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Health informatics — Identification of medicinal products — Implementation guidelines 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 des éléments de données et structures pour l'identification unique et l'échange d'informations réglementées sur les substances

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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 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 second edition cancels and replaces the first edition (ISO/TS 19844:2015), 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 harmonised 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, *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 — Implementation guidelines for data elements and structures for the unique identification and exchange of regulated information on substances

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 second 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 and H. 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 may be covered in the Annexes of this document. This information, although not defining of either a Substance or a Specified Substance Group 1, may 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;
- Nomenclature standards for substances.

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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 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*

3 General background and history

Due to the lack of a common and harmonised 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.

The objectives of the IDMP standards are to address the issues outlined above by developing harmonised 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.

Harmonised standards will stimulate vendors to develop “off-the-shelf” tools (that are interoperable due to the standard itself). Harmonised standards will also help to maximise forward compatibility of data and minimise 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 organisation. The maintenance organisation may also create alternative methods to submit information consistent with the ISO model.

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

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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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4 Substance (Mandatory)

4.1 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:

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- 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;

- Mixture Substance consists of a simple combination of Single Substances that are either isolated together or are the result of the same synthetic process. 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 Substance 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.

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 substances;
- Additional information regarding herbal and allergenic extracts;
- Physical state, including polymorphic forms;
- Detailed glycosylation information.

Specified Substance Group 2 is typically used to define:

- Manufacturer and the overall manufacturing process and critical process version number;

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- In addition, there is the possibility to make use of the reference source document class to store Release specifications of the intended manufactured substance.

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 Analytical Data;
- Detailed Manufacturing Information.

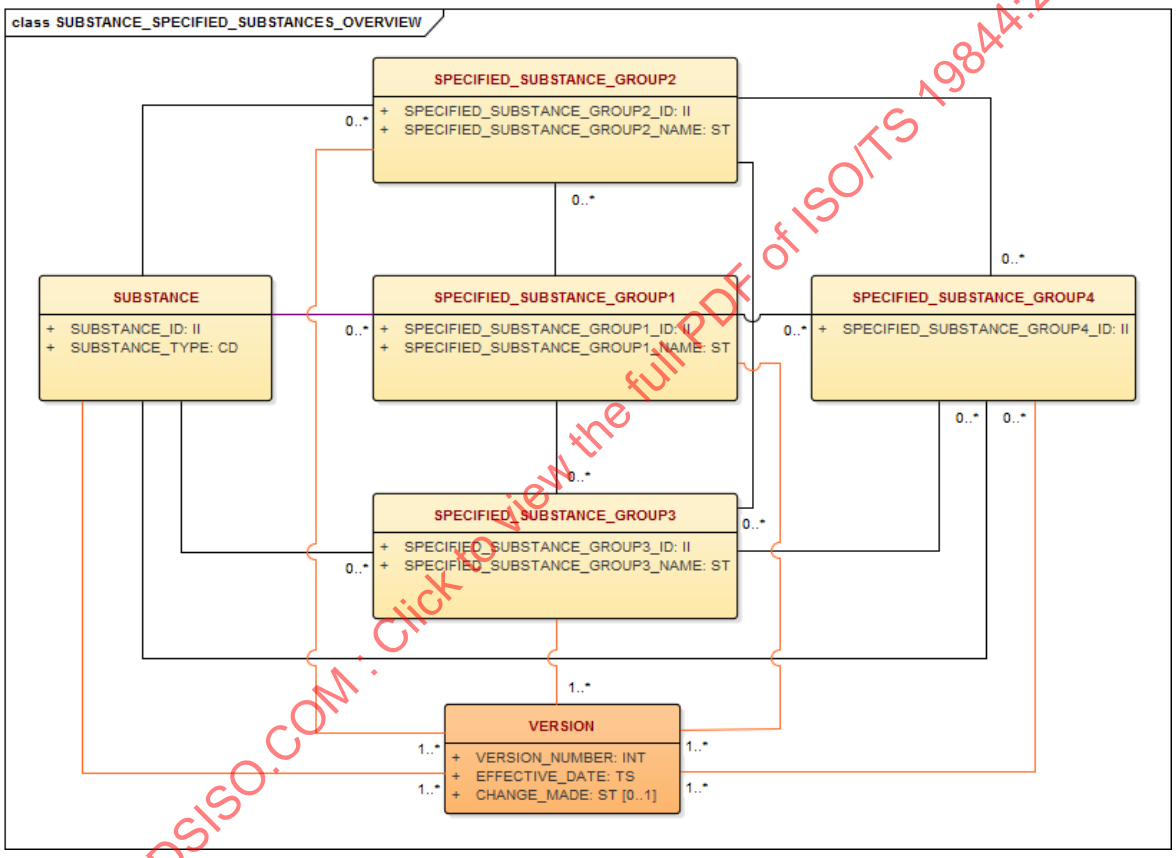


Figure 1 — High-level Substance-Specified Substance information model

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4.2 Defining substances

A substance is any matter that has a discrete existence, irrespective of origin, which may be biological 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, microorganisms or inorganic matrices that are not definable by a single or limited number of molecular structures. Substances may be active moieties, salts, solvates, stoichiometric complexes or mixtures of compounds that are isolated or

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synthesised/obtained or produced in a process together. Materials that are combined from multiple sources to form a product are not considered 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 recognised 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 that is permanently associated with that substance will be assigned. 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.

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.

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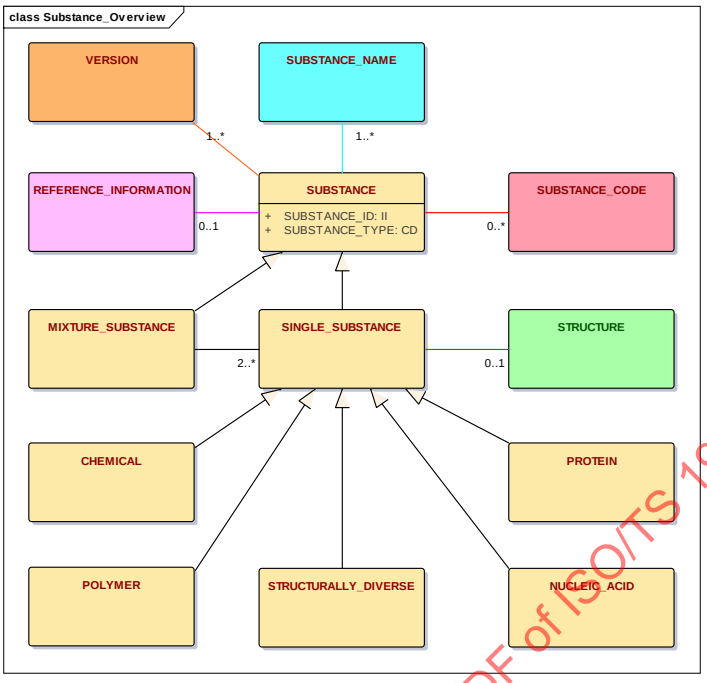


Figure 2 — High-level information model for substances

4.2.1 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. For the purposes of definition, all single substances are of one of the following types:

- (simple) chemical;
- protein;
- nucleic acid;
- polymer;
- structurally-diverse.

Each of these different types of substances has distinct elements essential for definition. Substances can also be a **mixture of single substances,** typically related and of the same type. Some materials may appear to have elements from multiple types of substances e.g. PEGylated proteins, drugs covalently linked to polymeric matrices or proteins, etc., to fully define the substance. Each of these substances will

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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.

EXAMPLE 2: Desmopressin can either be defined as a modified peptide or as a chemical substance.

Mixtures consist of a combination of related single substances where the source material and essential properties are also captured but proportions are not. 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 of single substances or a Specified Substance Group 1. A mixture substance 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 related and not synthesised or isolated together 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 Substances are defined in the ISO 11238 standard as a simple combination of single substances that are either isolated together or are the result of the same synthetic process.

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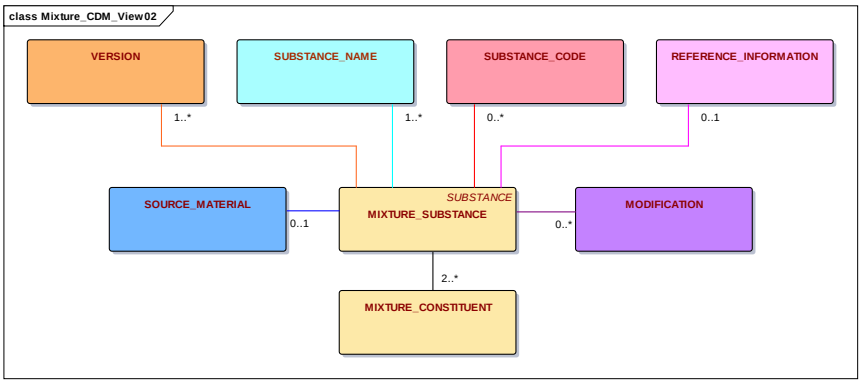
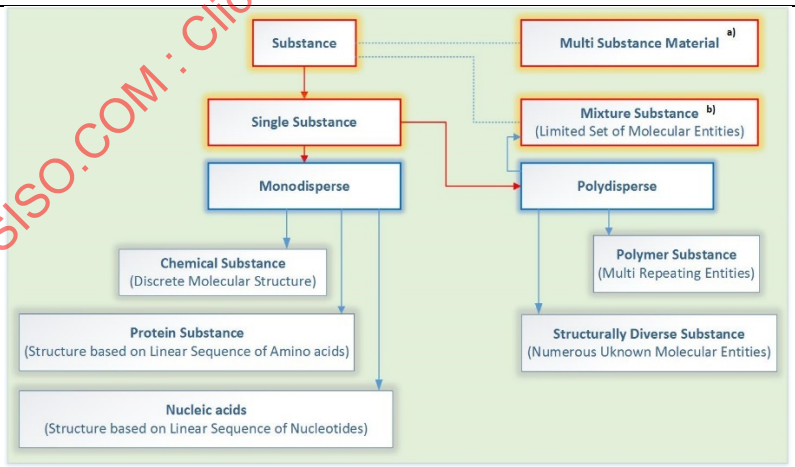


Figure 3 — High-level information model for Mixture Substance

For mixture substances in which multiple related substances are isolated together from a single source, the source will be a defining element. Starches are typically a mixture substance of the two distinct polymers amylose and amylopectin. Corn, whexat, 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 4 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).



a) Multi-substance material: Multi Substances and/or Specified Substances of diverse origin.

b) Mixture Substance: Type of polydisperse substance that is a combination of single substances isolated together or synthesised/obtained or produced in the same process.

Figure 4 — Decision tree or process by which the type of substance is determined

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Table 2 — Substance types

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"
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

4.2.2 Substance ID (Mandatory)

Every substance will 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. A submitter should always submit the ID 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 will 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 will 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[1] (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 will be identified by a single ID. 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 organisation 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 4.4. Defining information found in patents will usually not be sufficient to release the ID to the public.

4.3 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 basically eight types of names, Official names, systematic names, other names, brand names, company codes, homeopathic names, specified homeopathic names and plasma-derived names.

At least one name or company code should be associated with each substance. Names for a given substance and/or standardised 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 may be its company code. In later stages an INN name may be associated with the substance and become the preferred term for that substance.

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

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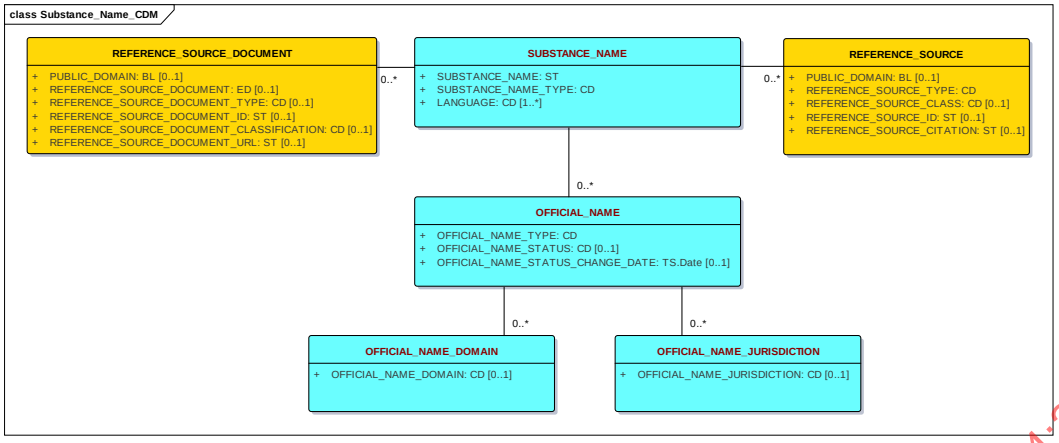


Figure 5 — Information model for Substance Names

4.3.1 Substance name

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 polymerisation, and viscosity, should be indicated in the names of these substances. Standardisation 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 name 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 polymerisation.

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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 infraspecies, 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 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.

4.3.2 Substance name type

Every name shall have one and only one name type. Official names are typically non-proprietary 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 a type.
Example(s)	Official name, systematic name, scientific name, other name, brand name, company code, homeopathic name, specified homeopathic name, plasma-derived name, preferred name
Conformance	MANDATORY
Data Type	CD

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Table 5 *(continued)*

Values Allowed	OFFICIAL, SYSTEMATIC, SCIENTIFIC, COMPANY CODE, OTHER, BRAND, HERBAL, HOMEOPATHIC, SPECIFIED HOMEOPATHIC, PLASMA-DERIVED, PREFERRED 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'.

4.3.3 Language

All names shall be associated with at least one language. Often the name, particularly INN names, 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, microorganism 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 name alisertib is identical in English, French and Spanish.

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.

4.3.4 Official name (Conditional

Each official name shall have one or more official name types. The official name type reflects the organisation that assigns or recognises the name associated with the substance. These names are typically non-proprietary 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

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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 optional and shall be repeated as necessary.

4.3.4.1 Official name type

Any authority which assigns official names will 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 7 — Official name type

User Guidance	Designation of which authority assigned the Official Name. 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, a separate <asNamedEntity> is specified for each authority that needs to be listed.

4.3.4.2 Official name status

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 names would be considered to be the Official name in many jurisdictions.

Table 8 — Official name status

User Guidance	The status of the official name.
Example(s)	Current, Alternate, Superseded, Proposed, Primary
Conformance	OPTIONAL
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.

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4.3.4.3 Official name status change date

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 9 — Official name status change date

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

4.3.4.4 Official name domain (CONDITIONAL)

Official 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 DRUGS or BIOLOGICS in the US and Japan.

Table 10 — Official name domain

User Guidance	Specifies when and for what purpose the official name is to be used. All official 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
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	Used if different names exist that are not appropriate to be used across all domains.

4.3.4.5 Official name 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. The Official Name Jurisdiction class is optional; when necessary the following conformances apply:

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Table 11 — Official name jurisdiction

User Guidance	The jurisdiction of the official name shall be provided.
Example(s)	US, EU, JA
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.

4.4 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 of public databases such as chemical abstracts. A source can refer to multiple data elements and a given element can have multiple sources.

4.4.1 Public domain

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 should be taken 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.

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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 chemical abstracts (CAS), a journal article, or a poster at scientific meeting attributable to the company.
Example(s)	Yes, No
Conformance	OPTIONAL
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.

4.4.2 Reference source type

All reference sources will be associated with a type. The type may 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), INN, ITIS, JAN, JOURNAL, JP, KEGG, MARTINDALE, NDA, PERSONAL CARE PRODUCTS COUNCIL (PCPC), PUBCHEM, USAN, USP, WEB PAGE, CAS Registry, FDA-(G)-SRS, WHO Collaborating Centre for Drug Statistics methodology (WHOCC), CHEMICAL BOOK, ORANGE BOOK, JAVA APPLICATION, MAA (Marketing Authorisation Application), Allegome-A database of allergenic molecules, Uniprot
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	All names should have at least one source and hence source type.

4.4.3 Reference source class

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

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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.

4.4.4 Reference source ID

Many sources such as regulatory submissions, INN lists and others will 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, INN list; PMID (PubMed Identifier).
Conformance	CONDITIONAL
Data Type	ST

4.4.5 Reference source citation

A citation should be captured for a literature reference. The specific format for a given citation may be defined at regional level. In case the Reference source citation is a Web Page or Public Database, the URL should be provided.

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

4.5 Reference source document (Conditional)

4.5.1 Public domain

Most 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

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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.

Table 17 — Public domain

User Guidance	Indication of whether the source is in the public domain.
Example(s)	Yes, No
Conformance	OPTIONAL
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.

4.5.2 Reference source document

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

Table 18 — 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 visualised and searched.

4.5.3 Reference source document type

Table 19 — 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

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4.5.4 Reference source document ID

Table 20 — Reference source document ID

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

4.5.5 Reference source document classification

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.

Table 21 — Reference source document classification

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

4.5.6 Reference source document URL

Table 22 — Reference source document URL

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

4.6 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 recognised 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

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used public codes such as CAS registry numbers with a given substance should be provided and associated to the substance.

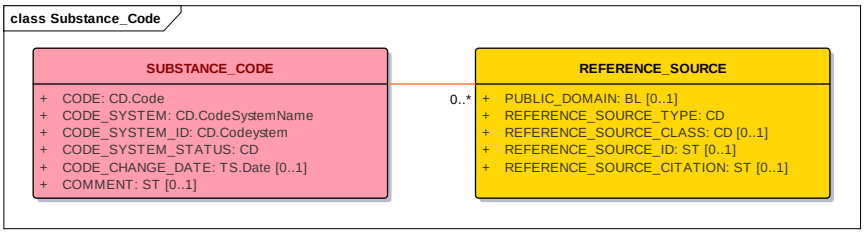


Figure 6 — Information model for substance codes

4.6.1 Code

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.

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 recognised 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.

4.6.2 Code system

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 organisation.

Examples CAS registry numbers, EC numbers, FDA UNII codes, EMA XEVMPD codes, ASK numbers, EPA Pesticide codes.

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Table 24 — Code system

User Guidance	Name of the code system.
Example(s)	CAS, EINECS, NSC, ASK, ATC, NDF-RT; RX-CUI ; INN BQ ; ETC.
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.

4.6.3 Code system ID

The code system ID shall be an OID or an ID as applicable. The ID is associated with code system and need not be submitted.

Table 25 — Code system ID

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

4.6.4 Code system status

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.

Table 26 — Code system status

User Guidance	The status of the code assignment
Example(s)	Current, Alternate, Superseded, Proposed
Conformance	MANDATORY
Data Type	CD
Values Allowed	Current, Alternate, Superseded, Proposed

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4.6.5 Code change date

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

4.6.6 Comment

Table 28 — Comment

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

4.6.7 Reference source

The reference source information should be captured as described in 4.4.

4.7 Reference information (Conditional)

Reference information should be captured for all types of substances and specified Group 1 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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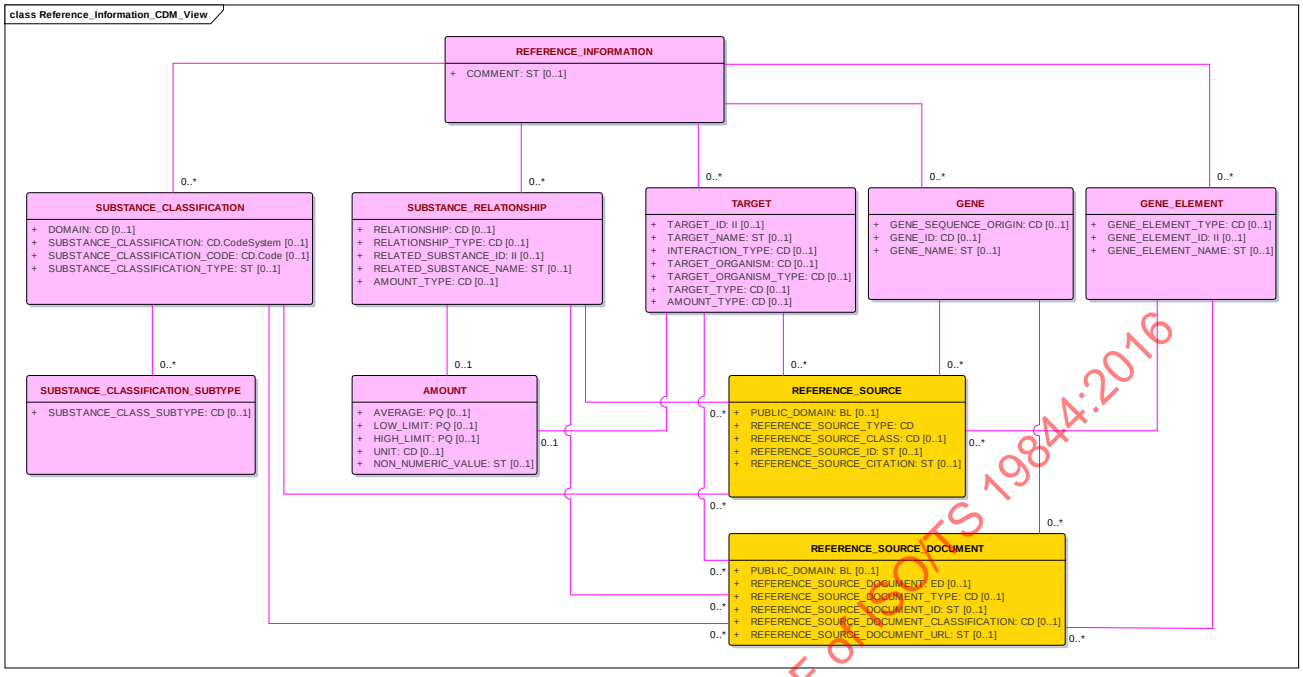


Figure 7 — Information model for Reference Information

4.7.1 Comment

Table 29 — Comment

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

4.7.2 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 shall have the ability to capture multiple classifications and variable levels of classification. Although most classification 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 8:

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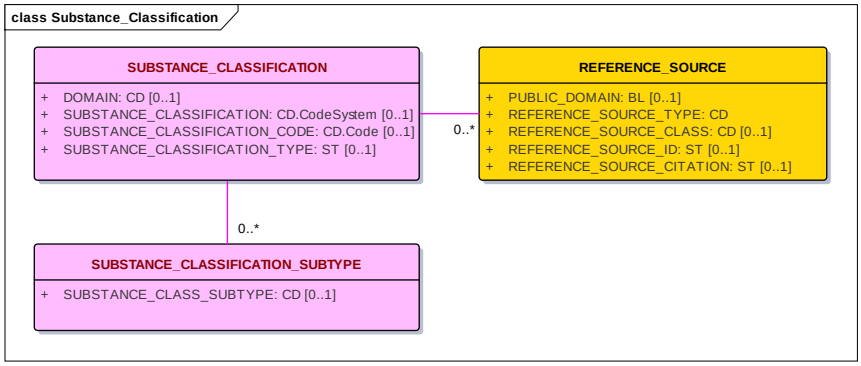


Figure 8 — Information model for substance classification

4.7.2.1 Domain

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 pharmaceuticals, human vaccine, animal drug, animal vaccine, food, food additive, colorant, pesticide; tobacco additive; flavour, excipient
Conformance	OPTIONAL
Data Type	CD

4.7.2.2 Substance classification

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, NCI, AHPA, MESH; Therapeutic Category of Drugs in Japan
Conformance	OPTIONAL
Data Type	CD.CodeSystem

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4.7.2.3 Substance classification code

Classification code with map 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 recognised classification system.

4.7.2.4 Substance classification type

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 initial type or highest level of a classification system.
Example(s)	Organ system 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.

4.7.2.5 Substance classification subtype

Table 34 — Substance classification 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	ST

4.7.2.6 Reference source (Conditional)

The reference source information should be captured as described in 4.4.

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4.7.2.7 Reference source document (Optional)

The reference source document information should be captured as described in 4.5.

4.7.3 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(s)	N/A
Conformance	CONDITIONAL
Data Type	N/A

4.7.3.1 Relationship

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 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 36 — 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, radiolabelled, prodrug, metabolite, enantiomer, starting material, processing material, resultant material
Conformance	CONDITIONAL
Data Type	CD

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4.7.3.1 Relationship type

Table 37 — Relationship type

User Guidance	The Type of interaction between the substances.
Example(s)	IONIC, Van der Waals interaction, Impurity, adjuvant absorption agent, active mooety
Conformance	OPTIONAL
Data Type	CD

4.7.3.2 Related substance ID

Table 38 — 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

4.7.3.3 Related substance name

Table 39 — Related substance name

User Guidance	Preferred term or primary name of related substance.
Conformance	CONDITIONAL
Data Type	CD
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.

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4.7.3.4 Amount type

Table 40 — Amount type

User Guidance	Most elements that require a quantitative value will also have a field called amount type. Amount type should always be specified because the actual value of the amount is often dependent on it. EXAMPLE: In capturing the actual relative amounts of substances or molecular fragments it is essential to indicate whether the amount refers to a mole ratio or weight ratio. For any given element an effort should be made to use same the amount type for all related definitional elements.
Example(s)	Mole per cent; Weight per cent; Mole ratio; Weight ratio, Weight, Moles, Exact, Non-Numeric value, SRU/Polymer Ratio, Monomer/Polymer Ratio
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	SRU/Polymer Ratio and Monomer/Polymer Ratio are applicable to polymers.

4.7.3.5 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 shall be captured according to 4.9.

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

4.7.3.6 Reference source (Optional)

The reference source information should be captured as described in 4.4.

4.7.3.7 Reference source document (Optional)

The reference source document information should be captured as described in 4.5.

4.7.4 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. GENE, 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.

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4.7.4.1 Target ID

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.

4.7.4.2 Target name

At least one name of the target shall be provided when target information is submitted. Target names will typically be handled no 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. Gene bank and Uniprot codes can be particularly useful for identifying and tracking targets. The ISO 11238 standard will be updated to rename Target Gene Name element as Target Name.

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.

4.7.4.3 Interaction type

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 will 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

4.7.4.4 Target organism

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 etc.
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	At least one organism type should be associated.

4.7.4.5 Target organism type

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.

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4.7.4.6 Target type

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

4.7.4.7 Amount type (Conditional)

Amount type should be captured as described in 4.7.3.4.

4.7.4.8 Amount (Conditional)

Amount should be captured as described in 4.9.

4.7.4.9 Reference source (Optional)

The reference source information should be captured as described in 4.4.

4.7.4.10 Reference source document (Optional)

The reference source document information should be captured as described in 4.5.

4.7.5 Gene (Conditional)

The gene subclause will 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.

4.7.5.1 Gene sequence origin

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

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EXAMPLES For monoclonal antibodies the typical values can be HUMAN, HUMANISED MOUSE; HUMANISED RAT; CHIMERIC MOUSE-HUMAN; CHIMERIC RAT-HUMAN.

Table 47 — Gene sequence origin

User Guidance	Common name for the organism from which the final gene sequence originated.
Example(s)	Human, Bovine, Human; Humanised; Mouse-Human Chimeric; Mouse
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	Typically, from the NCBI Gene database.
Business Rule(s)	NOTE it applies primarily to proteins.

4.7.5.2 Gene ID

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.

4.7.5.3 Gene name

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.

4.7.5.4 Reference source (Conditional)

The reference source information should be captured as described in 4.4.

4.7.5.5 Reference source document (Conditional)

The reference source document information should be captured as described in 4.5.

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4.7.6 Gene element (Conditional)

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

4.7.6.1 Gene element type

Table 50 — Gene element type

User Guidance	Type of the gene element. Should be captured for all genes that are transduced into cells and are intended to be expressed.
Example(s)	enhancer, promoter, silencer, terminator, repressor
Conformance	CONDITIONAL
Data Type	CD

4.7.6.2 Gene element ID

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.

4.7.6.3 Gene element name

Table 52 — Gene element name

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

4.7.6.4 Reference source (Conditional)

The reference source and related information will be captured according to 4.4. One or more reference sources could be cited.

4.7.6.5 Reference source document (Conditional)

The reference source document information should be captured as described in 4.5.

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4.8 Structure

4.8.1 Structural Representation (Conditional)

Structural information is an essential element for all chemical substances 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 standardised 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 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

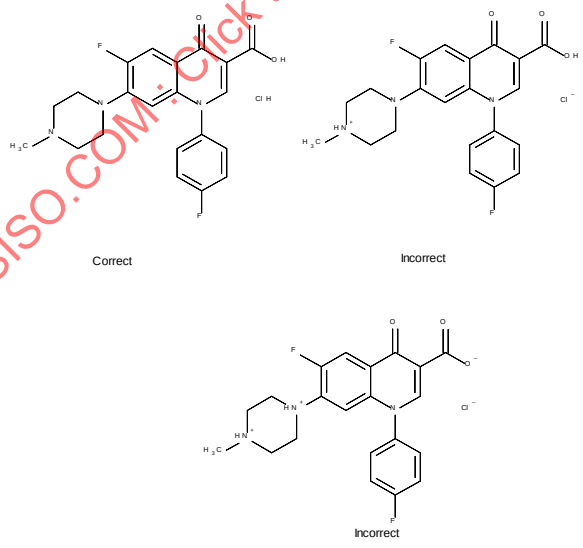


Figure 9 — Correct and incorrect graphical images of the molecular structure of difloxacin hydrochloride

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Metal and ammonium salts: All metal and ammonium salts (NH4+) shall be represented in a charged configuration with all equivalent functional groups ionised. Charge balance will be achieved when necessary by adding hydrogen ions (protons).

EXAMPLE: MONOSODIUM CITRATE

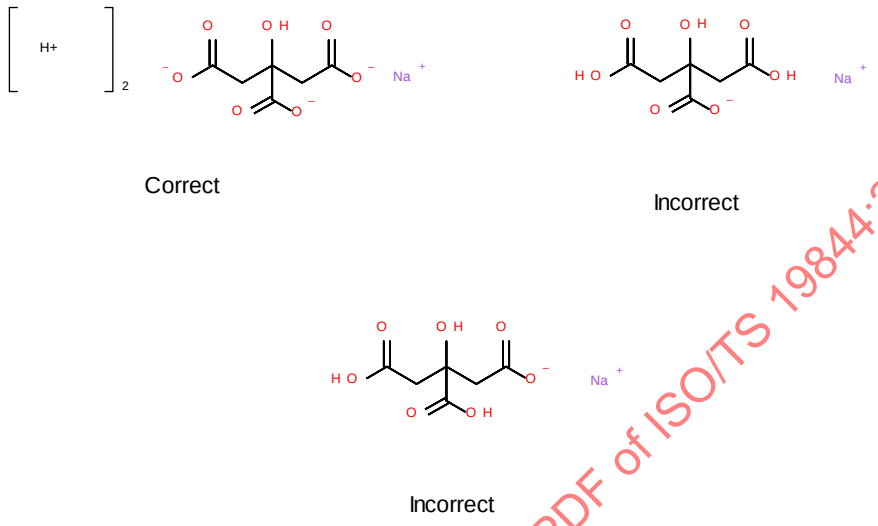


Figure 10 — Correct and incorrect graphical images of the molecular structure of monosodium citrate

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.

EXAMPLE: OFLOXACIN

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

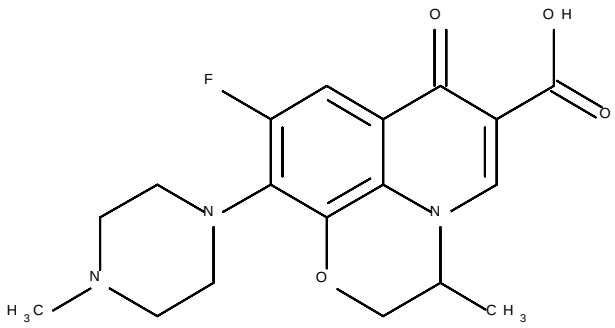


Figure 11 — Graphical image of the molecular structure of difloxacin hydrochloride

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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.

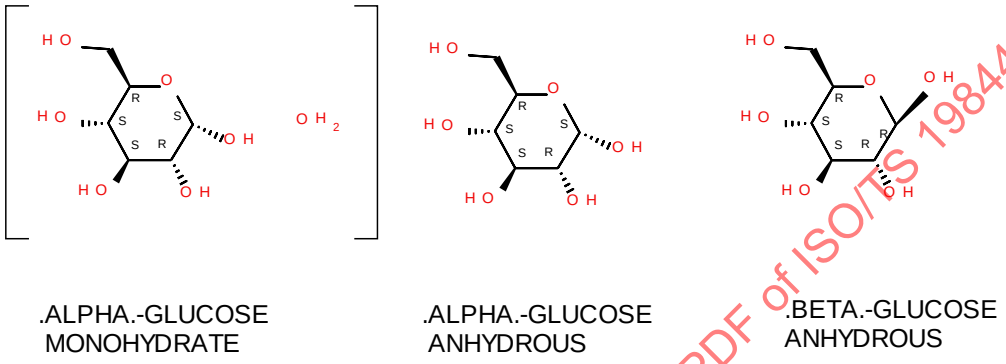


Figure 12 — Graphical images of the molecular structure of the three crystalline states of dextrose

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 13 the pyranose and furanose structures have one site of stereochemical ambiguity.

