATC code for CRM_{197} available. NOTE 8 The actual value should be provided but this information is confidential. NOTE 9 Protein Bank. NOTE 10 Protein Bank Europe. NOTE 11 The full sequence is to be provided as written in the text of the Figure I.15.			

I.7.1 Specified Substance Group 1 Information for *Corynebacterium diphtheriae* CRM_{197} protein

Tabular information of the Specified Substance Group 1 information of the *Corynebacterium diphtheriae* C7(β197)$^{tox-}$ strain is considered as confidential information and cannot be provided in this technical specification. In general, the pattern for description of the Master seed and the Working seed shall be followed as described by the example in Table I.21.

I.7.2 Specified Substance Group 2 Information for *Corynebacterium diphtheriae* CRM_{197} protein

Table I.18 — Tabular Manufacturing information for *Corynebacterium diphtheriae* CRM_{197} protein at the Specified Substance Group 2 information level

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2– Company NZS			
Specified Substance Group 2 ID	JKHGF98564(Artificial ID)	II	
Element Group: Substance Name			
(Specified) Substance (Group 2) Name	*Corynebacterium diphtheriae* CRM_{197} protein — Company NZS	ST	
Substance Name Type	Specified Substance Group 2	CD	
Language	en	CD	
(Parent) Substance ID	CRM19798S0 (Artificial ID)	II	1)

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Element Name	Value	Data Format	Note #
Element Group: Manufacturing			
Manufacturing Type	Manufacturer	CD	
Production Method Type	Vaccine production	CD	
Production Method Description	Fermentation of the *C. diphtheriae* C7(β197)$^{tox-}$ strain. The protein is secreted into the supernatant, which is recovered by centrifugation, filtration, and concentration and purification.	ST	
Production System Type	Fermentation, Harvesting and Purification	CD	
Production System	Bacteria	CD	
Critical Process Version Number	1	INT	2)
Version	ManCRM002	ST	
Version Date	21070406	TS.Date	
Element Group: Organization			
Manufacturer ID	DUNSCRM786(Artificial ID)	II	
Manufacturer Name	Company NZS	ST	
Issuer of ID	EMA OMS	CD	
Manufacturer Role	Manufacturer	CD	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	Marketing Authorization Application	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	FINAL12345 (Artificial ID)	ST	
Reference Source Citation	CBG453897 (Artificial CBG-Case number)	ST	
Element Group: Reference Source Document			
Public Domain	No	BL	
Reference Source Document	PDF	ED	
Reference Source Document Type	Release Specification	CD	

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Element Name	Value	Data Format	Note #
Reference Source Document ID	CRMFINAL45 (Artificial ID)	ST	
Reference Source Document Classification	In-house/Final lot release specification	CD	
NOTE 1 This (Parent) Substance ID refers to the Substance Name *Corynebacterium diphtheriae* CRM_{197} protein NOTE 2 The Critical Process Number Version Number would change if a substantial change in the (biological) manufacturing process occurred. These would include a change in the chemistry or biological production steps by means of additional passages, addition or elimination of a purification step. The change in a version number is tied to the production system type.			

I.7.3 Specified Substance Group 3 Information for *Corynebacterium diphtheriae* CRM_{197} protein

Table I.19 — Tabular information for *Corynebacterium diphtheriae* CRM_{197} protein at the Specified Substance Group 3 information level

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 3			
Specified Substance Group 3 ID	IOUTY89765 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Corynebacterium diphtheriae* CRM_{197} protein - Ph.Eur.	ST	
Substance Name Type	Specified Substance Group 3	CD	
Language	en	CD	
(Parent) Substance ID	CRM197S0 (Artificial ID)	II	1)
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name	Carrier Proteins for the Production of Conjugated Polysaccharide Vaccines for Human Use, CRM_{197} diphtheria protein	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia, monograph 01/2015:50211	ST	
NOTE This (Parent) Substance ID refers to the Substance Name *Corynebacterium diphtheriae* CRM_{197} protein.			