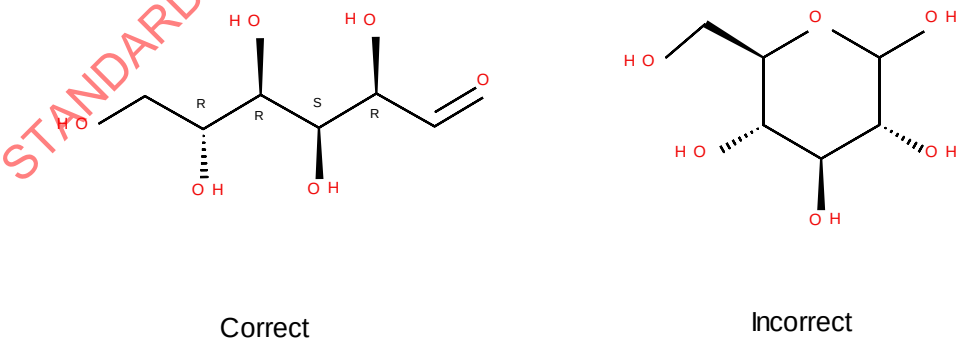


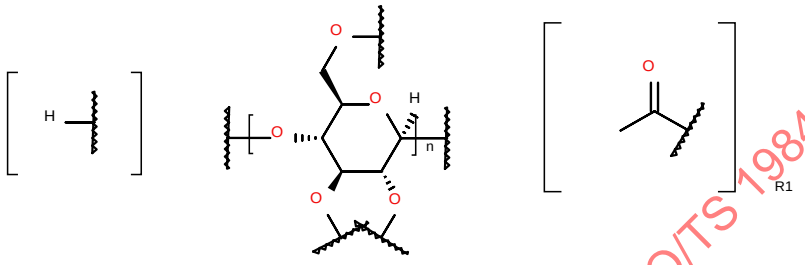
Figure 13 — Correct and incorrect graphical images of the molecular structure of (liquid) dextrose

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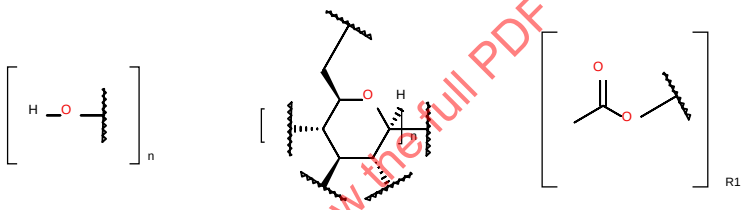
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Structural representations will also be used to represent fragments of molecules. Fragments will be used in describing partially modified polymers and are typically generated to describe partially acylated polymers, proteins or even nucleic acids.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

EXAMPLE: Cellulose Acetate



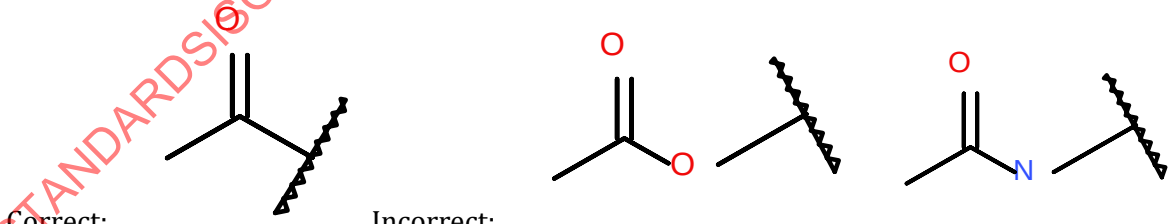
Correct



Incorrect

Figure 14 — Correct and incorrect graphical images of the molecular structure of cellulose acetate

The acetyl fragment is represented in Figure 15.



Correct: Incorrect:

Figure 15 — 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

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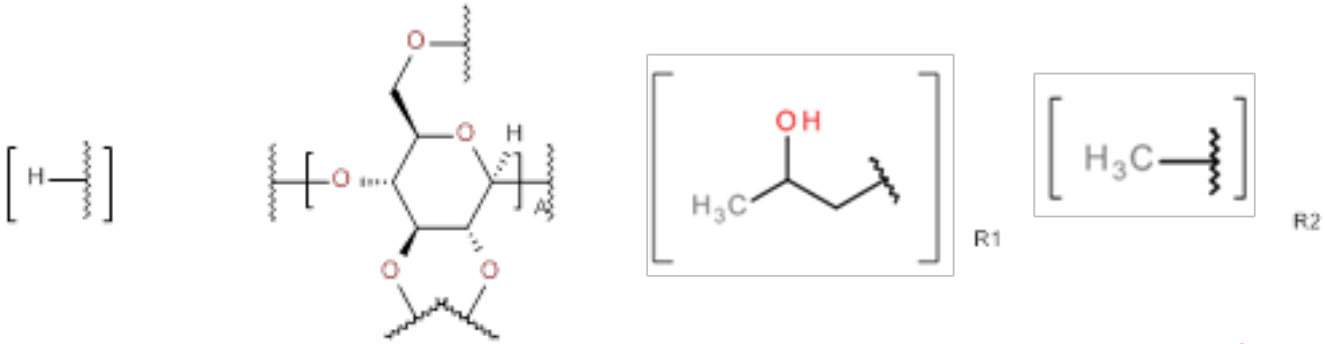


Figure 16 — Graphical images of the molecular structure of hypromelloses

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

In the Class Structure the Element Group 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.

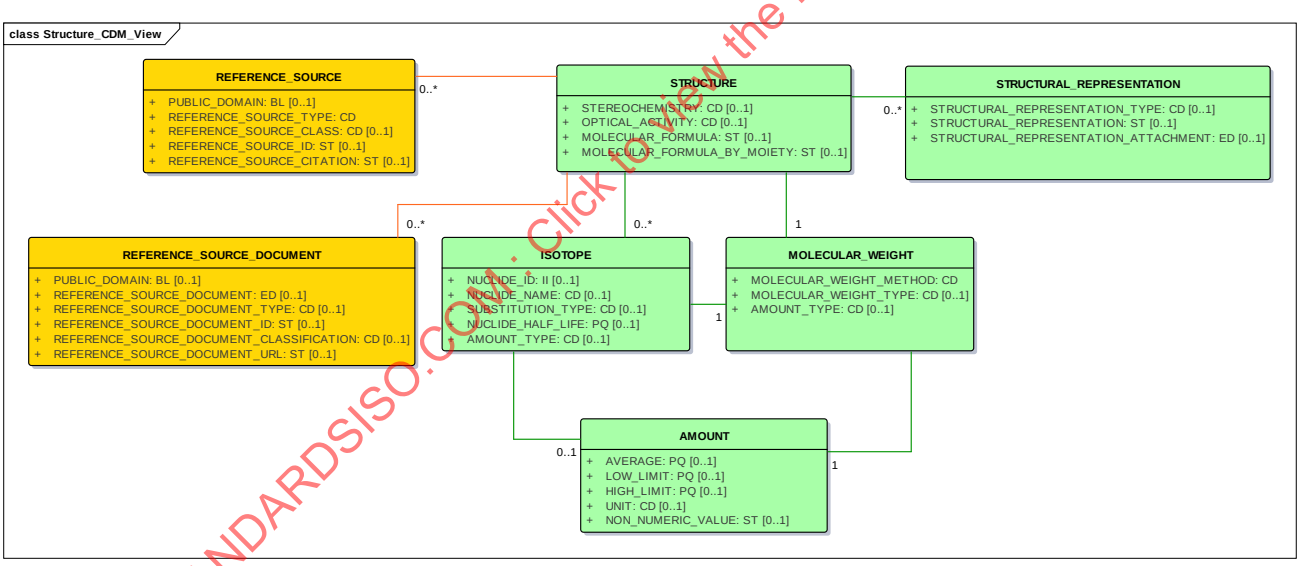


Figure 17 — Information model for structure and isotope

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

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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 4.2.1, is either chemical or polymer this class becomes MANDATORY and the following data elements should be described:

4.8.1.1 Structural representation type

Table 53 — 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
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	A structure can only be of one type. Field is mandatory when structural elements are present. When the Substance type, as defined in 4.2.1 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	application/x-InChI
MOLFILE	application/x-mdl-molfile
SMILES	application/x-smiles
CHIME	application/x-mdl-chime

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4.8.1.2 Structural representation

Table 54 — Structural representation

User Guidance	The structural representation shall be provided as text string, the following formats are acceptable: InChI, SMILES, MOLFILE, CDX.
Example(s)	InChI, MOLFILE, SMILES, CDX
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 4.2.1 is either chemical or polymer, this element becomes MANDATORY. The preferred representation type is MOLFILE v 2000.

4.8.1.3 Structural representation attachment

Table 55 — 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

4.8.2 Stereochemistry

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

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Table 56 — Stereochemistry

User Guidance	The stereochemistry of the substance shall 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)	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	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 4.2.1 is either chemical, protein, polymer or nucleic acid, this class becomes MANDATORY

4.8.3 Optical activity

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 57 — Optical activity

User Guidance	The optical activity shall be described based on a controlled vocabulary.
Example(s)	(+/-), (+), (-)
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	(+/-), (+), (-)
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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4.8.4 Molecular Formula

Table 58 — Molecular formula

User Guidance	Molecular formula is written as a sequence of pairs of atom symbol and stoichiometric number without any text formatting or special characters. This formal notation is essentially a code system. Specified according to the Hill system, i.e. first C, then H, then alphabetical.
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

4.8.5 Molecular Formula by Moiety

Table 59 — 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.
Example(s)	$C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S \,.H_2O$
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	Can be implicitly derived from the structure; Validity check for identity and structural representation

4.8.6 Molecular weight (Mandatory)

This information shall be captured as described in 5.2.7.

4.8.7 Isotope (Conditional)

Applicable for single substances that contain a radionuclide or a non-natural isotopic ratio, e.g. C-13 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.

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4.8.7.1 Nuclide ID

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.

4.8.7.2 Nuclide name

Table 61 — Nuclide name

User Guidance	The name for each isotope shall 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.

4.8.7.3 Substitution type

Applicable for single substances that contain a radionuclide or a non-natural isotopic ratio, e.g. C-13 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.

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4.8.7.4 Nuclide Half Life

Table 63 — Nuclide Half Life

User Guidance	The half life of a non natural nuclide.
Example(s)	109.77 min (18F)
Conformance	OPTIONAL
Data Type	PQ
Business Rule(s)	This field can be calculated from the Isotopes table.

4.8.7.5 Amount type (Optional)

Amount type should be captured as described in 4.7.3.4.

4.8.7.6 Amount (Optional)

Amount shall be captured as described in 4.9.

4.8.7.7 Molecular weight (Mandatory)

This information shall be captured as described in 5.2.7.

4.9 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. This amount subclause will be used throughout the standard for any properties or elements where quantitative, semi- quantitative or qualitative values apply. An amount type will usually be associated with each amount and the same amount type will typically apply to all of the quantitative values in a given subclause (i.e. for multiple fragment substitution either mole per cent, weight per cent or degree of substitution should be applied to each fragment they should not be mixed).

4.9.1 Average

Table 64 — Average

User Guidance	Used to capture quantitative values for a variety of elements. If only limits are given, the arithmetic mean would be the average. If only a single definite value for a given element is given, it would be captured in this field.
Example(s)	Average, Exact, Numeric Value
Conformance	CONDITIONAL
Data Type	PQ
Values Allowed	Single quantitative values or an average value for a given element.
Business Rule(s)	

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4.9.2 Low limit

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. Both these limits can be captured and type of lower limit should be indicated either in the amount type for a given element or in the units indicated for the amount. The low limit can be used alone to express one-sided ranges greater than or equal to this limit.

Table 65 — Low limit

User Guidance	Lower limit for a given quantitative value.
Conformance	CONDITIONAL
Data Type	PQ
Business Rule(s)	To be used to express the lower limit of a range of values, if applicable

4.9.3 High limit

Similar to the low limit, the high limit should indicate whether the value refers to a range of values or a range of averages. The high limit can also be used to express one-sided limits.

Table 66 — High limit

User Guidance	Higher limit for a given quantitative value.
Conformance	CONDITIONAL
Data Type	PQ
Business Rule(s)	To be used to express the higher limit of a range of values

4.9.4 Unit

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 organisation should maintain them. Units may be dependent on the method of measurement or calculation to determine the property.

EXAMPLE The hydrophobic-lipophilic balance can be a defining property for amphiphilic polymers particularly when the exact ratio of monomers or structural repeat units is not provided. There are at least two methods of calculation for this property and the method may be indicated in the unit (i.e. Davies Method; Griffin's Method).

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Table 67 — Unit

User Guidance	The unit of measure
Example(s)	1, g, mg, mol, mmol, L, [IU], mg/L, mol/L, g/mol, [IU]/g
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	UCUM/ISO 11240 units
Business Rule(s)	The Unit is mandatory for amount expressed as numeric value. When used with limits, both limits shall have the same dimension (and usually will have the same unit.)

4.9.5 Non-numeric Value

Table 68 — Non-numeric value

User Guidance	Qualitative, coded property value. To be used to capture qualitative values.
Example(s)	Positive, negative, Yes, No, complete, partial
Conformance	CONDITIONAL
Data Type	ST

4.9.6 Reference Source (Conditional)

The reference source information should be captured as described in 4.4.

4.9.7 Reference source document (Conditional)

The reference source document information should be captured as described in 4.5.

4.10 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 polymer substances isolated from biological matrices. Taxonomic and anatomical origins shall be described using a controlled vocabulary as required. This information is captured for naturally derived 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 infraspecies, 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.

The information model for the source material is shown in Figure 18.

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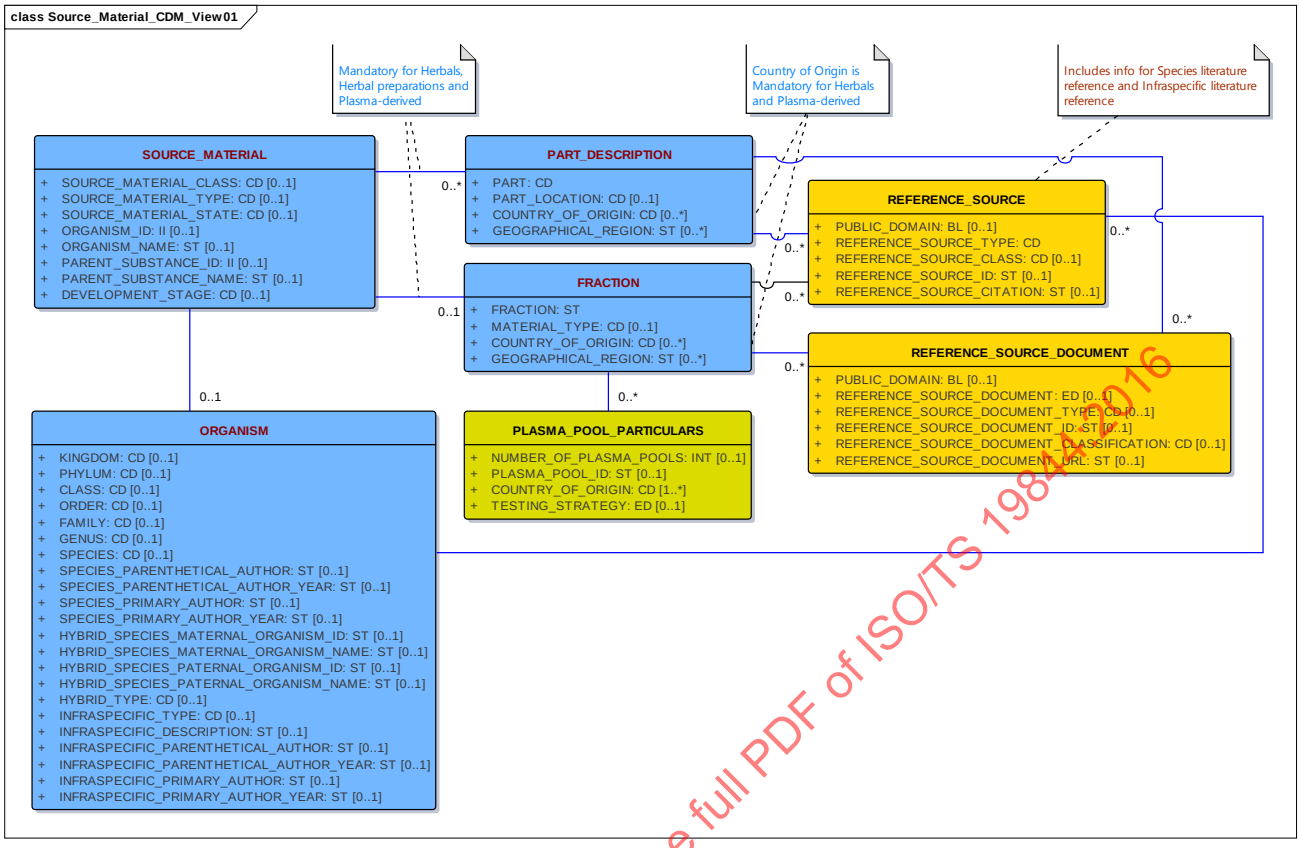


Figure 18 — Information model for source material

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

4.10.1 Source material class

Table 69 — 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
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	For Herbals this class shall be Mandatory

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4.10.2 Source material type

Table 70 — 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)	bacterium, human, mammal, fungus, virus, plant, animal
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.

4.10.3 Source material state

Table 71 — Source material state

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

4.10.4 Organism ID

Table 72 — Organism ID

User Guidance	The unique identifier associated with the source material parent organism shall be specified.
Conformance	CONDITIONAL
Data Type	II
Business Rule(s)	For Herbals this element shall be Mandatory.

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4.10.5 Organism name

Table 73 — Organism name

User Guidance	The organism accepted Scientific name shall 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's Medicinal Plant Names Services (MPNS). The names for other organisms will be provided by other authoritative sources.

4.10.6 Parent substance ID

Table 74 — Parent substance ID

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

4.10.7 Parent substance name

Table 75 — 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., Leaf
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	For Herbal Drugs or Herbal preparations this element shall be Mandatory.

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4.10.8 Development stage

Table 76 — Development stage

User Guidance	Stage of life for animals, plants, insects and microorganisms. This information shall 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, etc.
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	If it is a distinguishing factor, even if it is implicitly understood by experts.

4.10.9 Part Description (CONDITIONAL)

Information of the part of the material used to produce the substance shall always be provided by means of the following data elements:

4.10.9.1 Part

Table 77 — 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
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	For Herbals this element shall be Mandatory. 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's Medicinal Plant Names Services.

4.10.9.2 Part location

Table 78 — Part location

User Guidance	The detailed anatomic location when the part can be extracted from different anatomical locations of the organism. Multiple alternative locations may apply.
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.

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4.10.9.3 Country of origin

Table 79 — Country of Origin

User Guidance	The country where the plant material is harvested or the countries of which the plasma is collected and with reference to the tests. For "Plasma-derived substances" the attribute country of origin in the Part class will include the countries sourced for the manufacturing of the cryopoor plasma or cryoprecipitate as mentioned in the plasma master file document.
Example(s)	NL, DE, FR, ES, US, CN. 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, Homeopathic, 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.

4.10.9.4 Geographical region

Table 80 — Geographical region

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

4.10.9.5 Reference Source (Conditional)

The reference source information should be captured as described in 4.4.

4.10.9.6 Reference source document (Conditional)

The reference source document information should be captured as described in 4.5.

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4.10.10 Fraction (Conditional)

Table 81 — Fraction

User Guidance	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. At the Substance level, the additional class "Blood Plasma Pool Particulars" (see 4.10.10.7) is linked to the fraction. This class is used to capture information on the cryoprecipitate or the cryopoor plasma pool. Additional classes linked to the fraction at the Specified Substance Group 1 level are described in the relevant annexes of this document. In particular: For Herbal Specified Substance Group 1, the "Herbal preparation Property Particulars" is used to capture additional information for Herbal preparation extraction solvents and Herbal substance/Herbal preparation Mass Ratio. For Plasma-derived Specified Substance Group 1, the "Blood Plasma-derived Fraction Particulars" is used to capture the specific information of the country of plasma origin, testing and safety information.
Conformance	CONDITIONAL
Business Rule(s)	When the Name Type is Herbal, Homeopathic or Plasma-derived this class is mandatory at the Substance level. When the Name_type is Herbal or Plasma-derived this class is conditional at the Substance Group 1 information level based on jurisdictional legislation.

4.10.10.1 Fraction

Table 82 — 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
Conformance	MANDATORY
Data Type	ST

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4.10.10.2 Material type

Table 83 — Material type

User Guidance	The specific type of the material constituting the component. For Herbal preparations the particulars of the extracts (liquid/dry) is described in Specified Substance Group 1.
Example(s)	Lipid, Phospholipid, Protein, Nucleic acid, Herbal, Liquid/ Dry Herbal extract, Herbal part
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	

4.10.10.3 Country of Origin

Table 84 — Country of origin

User Guidance	For a Herbal substance, the country where the plant material is harvested. This information is not necessary when, in case of the Herbal substance, the information is already captured in the element class Part description.'. For "Plasma-derived substances" the attribute country of origin in the Fraction class will include the countries sourced for the manufacturing of the cryopoor plasma (Minipool) or cryoprecipitate (Minipool) as mentioned by the testing organisations.
Example(s)	NL, DE, FR, CN
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	This attribute is mandatory when the Substance Name Type is Herbal, Homeopathic, Plasma-derived. NOTE: Note that we only capture the countries of origin at the 'Part" which are mentioned in the Plasma Master file; not those who are sourced for the manufacture of the Minipool.

4.10.10.4 Geographical region

Table 85 — Geographical region

User Guidance	For a Herbal substance, the place/region where the plant material is harvested.
Example(s)	Shaanxi Province China
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	This element is not applicable for Blood plasma-derived.

4.10.10.5 Reference Source (Conditional)

The reference source information should be captured as described in 4.4.

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4.10.10.6 Reference source document (Conditional)

The reference source document information should be captured as described in 4.5.

4.10.10.7 Blood plasma pool particulars (Conditional)

This class should be used to capture information on the cryoprecipitate or the cryopoor plasma pool. The class is mandatory if the 'SUBSTANCE NAME TYPE' is plasma-derived.

4.10.10.7.1 Number of plasma pools

Table 86 — Number of plasma pools

User Guidance	The number of plasma pools of the Minipool for cryopoor plasma or cryoprecipitate.
Example(s)	3
Conformance	CONDITIONAL
Data Type	INT
Business Rule(s)	The element is mandatory if the value of the element SUBSTANCE NAME TYPE is plasma-derived.

4.10.10.7.2 Plasma pool ID

Table 87 — Plasma pool ID

User Guidance	The plasma pool ID.
Example(s)	PLASM9876P
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	The element is mandatory if the the value of the element SUBSTANCE NAME TYPE is plasma-derived.

4.10.10.7.3 Country of origin

Table 88 — Country of origin

User Guidance	The Country of Origin is directly coupled to the plasma pool and the manufacturer.
Example(s)	NL, DE, FR
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	

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4.10.10.7.4 Testing strategy

Table 89 — Testing strategy

User Guidance	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.
Example(s)	
Conformance	CONDITIONAL
Data Type	ED
Business Rule(s)	

4.10.11 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 infraspecies), 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 (see E.1.2 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 infraspecifics 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. Infraspecific 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,

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part and viral strain characteristics should be associated with separate identifiers that refer back to the whole organism parent substance.

4.10.11.1 Kingdom

Table 90 — Kingdom

User Guidance	The kingdom of an organism shall 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.

4.10.11.2 Phylum

Table 91 — Phylum

User Guidance	The phylum of an organism shall 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.

4.10.11.3 Class

Table 92 — Class

User Guidance	The class of an organism shall 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.

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4.10.11.4 Order

Table 93 — Order

User Guidance	The order of an organism shall 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.

4.10.11.5 Family

Table 94 — Family

User Guidance	The family of an organism shall 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's Medicinal Plant Names Services for plants. Catalogue of Life typically captures complete taxonomy in a manner consistent with this standard.

4.10.11.6 Genus

Table 95 — Genus

User Guidance	The genus of an organism shall 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 infraspecies.
Example(s)	*Ginkgo; Harpagophytum*
Conformance	CONDITIONAL
Data Type	CD

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4.10.11.7 Species

Table 96 — Species

User Guidance	The species of an organism shall be specified; refers to the Latin epithet of the species of the plant/animal; it is present in names for species and infraspecies.
Example(s)	*Bbiloba; 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, or Kew's Medicinal Plant Names Services for plants NCBI Taxonomy ID).

4.10.11.8 Species parenthetical author

The species parenthetical author should be captured as reported. For herbal substances the author will be captured according to the MPNS of Kew Gardens.

Table 97 — Species parenthetical author

User Guidance	The parenthetical author of an organism species shall be specified; refers to the first author who published the plant/animal name (of any rank).
Example(s)	L.
Conformance	CONDITIONAL
Data Type	ST

4.10.11.9 Species parenthetical author year

Table 98 — Species parenthetical author year

User Guidance	The parenthetical author year of an organism species an organism shall be specified; refers to the year in which the first author published the plant/animal name (of any rank).
Example(s)	2010, 2011
Conformance	OPTIONAL
Data Type	ST

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4.10.11.10 Species primary author

Table 99 — Species primary author

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

4.10.11.11 Species primary author year

Table 100 — Species primary author year

User Guidance	The primary author year of an organism species shall be specified; refers to the year in which the first author(s) published the plant/animal name.
Example(s)	2010
Conformance	OPTIONAL
Data Type	ST

4.10.11.12 Hybrid species maternal organism ID

Table 101 — Hybrid species maternal organism ID

User Guidance	The identifier of the maternal species constituting the hybrid organism shall 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

4.10.11.13 Hybrid species paternal organism ID

Table 102 — Hybrid species paternal organism ID

User Guidance	The identifier of the paternal species constituting the hybrid organism shall be specified based on a controlled vocabulary.
Conformance	OPTIONAL
Data Type	ST

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4.10.11.14 Hybrid type

Table 103 — Hybrid type

User Guidance	The hybrid type of an organism shall be specified.
Example(s)	HYBRID UNKNOWN LINEAGE, HYBRID KNOWN LINEAGE
Conformance	OPTIONAL
Data Type	CD
Business Rule(s)	If the hybridisation step is present, the type of hybridization should be provided.

4.10.11.15 Infraspecific type

Table 104 — Infraspecific type

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

4.10.11.16 Infraspecific description

Infraspecific information will be used to describe strains, serotypes, varieties, cultivars and cell lines. Often there is not a naming or taxonomic authority for this information. Standardised formats for this information may be developed. The actual infraspecific information should also be captured in the naming of these substances and synonyms should be maintained to help to identify infraspecific information and avoid duplication. For plants, the infraspecific 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 105 — Infraspecific description

User Guidance	The infraspecific description of an organism shall be specified based on a controlled vocabulary. For Influenza Vaccine, the infraspecific 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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4.10.11.17 Infraspecific parenthetical author

Table 106 — Infraspecific parenthetical author

User Guidance	The infraspecific parenthetical author of an organism shall be specified; refers to the first author(s) who published the infraspecific plant/animal name at any rank.
Conformance	OPTIONAL
Data Type	ST

4.10.11.18 Infraspecific parenthetical author year

Table 107 — Infraspecific parenthetical author year

User Guidance	The infraspecific parenthetical author year of an organism shall be specified; refers to the year in which the first author published the infraspecific plant/animal name (of any rank).
Example(s)	2011
Conformance	OPTIONAL
Data Type	ST

4.10.11.19 Infraspecific primary author

Table 108 — Infraspecific primary author

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

4.10.11.20 Infraspecific primary author year

Table 109 — Infraspecific primary author year

User Guidance	The infraspecific primary author year of an organism shall be specified; refers to the year in which the first author published the infraspecific plant/animal name (of any infraspecific rank).
Example(s)	2009
Conformance	OPTIONAL
Data Type	ST

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4.10.11.21 Reference Source (Conditional)

The reference source information should be captured as described in 4.4. Species literature reference and Infraspecific literature reference should be captured by this class.

NOTE Species are described by original articles and the taxonomy may vary over time so the reference to the original article is critical. A reference to an article should be complete and not just use author name abbreviations.

4.11 Modification (Conditional)

The Modification subclause is to be used to describe irreversible modifications to material (e.g. PEGylation, phosphorylation, hydrogenation). 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).

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 19.

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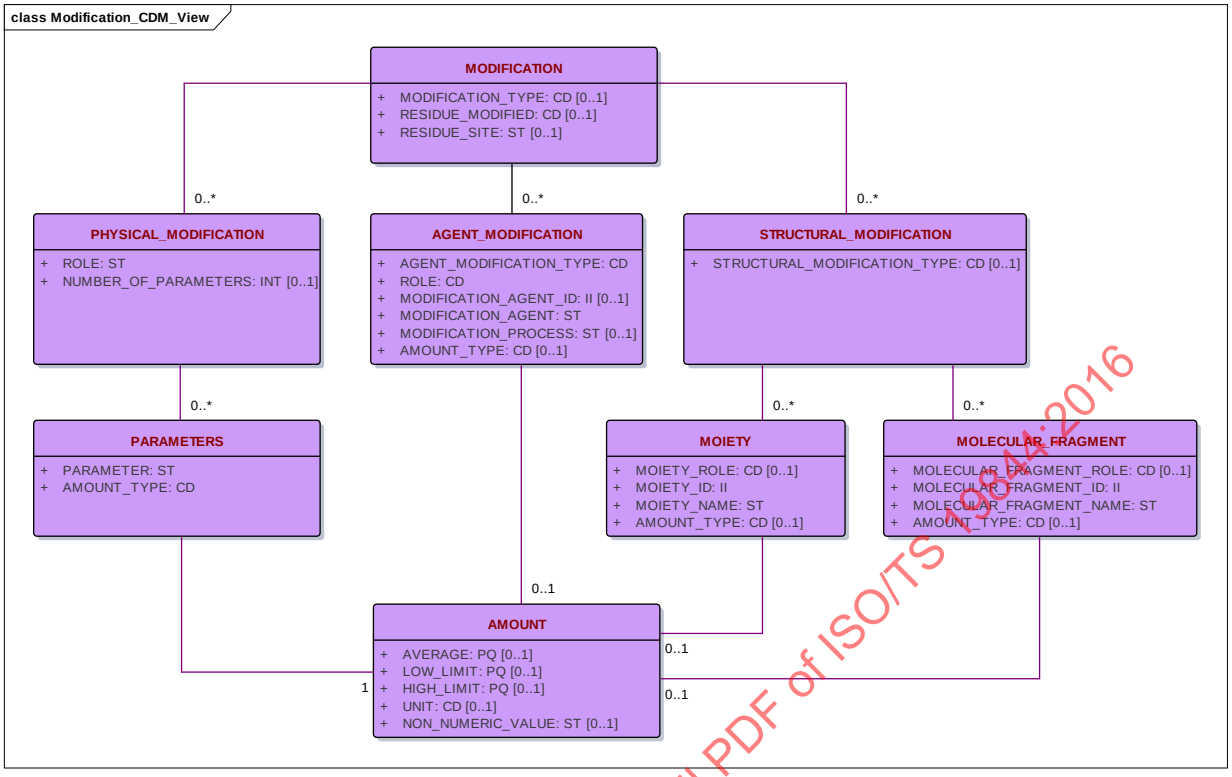


Figure 19 — Information model for modifications

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 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:

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4.11.1 Modification type

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 110 — 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 modifications, agent modifications, moiety, 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.

4.11.2 Residue modified

Table 111 — 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.
Example(s)	Lysine
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.

4.11.3 Residue sites

Table 112 — Residue sites

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.

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4.11.4 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 of 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. The microheterogeneity of proteins can be captured at the Specified Substance Group 1 the level and 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 4.11.1 refers to a structural modification, then the following specifications apply:

4.11.4.1 Structural modification type

Table 113 — 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
Conformance	CONDITIONAL
Data Type	CD

4.11.4.2 Moiety

For structural modifications, the moiety shall be provided based on the specifications provided in 5.1.5.2.

4.11.4.2.1 Amount type

Amount type should be captured as described in 4.7.3.4.

4.11.4.2.2 Amount

Amount shall be captured as described in 4.9.

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4.11.4.3 Molecular fragment

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.

4.11.4.3.1 Molecular fragment role (CONDITIONAL)

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

Table 114 — Molecular fragment role

User Guidance	The role of the fragment.
Example(s)	N-Terminal Pyroglu Formation
Conformance	CONDITIONAL
Data Type	CD

4.11.4.3.2 Molecular fragment ID

Each fragment will be identified with a Substance ID if available. If not available a new ID will be assigned with the submission.

Table 115 — 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

4.11.4.3.3 Molecular fragment name

Each fragment will also have at least one name associated with the fragment.

Table 116 — Molecular fragment 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 5.1.5.2.2.

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4.11.4.3.4 Amount type

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. The Amount type should be captured as described in 4.7.3.4.

4.11.4.3.5 Amount

Amount shall be captured as described in 4.9.

4.11.5 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.

4.11.5.1 Agent modification type

Table 117 — Agent modification type

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

4.11.5.2 Role

Table 118 — 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).
Example(s)	antigen, linker, conjugate, inactivation, antigen priming
Conformance	MANDATORY
Data Type	CD

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4.11.5.3 Modification agent

Table 119 — Modification agent

User Guidance	Established or primary name of the modifying agent.
Example(s)	Formaldehyde
Conformance	MANDATORY
Data Type	ST
Values Allowed	ISO 11238 substance name
Business Rule(s)	Implicitly derived from the value of the Modification Agent ID.

4.11.5.4 Modification agent ID

Table 120 — Modification agent ID

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

4.11.5.5 Modification process

Table 121 — Modification process

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

4.11.5.6 Amount type

Amount type should be captured as described in 4.7.3.4.

4.11.5.7 Amount

Amount shall be captured as specified in Subclause 4.9**.**

4.11.6 Physical Modification (Conditional)

The physical modification is optional; when applicable the information shall be provided by means of the following descriptors:

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4.11.6.1 Role

Table 122 — Role

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

4.11.6.2 Number of parameters

Table 123 — Number of parameters

User Guidance	The number of parameters that is going to be described as a result of the modification shall 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.

4.11.6.3 Parameters (Conditional)

Primarily used for nonspecific modification, specifies how a modification is quantified or extent of physical treatment.

4.11.6.3.1 Parameter

Table 124 — Parameter

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

4.11.6.3.2 Amount type (Mandatory)

Amount type shall be captured as described in 4.7.3.4.

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4.11.6.3.3 Amount (Mandatory)

Amount shall be captured as described in 4.9.

4.12 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; viscosity is used to distinguish many polymers and should always be reported if known. 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.

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

Property information is typically used for distinguishing Substances or Specified Substances Group 1 from one another. It is possible however that a request for specific general property information that may be independent of defining information may be requested. Some of this information may be used to determine if two Substances or Specified Substances are the same.

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

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

4.12.1 Property type

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

Table 125 — 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.

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4.12.2 Property name

Table 126 — Property name

User Guidance	The name of the property shall be specified based on a controlled vocabulary.
Example(s)	VISCOSITY, PH, CELL SURFACE ANTIGEN, SPECTRA, pK_a, UV absorption maxima
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	A fully defined coded concept shall always be provided.

4.12.3 Property parameters

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

Table 127 — 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 -10.5
Conformance	CONDITIONAL
Data Type	ST

4.12.4 Substance ID

Table 128 — 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

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4.12.5 Substance name

Table 129 — 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	CD
Values Allowed	ISO 11238 substance name
Business Rule(s)	The preferred term will be the default value implicitly derived from the Substance ID (4.3.2).

4.12.6 Amount type (Mandatory)

Amount type should be captured as described in 4.7.3.4.

4.12.6.1 Amount (Mandatory)

The information related to the amount shall be provided as per specification described in 4.9. The non-numeric value in the case of spectra would be the actual spectra or a reference to the document containing the actual spectra.

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

4.13.1 Version number

Table 130 — 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.

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4.13.2 Effective date

Table 131 — 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.

4.13.3 Change made

Table 132 — 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

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5 Substance definitions

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

If the substance type as defined in 4.2.1 is equal to Chemical substance, the following data elements and conformances apply.

5.1 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) 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.

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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 counterions or solvates 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 non-proprietary 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.

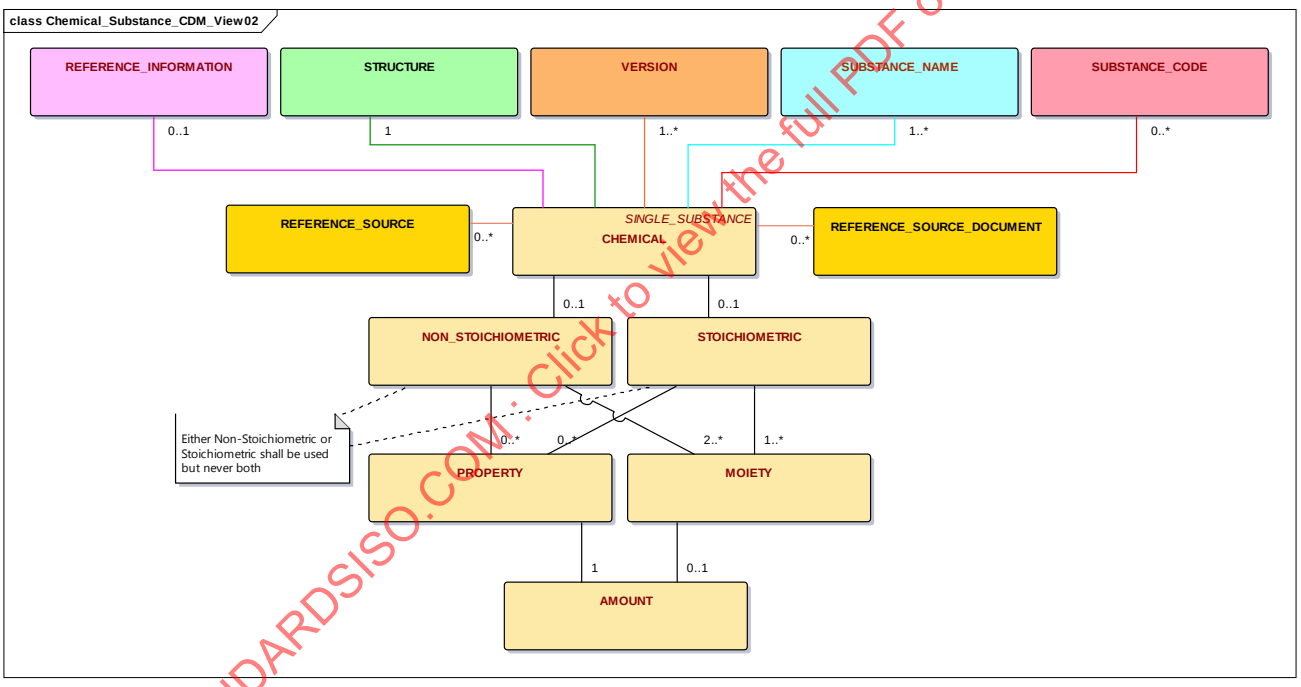


Figure 20 — Information model for the chemical substance

5.1.1 Comment

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.

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Table 133 — Comment

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

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 is also captured. 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.

The Element Group Moiety is connected with the stoichiometric chemical substance.

5.1.2 Structure

The information related to the structure shall be provided as per specification described in 4.8.

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 (mol, 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.

5.1.3 Stoichiometric/Non-stoichiometric chemicals

Stoichiometric chemical substances are substances that contain complete chemical structures and definite stoichiometric ratios among moieties (see 5.1.4 for details). Non-stoichiometric chemical substances are substances that do not have defined stoichiometry (see 5.1.5 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 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.

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Depending on the chemical substance information, either the Stoichiometric Subclause or the Non-stoichiometric subclauses should be described.

5.1.4 Stoichiometric chemicals

As decribed 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)

Mol representation STRUCTURAL REPRESENTATION TYPE: "MOL"

STRUCTURAL REPRESENTATION:

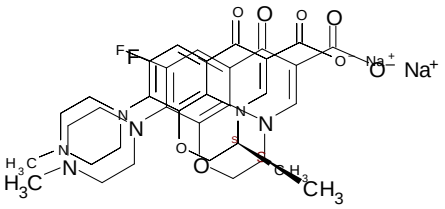
```
  3  2  0  0  0  0  0  0  0  0999 V2000
    3.9063   -7.3125    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
    4.6223   -6.8991    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
    5.3383   -7.3125    0.0000 O   0  0  0  0  0  0  0  0  0  0  0  0
  1  2  1  0  0  0  0
  2  3  1  0  0  0  0
M 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

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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]1COc2c3n1cc(c(=O)c3cc(c2N4CCN(CC4)C)F)C(=O)[O-].[Na+]”

STEREOCHEMISTRY: “CHIRAL”

Mol Representation STRUCTURAL REPRESENTATION TYPE: “MOL”

STRUCTURAL REPRESENTATION:

```
 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
```

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```
  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”

5.1.4.1 Number of moieties (Conditional)

This information should be captured as described in the 5.1.5.1.

5.1.4.2 Moiety (Mandatory)

This information should be captured as described in the 5.1.5.2. If the numeric value of the “number of moieties” is equal to 1, the Moiety class is not used.

5.1.4.2.1 Amount (Conditional)

Amount shall be captured as described in 4.9.

5.1.4.3 Property (Conditional)

Property shall be captured as specified in 4.12.

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5.1.4.3.1 Amount (Mandatory)

Amount shall be captured as described in 4.9.

5.1.5 Non-stoichiometric chemicals (Conditional)

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.

5.1.5.1 Number of moieties

Table 134 — Number of moieties

User Guidance	The number of moieties specified shall 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 Moiety classes as described in 5.1.5.2). If the numeric value is equal to 1, the moiety class shall not be used.

5.1.5.2 Moiety (Mandatory)

The moiety subclause serves for the description of both the moiety and the other fragment constituting the substance. 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:

The Element Group Moiety should be attached also to the element class Chemical, 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.

The Element Groups Moiety and Amount should also be tied to the Element Group stoichiometric substances.

This will help to describe salts and solvates and hydrated substances in a more unambiguous way with respect to the description of the molecular formula and sometimes official names, as in Figure 20.

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

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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.

5.1.5.2.1 Moiety role

For many peptides the moiety role of counterions such as acetate should be indicated.

Table 135 — 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
Conformance	CONDITIONAL
Data Type	CD

5.1.5.2.2 Moiety ID

Each moiety in a non-stoichiometric substance will be identified with a Substance ID if available. If not available a new ID will be assigned with the submission.

Table 136 — 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

5.1.5.2.3 Moiety name

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

Table 137 — 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 5.1.5.2.2.

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5.1.5.2.4 Amount type (Optional)

Typically, there will be an amount type relationship that will be consistent for all of the moieties. A single moiety will typically be assigned the value 1. Ranges of moieties that are stoichiometric will be assigned successive values. Amount type should be captured as described in 4.7.3.4.

5.1.5.2.4.1 Amount (Optional)

Amount shall be captured as described in 4.9.

5.1.5.3 Property (Conditional)

Property shall be captured as specified in 4.12.

5.1.5.3.1 Amount (Mandatory)

Amount shall be captured as described in 4.9.

5.1.6 Substance Name (Mandatory)

Names associated with a Specified Substance Group 1 shall be captured as described in 4.3. The name type shall be specified and, for Official Names, the same format should be followed 4.3.4).

5.1.7 Substance Code (Conditional)

Substance Code should be captured as described in 4.6.

5.1.8 Version (Mandatory)

Version information shall be captured as described in 4.13.

5.1.9 Reference information

Reference information should be captured as described in 4.7.

5.1.10 Reference source (Conditional)

The reference source information should be captured as described in 4.4.

5.1.11 Reference source document (Conditional)

The reference source document information should be captured as described in 4.5.

5.2 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.

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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 synthesised, 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 synthesised 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.

5.2.1 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. Detailed guidelines on

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capturing this information may be given in subsequent editions of this document and Protein Annex.

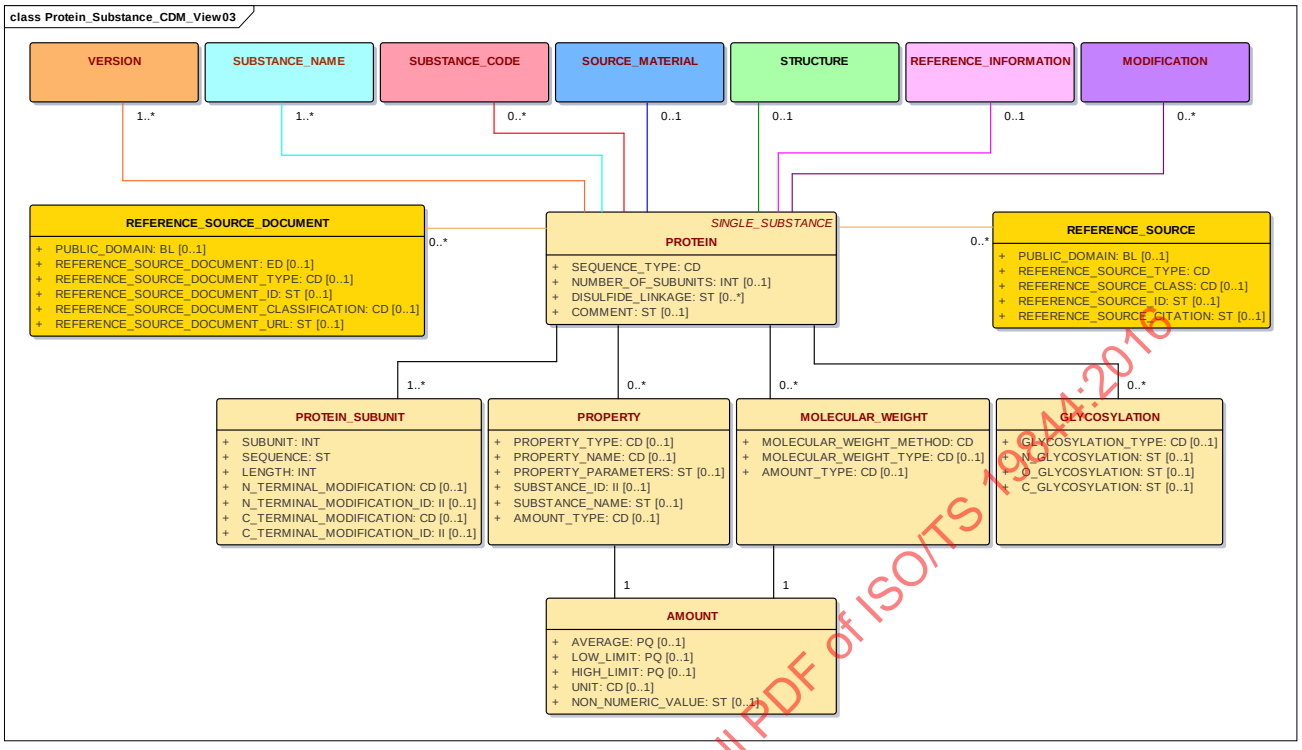


Figure 21 — Information model for the protein substance

If the substance type as defined in 4.2.1 is equal to *Protein substance*, the following data elements and conformances apply in order to assign Substance IDs.

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5.2.2 Sequence type

Table 138 — 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

5.2.3 Number of subunits

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 139 — 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	CONDITIONAL
Data Type	INT
Business Rule(s)	This number is implicit and derived from number of protein subunits.

5.2.4 Disulfide linkage

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).

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Table 140 — Disulfide linkage

User Guidance	The disulphide 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 Annex C.

5.2.5 Comment

Table 141 — Comment

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

5.2.6 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 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.

5.2.6.1 Subunit

Table 142 — 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

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5.2.6.2 Sequence

Table 143 — 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

5.2.6.3 Length

Table 144 — Length

User Guidance	Length of linear sequences of amino acids contained in the subunit
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.

5.2.6.4 N_Terminal modification

Table 145 — N_Terminal modification

User Guidance	The name of the fragment modified at the N-terminal of the protein shall be specified.
Example(s)	N-Terminal Pyroglu Formation; Pyroglutamic acid (pE),
Conformance	CONDITIONAL
Data Type	CD
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.

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5.2.6.5 N_Terminal modification ID

Table 146 — 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.

5.2.6.6 C_Terminal modification

Table 147 — C_Terminal modification

User Guidance	The modification at the C-terminal shall be specified.
Example(s)	amide, ethyl ester etc., C_Terminal Lysine removal
Conformance	CONDITIONAL
Data Type	CD
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.

5.2.6.7 C_Terminal modification ID

Table 148 — 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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5.2.7 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:

5.2.7.1 Molecular weight method

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

Table 149 — 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 centrifugation, End-group analysis, End-group titration, Size-exclusion chromatography
Conformance	MANDATORY
Data Type	CD

5.2.7.2 Molecular weight type

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 150 — 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	M_n; viscosity average, M_v; weight average, M_w; and Z-average M_z. Polydispersity
Business Rule(s)	If known, it shall be provided

5.2.7.3 Amount type (Conditional)

Amount type should be captured as described in 4.7.3.4.

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5.2.7.3.1 Amount (Mandatory)

Amount shall be captured as described in 4.9.

5.2.8 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 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 characterise 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.

5.2.8.1 Glycosylation type

The different glycosylation types are determined by the cell that either the protein or Specified Substance was synthesised 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 cell or old world monkey cells. The glycosylation type will often have substantial effects on the immunogenicity of the protein or vaccine.

Table 151 — Glycosylation type

User Guidance	The type of the glycan shall be specified based on a controlled vocabulary.
Example(s)	HUMAN, OLD WORLD MONKEY, MAMMALIAN, AVIAN, REPTILIAN; FUNGAL, BACTERIAL, PLANT, INSECT, MAMMALIAN AFUCOSYLATED, YEAST HUMANISED
Conformance	CONDITIONAL
Data Type	CD

5.2.8.2 N_Glycosylation

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 152 — N-Glycosylation

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.

5.2.8.3 O-Glycosylation

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 153 — O-Glycosylation

User Guidance	Information on the site of o-glycosylation (serine, threonine, tyrosine, hydroxylysine, hydroxyproline) shall 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).

5.2.8.4 C-Glycosylation

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

Table 154 — C-Glycosylation

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

5.2.9 Property (Conditional)

Property shall be captured as specified in 4.12.

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5.2.9.1 Amount (Mandatory)

Amount shall be captured as described in 4.9.

5.2.10 Structure (Mandatory)

The information related to the structure shall be provided as per specification described in 4.8. 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[2].

5.2.11 Substance name (Mandatory)

Information shall be captured as described in 4.3.

5.2.12 Modification (Conditional)

The information should be captured as described in 4.11.

5.2.13 Substance code (Conditional)

Substance Code should be captured as described in 4.6.

5.2.14 Source material (Conditional)

Source Material should be captured as described in 4.10.

5.2.15 Version (Mandatory)

Version information shall be captured as described in 4.13.

5.2.16 Reference information (Conditional)

Reference information should be captured as described in 4.7.

5.2.17 Reference source (Conditional)

The reference source information should be captured as described in 4.4.

5.2.18 Reference source document (Conditional)

The reference source document information should be captured as described in 4.5.

5.3 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.

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

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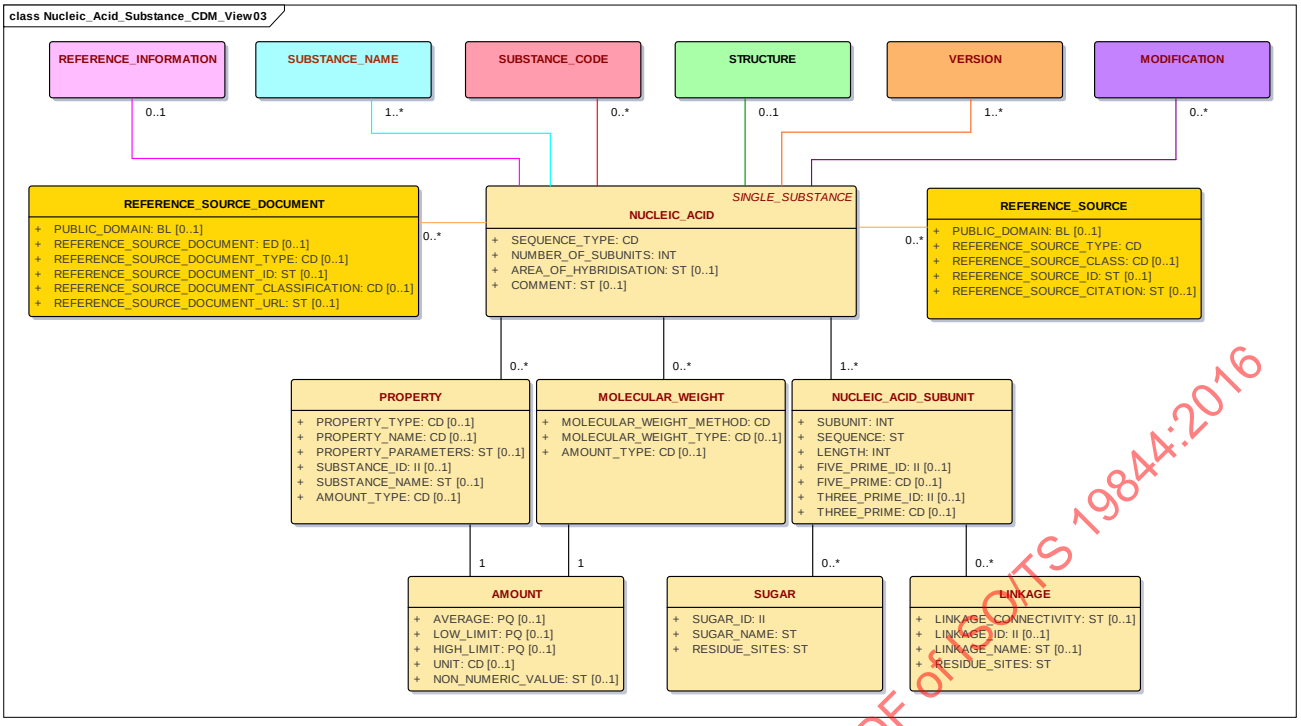


Figure 22 — Information model for nucleic acid

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 aptomers

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.

5.3.1 Structure (Conditional)

There are multiple alternative ways of representing the structure of nucleic acids. Figure 23 provides an example of one of the possible structural representations. While the sequence of nitrogenous bases is

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given as a single letter notation, the backbone structure is represented as a polymeric single repeat unit (5.4 “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.

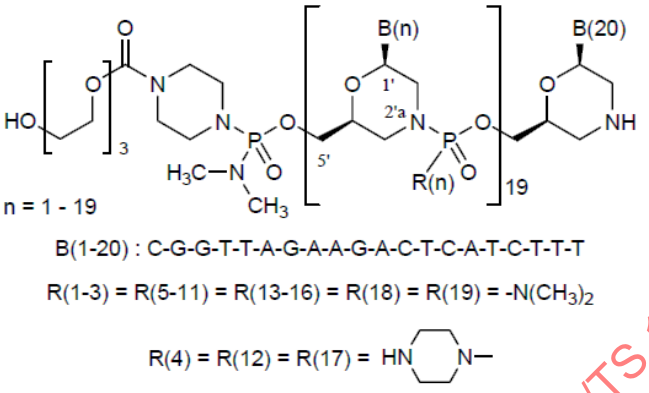


Figure 23 — Representative Structural Representation of nucleic acids

Information shall be captured as described in 4.8.

5.3.2 Sequence type

Table 155 — 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

5.3.3 Number of subunits

Table 156 — 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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5.3.4 Area of hybridisation

Table 157 — Area of hybridisation

User Guidance	The area of hybridisation shall 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

5.3.5 Comment

Table 158 — Comment

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

5.3.6 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.

5.3.6.1 Subunit

Table 159 — 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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5.3.6.2 Sequence

Table 160 — 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

5.3.6.3 Length

Table 161 — Length

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

5.3.6.4 Five prime ID

Table 162 — Five prime ID

User Guidance	
Example(s)	JKUHT76541 (Artificial ID)
Conformance	CONDITIONAL
Data Type	II
Business Rule(s)	

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5.3.6.5 Five prime

Table 163 — Five prime

User Guidance	The nucleotide present at the 5’ terminal shall 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	CD
Business Rule(s)	Implicit NOTE: If not specified in the available reference source this value shall be derived from the nucleic acid sequence.

5.3.6.6 Three prime ID

Table 164 — Three prime ID

User Guidance	
Example(s)	JKUHT76541 (Artificial ID)
Conformance	CONDITIONAL
Data Type	II
Business Rule(s)	

5.3.6.7 Three prime

Table 165 — Three prime

User Guidance	The nucleotide present at the 3’ terminal shall 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)	Tymidine (T)
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	NOTE: If not specified in the available reference source this value is derived from the nucleic acid sequence.

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5.3.6.8 Sugar (Conditional)

5.3.6.8.1 Sugar ID

The Substance ID 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.

Table 166 — Sugar ID

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

5.3.6.8.2 Sugar name

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 167 — Sugar name

User Guidance	The name of the sugar or sugar-like component that make up the nucleotide
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.

5.3.6.8.3 Residue sites

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

Table 168 — Residue sites

User Guidance	The residues that contain a given sugar will 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
Values Allowed	ISO 11238 Substance ID

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5.3.6.9 Linkage (Conditional)

The linkages between sugar residues will also be captured.

5.3.6.9.1 Linkage connectivity

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

Table 169 — 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.

5.3.6.9.2 Linkage ID

Table 170 — Linkage ID

User Guidance	Each linkage will be registered as a fragment and have an ID.
Conformance	CONDITIONAL
Data Type	II

5.3.6.9.3 Linkage name

Table 171 — Linkage name

User Guidance	Each linkage will be registered as a fragment and have at least one name. A single name shall be assigned to each linkage.
Example(s)	Phosphothioate
Conformance	CONDITIONAL
Data Type	ST

5.3.6.9.4 Residue sites

Residues shall be captured as described in 5.3.6.8.3.

5.3.7 Modification (Conditional)

The information should be captured as described in 4.11.

5.3.8 Property (Conditional)

Property shall be captured as specified in 4.12.

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5.3.8.1 Amount (Mandatory)

Amount shall be captured as described in 4.9.

5.3.9 Molecular weight (Conditional)

This information shall be captured as described in 5.2.7.

5.3.9.1 Amount (Mandatory)

Amount shall be captured as described in 4.9.

5.3.10 Substance Name (Mandatory)

Information shall be captured as described in 4.3.

5.3.11 Substance Code (Conditional)

Substance Code should be captured as described in 4.6.

5.3.12 Version (Mandatory)

Version information shall be captured as described in 4.13.

5.3.13 Reference information (Conditional)

Reference information should be captured as described in 4.7.

5.3.14 Reference source (Conditional)

The reference source information should be captured as described in 4.4.

5.3.15 Reference source document (Conditional)

The reference source document information should be captured as described in 4.5.

5.4 Polymers

Polymers are polydisperse molecular ensembles defined using combination 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 polymerisation, 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 matrixes, the source of the polymer should also be provided.

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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.

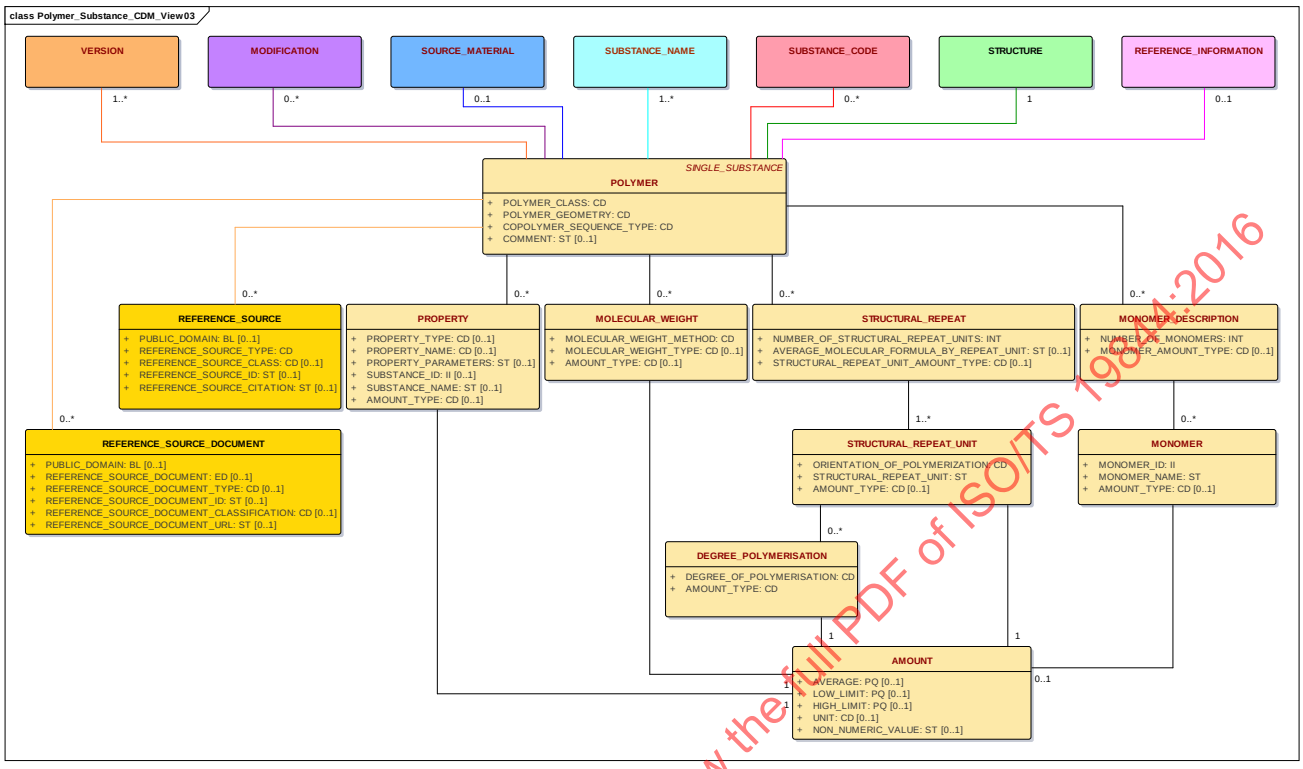


Figure 24 — Information model for polymer substance

For the description of polymer substances, 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
- Degree of Polymerisation
- 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

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

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5.4.1 Polymer class

Table 172 — Polymer class

User Guidance	Type of polymer.
Example(s)	homopolymer, copolymer
Conformance	MANDATORY
Data Type	CD

5.4.2 Polymer geometry

Table 173 — 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

5.4.3 Copolymer sequence type

Table 174 — Copolymer sequence type

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

5.4.4 Comment

Table 175 — Comment

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

5.4.5 Substance name (Mandatory)

The information related to the name of the substance shall be provided as described in 4.3. 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.

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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).

5.4.6 Structure (Mandatory)

The information related to the structure shall be provided as per specification described in 4.8. 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 repeating units. MolFile are the preferred format for the molecular structure of the repeat unit.

5.4.7 Monomer description (Conditional)

For synthetic 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 shall be provided by means of the following data elements:

5.4.7.1 Number of monomers

Table 176 — Number of monomers

User Guidance	The number of diverse monomers used to synthesise the polymer shall be specified.
Example(s)	2
Conformance	MANDATORY
Data Type	INT
Business Rule(s)	This number can be counted and is never explicitly represented.

5.4.7.2 Monomer Amount type

Table 177 — Monomer Amount type

User Guidance	This element captures 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

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5.4.7.3 Monomer (Conditional)

This subclause identifies and quantifies the monomer(s) used in the synthesis of the polymer.

5.4.7.3.1 Monomer ID

Table 178 — Monomer ID

User Guidance	The unique identifier assigned to the monomer.
Conformance	MANDATORY
Data Type	II

5.4.7.3.2 Monomer name

Table 179 — Monomer name

User Guidance	The name of the monomer shall be provided; established or primary name of monomer.
Conformance	MANDATORY
Data Type	ST

5.4.7.3.3 Amount Type

Amount type should be captured as described in 4.7.3.4.

5.4.7.3.3.1 Amount (Conditional)

Amount shall be captured as described in 4.9.

5.4.8 Structural repeat (Conditional)

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

5.4.8.1 Number of structural repeat units

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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5.4.8.2 Average molecular formula by repeat unit

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.

5.4.8.3 Structural repeat unit amount type

The information should be captured as described in 4.7.3.4. Indicate how the quantitative amount of Structural Repeat Units is captured (e.g. mole ratio, weight ratio, mole per cent, weight per cent).

5.4.8.4 Structural repeat unit (Mandatory)

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

5.4.8.4.1 Orientation of polymerisation

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

Table 182 — Orientation of polymerisation

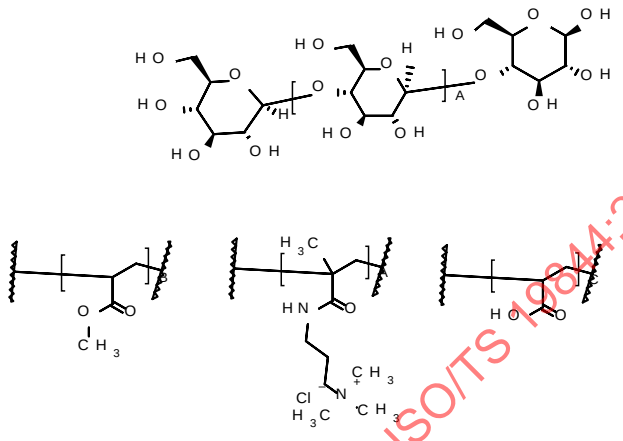
User Guidance	The orientation of the polymerisation shall be described.
Example(s)	head-tail, head-head, random
Conformance	MANDATORY
Data Type	CD

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5.4.8.4.2 Structural repeat unit

Table 183 — Structural repeat unit

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

5.4.8.4.3 Amount Type

Amount type should be captured as described in 4.7.3.4.

5.4.8.4.4 Amount (Mandatory)

Amount shall be captured as described in 4.9.

5.4.8.4.5 Structural representation (Mandatory)

Structural repeat unit representation information for each SRU should be captured as described in 4.8.1.

5.4.8.4.6 Degree of polymerization (Conditional)

This subclause applies to homopolymer and block co-polymers where the degree of polymerisation within a block can be described. The following information shall be provided where available:

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5.4.8.4.6.1 Degree of polymerisation

Table 184 — Degree of polymerisation

User Guidance	The type of the degree of polymerisation shall be described.
Example	"Structural Repeat unit: <A><amount or number of SRU/per polymer ratio>"
Conformance	MANDATORY
Data Type	CD

5.4.8.4.6.2 Amount Type

Amount type should be captured as described in 4.7.3.4.

5.4.8.4.6.2.1 Amount (Conditional)

Amount shall be captured as described in 4.9.

5.4.9 Molecular weight (Mandatory)

This information shall be captured as described in 5.2.7.

5.4.9.1 Amount (Mandatory)

Amount shall be captured as described in 4.9.

5.4.10 Property (Conditional)

Property shall be captured as specified in 4.12.

5.4.10.1 Amount (Mandatory)

Amount shall be captured as described in 4.9.

5.4.11 Substance code (Conditional)

Substance Code should be captured as described in 4.6.

5.4.12 Version (Mandatory)

Version information shall be captured as described in 4.13.

5.4.13 Reference information (Conditional)

Reference information should be captured as described in 4.7.

5.4.14 Modification (Conditional)

The information should be captured as described in 4.11.

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5.4.15 Source material (Conditional)

This information shall be captured as described in 4.10.

5.4.16 Reference source (Conditional)

The reference source information should be captured as described in 4.4.

5.4.17 Reference source document (Conditional)

The reference source document information should be captured as described in 4.5.

5.5 Structurally diverse substances

There are a wide variety of substances described as structurally diverse substances. Structurally diverse substances are typically substances that have a variety of structurally diverse constituents that cannot be captured as a mixture of a limited number of related single substances. This category would be used to describe the following class of substances:

- Herbals -- The Herbal preparation OIL is discussed in B.8.2 of the Chemical Annex B. The Herbal preparation, Extract, exudates as well as the (Herbal) Substance (fresh), Herbal Drug are discussed in the Herbal Annex E.
- Homeopathic Substances are discussed in Annex F.
- Vaccines — to be addressed in the next edition of this document.
- Plasma-derived substances used in Blood products are discussed in Annex G.
- 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.

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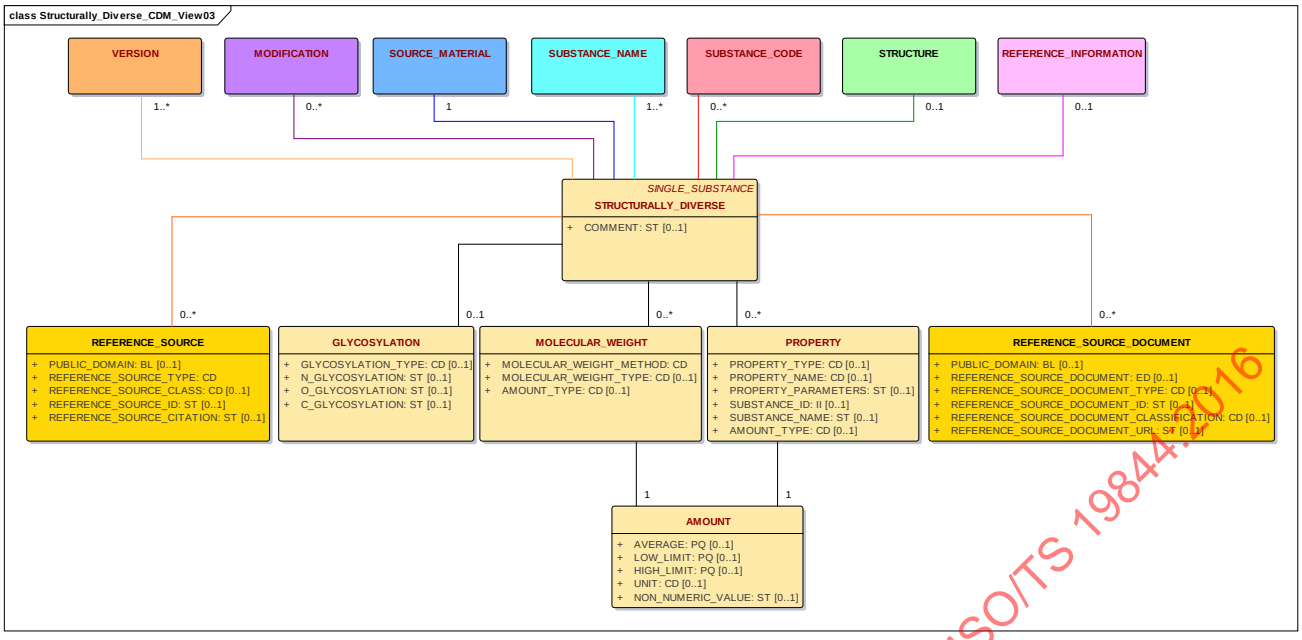


Figure 25 — Information Model for Structurally-Diverse Substance

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.

5.5.1 Comment

Table 185 — Comment

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

5.5.2 Substance name (Mandatory)

Information shall be captured as described in 4.3.

5.5.3 Structure (Mandatory)

If applicable, the modification should be described based on specification provided in 4.10.

5.5.4 Property (Conditional)

Property shall be captured as specified in 4.12.

5.5.4.1 Amount (Mandatory)