I.8 Tabular information for Meningococcal ACWY conjugate vaccine

I.8.1 Registration of Tabular Information *N. meningitidis* group A oligosaccharide conjugated to CRM_{197} protein

Table I.20 — Description of *N. meningitidis* group A polysaccharide (pre-registration)

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Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance Type	Polymer	CD	
Substance ID	SGERSA8976 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Neisseria Meningitidis* group A polysaccharide	ST	
Substance Name Type	Preferred Name	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU	CD	
Element Group: Official Name			
Official Name Type	Ph. Eur.	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Ph. Eur.	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	Ph. Eur. monograph 01/2008:0250	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Meningococcal serogroup A	ST	
Substance Name Type	Other Name	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU	CD	
Element Group: Substance Name (Repeat)			
Substance Name	MenA polysaccharide	ST	
Substance Name Type	Other Name	CD	
Language	en	CD	
Substance Name Domain	Drug	CD	
Jurisdiction	EU	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	

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Element Name	Value	Data Format	Note #
Reference Source Type	CAS Registry	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	https://stneasy.fiz-karlsruhe.de/tmp/01215091061464/625553958.html	ST	3)
Element Group: Substance Name (Repeat)			
Substance Name	NEISSERIA MENINGITIDIS GROUP A CAPSULAR POLYSACCHARIDE ANTIGEN	ST	
Substance Name Type	Preferred Name	CD	
Language	en	CD	
Substance Name Domain	Biologic	CD	
Jurisdiction	US	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	FDA GSRS	CD	
Reference Source Class	Public Database	CD	
Element Group: Substance Name (Repeat)			
Substance Name	Meningococcal group A Polysaccharide	ST	
Substance Name Type	Official Name	CD	
Language	en	CD	
Substance Name Domain	Biologic	CD	
Jurisdiction	US	CD	
Element Group: Official Name			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	USP 40 <1234> Vaccines for Human Use-Polysaccharide and Glycoconjugate vaccines, p 1888 - 1905	ST	
Element Group: Substance Code			
Code	1714127-90-8	CD.Code	

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Element Name	Value	Data Format	Note #
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	1I86B47NY4 (UNII)	CD.Code	
Code System	FDA GSRS	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.CodeSystem	
Substance Classification Code	J07AH01	CD.Code	
Substance Classification Type	meningococcus A, purified polysaccharides antigen	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC	CD	
Reference Source Class	Public Database	CD	
Reference Source URL	https://www.whocc.no/atc_ddd_index/?code=J07AH	ST	
Element Group: Polymer			
Polymer Class	Homopolymer	CD	
Polymer Geometry	Linear	CD	
Copolymer Connectivity	N/A	CD	

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Element Name	Value	Data Format	Note #
Element Group: Monomer Set Description			
Number of Monomers	3	INT	
Monomer Amount Type	Monomer/Polymer Ratio	CD	
Element Subgroup: Polymer Starting Material			
Starting Material ID	NACMANAP87 (Artificial ID); [CHEBI:62165]	II	
Starting Material Name	*N*-acetyl-α-D-mannosamine 6-phosphate	ST	1)
Starting Material Type	Biological Substance	CD	
Is Defining	Yes	BL	
Element Subgroup: Polymer Starting Material (Repeat)			
Starting Material ID	NACMANAP88 (Artificial ID); [CHEBI:62165]	II	
Starting Material Name	3-*O*-acetylated *N*-acetyl-α-D-mannosamine 6-phosphate	ST	1)
Starting Material Type	Biological Substance	CD	
Is Defining	Yes	BL	
Element Subgroup: Polymer Starting Material (Repeat)			
Starting Material ID	NACMANAP89 (Artificial ID); [CHEBI:62165]	II	
Starting Material Name	4-*O*-acetylated *N*-acetyl-α-D-mannosamine 6-phosphate	ST	1)
Starting Material Type	Biological Substance	CD	
Is Defining	Yes	BL	
Element Group: Structural Repeat			
Number of Structural Repeat Units	1	INT	
Average Molecular Formula by Repeat Unit	$C_8H_{13}NO_8P.C_2H_3O.H.HO$	ST	
Structural Repeat Unit Amount Type	Average	CD	
Element Group: Structure			
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	See below	ED	

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Element Name	Value	Data Format	Note #

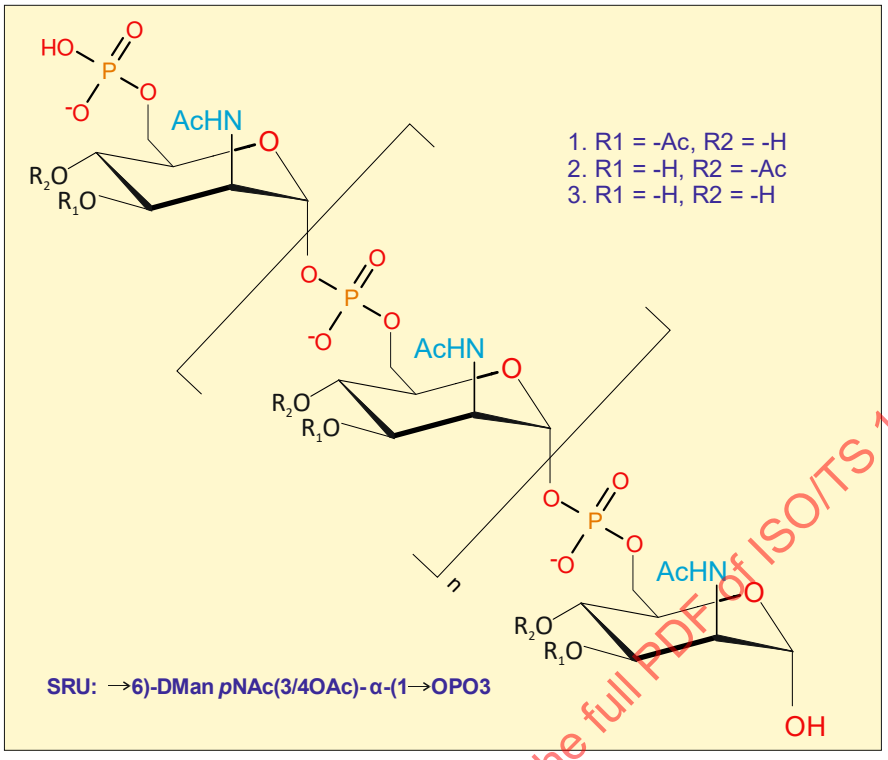


Figure I.16 — Structural representation of *N. meningitidis* group A polysaccharide

Element Group: Structural Repeat Unit			
Orientation of Polymerization	Head-tail	CD	
Structural Repeat Unit	→6)-DMan*p*NAc(3/4OAc)-α-(1→OPO3)	ST	
Element Group: Degree Polymerization			
Degree of Polymerization	→6)-DMan*p*NAc(3/4OAc)-α-(1→OPO3	CD	
Element Group: Amount			
Amount Type	NMT	CD	
Quantity	As Marketing Authorization	PQ	3)
High Limit	0.40	PQ	
Amount Text	Molecular Size Distribution constant (K_D)	ST	2)
Element Group: Molecular Weight (N/A)			
Element Group: Property			
Property Type	Physical	CD	
Property Name	Percent MenA Polysaccharide eluted before K_D = 0.50	CD	2)
Property Parameters	Observed K_D Value	ST	

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Element Name	Value	Data Format	Note #
Property Substance ID	NEISSA8976 (Artificial ID)	II	
Property Substance Name	*Neisseria Meningitidis* group A polysaccharide	ST	
Element Group: Amount			
Amount Type	Exact	CD	
Quantity	0,70	PQ	
Amount Text	Percent MenA Polysaccharide eluted before K_D = 0,50	ST	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Protein Content	CD	
Property Parameters	N/A		
Property Substance ID	NEISSA8976 (Artificial ID)	II	
Property Substance Name	*Neisseria Meningitidis* group A polysaccharide	ST	
Element Group: Amount			
Amount Type	NMT	CD	
Quantity	10	PQ	
Unit	mg/g	CD	
Amount Text	mg/g Polysaccharide	ST	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	*O*-Acetyl groups	CD	
Property Parameters	N/A		
Property Substance ID	NEISSA8976 (Artificial ID)	II	
Property Substance Name	*Neisseria Meningitidis* group A polysaccharide	ST	
Element Group: Amount			
Amount Type	NLT	CD	
Quantity	2	PQ	
Unit	mmol/g	CD	
Amount Text	mmol/g Polysaccharide	ST	