Amount shall be captured as described in 4.9.

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5.5.5 Molecular weight

This information shall be captured as described in 5.2.7.

5.5.5.1 Amount (Mandatory)

Amount shall be captured as described in 4.9.

5.5.6 Glycosylation (Conditional)

This information should be captured as described in 5.2.8.

5.5.7 Modification (Conditional)

The information should be captured as described in 4.11.

5.5.8 Source material (Conditional)

This information shall be captured as described in 4.10.

5.5.9 Substance code (Conditional)

Substance Code should be captured as described in 4.6.

5.5.10 Reference information (Conditional)

Reference information should be captured as described in 4.7.

5.5.11 Version (Mandatory)

Version information shall be captured as described in 4.13.

5.5.12 Reference source (Conditional)

The reference source information should be captured as described in 4.4.

5.5.13 Reference source document (Conditional)

The reference source document information should be captured as described in 4.5.

5.5.14 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

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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 in 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 or 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 fertilisers, pesticides and herbicides, the amount of daylight and water, although important they 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 of the extract will be defined at the Specified Substances Group 1 information level. Fractions of plants 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 Drug 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, 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. Although Annex E doesn't include any examples, algae, fungi, animals and minerals are also classified as herbals.

5.5.14.1 Naming vegetable oils

The business rules for naming of vegetable oils are described in subclause Structurally Diverse Substance, Herbals, 5.5.14.1 and in the subclause Source material (see 4.10).

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 infraspecies (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

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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.

5.5.14.1.1 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 the 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 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 (infraspecies 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 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 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).

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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.

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.

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

5.5.15 Vaccines

Annex I will address this information and will be included in the next edition of this document. Annex I will provide 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 microorganism and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins.

5.5.16 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.

5.5.17 Allergens

Annex J will address this information and will be included in the next edition of this document. Annex J will provide guidance to describe the elements that are necessary to define allergenic extracts. The

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active allergens are structurally-diverse substance derived from biological matrices. In several instances, the allergenic proteins responsible for the allergenic response in the majority of patients have beeb isolated and characterised, e.g. Fel d 1 in cat saliva.

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

Annex K will address this information and will provide guidance to describe the elements that are necessary to define what are typically referred to as advanced therapies. 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 proteins. 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.

5.5.19 Minerals

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

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

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5.6 Mixture substance

Material that contains multiple substances can be mixture substance if the substances are either isolated or synthesised 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).

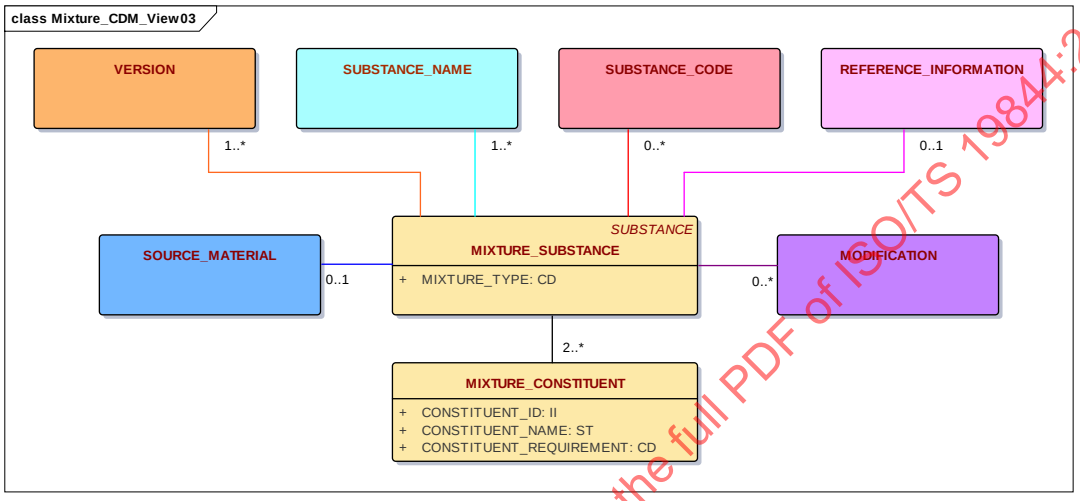


Figure 26 — Information Model for mixture substance

The following information on mixture shall be provided:

5.6.1 Mixture type

Table 186 — 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

5.6.2 Mixture constituent (Mandatory)

The mixture constituent set of elements aims to describe the constituents of the mixture substance. Such information shall be provided by means of the following data elements:

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5.6.2.1 Constituent ID

Table 187 — Constituent ID

User Guidance	The unique identifier assigned to the constituent 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.
Conformance	MANDATORY
Data Type	II

5.6.2.2 Constituent name

Table 188 — Constituent name

User Guidance	The name of the constituent of the mixture shall be described; 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

5.6.2.3 Constituent requirement

Table 189 — Constituent requirement

User Guidance	A flag indicating if this component is required.
Example(s)	Always present, may be present.
Conformance	MANDATORY
Data Type	CD

5.6.3 Modification (Conditional)

The information should be captured as described in 4.11.

5.6.4 Source material (Conditional)

This information shall be captured as described in 4.10.

5.6.5 Substance name (Mandatory)

Information shall be captured as described in 4.3.

5.6.6 Substance code (Conditional)

Substance Code should be captured as described in 4.6.

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5.6.7 Reference information (Conditional)

Reference information should be captured as described in 4.7.

5.6.8 Version (Mandatory)

Version information shall be captured as described in 4.13.

6 Specified substance (Optional)

There are a number of regulatory needs when defining materials in medicinal products. The globalisation 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 optional. Should a region implement any of the Specified Substance Groups, the following conformances as described in this subclause are applicable.

6.1 Specified Substance Group 1 (repeat as necessary)

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 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 (Vechicle, Dilution and Potentisation) etc.

The information model for Specified Substances Group 1 is listed in Figure 27.

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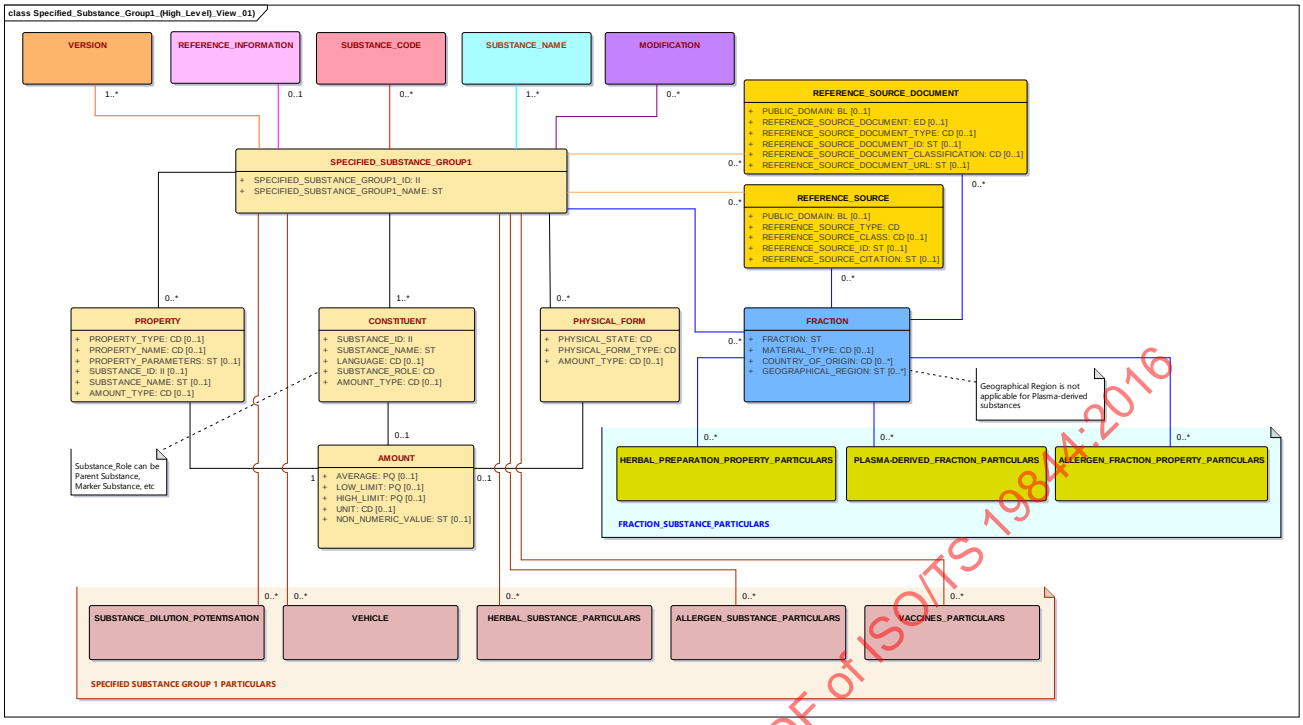


Figure 27 — Information model for the Specified Substance Group 1

6.1.1 Specified substance Group 1 ID

Table 190 — 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

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6.1.2 Specified substance Group1 Name

Table 191 — Specified substance Group 1 name

User Guidance	The name of the Specified Substance Group 1 shall be provided in this field. [Scientific genus/binomial/trinomial **without** Author] [Part(s)] [Fraction][Extraction solvent composition][Herbal Drug/Native Herbal preparation(DER)]
Example(s)	*Ginkgo biloba,* Leaf, Dry Extract Acetone-Water (60 — 40, w/w), (37-65:1) *Harpagophytum zeyheri,* Root, Dry Extract Ethanol-Water (60 – 40, v/v),(1.5 – 3.0:1)
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	Name conventions shall follow the pattern described for herbals as described in the user guidance and the Naming Overview for Herbals as described in E.1.5.4.

6.1.3 Substance Name (Mandatory)

Names associated with a Specified Substance Group 1 shall be captured as described in 4.3. The Substance Name Type shall be specified and, for Official Names, the same format shall be followed (see 4.3.4).

6.1.4 Substance Code (Conditional)

Codes associated with a Specified Substance Group 1 should be captured as described in 4.6.

6.1.5 Version (Mandatory)

Version associated with a Specified Substance Group 1 Version information shall be captured as described in 4.13.

6.1.6 Reference source (Conditional)

The reference source information should be captured as described in 4.4.

6.1.7 Reference source document (Conditional)

The reference source document information should be captured as described in 4.5.

6.1.8 Property (Conditional)

Property values should be captured as described for substances in 4.12. It is possible to capture both definitional properties and properties that provide additional information about a substance. For example, 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.

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6.1.9 Fraction (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 4.10.10.7), (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 4.10.10.7) and the Specified Substance Group 1 level (see 6.1.9.4).

For the Herbal Specified Substance Group 1, the Herbal preparation Property Particulars (see 6.1.9.3) is used to capture additional information for Herbal preparation extraction solvents and Herbal substance/Herbal preparation Mass Ratio. For Plasma-derived Specified Substance Group 1, the Blood Plasma-derived Fraction Particulars (see 6.1.9.4) is used to capture the specific information of the country of plasma origin, testing and safety information.

Table 192 — Fraction

User Guidance	The elements for capturing the Fration element Group should be captured as described in 4.10.10. In addition, 'Fraction Particular Element Groups' should be captured at the Specified Substance Group 1 level corresponding to structurally diverse substance specific information according to the relevant annexes).
Example(s)	
Conformance	CONDITIONAL
Data Type	N/A
Business Rule(s)	When the herbal substance is derived from a fraction of the plant, the description of the fraction is required. For Blood/Plasma-derived, the element 'GEOGRAPHICAL REGION' in Class 'FRACTION' in SSG1 is not applicable.

6.1.9.1 Reference Source (Conditional)

The reference source information should be captured as described in 4.4.

6.1.9.2 Reference source document (Conditional)

The reference source document information should be captured as described in 4.5.

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6.1.9.3 Herbal preparation property particulars

Table 193 — Herbal preparation property particulars

User Guidance	This Element Group is used to capture further information about the Herbal preparation (Extract), such as the Extraction solvent composition(s) 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. In this context, 'Herbal Substance' can be either a Substance (fresh) or a Herbal Drug.
Example(s)	N/A
Conformance	CONDITIONAL
Data Type	N/A
Values Allowed	N/A
Business Rule(s)	Mandatory, when the the value of the attribute 'Material Type' of the Element Group 'Fraction' is 'Herbal'.

6.1.9.3.1 Extraction solvent composition

Table 194 — Extraction solvent composition

User Guidance	This attribute is used to capture additional information for Herbal preparation (Extract). The Herbal preparation (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.
Example(s)	Ethanol – water (60-40 v/v); Ethanol 50% v/v; Acetone-Water (60-40 w/w)
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	N/A
Business Rule(s)	

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6.1.9.3.2 Drug Extract Ratio (DER)

Table 195 — Drug Extract Ratio (DER)

User Guidance	This attribute is used to capture additional information for Herbal preparation (Extract). 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.
Example(s)	37 – 65 part Herbal Substance = 1 part Herbal Extract (e.g. *Ginkgo biloba*, Leaf, Dry Extract) 1 part Herbal Substance = 1.5 – 2.5 part Extract (e.g. *Iberis amara*, Whole Plant, Extract Ethanol – Water (50-50, v/v).
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	N/A
Business Rule(s)	

6.1.9.3.3 Substance ID

Table 196 — Substance ID

User Guidance	The Substance ID for each extraction solvent should be captured.
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)	

6.1.9.3.4 Substance name extraction solvent

Table 197 — Substance name extraction solvent

User Guidance	The substance name of the extraction solvent should be captured.
Example(s)	Ethanol; Water; Acetone – Water (60 – 40, w/w)
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	The preferred term is the default value implicitly derived from the Substance ID.
Business Rule(s)	

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6.1.9.3.5 Amount type (Mandatory)

Amount type should be captured as described in 4.7.3.4.

6.1.9.3.6 Amount (Mandatory)

Amount shall be captured as described in 4.9.

6.1.9.4 Blood Plasma-derived fraction particulars (Conditional)

Table 198 —Blood Plasma-derived fraction particulars

User Guidance	This class captures information on the specific information of the country of plasma origin, testing and safety information.
Example(s)	N/A
Conformance	CONDITIONAL
Data Type	N/A
Values Allowed	N/A
Business Rule(s)	

6.1.9.4.1 Cryopoor plasma process flow N

Table 199 — Cryopoor plasma process flow N

User Guidance	This attribute should capture the process flow from which the cryo poor plasma flow N is obtained.
Example(s)	See Table G.9, Annex Plasma-derived substance, Table Specified Substance Group 1
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	N/A
Business Rule(s)	

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6.1.9.4.2 Cryoprecipitate process flow N

Table 200 —Cryoprecipitate process flow N

User Guidance	This attribute should capture the process flow from which the cryoprecipate flow N is obtained.
Example(s)	
Conformance	CONDITIONAL
Data Type	ST
Values Allowed	N/A
Business Rule(s)	

6.1.9.4.3 Country of origin

Table 201 —Country of origin

User Guidance	The countries of plasma origin applied in the production of cryopoor plasma and cryoprecipitate are captured and specified at the Specified Substance Group 1. At the Specified Substance Group 1 level/Element Group 'Blood Plasma-derived Fraction Particulars', the attribute 'Country of Origin' could be captured as a subset of country(ies) referenced in the parent substance (cryoprecipitate or cryopoor plasma).
Example(s)	
Conformance	MANDATORY
Data Type	CD
Values Allowed	N/A
Business Rule(s)	

6.1.10 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 4.11).

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.

6.1.11 Reference Information (Conditional)

Reference information should be captured as described in 4.7.

6.1.12 Constituent (Mandatory)

The Constituents group of elements serves several roles, each substance in multiple substance materials is captured as a component. Signature, active markers, and limit substances and extraction solvents are also captured for herbal extracts. The amount of components, constituents and extraction solvents are

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captured, too. A different Specified Substance Group 1 will be created if these amounts consistently vary.

At least one constituent is necessary for every Specified Substance Group 1 (i.e. the parent Substance ID).

6.1.12.1 Substance ID

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

Table 202 — Substance ID

User Guidance	Every Specified Substance Group 1should 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.

6.1.12.2 Substance name

Table 203 — 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.
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.

6.1.12.3 Language

Table 204 — 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)	

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6.1.12.4 Substance role

Table 205 — 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, component, degradant, metabolite, active moiety, parent substance, parent specified substance
Conformance	MANDATORY
Data Type	CD
Values Allowed	COMPONENT, EXTRACTION SOLVENT, SIGNATURE SUBSTANCE, MARKER SUBSTANCE
Business Rule(s)	Markers for herbal Specified Substance are conditional, when the available information on markers shall be provided.

6.1.12.5 Amount type (Conditional)

Amount type should be captured as described in 4.7.3.4.

6.1.12.5.1 Amount (Conditional)

Amount shall be captured as described in 4.9.

6.1.13 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 one example of a crystal in which part is dissolved and part is in solution. 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. If two polymorphs are distinguished by crystalline type, the symmetry group that distinguishes the crystalline types should be captured as a property.

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:

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6.1.13.1 Physical state

Table 206 — Physical state

User Guidance	The actual state of the substance in packaged product or administered product
Example(s)	solid, liquid
Conformance	MANDATORY
Data Type	CD
Values Allowed	SOLID, LIQUID, GAS, EMULSION, GEL
Business Rule(s)	This information is implicit and derived from the Physical Form Type

6.1.13.2 Physical form type

Table 207 — Physical form type

User Guidance	Type of the physical form
Example(s)	crystalline, amorphous, tincture, dry, extract
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	When the physical state is available, it shall be provided as it defines a new Specified Substance Group 1 ID

6.1.13.3 Amount type (Conditional)

Amount type should be captured as described in 4.7.3.4.

6.1.13.4 Amount (Conditional)

Amount shall be captured as described in 4.9.

When there is an amount, it shall be specified as an observation with a measurable property code.

6.1.14 Specified substance particulars

This subclause describes additional information related to Specified Substance particulars depending on the Specified Substance Group 1 category. For herbal substances, refer to Herbal Substance Particulars, described in 6.1.14.1. For substances with substance name type Specified Homeopathic, refer to 6.1.14.2 Vehicle and 6.1.14.3 for Dilution and Potentisation.

6.1.14.1 Herbal Substance particulars (Conditional)

The Element Group 'Herbal Substance Particulars' is used for the further description of the characteristics of the Substance (fresh) and the Substance (Herbal Drug).

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6.1.14.1.1 Degree of comminution

Table 208 —Degree of comminution

User Guidance	The degree of comminution should be specified.
Example(s)	Cut, fragmented, sliced and sifted leaves; cut into slices of 2-4 cm
Conformance	OPTIONAL
Data Type	ST
Business Rule(s)	

6.1.14.1.2 Process state

Table 209 — Process state

User Guidance	Description of conditions of drying and storage of the herbal material.
Example(s)	Natural dried at 20°C for 6 hours; Dried indoors, well ventilated
Conformance	OPTIONAL
Data Type	ST
Business Rule(s)	

6.1.14.1.3 Wild_Cultivated

Table 210 — Wild_Cultivated

User Guidance	This element should be used to capture if the herbal is wild or cultivated.
Example(s)	Wild; Cultivated
Conformance	OPTIONAL
Data Type	CD
Business Rule(s)	

6.1.14.1.4 Growth state

Table 211 — Growth state

User Guidance	The growth state of the plant should be specified.
Example(s)	Before leaves turn yellow; Mature plant
Conformance	OPTIONAL
Data Type	ST
Business Rule(s)	

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6.1.14.1.5 Harvesting time

Table 212 — Harvesting time

User Guidance	The time of harvesting should be specified.
Example(s)	June – October; Plants are harvested during the whole year after they have been cultivated for at least two growth periods; In Autumn of the next year after seeding
Conformance	OPTIONAL
Data Type	ST
Business Rule(s)	

6.1.14.1.6 Decontamination Process

Table 213 — Decontamination Process

User Guidance	The decontamination process should be described.
Example(s)	
Conformance	OPTIONAL
Data Type	ST
Business Rule(s)	

6.1.14.1.7 Country of origin

Table 214 — Country of origin

User Guidance	The country of origin should be specified.
Example(s)	China, South Africa and Namibia, US, CA
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	

6.1.14.1.8 Geographical region

Table 215 — Geographical region

User Guidance	The place/region of origin should be specified.
Example(s)	Provinces Shandong, Jiangsu, Sichuan, North America
Conformance	OPTIONAL
Data Type	ST
Business Rule(s)	

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6.1.14.1.9 Storage time

Table 216 — Storage time

User Guidance	The storage time should be specified.
Example(s)	NMT 6 month; 2 years
Conformance	OPTIONAL
Data Type	ST
Business Rule(s)	

6.1.14.1.10 Storage conditions

Table 217 — Storage conditions

User Guidance	The conditions of storage should be specified.
Example(s)	Stored protected from light at 0°C, until processed; Protected from light at -20°C to -24°C for maximum 24 months
Conformance	OPTIONAL
Data Type	ST
Business Rule(s)	

6.1.14.2 Vehicle (Conditional)

Table 218 — Vehicle

User Guidance	Excipients used for the preparation of certain stocks or for the potentisation process.
Example(s)	Purified water; additives; ethanol of a suitable concentration, glycerol 85 per cent; lactose monohydrate
Conformance	CONDITIONAL
Business Rule(s)	

6.1.14.2.1 Vehicle composition

Table 219 — Vehicle composition

User Guidance	The composition of the diluent used in the potentiation of the homeopathic substance.
Example(s)	Ethanol, Ethanol-water, Glycerol-ethanol-water.
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	When the physical state is available, it shall be provided as it defines a new Specified Substance Group 1 ID.

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6.1.14.2.2 Substance ID

Table 220 — Substance ID

User Guidance	Every vehicle substance should have a substance ID.
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 vehicle is a substance.

6.1.14.2.3 Substance Name

Table 221 — Substance name

User Guidance	The name of the substance of the vehicle shall be described.
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.

6.1.14.2.4 Amount type (Conditional)

The Amount type should be captured as described in 4.7.3.4.

6.1.14.2.5 Amount (Conditional)

Amount should be captured as described in 4.9.

6.1.14.3 Substance Dilution Potentisation (Conditional)

This subclause describes the dilutions of triturations of homeopathic stocks and should be populated when describing homeopathic preparations. Decimal, Centimal dilutions and LM dilutions shall be included in the Specified Substance Group 1 Information level. These elements appear when the 'Substance Name Type' has the value 'homeopathic' at the Substance Information level.

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6.1.14.3.1 Dilution Potentisation Type

Table 222 —Dilution Potentisation Type

User Guidance	This element should be used to capture the dilution/potentisation type.
Example(s)	“Decimal, DH”, “Decimal, D”, “Centesimal, C”, K (Korsakovian),
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	“Decimal, DH”, “Centesimal, CH”
Business Rule(s)	

6.1.14.3.2 Dilution Grade

Table 223 — Dilution grade

User Guidance	Number of Dilution
Example(s)	6
Conformance	CONDITIONAL
Data Type	INT
Values Allowed	Integer numbers
Business Rule(s)	

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6.2 Specified substance Group 2

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 Type and the Production System that describes the cell line or animal from which a given substance is isolated from.

The manufacturer is not necessarily the entity that has market authorisation, but the entity that manufactures or repackages 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

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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 28, 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.

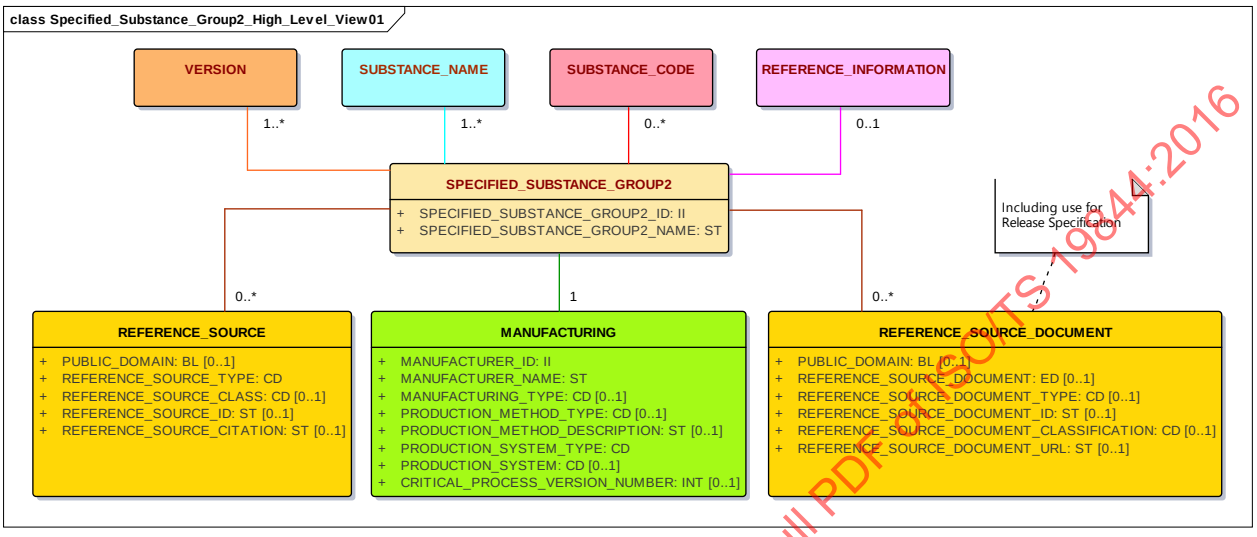


Figure 28 — Information model for the Specified Substance Group 2

In this version of the ISO/TS 19844 Implementation Guidance, only the Element Group Manufacturing (class in green colour in Figure 28) shall be implemented to include only the attributes within the class. However, in this version of the document, the Manufacturing class shall be extended to cover extended manufacturing information, e.g. see Figure E.10 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 29 as part of the Specified Substance Group 4.

In Annex E the model for a 'Limited' extended information for Manufacturing is provided to serve the Herbal use cases for the Herbal preparation Extracts.

NOTE In the class ‘Manufacturing’ (green box) the elements ‘Manufacturer ID' and 'Manufacturer Name’ are corresponding to the information provided in accordance with the eCTD module M3, Manufacturing. This means when the production method type is the same for different manufacturing sites, the SSG2 ID is the same. 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.10) the SSG2 ID will be site specific and trigger a different ID (also in the case when the same production method is used)..

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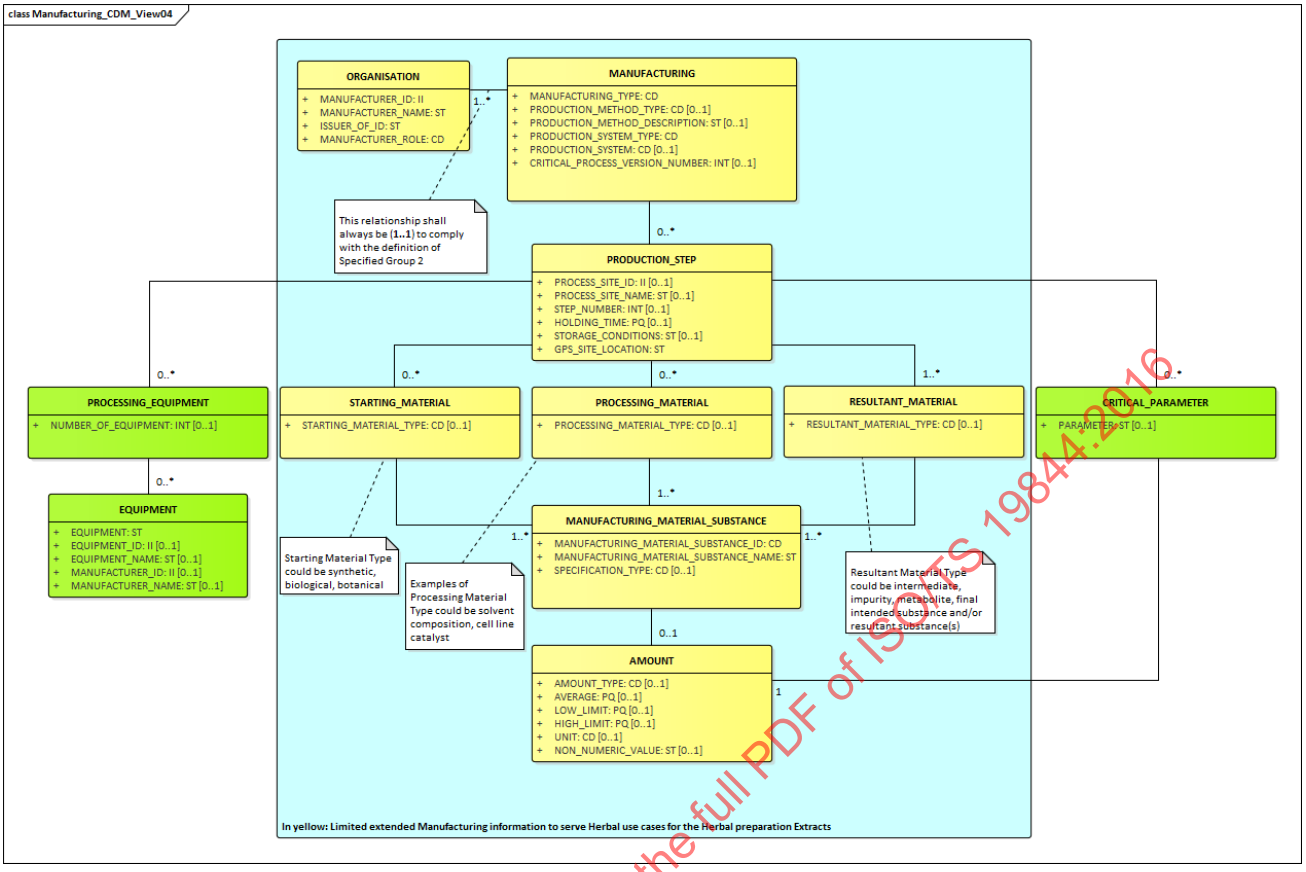


Figure 29 — Information Model for Manufacturing

NOTE Figure 29 has been updated in accordance to the next version of the ISO 11238 substance standard.

6.2.1 Specified Substance Group2 ID

Table 224 — Specified Substance Group2 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.
Conformance	MANDATORY
Data Type	II
Business Rule(s)	NOTE: The Specified Substance ID is NOT SPECIFIED for Specified Substance ID Request

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6.2.2 Specified Substance Group2 Name

Table 225 — Specified Substance Group 2 name

User Guidance	The name of the Specified Substance Group 2 shall be provided in this field. The name should be coined from the preferred term of the substance and the manufacturer.
Example(s)	Human Insulin Drugco
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	The name should be coined from a concatenation of the preferred term of the parent substance and the manufacturer (i.e. Human Insulin Drugco). Regions may provide additional guidance as the latest version of the Naming Conventions document (Ref. Doc.: EMA/720247/2011).

6.2.3 Parent Substance ID

The Parent Substance ID corresponds to the Substance or Specified Substance Group 1 ID that identifies the manufactured substance. The ID of the parent for the Specified Substance Group 2 may refer to either a Substance ID or a Specified Substance Group 1 ID.

6.2.4 Reference source (Conditional)

The reference source information should be captured as described in 4.4.

6.2.5 Reference source document (Conditional)

The reference source document information should be captured as described in 4.5.

6.2.6 Manufacturing (Mandatory)

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

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6.2.6.1 Manufacturer ID

Table 226 — Manufacturer ID

User Guidance	The unique code used to track manufacturers be provided.
Conformance	MANDATORY
Data Type	II
Business Rule(s)	For substance (active ingedients intented 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. A necessary condition for the Specified Substance Group 2 to exist is: either the Manufacturer ID, Name and type is available AND/OR the production method type, product system type and production system exist. The manufacturer and production description can coexist, at least one of those shall be provided. The Manufacturer ID for SSG2 shall be linked to the actual Manufacturing site where the substance is manufactured. If necessary, bulk substance manufacturing site and further steps (e.g. micronisation 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.

6.2.6.2 Manufacturer name

Table 227 — Manufacturer name

User Guidance	The name of the manufacturer of the Specified Substance.
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	For substance (active ingedients intented 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.

NOTE Organisation information is captured as described in ISO/TS 20443, the implementation guide for ISO 11615.

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6.2.6.3 Manufacturing type

Table 228 — Manufacturing type

User Guidance	The type of operation performed by the entity associated with the substance.
Example(s)	Manufacturer (of Substance or Specified Substance), Hervester
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	For substance (active ingedients intented to be used in the medicinal product) the element is always mandatory. For excipients (non-active ingredients intented to be used in the medicinal product) the information is optional. If a repackager the original manufacturer should also be captured.

6.2.6.4 Production method type

Table 229 — Production method type

User Guidance	The overall type of production system, synthetic, extraction, biosynthetic, extraction and potentisation, chemical solubility and potentisation, chemical mixing and potentisation.
Example(s)	synthetic, extraction, percolation, biosynthetic, semi-synthetic, extraction and potentisation, chemical solubility and potentisation, chemical mixing and potentisation, harvesting, fractionation, fermentation and chemical synthesis
Conformance	CONDITIONAL
Data Type	CD
Business Rule(s)	For substance (active ingedients intented 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.

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6.2.6.5 Production method description

Table 230 — Production method description

User Guidance	The production method description shall be captured.
Example(s)	"Chemical synthesis from starting materials, purification steps and recrystallisation to obtain crystalline form 1". "Nuclide production by bombardment of [18O] by accelerated protons in a Cyclotron: 18O(p,n)18F, followed by radiolabelling of a precursor substance by a chemical substitution on a radio synthesiser. 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".
Conformance	CONDITIONAL
Data Type	ST
Business Rule(s)	For substance (active ingedients intented 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. The production method description shall be captured when the Substance name type is provided as Specified Homeopathic, or Herbal.

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6.2.6.6 Production system type

Table 231 — Production system type

User Guidance	This element shall 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 deomposition.
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	For substance (active ingedients intented 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. 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.

6.2.6.7 Production system

Table 232 — 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
Conformance	CONDITIONAL
Data Type	CD
Values Allowed	
Business Rule(s)	For substance (active ingedients intented 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. Production System, System Type and Method 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 E.1.7)

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6.2.6.8 Critical process version number

Table 233 — Critical process version number

User Guidance	Should be captured for material derived from both extractive and biosynthetic production method, for synthesised peptides and nucleic acids, chemical and polymer substances.
Example(s)	2
Conformance	CONDITIONAL
Data Type	INT
Values Allowed	Start at one and increases if a major critical process changes occur (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 (active ingredients intented 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. Production System, System Type and Method 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**.

6.2.6.9 Substance name (Mandatory)

Names associated with a Specified Substance Group 2 shall be captured as described in 4.3. Trade names associated with the manufacturer will be captured at this level.

6.2.6.10 Substance code (Conditional)

Codes associated with a Specified Substance Group 2 Substance Code should be captured as described in 4.6.

6.2.6.11 Reference source

The reference source information should be captured as described in 4.4.

6.2.6.12 Version (Mandatory)

Version information associated with a Specified Substance Group 2 shall be captured as described in 4.13.

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6.3 Specified Substance Group 2 for Herbal preparations

6.3.1 Specified Substance Group2 ID

Table 234 — 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
Conformance	MANDATORY
Data Type	II
Business Rule(s)	NOTE the Specified Substance ID is NOT SPECIFIED for Specified Substance ID Request

6.3.2 Specified substance Group2 Name

Table 235 — Specified substance Group 2 Name

User Guidance	The name of the Specified Substance Group 2 shall be provided in this field. The name should be coined from the preferred term of the substance and the manufacturer. The Name Extract and Parent relationship with the Herbal preparation. Coupling to the manufacturer.
Example(s)	*Harpagophytum procumbens*, Root, Dry Extract Ethanol-Water (60-40) (1.5–3.0 = 1 w/w) — Manufacturer Ex.
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	The name should be coined from a concatenation of the preferred term of the parent substance and the manufacturer (i.e. Human Insulin Lilly).

6.3.3 Parent Substance ID

The concept of the Parent Substance ID follows the logic described above (see 6.2.3) and corresponds to the Substance or Specified Substance Group 1 ID that identifies the manufactured substance. The ID of the parent for the Specified Substance Groups 1, 2 or 3 may refer to either a Substance ID or a Specified Substance Group 1 or 2 ID.

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6.3.4 Manufacturing

6.3.4.1 Manufacturer ID

Table 236 — Manufacturer ID

User Guidance	The unique code used to track manufacturers.
Conformance	MANDATORY
Data Type	II
Business Rule(s)	The Manufacturer ID for SSG2 shall be linked to the actual Manufacturing site where the Herbal preparation is manufactured, or where the Herbal substance is collected, communicated and stored till further processing. The Manufacturer ID is primarily linked to the manufacturing of the Herbal substance or Herbal preparation. When other sites are needed to describe additional production steps this information shall be captured in the Reference Source Document class.

6.3.4.2 Manufacturer name

Table 237 — Manufacturer name

User Guidance	The name of the manufacturer of the Substance or the Specified Substance Group 1 shall be provided.
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	

6.3.4.3 Manufacturing type

Table 238 — Manufacturing type

User Guidance	The type of operation performed by the entity associated with the substance.
Example(s)	Manufacturer (of the Substance or Specified Substance), Harvester of the botanical material
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	

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6.3.4.4 Production method type

Table 239 — Production method type

User Guidance	The overall type of production system, synthetic, extractive, biosynthetic.
Example(s)	Extraction
Conformance	MANDATORY
Data Type	CD
Business Rule(s)	

6.3.5 Version

Version information associated with a Specified Substance Group 2 version information shall be captured as described in 4.13.

6.4 Specified Substance Group 3

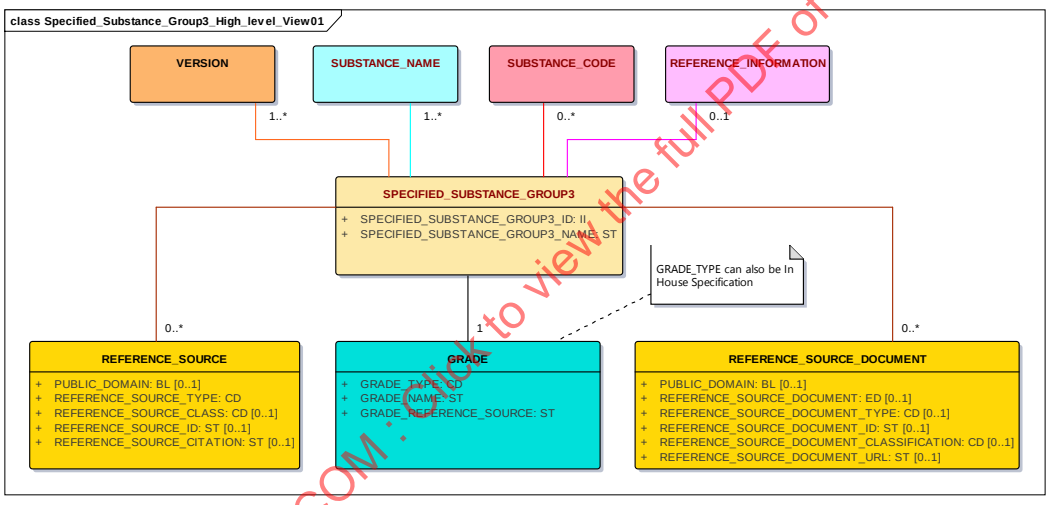


Figure 30 — Information model for the Specified Substance Group 3

Figure 30 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.

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

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6.4.1 Specified Substance Group 3 ID

Table 240 — 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. 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

6.4.2 Specified Substance Group3 Name

Table 241 — Specified Substance Group 3 name

User Guidance	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(s)	Name in monograph appended to Grade Type (i.e. sterile water for injection USP)
Conformance	MANDATORY
Data Type	ST
Business Rule(s)	Every reference to Pharmacopoeia generates a separate Secified Group 3 identifier

6.4.3 Parent Substance ID

The ID of the parent for the Specified Substance Group 3 may refer to either a Substance ID or Specified Substance Group 1 ID, or Specified Substance Group 2 ID.

6.4.4 Grade (Mandatory)

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

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6.4.4.1 Grade type

Table 242 — 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 specication 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.

6.4.4.2 Grade name

Table 243 — Grade name

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

6.4.4.3 Grade reference source

Table 244 — Grade reference source

User Guidance	Refers to the relevant reference source of the grade or specific source of monograph.
Example(s)	Ph.Eur., Ed 7th 2011 (7.2), USP
Conformance	MANDATORY
Data Type	ST

6.4.5 Version (Mandatory)

Version information associated with a Specified Substance Group 3 shall be captured as described in 4.13.

6.4.6 Reference source (Conditional)

The reference source information should be captured as described in 4.4.

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6.4.7 Reference source document (Conditional)

The reference source document information should be captured as described in 4.5.

6.4.8 Substance name (Mandatory)

Names associated with a Specified Substance Group 3 shall be captured as described in 4.3.

6.4.9 Substance code (Conditional)

Codes associated with a Specified Substance Group 3 should be captured as described in 4.6.

6.4.10 Version (Mandatory)

Version associated with a Specified Substance Group 3 Version information shall be captured as described in 4.13.

7 Description of the information modelling principles and practices

TBD.

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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 will 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 name will frequently map to different substances. INN names 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 the ISO IDMP 11615 standard, 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 organisation 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 organisation.

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

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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 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
(normative)

Chemical substance

B.1 General

In Figure B.1 a high level information is provided regarding chemical substances.

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 4.2.1-Substance types).

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.

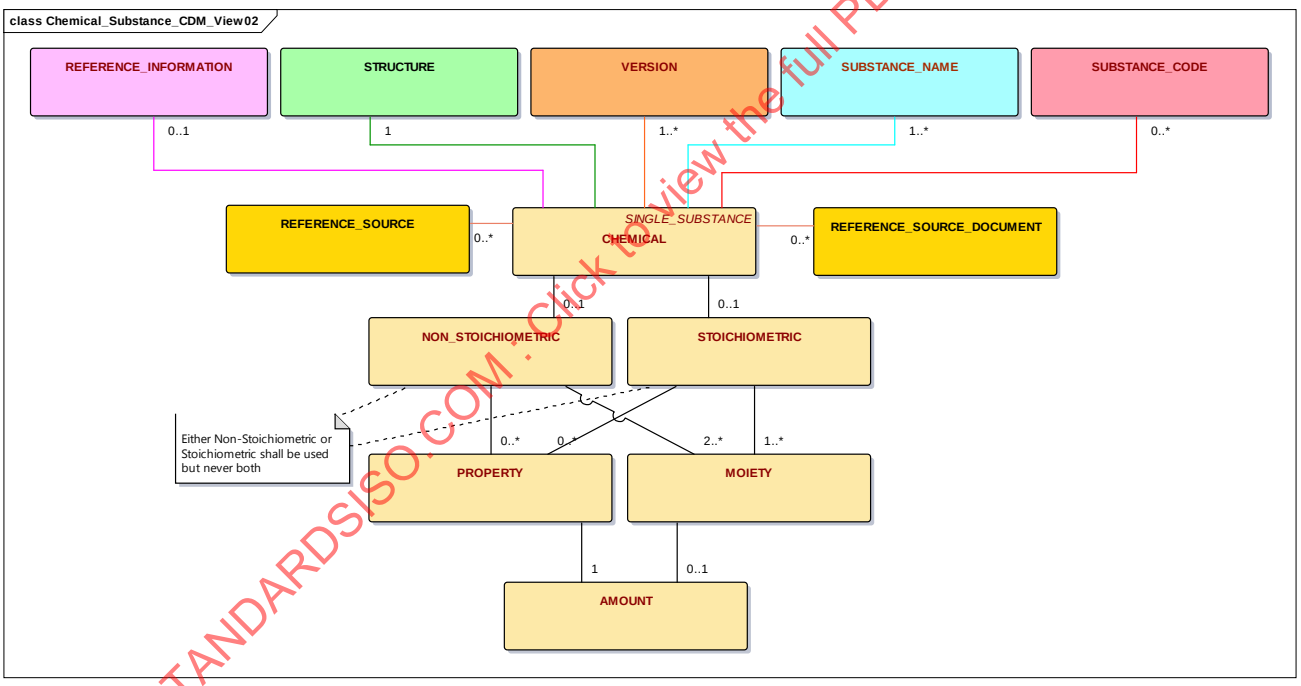


Figure B.1 — High level overview of Chemical Substance information

NOTE All element names are defined within the Terms and Definitions (B.5) of this Annex.

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 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.

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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:

Molecular formula: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$

NOTE 1 The molecular formula (see 4.8.4 and 4.8.5) 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 5.2.7 of this document.

Element Group: Amount

Average [Numeric Value]: 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 should be attached also to the element class Chemical, 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.

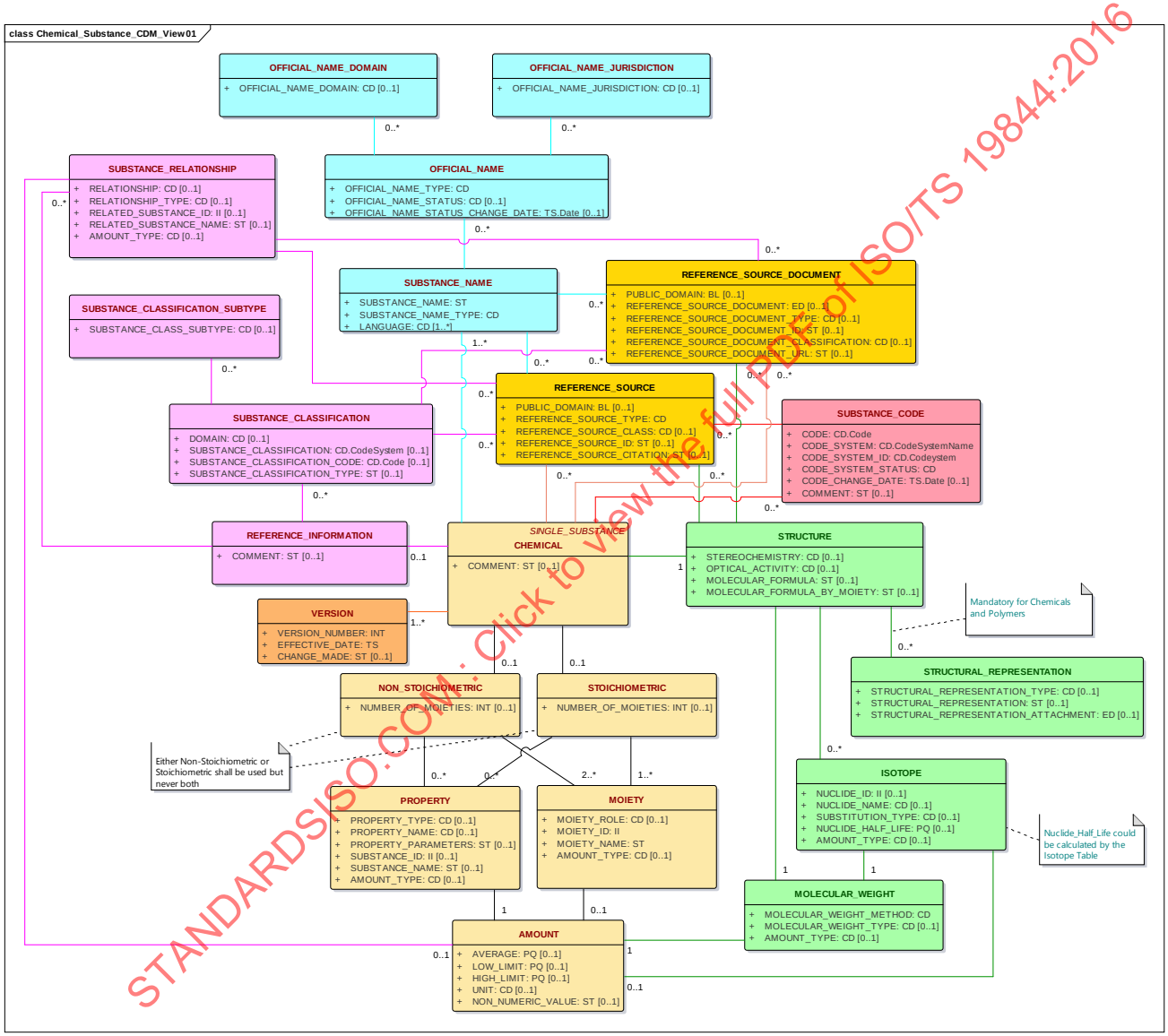
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B.2 Molecular Weight, Moiety and Amount for stoichiometric chemical substances

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 and solvates and hydrated substances 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[3] the qualitative and quantitative composition of a medicinal product should be described in terms of the active substances and constituents of the excipient.

[3] Directive 2001/83/EC on the Community code relating to medicinal products for human use.

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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 Moeity Group also tied to the Stoichiometric Chemical Substance: *e.g.*:

Describing Amlodipine besylate hydrate (1:1:1) in equal mol ratios with the molecular formula: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S \cdot H_2O$ 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 by Moiety: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S \cdot H_2O$
Molecular Formula: $C_{26}H_{33}ClN_2O_9S$, which is equal to the sum of the molecular formula of the moieties.

Relations with other Element Groups:

Element Group: Structural Modification

Structural Modification Type: Moiety

Element Group: Moiety

Moiety Role: Salt

Moiety ID: 685928Z18A (UNII)

Moiety Name: Benzenesulfonic acid

Amount Type: Mole Ratio to Amlodipine

Element Group: Amount

Average (Numeric value): 1

Element Group: Structural Modification

Structural Modification Type: Moiety

Element Group Moiety

Moiety Role: Solvate

Moiety ID: 059QF0KO0R (UNII)

Moiety Name: Water

Amount Type: Mole Ratio to Amlodipine

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Element Group Amount

Average (Numeric value): 1

Element Group Substance Relationship:

- The Active Moiety relationship is a one-way relationship;
- Parent molecule to a salt/solvate is a two-way relationship.
- Both one-and two-way relationships are possible.

Relationship: Active Moiety
Substance ID: PTYF75643O (Artificial ID); 1J444QC288 (UNII)
Substance Name: Amlodipine

NOTE The relationship from a parent molecule to a salt is an example of a two-way relationship

Relationship: Parent (Salt/Solvate)
Substance ID: PTYF75643O (Artificial ID); 1J444QC288 (UNII)
Substance Name: Amlodipine

Relationship: Salt
Substance ID: JUTYR9087S (Artificial ID); 685928Z18A (UNII)
Substance Name: Benzenesulphonic acid

NOTE For the further documentation in this Chemical Annex below it is assumed that the proposed changes of the ISO 11238 Substance Standard will be accepted for the addition of the element Molecular Weight and Amount Group and the change for the element Moiety also connected to stoichiometric chemical substances when applicable.

When requesting a Substance ID for a substance in the development stage or substance under investigation, only a minimum set of information should 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).

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B.3 Outline of Annex B

This Annex B 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 Substance**

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 substance

Captured at the Specified Substance level:

- Multi substance material

- **Key elements of a chemical substance are :**

- Substance name and Company-code
- Substance structure
- Substance molecular formula
- Substance molecular weight
- 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 Group 1, 2 or 3 Specified substance level when appropriate.**

- **Discussing Radionuclide Substance.**

B.4 Scope

This Annex provides guidance for Chemical Substance, Mixture Substance and Radionuclide to define elements that describe mandatory and conditional requirements/fields in order to generate ISO IDMP Substance Identifiers in view of 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.5 Terms and definitions

For the purposes of this Annex B, both the terms and definitions given in ISO 11238 and the following apply.

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B5.1
ATC Code, Substance classification code
Anatomic Therapeutic Chemical Classification code

NOTE 1 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 This pharmaceutical coding system divides drugs into different groups according to the organ or system on which they act and/or their therapeutic and chemical characteristics. Each bottom-level ATC code stands for a pharmaceutically used substance in a single indication (or use). This means that one drug can have more than one code: Acetylsalicylic acid (Aspirin), 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.

B5.2
boiling point
corrected temperature at which the vapour pressure of a liquid is equal to 101.3 kPa.

B5.3
co-crystals
multi-component crystals based on hydrogen bonding interactions without the transfer of hydrogen ions to form salts.

B5.4
CV
controlled vocabulary
finite set of values that represent the only allowed values for a data item.

NOTE 1 The allowed values can be codes, text, or numeric.

NOTE 2 Adapted from CDISC Clinical Research Glossary V8.0, 2009.

B5.5
CAS Index name
Chemical Abstracts Service Index Name, also referred to as CAS Registry name

B5.6
CAS Registry Number /CAS number
unique numerical identifier

NOTE The numbers are sequential and are assigned as a substance enters the registry system. The numbers do not have a common length and lengths vary from 5 digits to nine 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.

B5.7
Cahn-Ingold-Prelog priority rules, CIP system or CIP conventions
set of rules used in organic chemistry to name the stereoisomers of a molecule

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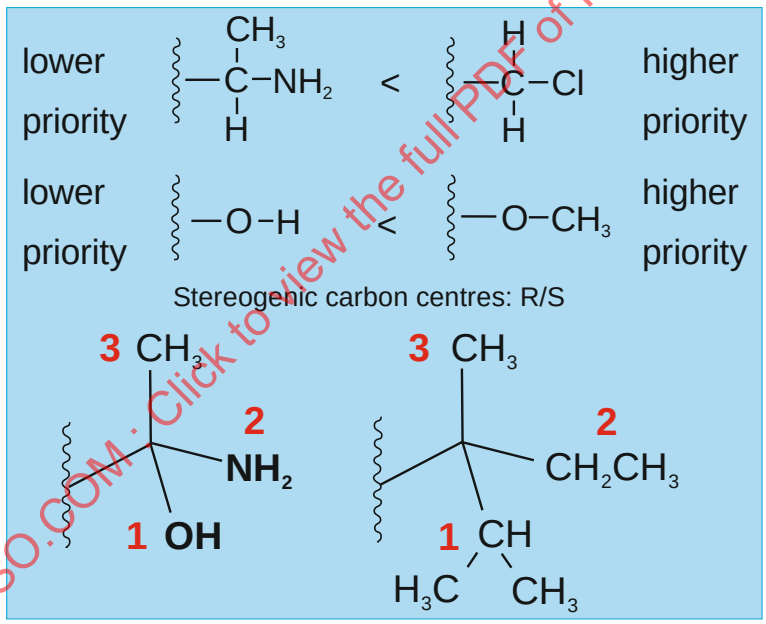
NOTE A molecule may contain any number of stereogenic carbon centres and any number of double bonds, and each gives rise to two possible configurations. The purpose of the CIP system is to assign an R or S descriptor to each stereogenic carbon centre and an E or Z descriptor to each double bond so that the configuration of the entire molecule can be specified uniquely by including the descriptors in its systematic name.

B5.8
configuration
method for indicating the three-dimensional arrangement of atoms at a stereogenic carbon centre

NOTE 1 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 If a decision about priority can't be reached by applying rule 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 Multiple-bonded atoms are considered equivalent to the same number of single-bonded atoms.

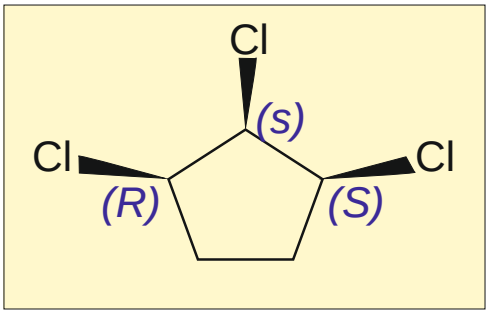


Two examples of stereogenic carbon centres: The lowest substituent is shown only by a wavy line, and is assumed to be behind the rest of the molecule. Both centres shown are S isomers.

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.

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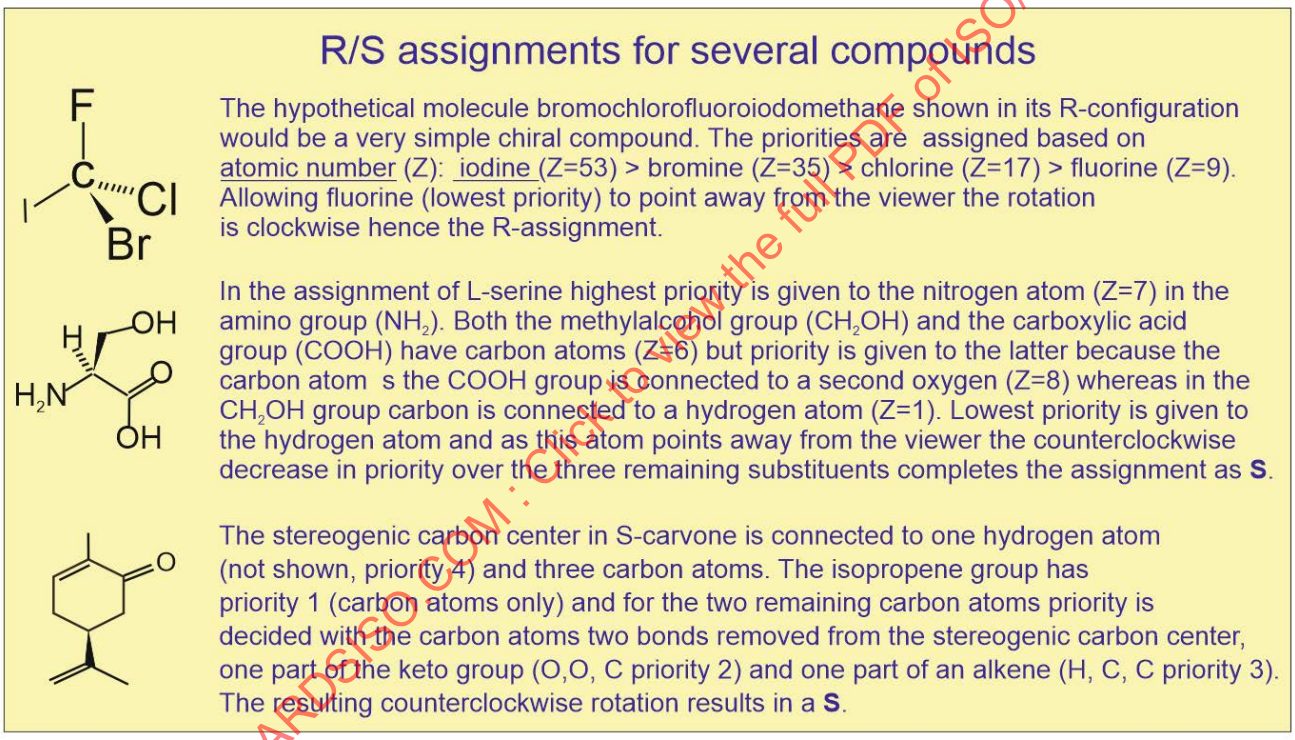
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(1*R*,2*s*,3*S*)-1,2,3-trichlorocyclopentane

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.

EXAMPLES:



B5.9
critical point, critical temperature, critical pressure
behaviour of a heated liquid

NOTE The behaviour of a heated in an open vessel differs from that of a liquid in a sealed vessel.

In an open vessel, the liquid vaporises from its surface as it is heated. At the temperature at which its vapour pressure would be equal to the external pressure, vaporisation can occur throughout the bulk of the liquid and the vapour can expand freely into the surroundings. The condition of free vaporisation throughout the liquid is called **boiling.** The temperature at which