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Element Name	Value	Data Format	Note #
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Phosphorous	CD	
Property Parameters	N/A		
Property Substance ID	NEISSA8976 (Artificial ID)	II	
Property Substance Name	*Neisseria Meningitidis* group A polysaccharide	ST	
Element Group: Amount			
Amount Type	NLT	CD	
Quantity	80	PQ	
Unit	mg/g	CD	
Amount Text	mg/g Polysaccharide	ST	
Element Group: Source Material			
Source Material Class	Biologic	CD	
Source Material Type	Bacteria	CD	
Source Material State	Polysaccharide, natural derived	CD	
Organism ID	NEIS87654A (Artificial ID)	II	
Organism Name	*Neisseria Meningitidis* (Albrecht and Ghon, 1901), Murray, 1929, Serogroup A	ST	
Parent Substance ID	BACHT6754N (Artificial ID)	II	
Parent Substance Name	*Neisseria meningitidis* (Albrecht and Ghon, 1901), Murray, 1929	ST	
Country of Origin	N/A		
Development Stage	N/A	CD	
Element Group: Organism			
Family	*Neisseriaceae*	CD	
Genus	*Neisseria*	CD	
Species	*Neisseria meningitidis*	CD	
Intraspecific Type	Strain	CD	
Intraspecific Description	Serogroup A	ST	

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Element Name	Value	Data Format	Note #
Element Group: Author			
Author Type	Species Primary Author, year	CD	
Author Description	(Albrecht and Ghon, 1901), Murray, 1929	ST	
Element Group: Organism General			
Kingdom	Bacteria	CD	
Phylum	Proteobacteria	CD	
Class	Betaproteobacteria	CD	
Order	Neisseriales	CD	
Element Group: Part Description			
Part	Whole	CD	
Part Location	N/A		
Element Group Reference Information			
Element Group: Gene			
Gene Sequence Origin	Bacterial	CD	
Gene ID	NEIS2157	CD	
Gene Name	*csaA*	ST	
Element Group: Gene Element			
Gene Element Type	Epimerase	CD	
Gene Element ID	JKHYD67543 (Artificial ID)	II	
Gene Element Name	UDP-*N*-acetyl-D-glucosamine 2-epimerase	ST	
Element Group: Gene (Repeat)			
Gene Sequence Origin	Bacterial	CD	
Gene ID	NEIS2158	CD	
Gene Name	*csaB*	ST	
Element Group: Gene Element			
Gene Element Type	Polymerase Linker	CD	
Gene Element ID	378RDFA86B (Artificial ID)	II	
Gene Element Name	Polymerase linking *N*-acetyl-D-mannosamine-6-phosphate monomers	ST	

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Element Name	Value	Data Format	Note #
Element Group: Gene (Repeat)			
Gene Sequence Origin	Bacterial	CD	
Gene ID	NEIS2159	CD	
Gene Name	*csaC*	ST	
Element Group: Gene Element			
Gene Element Type	Transferase	CD	
Gene Element ID	KLJH564312 (Artificial ID)	II	
Gene Element Name	*O*-acetyltransferase	ST	
Element Group: Gene (Repeat)			
Gene Sequence Origin	Bacterial	CD	
Gene ID	NEIS2160	CD	
Gene Name	*csaC*	ST	
Element Group: Gene Element			
Gene Element Type	Capsule Transporter	CD	
Gene Element ID	KLJH564312 (Artificial ID)	II	
Gene Element Name	Capsule transport	ST	

NOTE 1 The Polymer starting material is either 3-*O*-acetylated *N*-acetyl-α-D-mannosamine 6-phosphate or 4-*O*-acetylated *N*-acetyl-α-D-mannosamine 6-phosphate or *N*-acetyl-α-D-mannosamine 6-phosphate.

NOTE 2 The K_D is calculated according to the formula: $K_D = (V_e - V_0)/V_t - V_0)$; V_0 = Void volume of the column as determined by Blue Dextran 2000 and V_t is the total permeation volume as determined by ^{14}C-labelled Sodium Acetate solution containing 0,4 µCi or radioactivity or Sodium Azide. The elution volume V_t of the analyte is calculated from the peak of the absorbance curve. The percentage of sample eluted before a given K_D is calculated according to the following formula: area of sample elution curve before a given K_D / total area of the sample elution curve x 100 (see WHO requirements, TRS 594, Annex2 [78]).

NOTE 3 The actual value is provided but this information is confidential.

I.8.2 Specified Substance Group 1 Information for *N. Meningitidis* group A polysaccharide

Table I.21 — Tabular information *N. Meningitidis* group A polysaccharide at the Specified Substance Group 1 information (Passage information)

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