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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 (Figure B.3, Fig.2(A)). At the same time the density of the liquid decreases as a result of its expansion. (Figure B.3, Fig.2(B)) 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. (Figure B.3, Fig. 2(C)) The temperature at which the surface disappears is the **critical temperature T_c**. The corresponding vapour pressure is the **critical pressure p_c.**

B5.10
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.

B5.11
elemental composition
pure chemical substance 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 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 Methane CH_4 is [C, H] since it consists of two chemical elements.

B5.12
EV-Code
EudraVigilance Code
code for a substance used in the Extended EudraVigilance Medicinal Product Dictionary (XEVMPD), developed by the European Medicines Agency (EMA). The XEVMPD is designed to support the collection, reporting, coding and evaluation of authorised and investigational medicinal product information in a standardised and structural way.

B5.13
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.

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B5.14
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 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 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 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/C6H6 /c1-2-4-6-5-3-1/h1-6H.

B5.15
InChI Key
fixed length (25 characters) condensed digital representation of the InChI designed to allow for easy web searches of chemical compounds.

NOTE 1 The full InChI is too lengthy for easy searching, and therefore the InChIKey was developed.

NOTE 2 This is sometimes referred to as hashed InChI.

B5.16
InChI resolvers
lookup service to make the links between the InChI key and InChI.

NOTE 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.

B5.17
isomers

B5.17.1
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, diastereoisomers, geometric isomers or constitutional isomers.

B5.17.2
enantiomers
two stereoisomers related to each other by a reflection. They are mirror images of each other which are non-superimposable. Every stereogenic centre in one molecule has the opposite configuration in the other. Two compounds that are enantiomers of each other have the same

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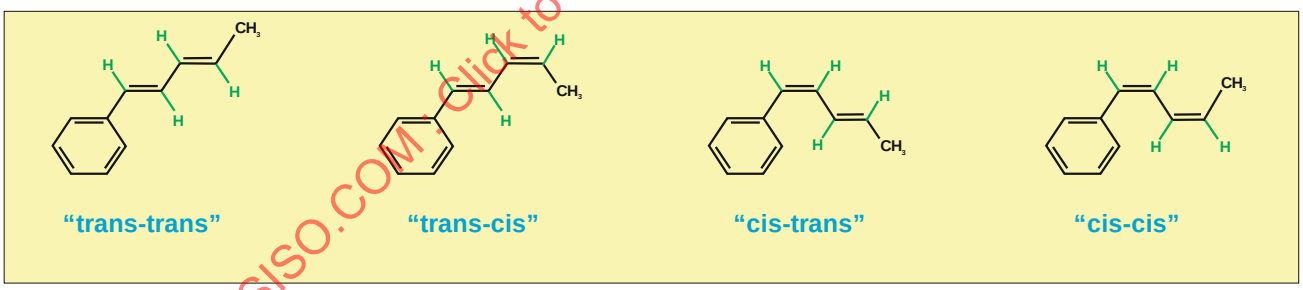
physical properties except for the direction in which they rotate polarised light and how they interact with different optical isomers of other compounds. As a result, different enantiomers of a compound may have substantially different biological effects. Pure enantiomers also exhibit the phenomenon of optical activity and can be separated only with the use of a chiral agent.

B5.17.3
diastereomers
stereoisomers not related through a reflection operation. Diastereomers are pairs of stereoisomers that are not mirror images of each other. 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**.

B5.17.4
geometric Isomers
sub-class of diastereomers which exist due to restricted rotation in a molecule and do not require stereogenic centres to exist. 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: 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



B5.17.5
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. 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.

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B5.17.6
constitutional isomers
isomers that share the same molecular formula, but the bond connections (atomic constitution) and/or their order differ(s) between different atoms/groups. (e.g.*n*-Butane and *iso*-Butane; Ethyl alcohol and Dimethyl ether; Isopropylamine and *n*-Propylamine).

B5.18
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)[4].

B5.19
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.

B5.20
mixture substance
type of polydisperse substance that is a combination of single substances isolated or synthesised/obtained in the process together.

EXAMPLE: Gentamicin would be defined as a mixture substance of Gentamicin C1, C1a, C2, C2a, and Gentamicin C2b. Glyceryl monoesters could be defined as a mixture substance of two single substances which differ in the position of esterification.

B5.21
moiety
moiety is an entity within a substance that has a complete and continuous molecular structure.

NOTE The strength of a medicinal product is often based on what is referred to as the active moiety and should be defined in a consistent manner across all products. To avoid ambiguity, the free acid and/or free base should be used as the moiety upon which strength is based.

B5.22
molecular formula
simplest type of formula, which uses only letters and numbers indicating atomic proportional ratios (the numerical proportions of atoms of one type to those of other types) of the chemical formula 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 also other symbols, such as parentheses, dashes, brackets, and plus (+) and minus (–) signs. These are limited to a single typographic line of symbols, which may

[4] 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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include subscripts and superscripts. A chemical formula contains no words. (*e.g.* Glucose $C_6H_{12}O_6$).

B5.23
molecular structure
unambiguous representation of the arrangement of atoms. For the purposes of defining substances, three dimensional conformations shall not be captured.

B5.24
molecular weight
mass of one molecule of a homogenous substance or the average mass of molecules that comprise a heterogeneous substance. The unified atomic mass unit is the unit of molecular weight and includes the type of molecular weight (g/mol).

B5.25
multi-substance material
single substances of diverse origin that are brought together and do not undergo a chemical transformation will be defined as multi-substance material (Group 1 Specified Substance) and not a mixture substance.

B5.26
official name type
INN: International Nonproprietary Name, also known as rINN, recommended International Nonproprietary Name or pINN, proposed International Nonproprietary Name.

WHO: World Health Organization**:**

WHO-application International Nonproprietary Name rules[5]

BAN: British Approved Name

Ph.Eur.: European Pharmacopoeia

JAN: Japanese approved name

JP: Japanese Pharmacopoeia

USAN: United States Adopted Names

USP: United States Pharmacopoeia

DAB (EAB): Deutsches Arzneibuch. This has been followed up by Europäisches Arzneibuch.

HAB: Homöopatisches Arzneibuch 2010, Ambtliche Ausgabe. Deutschen Apotheken Verlag, Stuttgart.

HP: Pharmacopoea Homoepathica polyglotta. 8th edition. Leipzig. Dr. Willmar Schwabe, 1911.

B5.27
optical rotation
property displayed by chiral substances of rotating the plane of polarisation of polarised light. The amount of rotation observed in a polarimetry experiment depends on the number of

[5] http://whoqlibdoc.who.int/hq/1997/WHO_PHARM_S_NOM_1570.pdf

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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 both sample concentration and sample path length.

NOTE Optical rotation is considered to be positive (+) for dextrorotatory substances and negative (-) for laevorotatory substances.

B5.27.1

specific optical rotation [αm]tλ

rotation, expressed in radians, measured at the temperature *t* (20°C) at a wavelength λ (usual D, light of 589,3 nanometer wavelength of the Sodium D-line, that is the yellow light emitted from common sodium lamps) and a path length of 1 decimeter (1 dm = 10 cm).

$$[\alpha]^{20}_{D} = \frac{\text{Observed rotation (degrees)}}{\text{Path length (dm) x Concentration C (g/ml)}}.$$

B5.28

phase transition

occurs spontaneous of one phase to another phase at a characteristic temperature for a given pressure. 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 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.

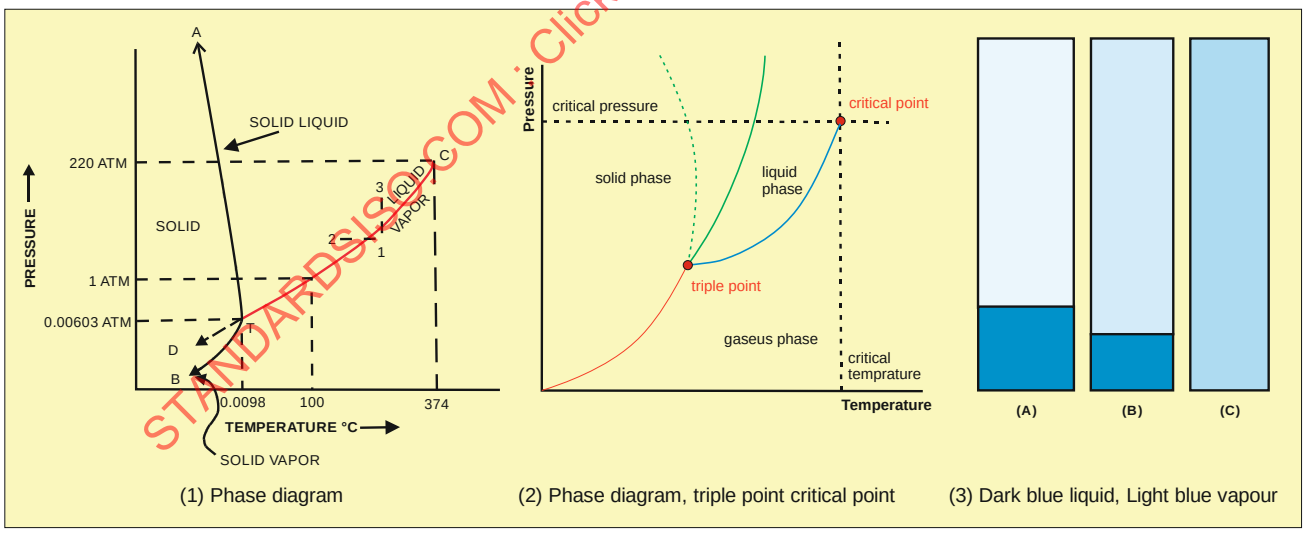


Figure B.3 — Phase diagrams

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

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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.

B5.29
physical form
physical state, either gas, liquid, or solid, and the type of organisation for solid matter. Solids can be either crystalline or amorphous and can show polymorphism. Amorphous material is characterised by the absence of distinct reflections in the X-ray powder diffraction (XRPD) pattern.

B5.30
polymorphism
ability of a compound in the solid state to exist in different crystalline forms having the same chemical composition

NOTE 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 crystallisation conditions (temperature, pressure, solvent, concentration rate of crystallisation, seeding of the crystallisation medium, presence and concentration of impurities etc.). Information about the 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 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.

B5.31
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 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).

B5.32
salt
ionic substances formed from the neutralisation reaction of an acid and base. Salts are ionic compounds composed of cations (positive ions) and anions (negative ions).

B5.33
solvate
substance formed through association of a solvent molecule (i.e. water, alcohol) with another moiety. Solvates can be either stoichiometric or non-stoichiometric and are predominately present in the solid form of substances.

B5.34

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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. The solubility of a substance fundamentally depends on the used solvent 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.

B5.35
stoichiometric substances
substances that contains moieties in simple integral ratios.

NOTE 1 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 Chemicals have defined stoichiometry when the ration of all moieties (ion, counter ion and solvate), can be represented as simple integral ratios.

B5.36
UNII
10 character, randomly generated alpha-numeric string that is currently used to identify substances in medicinal products. 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.

B5.37
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".

B5.37.1
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 m2 at a rate (v) of 1 m/s relative to a parallel layer at a distance (x) of 1 meter.

NOTE The unit of dynamic viscosity is the pascal second (Pa.s). The most commonly used submultiple is the millipascal second (mPa.s).

B5.37.2
Kinematic viscosity
ratio of the dynamic viscosity **η** to the density of the fluid ρ 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.

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B5.37.3
inherent viscosity

ratio of the natural logarithm of the relative viscosity to the mass concentration of the polymer . Inherent viscosity is defined as:

$$\eta_{inh} = \frac{\ln \eta_{rel}}{c}$$

where **c** is the mass concentration of the polymer (g/dL) and η_{rel} is the relative viscosity, which is defined as

$$\eta_{rel} = \frac{\eta}{\eta_0}$$

where η is the viscosity of the solution and η_0 is the viscosity of the neat solvent. The unit of inherent viscosity is dL/g.

B.6 Chemical Substance subtypes and Mixture Substance

B.6.1 Substance type, Chemical substance

B.6.1.1 Stoichiometric chemical substances

As stated in the Main Body of the ISO/TS 19844: 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.

Chemical substances are defined on the basis of their covalent molecular structure; the presence of a salt (counter-ion) and/or solvates (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 counterions 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 accompanied document or a structural representation type ‘Molfile’, ‘SMILES’, ‘InChI’.

The structural information typically provided to INN, USAN, BAN or JAN to assign a non-proprietary 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

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account when defining and distinguishing substances. Information beyond monograph requirements may occasionally be necessary to distinguish substances".

B.6.2 Solid state forms of the Substance

B.6.2.1 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 (compaction, followability, 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-crystallisation 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 paring.

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 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.6.2.2 Solvates and hydrates

Water or solvent act as a conformer. 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 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.

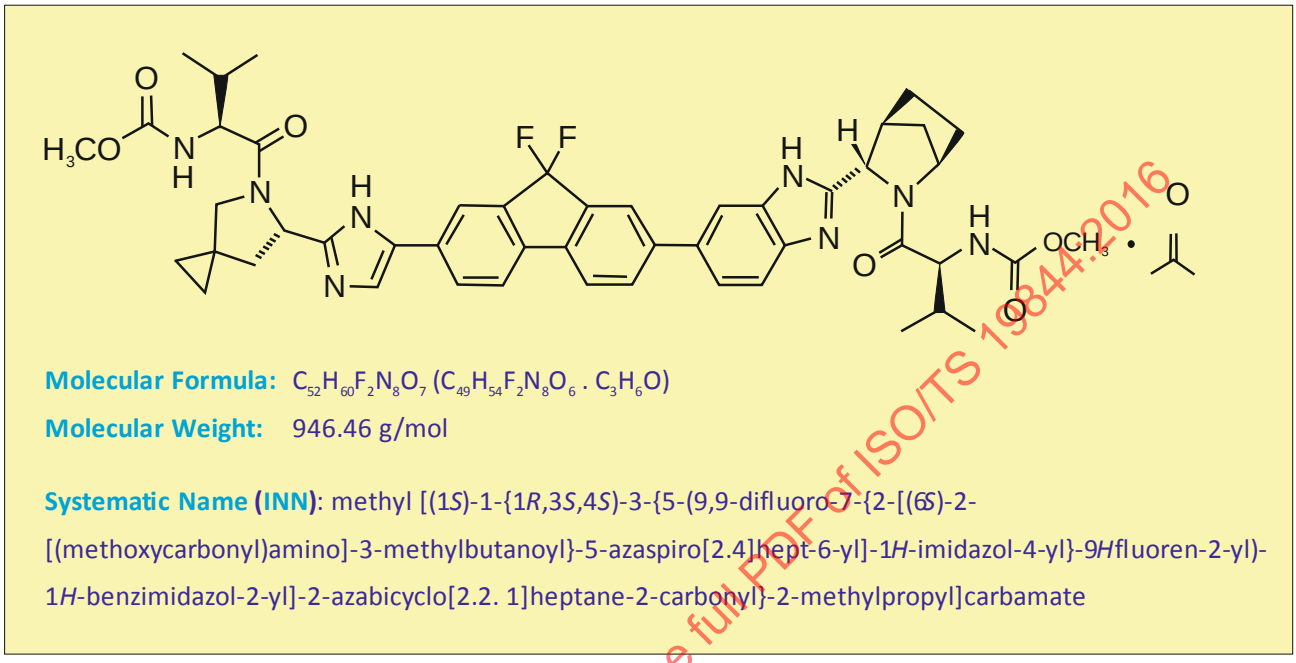
In ISO 11238 and ISO/TS 19844 these materials are considered as separate substances from the parent substance, describing the active moiety. Hydrates, solvates and co-crystals will have a separate Substance ID at the Substance level.

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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 **[$C_{49}H_{54}F_2N_8O_6$]**.



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.4 — Illustrative representation of Lepidasvir acetone solvate

EXAMPLE 3 Edoxaban tosilate monohydrate **[$C_{24}H_{30}ClN_7O_4S. C_7H_8O_3S. H_2O$]** will have a separate Substance ID from the parent substance Edoxaban [$C_{24}H_{30}ClN_7O_4S$] and from Edoxaban tosilate anhydrous **[$C_{24}H_{30}ClN_7O_4S. C_7H_8O_3S$]**, see Figure B.4.

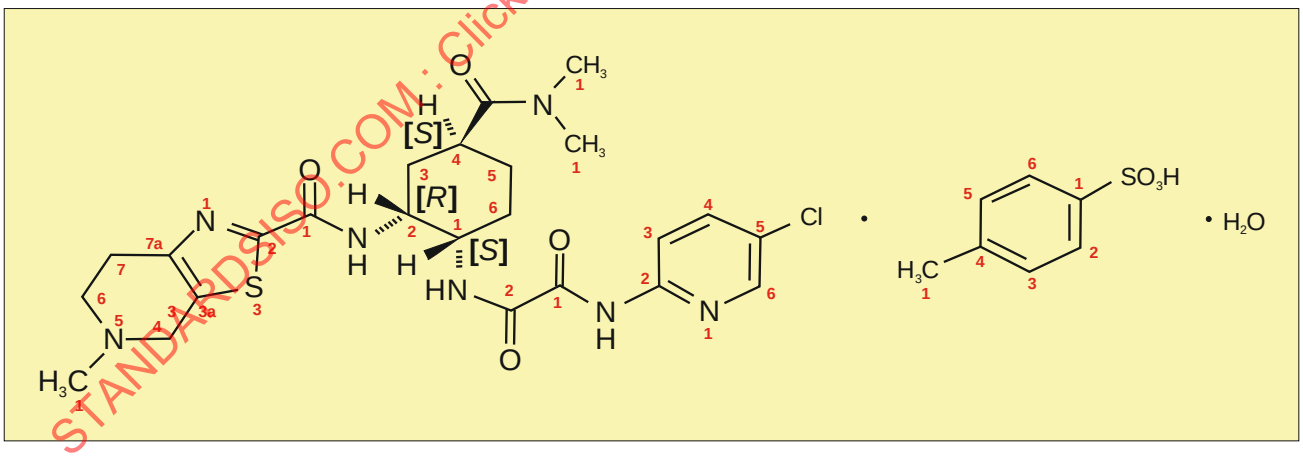


Figure B.5 — Full structural representation of Edoxaban tosilate monohydrate, 4.8.1

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

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solvate, where DMSO is fully incorporated into the crystal lattice. In solid state, one form has been identified (form 1). The active substance is a white to almost white solid, very slightly soluble in ethanol (non-solvated parent) and acetonitrile and slightly soluble in DMSO (solvated) and isopropyl acetate.

In Figure B.6 the structure of the parent substance Trametinib is provided as well as the structural relationship with its dimethyl sulfoxide solvate.

Structural representations of trametinib (parent), **figure A.1 and A.2 and its dimethyl sulfoxide solvate, figure B.1 and B.2.**

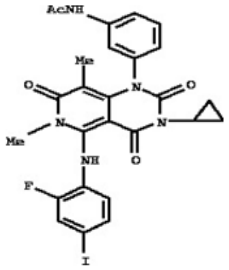


Fig: A.1 CAS Registry name and **CAS Number**: 871700-17-3 Acetamide, N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-3,4,6,7-tetrahydro-6,8-dimethyl-2,4,7-trioxopyrido [4,3-d]pyrimidin-1(2H)-yl]phenyl]-

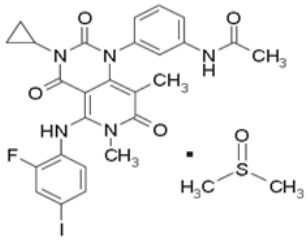


Fig: B.1: CAS Registry name and **CAS number** 1187431-43-1 Acetamide, N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino] -3,4,6,7-tetrahydro-6,8-dimethyl-2,4,7-trioxopyrido[4,3-*d*]pyrimidin-1(2*H*)-yl]phenyl]-,compound with 1,1'-sulfinylbis[methane] (1:1)

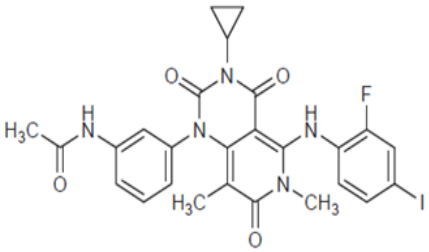


Fig: A.2 Recommended INN: List **67,** WHO Drug Information, Vol. 26, No. 1, 2012;
Trametinib; $C_{26}H_{23}FIN_5O_4$
N-(3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl]phenyl]acetamide; **Mw = 615.4**

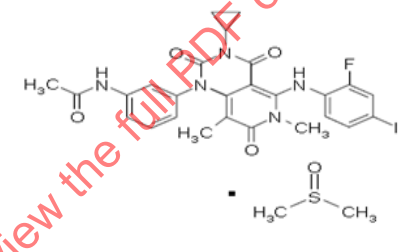


Fig: B.2: IUPAC name: Equimolecular combination of N-(3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)-yl]phenyl)acetamide with (methylsulfinyl)methane;
Trametinib dimethyl sulfoxide; $C_{26}H_{23}FIN_5O_4 . C_2H_6OS$;
Mw = 693.5 Da. (DMSO solvate of parent)

Figure B.6 — Structural representation of Trametinib and Trametinib dimethyl sulfoxide

NOTE Figure B.6/Fig.A.2, Figure B.6/Fig.B.1, Figure B.6/Fig.B.2 are correct structural representations as the complete chemical structures and definite stoichiometric ratios among moieties are described in 4.8.

B.6.3 Need to substantiate the chemical structure, molecular formula and molecular weight

When an INN-name 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 4.5) in order to substantiate the structure and molecular weight. The mass spectrum of trametinib dimethyl sulfoxide was obtained by positive ion electrospray ionisation 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.7.

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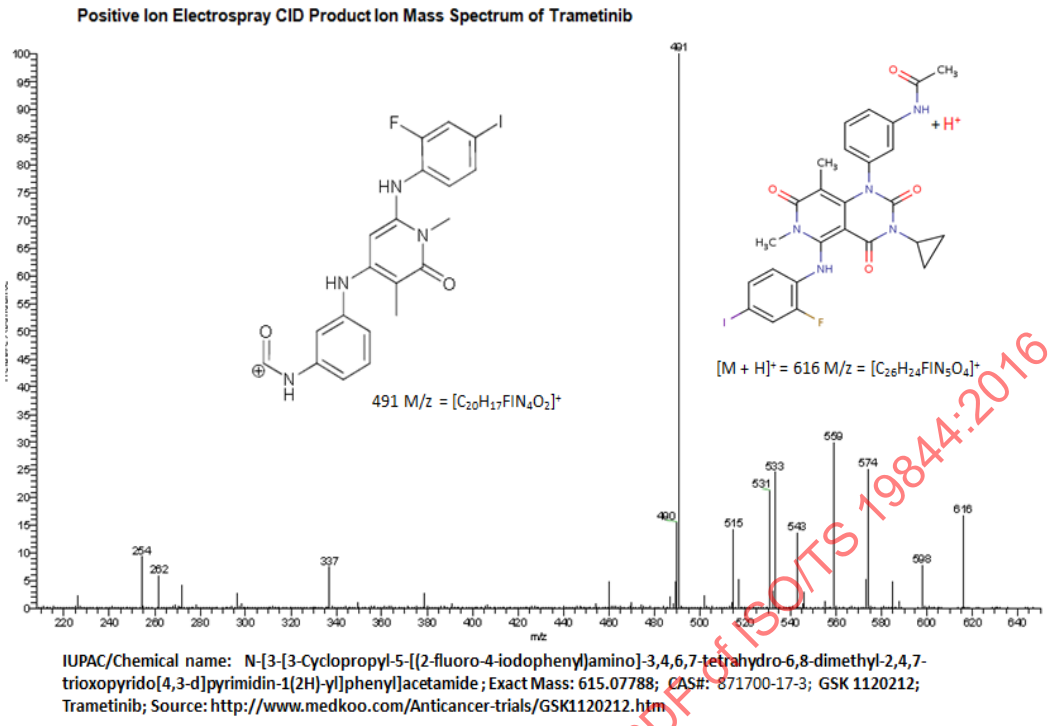


Figure B.7 — Mass Spectra and proposed structure of the molecular [M+1] ion and the [491]+ fragment Ion of Trametinib

B.6.4 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 the 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 6.1 and 6.1.12.

B.6.4.1 Example: Tibolone [$C_{21}H_{28}O_2$]

Tibolone is marketed 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

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Drug Products: Chemical Substance (ICH Topic Q 6A), 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.

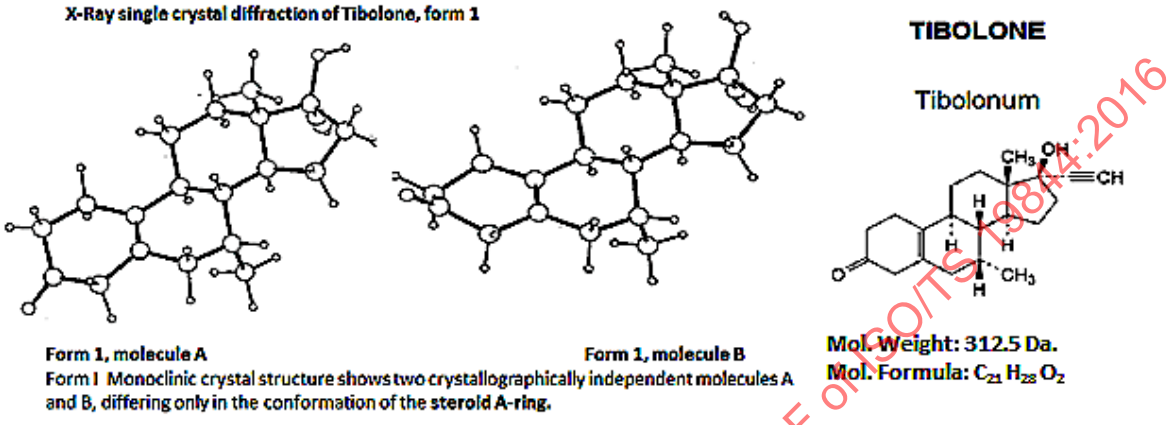


Figure B.8 — Representation of Tibolone monoclinic crystal structure and triclinic crystal structure

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 et al. "Thermal studies on polymorphic structures of Tibolone", Journal of Thermal Analysis & Calorimetry; Oct 2010, Vol. 102 Issue 1, p233; and Gabriel Lima Barros de Araújo; Solid state characterisation of tibolone polymorphs, Dissertation University São Paulo, 2009; http://www.teses.usp.br/teses/disponiveis/9/9139/tde-31032010-091615/es.php; (The results confirm that two pure polymorphic forms for Tibolone were crystallised: Form I, monoclinic, obtained by recrystallization from acetone and water and Form II, triclinic, recrystallised 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.6.5 Non-stoichiometric chemical substances

Non-stoichiometric chemical susbstances are substances having variable ratios among moieties; each moiety in itself has a discrete molecular structure. (E.g. The monosulfides of the transition metals are

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often nonstoichiometric. Iron(II) sulfide (the mineral Pyrrhotide) with a composition Fe(1-x) S (x = 0 to 0.2), see 5.1.5.

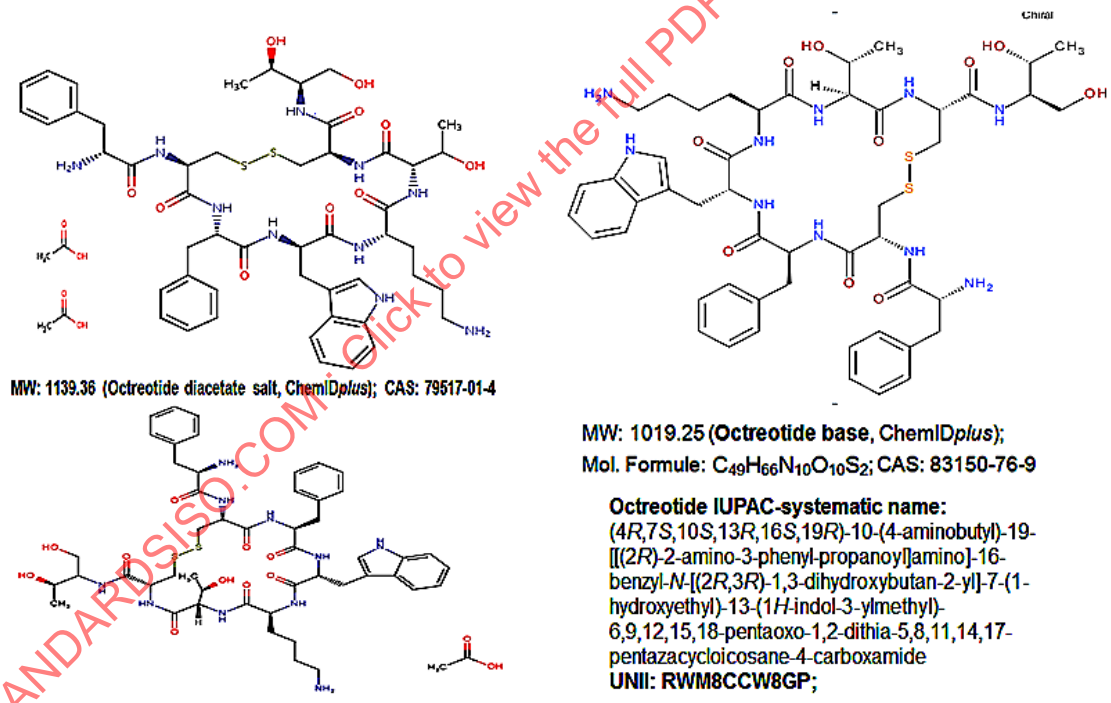
B.6.5.1 Example: USP monograph: Aluminium Chlorohydrex Propylene Glycol

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.6.5.2 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.8, Octreotide base **[$C_{49}H_{66}N_{10}O_{10}S_2$]**, Mol. weight 1019.25, Octreotide monoacetate **[$C_{49}H_{66}N_{10}O_{10}S_2 \cdot C_2H_4O_2$]**, and Octreotide diactetate **[$C_{49}H_{66}N_{10}O_{10}S_2 \cdot 2C_2H_4O_2$]** are shown obtained form FDA-SRS (base) and from Chem*IDplus* for the mono and diacetate salts.



MW: 1139.36 (Octreotide diacetate salt, Chem*IDplus*); CAS: 79517-01-4

MW: 1019.25 (**Octreotide base**, Chem*IDplus*);
Mol. Formule: $C_{49}H_{66}N_{10}O_{10}S_2$; CAS: 83150-76-9

Octreotide IUPAC-systematic name:
(4*R*,7*S*,10*S*,13*R*,16*S*,19*R*)-10-(4-aminobutyl)-19-[[(2*R*)-2-amino-3-phenyl-propanoyl]amino]-16-benzyl-*N*-[(2*R*,3*R*)-1,3-dihydroxybutan-2-yl]-7-(1-hydroxyethyl)-13-(1*H*-indol-3-ylmethyl)-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentazacycloicosane-4-carboxamide
UNII: RWM8CCW8GP;

CAS Reg. name and number: 79517-01-4
L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[(1R,2R)-2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2.fwdarw.7)-disulfide, acetate (1:?)
Mol. formule: $C_{49}H_{66}N_{10}O_{10}S_2 \cdot C_2H_4O_2$
Mol. weight for Octreotide monoacetate: 1079.25 Da.

Figure B.9 — Structural representation of Octreotide Acetate

In Figure B.9 the colored structures are in agreement with 4.8, but do not show the R,S-denominators. These are described in the systematic name.

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B.6.6 Mixture substance

A mixture substance is a type of polydisperse substance that is a combination of single substances isolated together or synthesised/obtained or produced in the same process. Two examples are provided:

B.6.6.1 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 substance contains as active multiple active components two pairs of constitutional isomers ($A_{2\text{-}4/5}$) and ($A_{2\text{-}2/3}$), see Figure B.9.

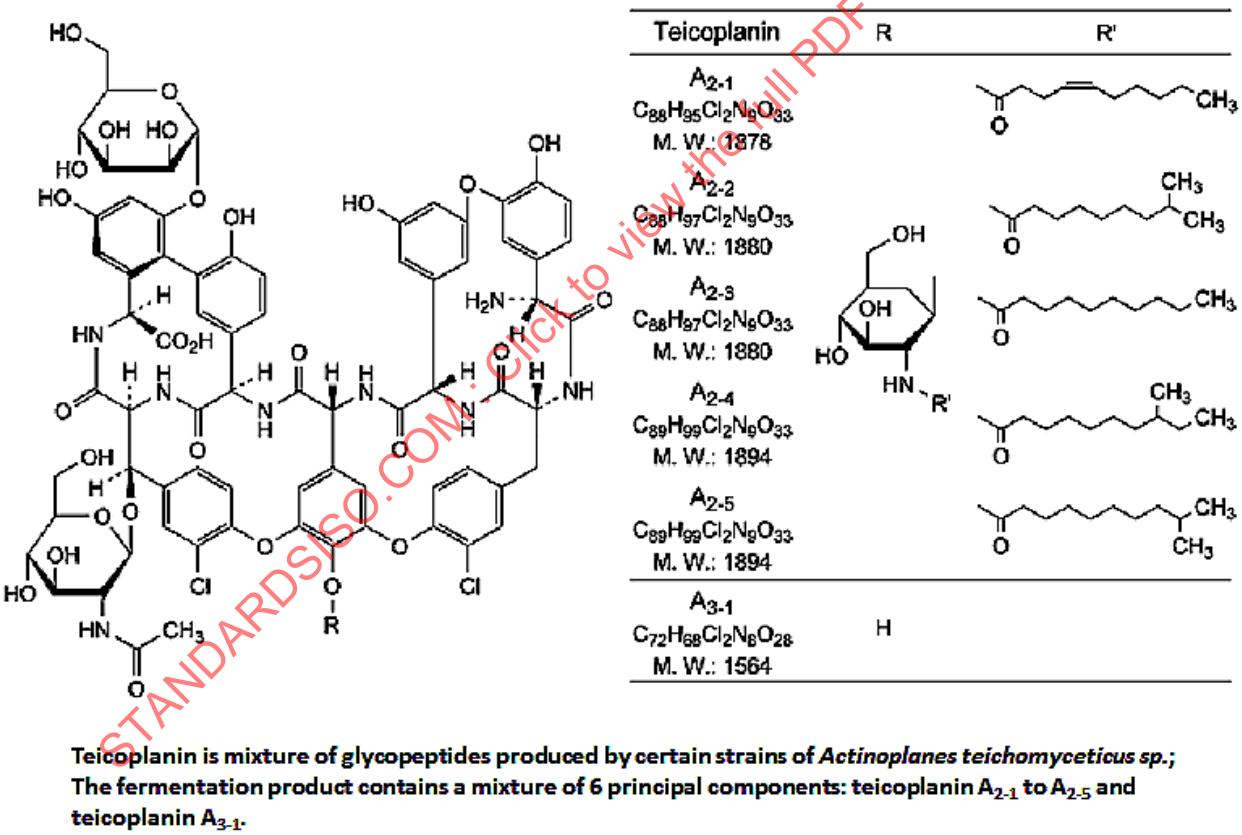


Figure B.10 — Structural representation of Teicoplanin (Ph.Eur.)

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B.6.7 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 synthesised together, but physically mixed together. They would be defined as a Specified Substance Group 1 substance.

B.6.7.1 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.11. 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 stabilisation to the paclitaxel nanoparticles to prevent aggregation. Stabilisation is achieved by the fact that albumin adsorbs onto the 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 stabilised 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.11.

In Figure B.12, the structure, names and molecular formula and molecular weight of Paclitaxel and Paclitaxel Poliglumex substances are presented.

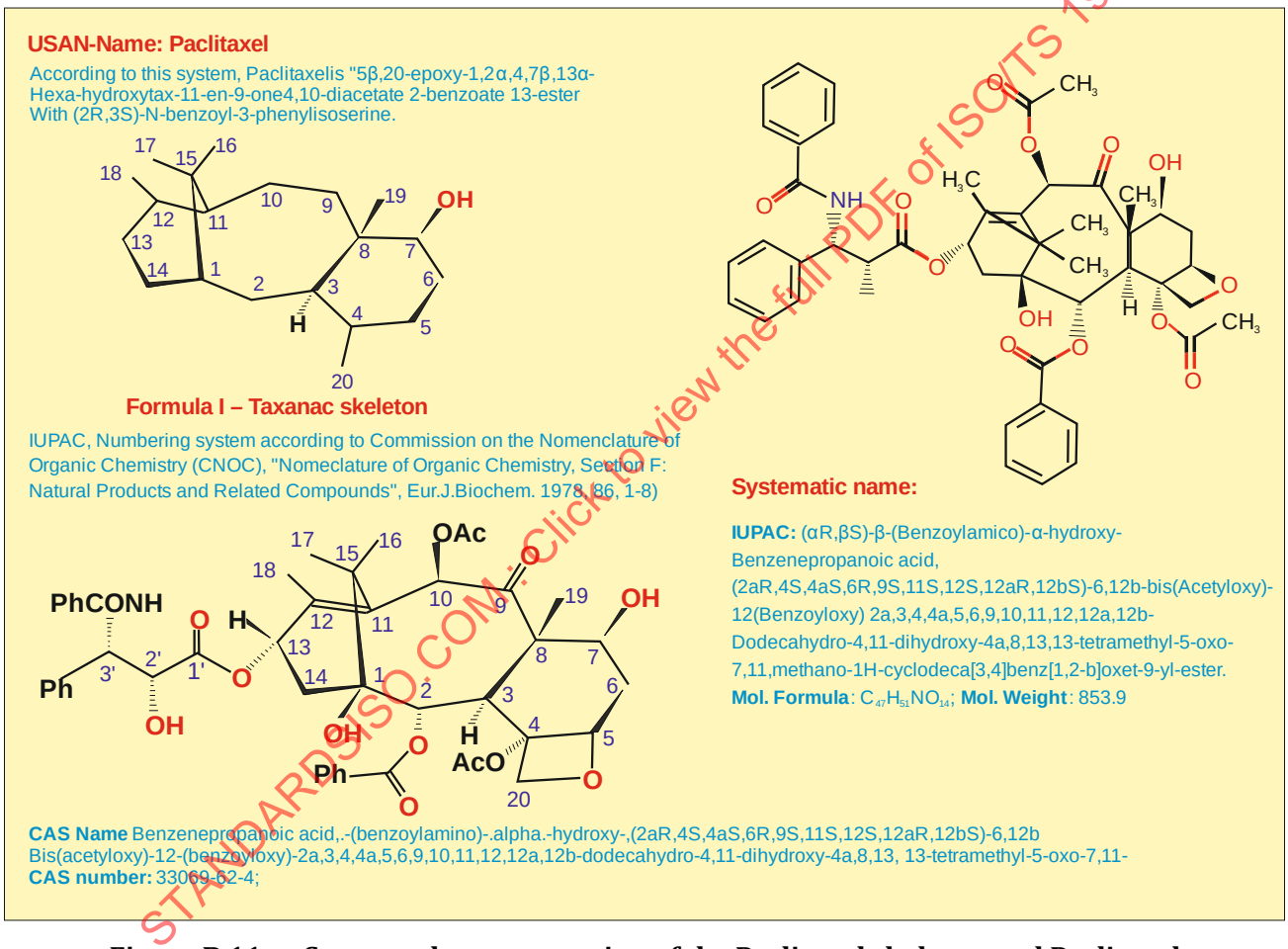
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Paclitaxel Poliglumex is a <u>covalent modification</u> of the Paclitaxel molecule. Paclitaxel Poliglumex is captured at the substance level.

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. The "coloured" structure is a structural representation of both the fragments. The "uncoloured" structure is the structural representation following the ISO/TS 19844 for polymers.

Paclitaxel Poliglumex is described in the FDA-SRS 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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Figure B.11 — Structural representation of the Paclitaxel skeleton and Paclitaxel

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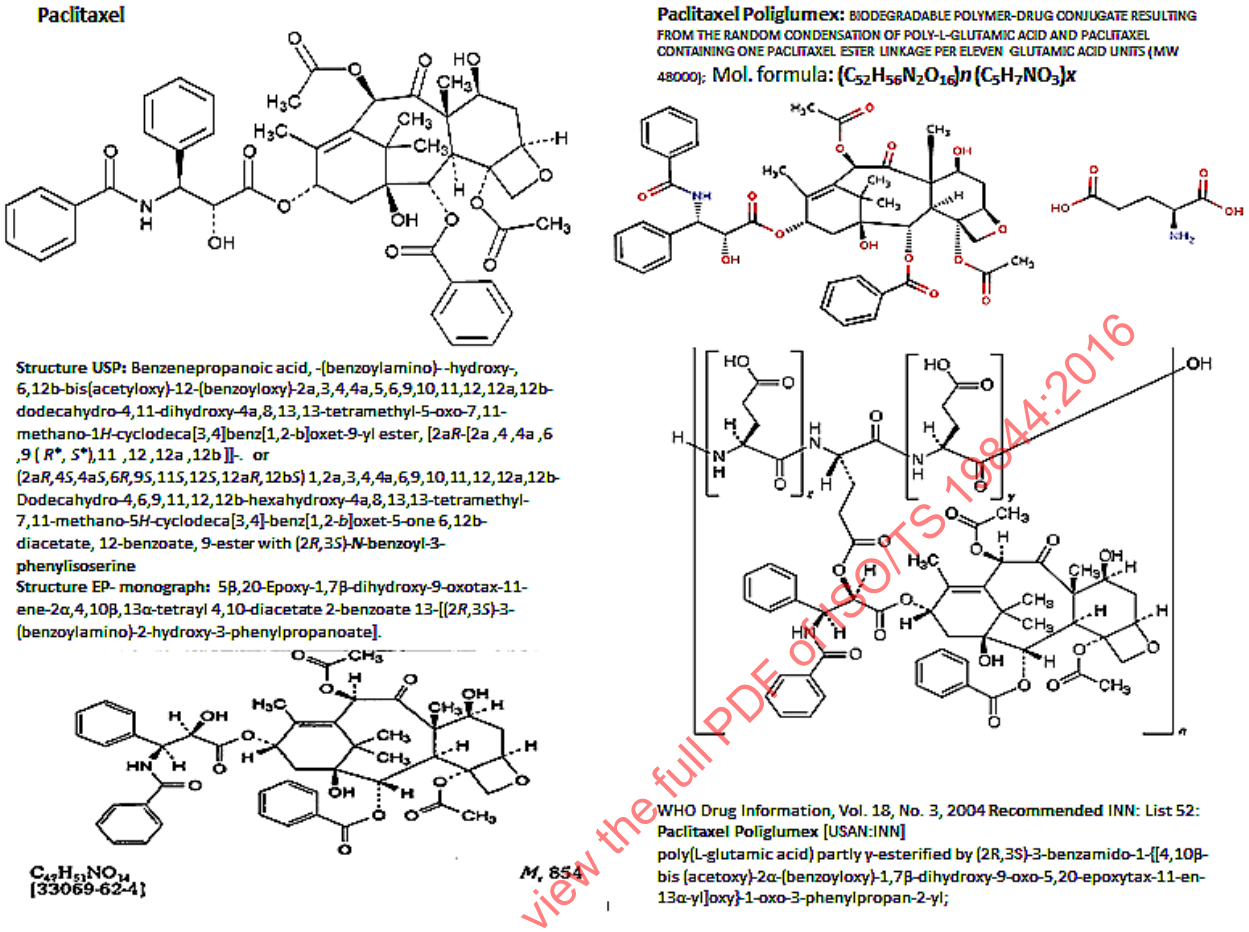


Figure B.12 — Structural representation of Paclitaxel and Paclitaxel Poliglumex

B.7 Discussion of the key elements of a chemical substance

B.7.1 Identity of material

The identity, nomenclature and chemical structure of the substance type chemical substance which is the subject of an application for marketing authorisation, or is under investigation, or is already marketed, is characterised by 5 key elements mentioned below of which in B.3 the solid state form already has been discussed:

- Substance name and/or Company-code
- Substance structure
- Substance molecular formula
- Substance molecular weight
- Physical form

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In the main body of this document the first two elements are extensively discussed in 4.3 (Substance names), 4.4 (Reference Source), 4.6 (Substance Code), 4.8.1 (Structural representation) whereas abbreviations and molecular formula and molecular weight are described.

The structural representation of the chemical substances shown in the figures inside Figure B.3 is discussed for each figure with respect to 4.8. Additional information will be discussed in the next clauses.

B.7.2 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 4.3.4.2) 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 non proprietary 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.

B.7.3 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 alphabetical order. When the formula contains no carbon, all the elements, including hydrogen, are listed alphabetically. In the 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: **$C_{26}H_{31}ClN_2O_8S$.**

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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 crystallisation 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 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.7.4 Molecular weight

Molecular mass or **molecular weight** refers to the mass of a molecule and is also directly derived from the molecular structure or the 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.

NOTE1 408.88 g/mol. (Parent Amlodipine), 158.18 g/mol. (Besilate).

NOTE 2 For a substance not described in a Pharmacopoeia (Ph.Eur., USP, JP) a mass spectrum should be provided to substantiate the calculated molecular weight.

B.7.5 Substance structure

Subclause 4.8 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 standardised formats (see 4.8.1).

A FULL structure is a structure in which the complete connectivity of the substance is known and the substance is monodisperse.

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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 Implementation Guidance.

The structure is “incomplete” to the definition of FULL structure and therefore called “illustrative” in the examples of Annex B.

B.7.5.1 Stereochemistry

The stereochemistry of the substance shall be indicated in the structure if it can be, as is stated in 4.8.4. Special cases of stereochemistry that cannot be indicated in the structure shall be described based on a controlled vocabulary. Figure B.13 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.

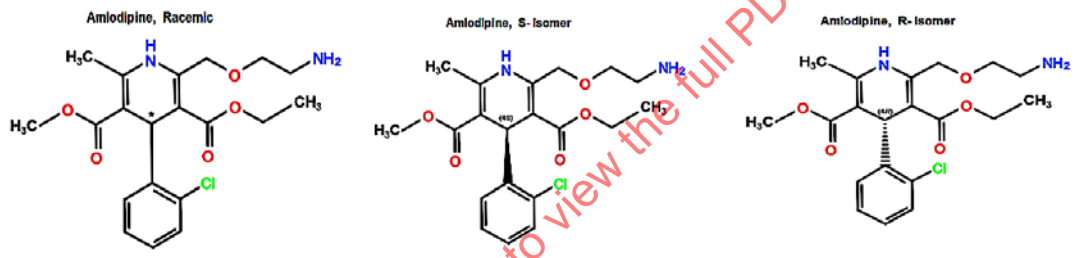


Figure B.13 — Full structural representation of Amlodipine

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, see Figure B.13.

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. See Figure B.13.

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The ISO/TS 19844 provides the following information in 4.8.2:

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

User Guidance	The stereochemistry of the substance are indicated in the structure and should be captured here. Special cases of stereochemistry that can't be indicated in the structure are described based on a controlled vocabulary. Mixtures of stereoisomers are 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, RACEMIC, MIXED, ACHIRAL, EPIMERIC, UNKNOWN
Conformance	CONDITIONAL
Data Type	CD
Value Allowed	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, ACHIRAL, ABSOLUTE, EPIMERIC, UNKNOWN
Business Rule(s)	When the Substance type (as defined in 4.2.1) is either chemical, protein, polymer or nucleic acid, this class becomes MANDATORY.
NOTE Clarification of the Value Allowed in conformance table 4.8.2, Source: NCI thesaurus: https://ncit.nci.nih.gov/ncitbrowser/	

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 counter clockwise direction
RACEMIC **Definition:**	**Racemate** An equimolar mixture of two enantiomers. A racemate is optically inactive.
EPIMERIC **Definition:**	**Epimeric Centres** A particular kind of diastereoisomers that differ in their stereochemistry at only one chiral centre; the stereochemistry at all other chiral centres is identical.
Cis-Trans Geometry	

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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 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.
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.

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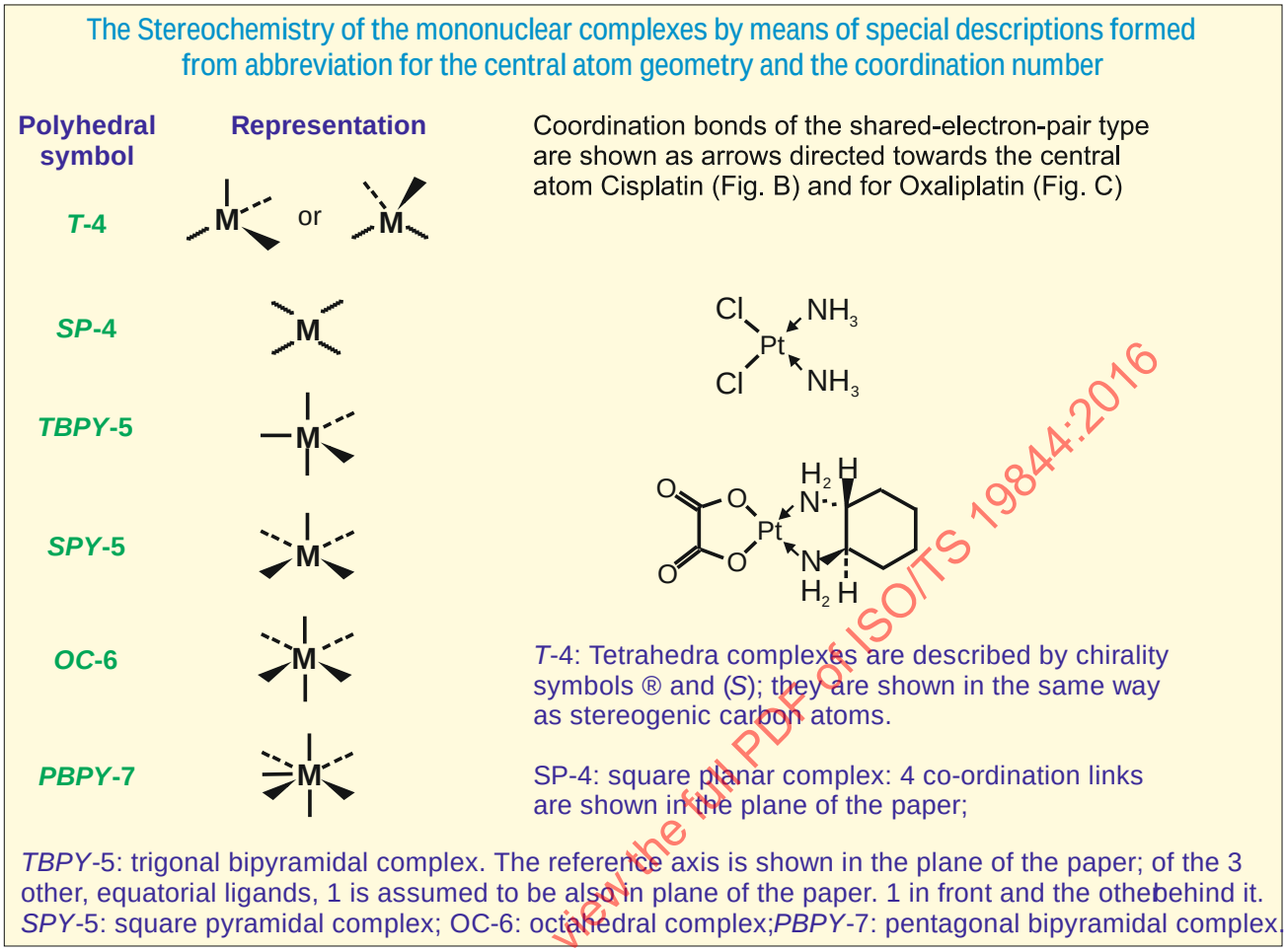


Figure B.14 — Stereochemistry of mononuclear complexes

B.7.5.2 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 special 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.14. Isomers can be classified in Stereoisomers (Enantiomers and Diastereomers), Geometric isomers, Conformers and Constitutional isomers. The definitions are described in B.5. In the following subclauses Stereoisomers and Geometric isomers will be discussed.

B.7.6 Geometric isomerism

B.7.6.1 (*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.15 presents example 1-Phenyl-1,3-pentadiene.

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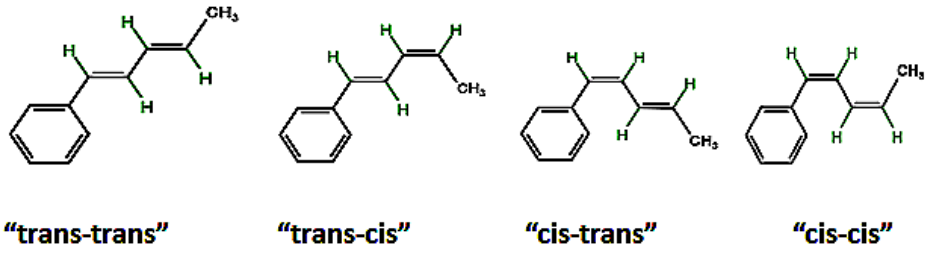


Figure B.15 — Stereochemistry of 1-Phenyl-1,3-pentadiene

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.16.

B.7.6.2 *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.16.

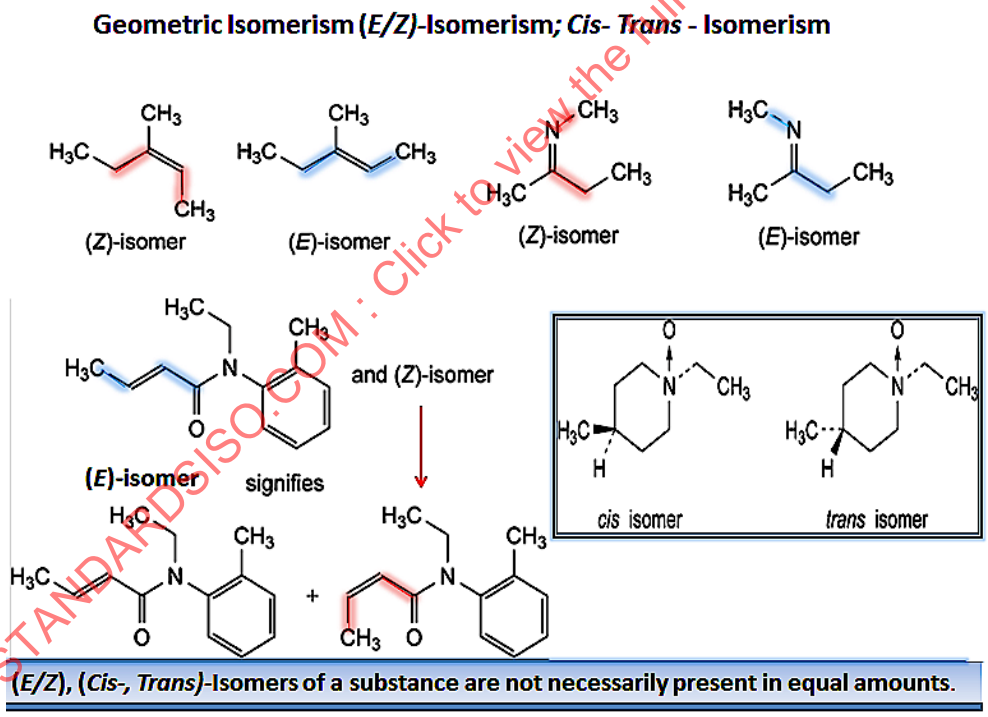


Figure B.16 — Geometric isomerismStereo-descriptors in systematic nomenclature: Substance with one centre of asymmetry

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)

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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.2. **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.12). The Element Groups capturing Amlodipine besilate are described in B.9.1, tabular example 1.

B.7.7 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.17 presents an example of the enantiomer and diasteriomers 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.

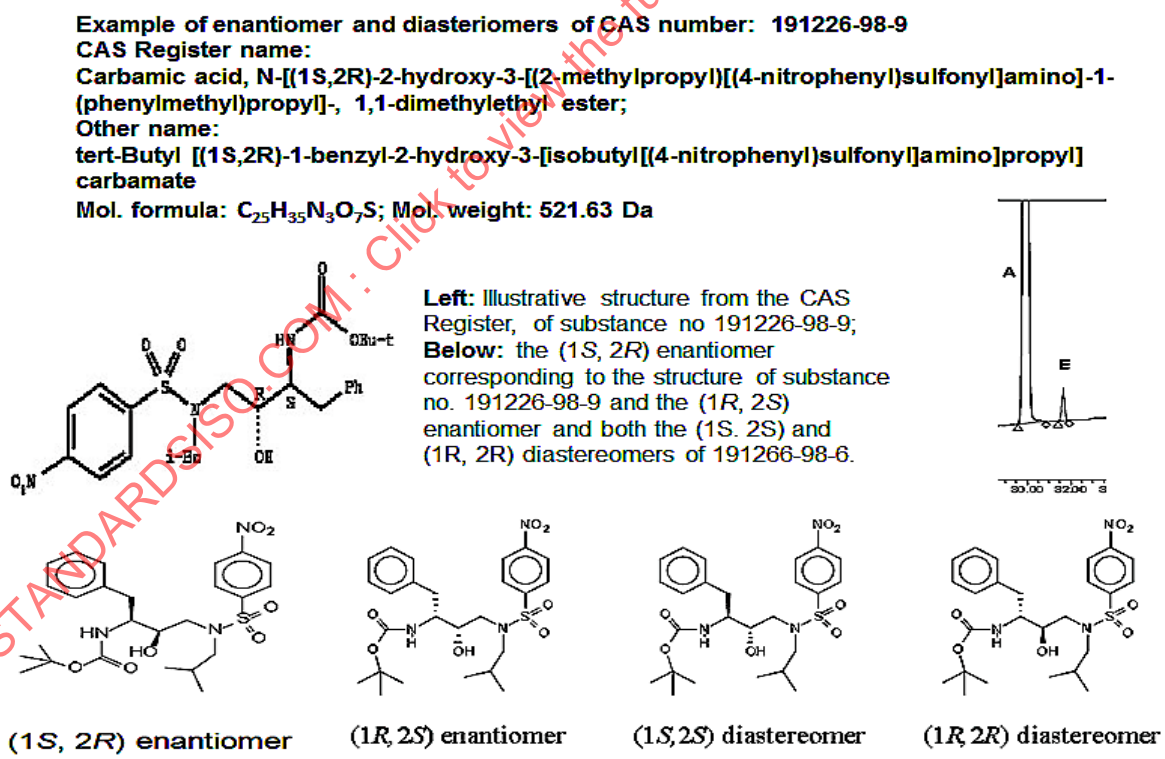


Figure B.17 — Structural representation of substances with two asymmetric centres

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B.7.8 Anomers

A special case of epimerism is that of anomerism of sugars. Anomers are defined as diastereoisomers 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 the Main Body of this document, 4.8.1 the structural representation of glucose in the crystalline state is provided as well as the introduction of an anomeric C_1-atom after cyclisation of D-glucose and representation of D-glucose in the Haworth projection, in Figure B.18. In Figure B.19 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.20 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, 4.8 Example α-, and β-Glucose anhydrous. The examples provided in Figure B.20 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.20 should be provided. Note that none of the electronic structural representation understands Haworth projections.

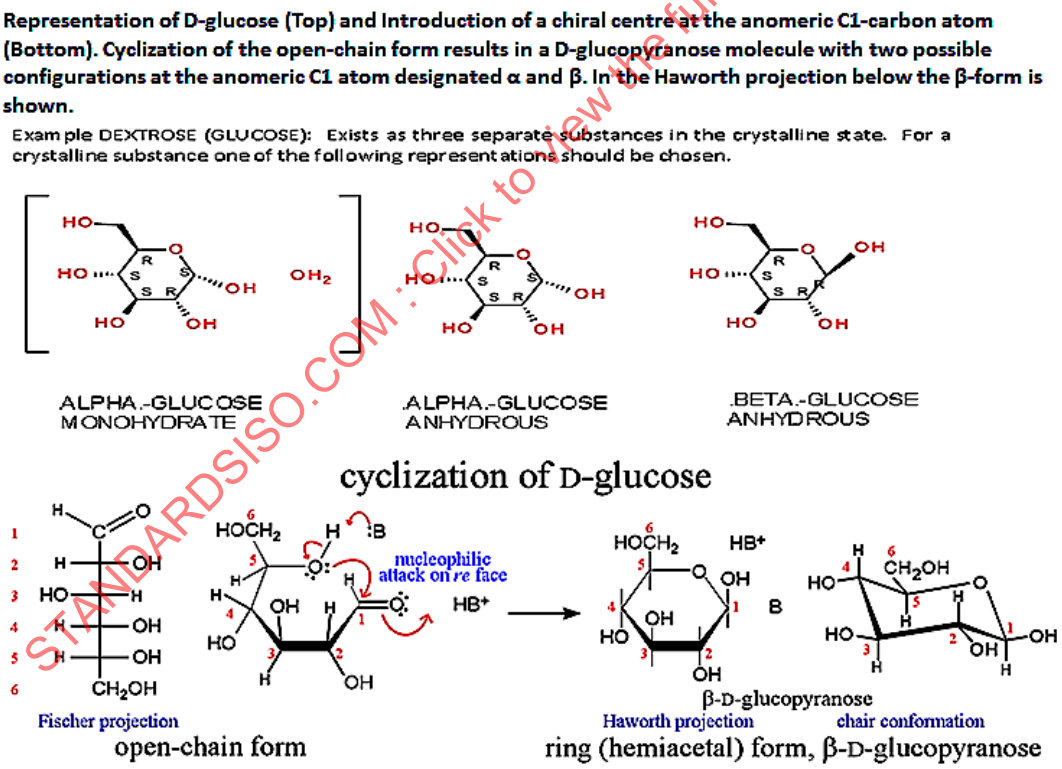


Figure B.18 — Structural representation of α- and β Glucose and α-Glucose monohydrate and in Haworth projection

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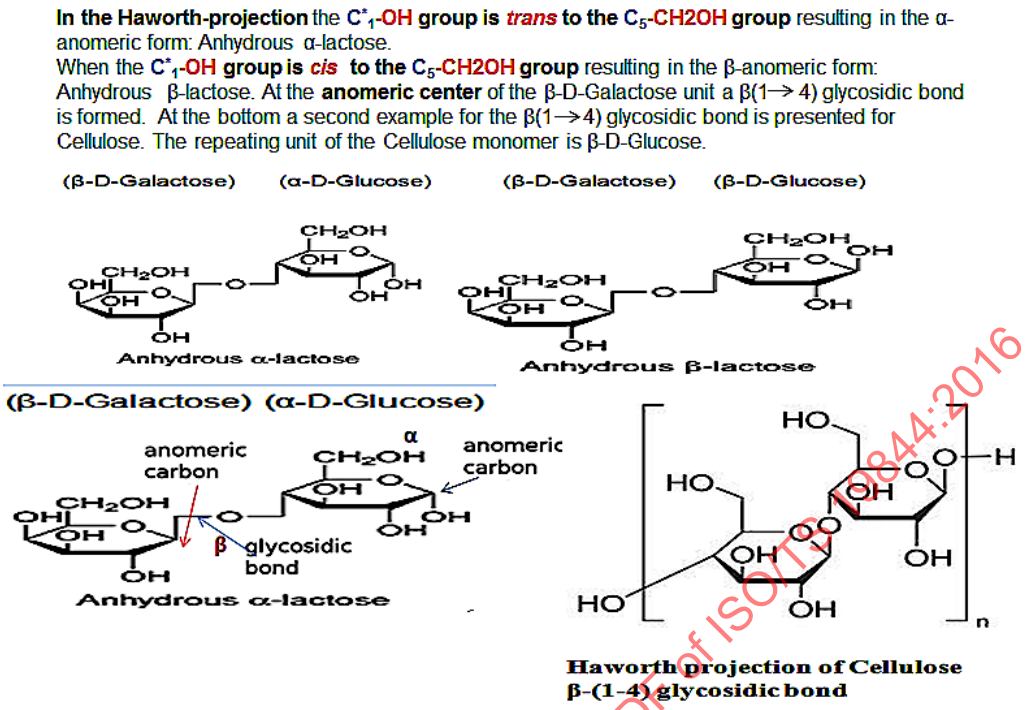


Figure B.19 — Haworth projection of α- and β Lactose anhydrous

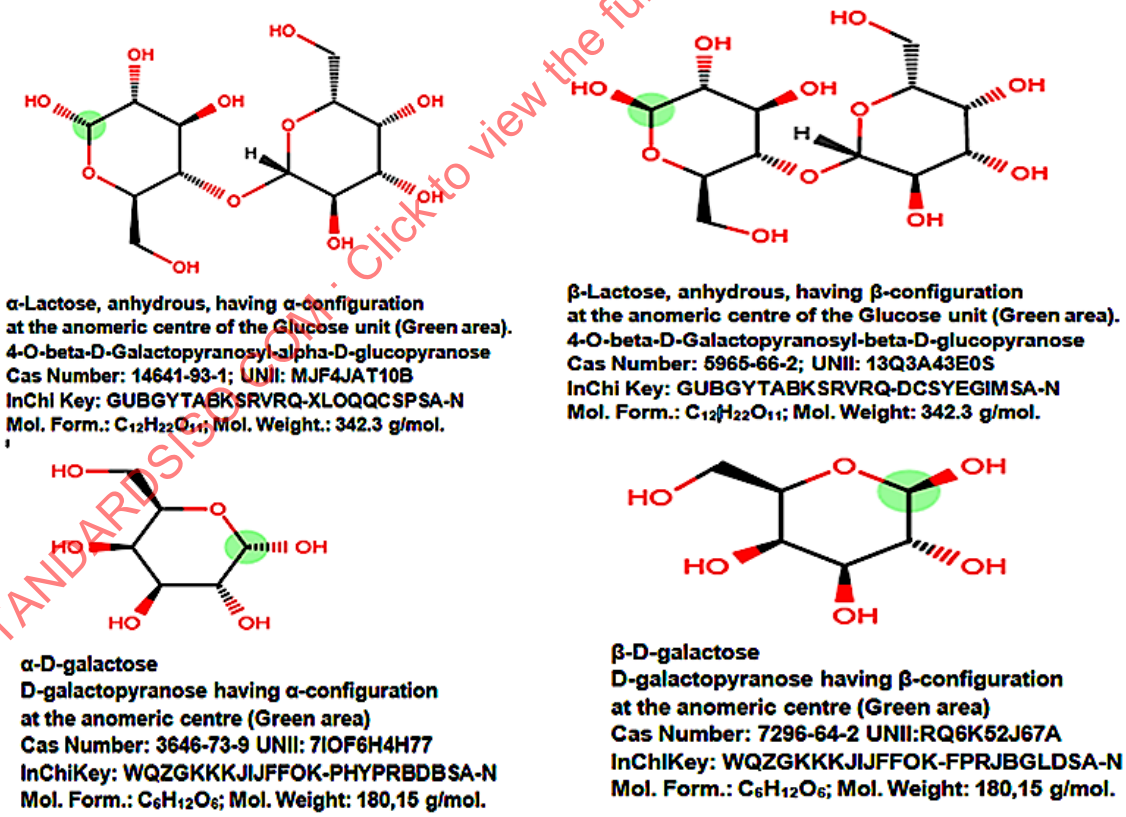


Figure B.20 — α- and β-Lactose, α-D- and β-D-Galactose in absolute Structural Representation in accordance with ISO/TS 19844

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B.7.9 Substance with more than two centres of Asymmetry (Mixture of stereoisomers)

In the Main Body of this document, 4.8.3, Table 54, 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".

Next **example of Misoprostol** will provide 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-SRS 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
CAS Registry Number	59122-46-2
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.21.

NOTE 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.

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INN: Misoprostol; Mol. form.: $C_{22}H_{38}O_5$; Mol. weight: 382.5 g/mol.; CAS: 59122-46-2
USAN: (±)-(11α, 13E)-11 ,16-dihydroxy-16-methyl-9-oxoprost-13-en-l-oic acid, methyl ester
EP: 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

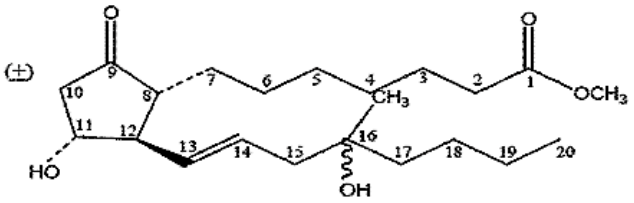
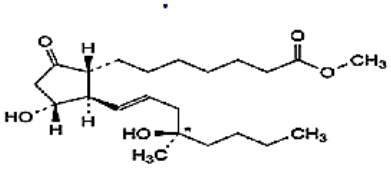
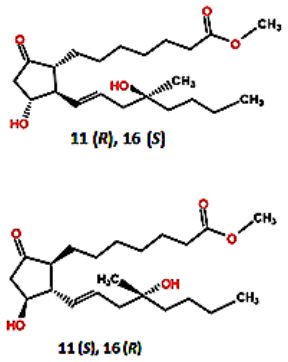


Fig. A, conventional prostoglandin numbering system



its epimer at C* and their enantiomers

EP. Representation of the epimeric mixture at C* (4RS)(4SR)



11 (*R*), 16 (*S*)

11 (*R*), 16 (*R*)

11 (*S*), 16 (*R*)

11 (*S*), 16 (*S*)

4 stereisomers:
Methyl 11(R), 16(S), 13 (*E*) - 11,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oate (active)
Methyl 11(R), 16(R), 13 (*E*) - 11,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oate
Methyl 11(S), 16(R), 13 (*E*) - 11,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oate
Methyl 11(S), 16(S), 13 (*E*) - 11,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oate

Figure B.21 — Structural representation of Misoprostol

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B.7.10 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 counterions or solvates present in the material should also be provided.

For all chemical substances a molecular representation (Mol file, SMILES, InChI, 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 accompanied document (see 4.8). In addition to the structure the molecular formula, molecular weight, and systematic name should be provided at the structural representation.

B.7.11 Decision tree for a new Substance ID

Figure B.22 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 (Triamcinolone, micronised)	YES
➢	6)	Same elemental composition, same molecular weight, same stereochemistry, same physical form, technical grade (Triamcinolone, micronised), Ph.Eur. or USP	YES

Figure B.22 — Decision tree for a new Substance ID

B.8 Discussing other elements of importance regarding the characteristics of a substance

B.8.1 Introduction

At the 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.8.2 Naming Vegetable Oils

The **business rules** for naming of vegetable oils are described in 5.5.14.1 (of Structurally Diverse Substance, herbals) and in the subclause Source material (see 4.10).

NOTE The information model for Structurally Diverse substances has been updated in the Main body of the ISO/TS 19844 as by the latest version and has to be updated in the ISO 11238 standard.

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As outlined in Annex E of this document 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.4). 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 regulation.

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 infraspecies (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) in this Annex. 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 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.23 the Substances subclasses are shown belonging to the Substance Type: Structurally Diverse.

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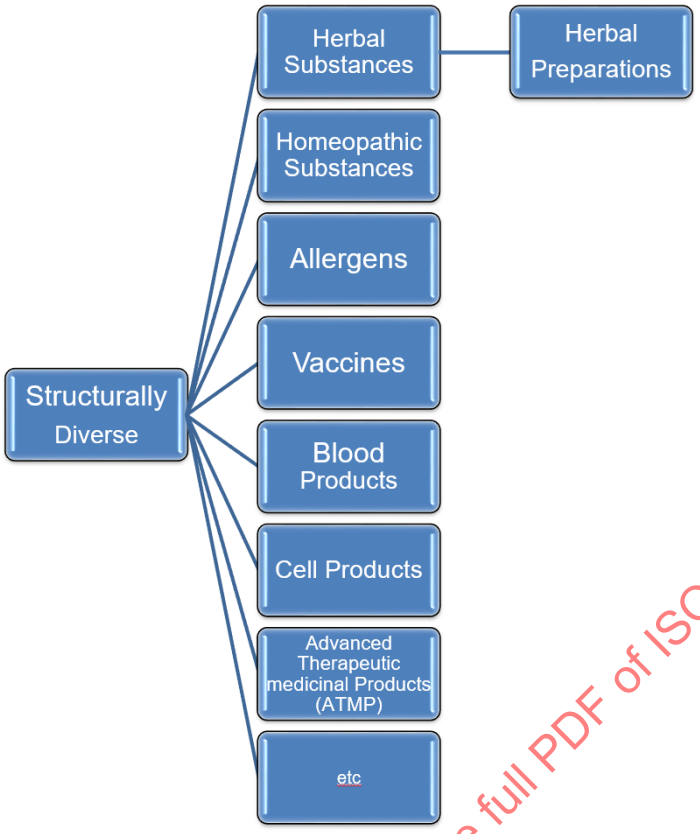


Figure B.23 — Examples of Substance classes belonging to Substance Type: Structurally Diverse

B.8.2.1 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 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,** giving the Substance Role the value <Parent>, 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 (infraspecies 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.

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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 **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 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 [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.	

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The relationships between the ISO 11238, ISO/TS 19844 Structurally diverse description and the Substance (fresh) and Substance (Herbal preparation) for Olive Oil, Virgin are represented in the Figure B.24.

For comparison, the relationships between the ISO 11238, ISO/TS 19844 Structurally diverse description, the Substance (fresh), the Substance (Herbal Drug) and the Substance (Herbal preparation) for Ginkgo biloba, Dry Extract are presented in Figure B.25.

Further details and discussion is described in the Annex E (Structurally Diverse/Herbal).

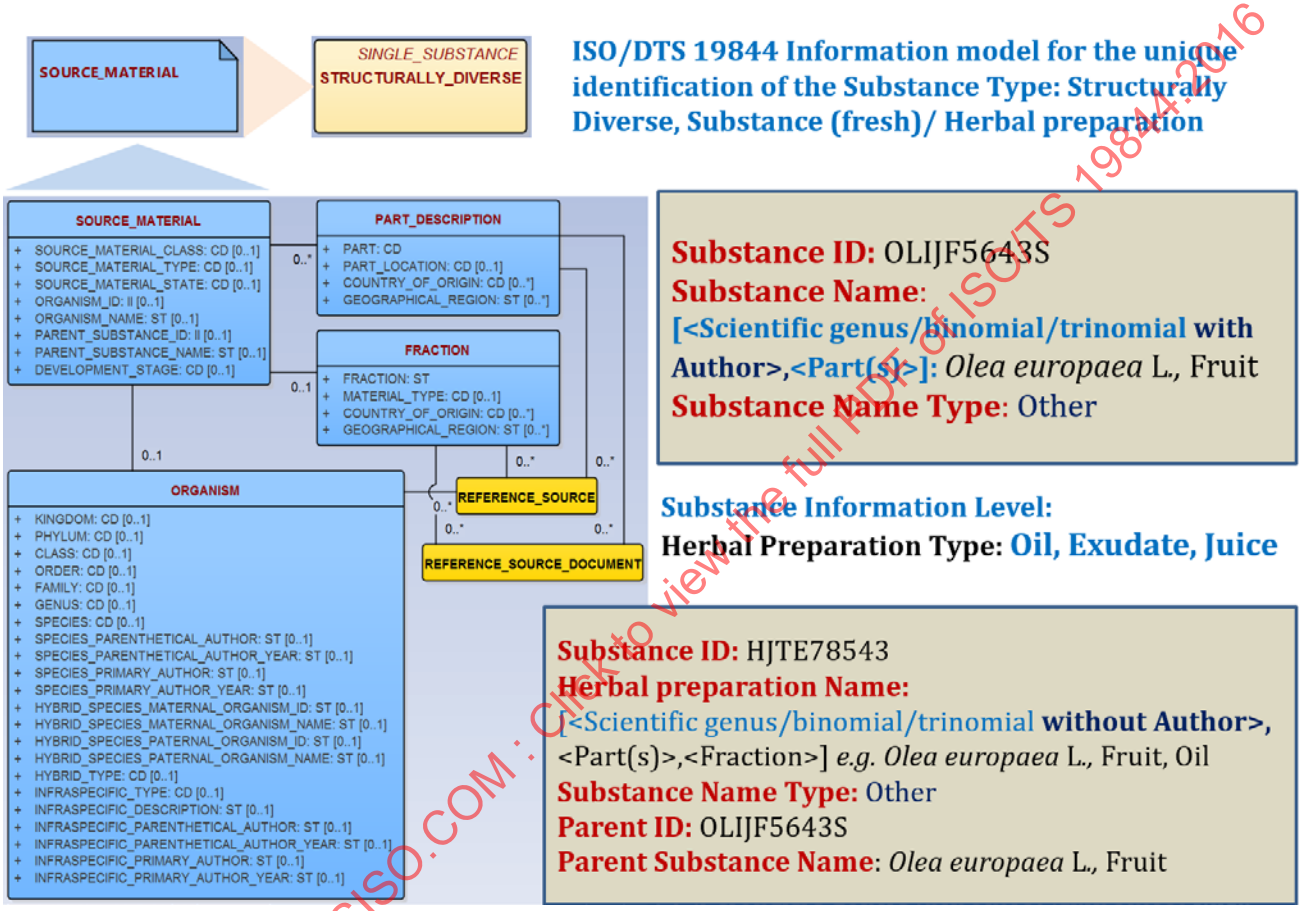


Figure B.24 — Information model for Structurally Diverse, Substance (fresh)/Herbal preparation

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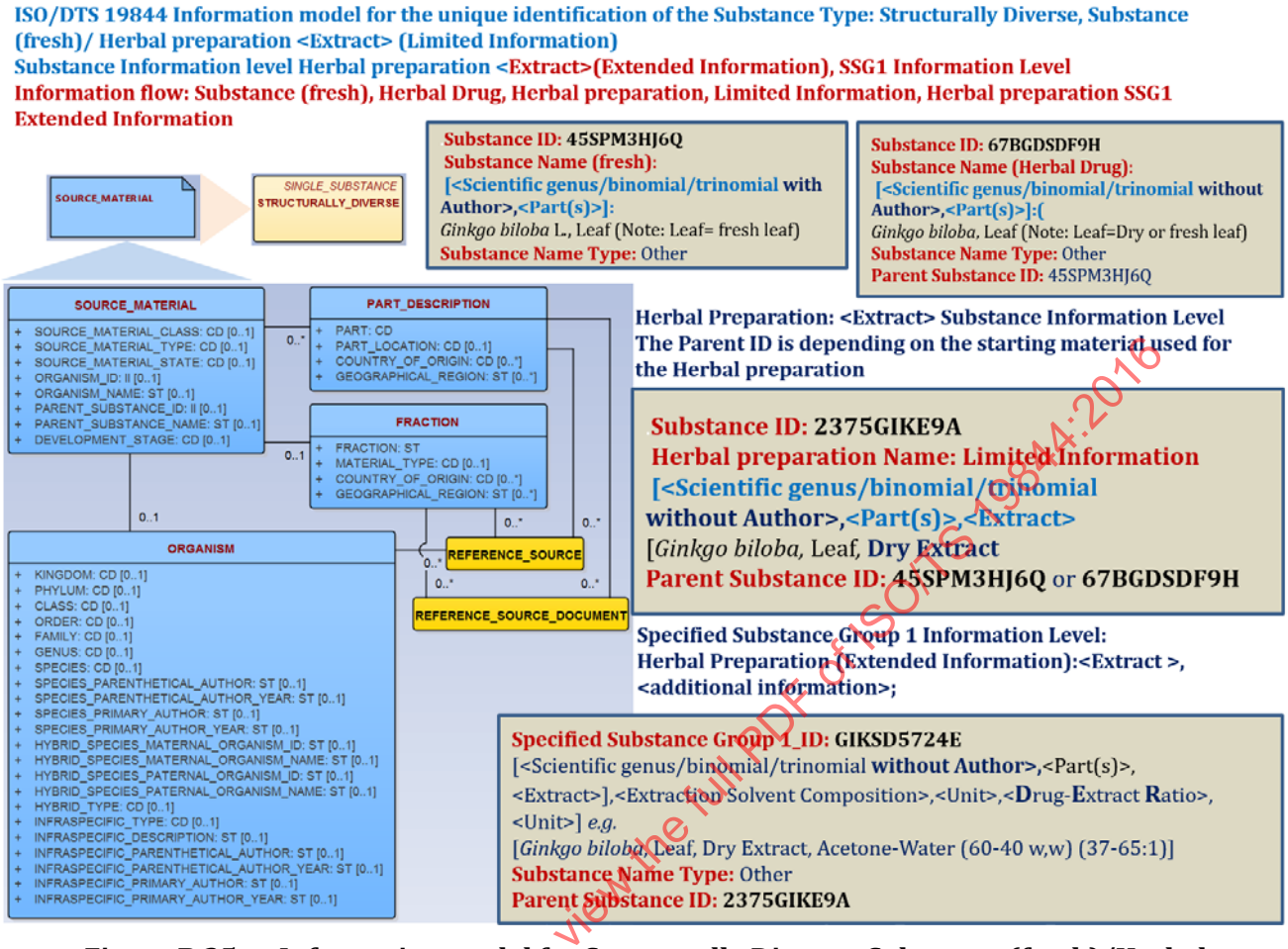


Figure B.25 — Information model for Structurally Diverse, Substance (fresh)/Herbal preparation and Herbal preparation at the Specified Substance Group 1 level

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)
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.26.

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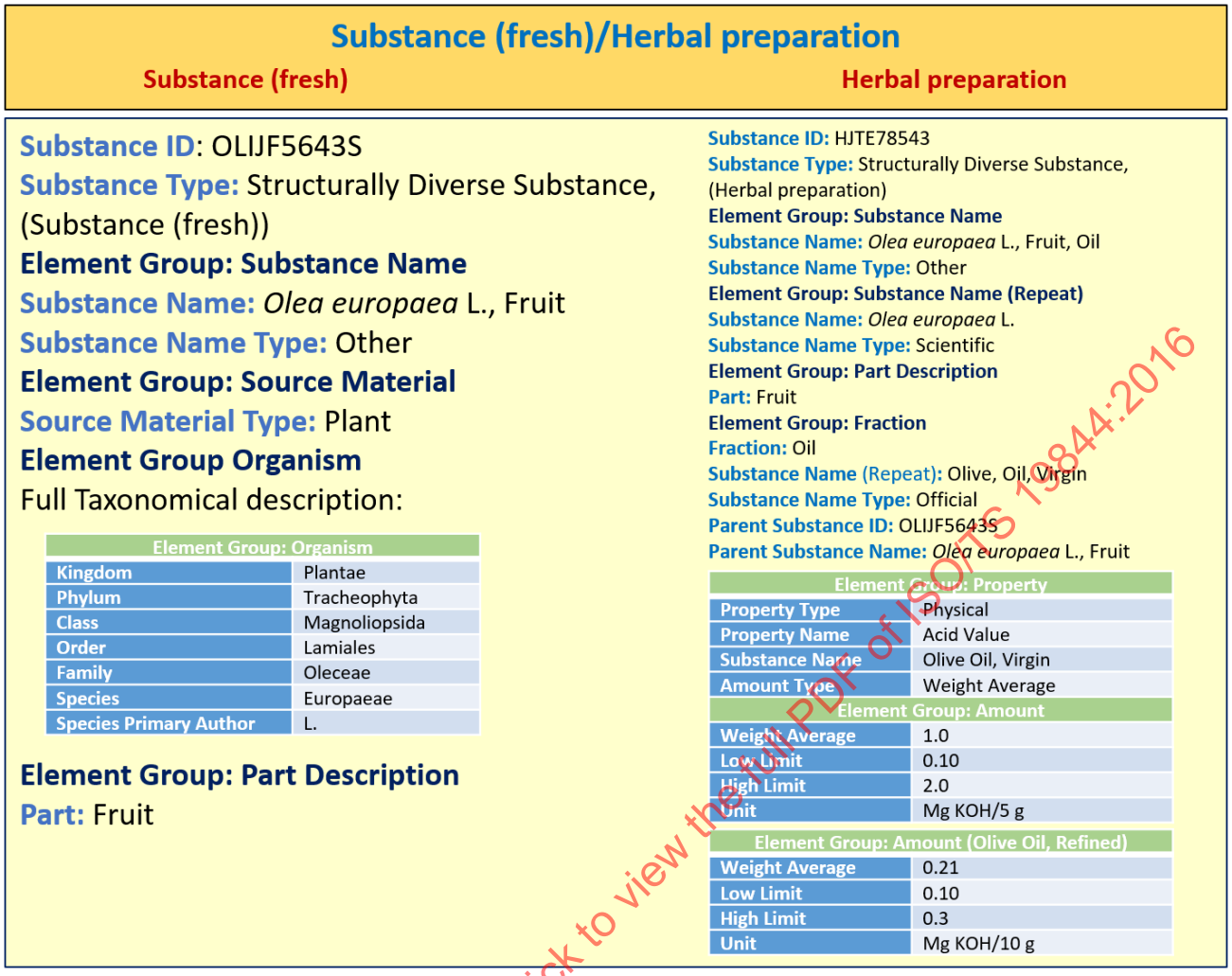


Figure B.26 — Substance (fresh)/Herbal preparation of Olive Oil, Virgin (Ph.Eur.)

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B.8.2.2 Description of Elements at the Specified Substance Group 1 Information level

The Element Group Properties 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.8.2.6 of this Annex.

NOTE The Specified Substance Group 1 does not have a connection with the Modification Group. So it will be proposed to introduce the 'Modification' Element Group at the Specified Substance Group 1 level in addition to its existing connection at the Substance level (proposed change to ISO 11238, in Figure B.27). Also, the 'Property Parameter' attribute has been added to the 'Property' class.

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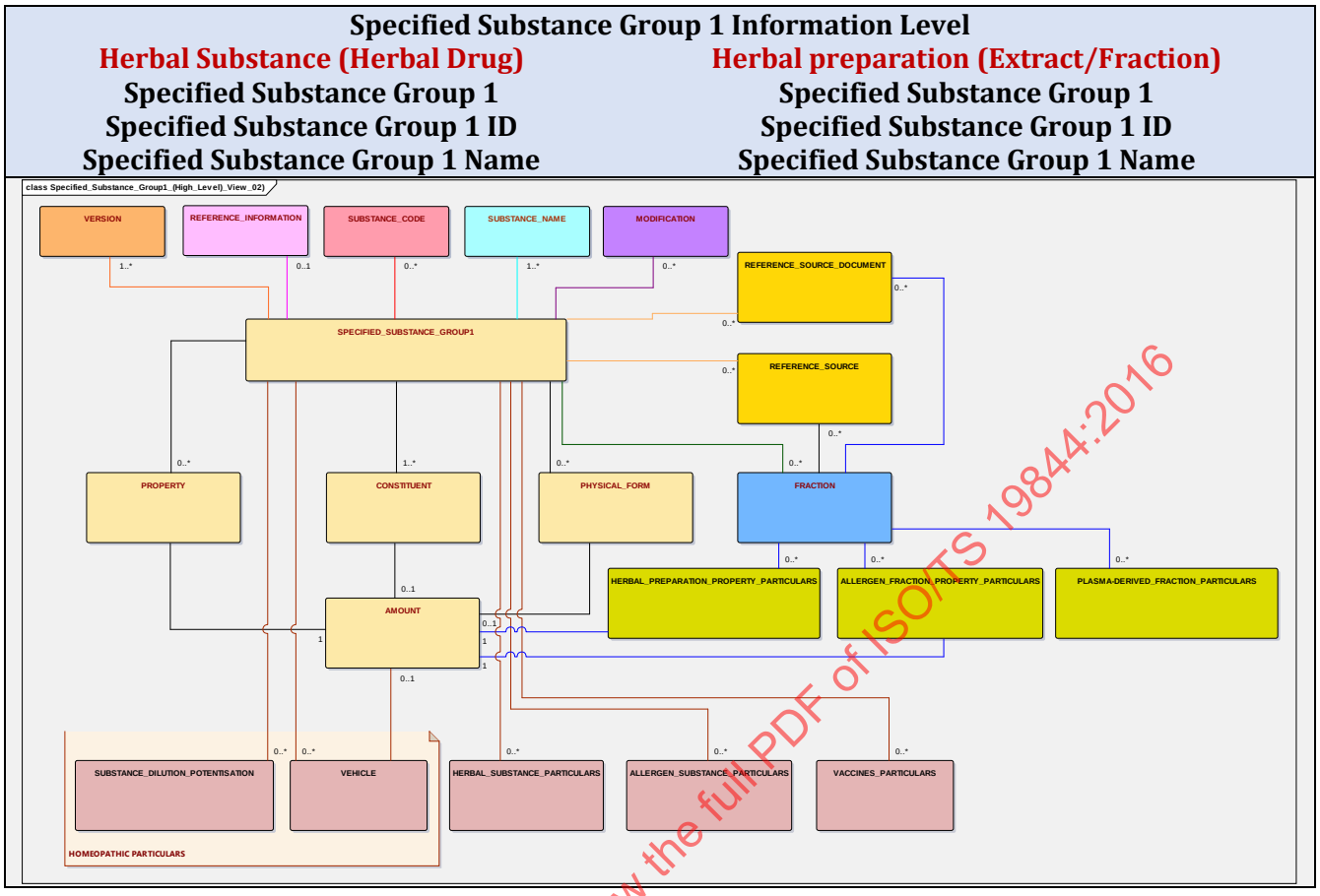


Figure B.27 — updated Specified Substance Group 1 information level

NOTE 1 In Figure B.27 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 standardised 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, the fraction Herbal preparation corresponds to a Specified Substance Group 1 ID and a Specified Substance Group 1 Name (see Figure B.24., Figure B.25 and Figure E.4).

NOTE 2 Further information and examples are provided in Annex E.

B.8.2.3 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 the 'Reference Source Document Type' provides the manufacturer to submit the Release Specification of the manufactured preparation. For more details, see 6.2 and Annex E.

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B.8.2.4 Description of Elements at the Specified Substance Group 3 Information level

At Specified Substance Group 3 information level (Figure 30) 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.

Specified Substance Group 3 ID: JFGDRW4526 (Artificial ID)
Specified Substance Group 3 Name: Olive Oil, Virgin Ph.Eur.
Reference Source Type: Ph.Eur.
Parent Substance ID: HJFTE78543 corresponding 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 30, 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., USP as well as the intended particle size.

B.8.2.5 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)
Substance name: *Olea europaea*, Fruit, **Oil Refined**
Substance Name Type: Other
Substance Name: Refined Olive Oil
Substance Name Type: Official
Parent Substance ID: HJFTE78543 corresponding to: the
Parent Substance: *Olea europaea*, Fruit, Oil (= Herbal preparation); Common name: Olive Oil, Virgin, and which in turn is related to the parent organism.
Parent Substance Name: *Olea europaea* L., Fruit and
Parent Substance ID: OLIJF5643S (= Substance (fresh)).

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NOTE 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 (Ph.Eur.).

The Specified Substance Group 3 name for Olive Oil, Refined (Ph.Eur.), will be:

Specified Substance Group 3 ID: SDAUT12543 (Artificial ID)

Specified Substance Group 3 Name: Olive Oil, Refined Ph.Eur.

Reference Source Type: Ph.Eur.

Parent Substance ID: KHJGHR4523 corresponding to the parent substance name

Parent Substance Name (Common Name): *Olea europaea*, Fruit, Oil Refined and is related to the

Parent Substance Name: *Olea europaea*, Fruit, Oil; Common name: Olive Oil, Virgin, with the

Parent Substance ID: HJFTE78543 (= Herbal preparation), which in turn is related by the relationship <parent organism> with the:

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

Parent Substance ID: OLIJF5643S (Substance (fresh))

B.8.2.6 Properties to be captured, related to liquids (vegetable oils)

In B4 and B5, the key elements for defining the substance are: Structure, Molecular formula, Molecular weight and Solid state characterisation.

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 Specified Substance, whether it is Virgin Olive Oil (Ph.Eur.), or Refined Olive Oil (Ph.Eur.), which is essential for use in parenteral preparations.

In Figure B.28 and Figure B.29 these elements are discussed regarding the definition of a vegetable oil. In Figure B.31, 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 Specified Substances in the sense of ISO 11238, since the Refined Olive Oil (Ph.Eur.) is sourced from the Virgin Olive Oil (Ph.Eur.), but has been refined by a modification process in order to remove or reduce free acids.

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

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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 and peroxide value.

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.29 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, colorless 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)** ***Unsaponifiable matter***: 1.5 % on 5.0 g	***Appearance***: Clear, colorless 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
Unsaponifable Matter	1.18 %
...	...

Figure B.28 — 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
Unsaponitable Matter	1.18 %
Color gardner	1.9
Color lovibond 5 ¼" yellow	10.0
Color lovibond 5 ¼" red	1.0
Sesameoil	complies
Alkalline 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 und delta 5.24-stigmastadienol

Identity	complies
Purity	Complies

Figure B.29 — Specifications for Olive Oil, Refined by the applicant (sponsor) documentation

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B.8.2.7 Example: Identity of material, combining the elements for Olive Oil, Virgin (Ph.Eur.) and Olive Oil, Refined (Ph.Eur.)

Table B.1 — Olive Oil, Virgin (Ph.Eur.)

Element Name	Value	Data Format	Note #
Element Group: Substance (fresh)			
Substance Type	Structurally Diverse, Herbal Substance	CD	
Substance ID	OLIJF5643S (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Olea europaea* L., Fruit	ST	1)
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Substance Name (Repeat)			
Substance Name	*Olea europaea* L.	CD	
Substance Name Type	Scientific	CD	
Language	en	CD	2)
Element Group: Source Material			
Source Material Class	Organic	CD	
Source Material Type	Plant	CD	
Source Material State	Live	CD	
Organism ID	LHJFG63421 (Artificial ID)	II	3)
Organism Name	*Olea europaea* L.	CD	3)
Development stage	Fruiting	CD	
Element Group: Organism			
Kingdom	Plantae	CD	
Phylum	Tracheophyta	CD	
Class	Magnoliopsida	CD	
Order	Lamiales	CD	
Family	Oleaceae	CD	
Genus	Olea	CD	
Species	europaea	CD	
Species Primary Author	L.	ST	
Element Group: Part Description			

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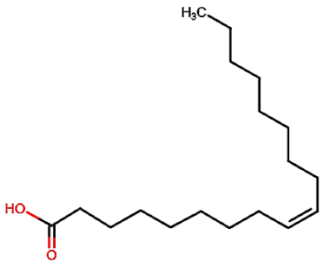
Table B.1 *(continued)*

Element Name	Value	Data Format	Note #
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	
Element Group: Substance Name (Repeat)			
Substance Name	Olive Oil, Virgin	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name 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	European Pharmacopoeia, monograph 07/2011:0518	ST	
Element Group: Source Material			
Parent Substance ID	OLIJF5643S (Artificial ID)	II	
Parent Substance Name	*Olea europaea* L., Fruit	ST	
Element Group: Fraction			
Fraction	Oil	CD	
Element Group: Structure			

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Table B.1 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment		ED	
Stereochemistry	Achiral	CD	
Optical activity	None	ST	
Molecular Formula	$C_{18}H_{34}O_2$.	ST	
Element Group: Molecular Weight			
Molecular Weight method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	282.5	PQ	
Unit	g/mol	CD	
Element Group: Property			
Property Type	Physical	CD	
Property Name	Relative density	ST	
Property Parameters	Measured at 20°C	ST	
Substance ID	HJFTE78543	II	4)
Substance Name	Olive Oil, Virgin	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	0.913	PQ	
Unit	Not applicable (dimensionless quantity)		
Element Group: Property (Repeat)			

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Table B.1 *(continued)*

Element Name	Value	Data Format	Note #
Property Type	Physical	CD	
Property Name	Acid value	ST	
Substance ID	HJFTE78543	II	4)
Substance Name	Olive Oil, Virgin	ST	
Amount Type	Weight average	CD	
Element Group: Amount			
Average [Numeric Value]	1.0	PQ	
Low Limit	0.10	PQ	
High Limit	2.0	PQ	
Unit	mg KOH/5 g	ST	
Element Group: Specified Substance Group 3 (Olive Oil, Virgin-Ph.Eur.)			
Specified Substance Group 3 ID	JFGDRW4526 (Artificial ID)	II	
Substance Type	Specified Substance Group 3	CD	
Specified Substance Group3 Name	*Olea europaea*, Fruit, Oil Ph.Eur.	ST	
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	
Grade Reference Source	Ph.Eur. monograph 07/2011:0518	ST	

[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.

[2] The language for the Substance Name Type 'Scientific' has the value en (see 4.3.3).

[3] The Organism ID and Name should be provided by The Kew Gardens Medicinal Plant Names Services (MPNS).

[4] Oleic Acid should be registered in the database with the minimal information for the Element Group Structure.

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Table B.2 — 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* L., Fruit, Oil Refined	ST	
Substance Name Type	Other	CD	
Language	en	CD	
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		
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name 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	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, Oil	ST	
Element Group: Fraction			

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Table B.2 *(continued)*

Element Name	Value	Data Format	Note #
Fraction	Oil Refined	CD	
Element Group: Property			
Property Type	Physical	CD	
Property Name	Relative density	ST	
Property Parameters	Measured at 20°C	ST	
Substance ID	KHJGHR4523	II	
Substance Name	Olive Oil, Refined	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	0.913	PQ	
Unit	Not applicable (dimensionless quantity)	ST	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Acid value	ST	
Substance ID	KHJGHR4523	II	
Substance Name	Olive Oil, Refined	ST	
Amount Type	Weight average	CD	
Element Group: Amount			
Average	0.21	PQ	
Low Limit	0.10	PQ	
High Limit	0.3	PQ	
Unit	mg KOH/10 g	CD	
Element Group: Specified Substance Group 3 (Olive Oil, Refined-Ph.Eur.)			
Specified Substance Group 3 ID	SDAUT12543 (Artificial ID)	II	
Substance Type	Specified Substance Group 3	CD	
Specified Substance Group 3 Name	*Olea europaea*, Fruit, Oil, Refined, Ph.Eur.	ST	
Parent Substance ID	KHJGHR4523 (Artificial ID)	II	
Element Group: Grade			

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Table B.2 *(continued)*

Element Name	Value	Data Format	Note #
Grade Type	Ph.Eur.	CD	
Grade Name	Olive Oil, Refined	ST	
Grade Reference Source	Ph.Eur. monograph 07/2011:1456	ST	

B.8.3 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 and Plant part and whether the substance is considered to be a mixture substance or another substance type e.g.:

- 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 substance depending on the manufacturing process.

B.8.3.1 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.) will be:

Substance name	*Ricinus communis,* Seed, Oil with
Substance ID	JKGSDE6452 (Artificial ID); D5340Y2I9G (UNII);
Substance Name Type	Other
Common Name	Castor Oil, Virgin
Substance Name Type	Official

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B.8.3.2 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 Pharmacopoea 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.) will be:

Substance Name	*Ricinus communis*, Seed, Oil Hydrogenated
Substance ID	CFDSW67453 (Artificial ID); ZD94AP8MEY(UNII)
Substance Name Type	Other
Common Name	Castor Oil, Hydrogenated
Substance Name Type	Official

B.8.3.3 Relationship Castor Oil, Virgin and Castor Oil, Hydrogenated

Castor Oil, Hydrogenated is **not** like Refined Olive Oil, a special grade of Castor Oil.

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 chains of the triglyceride ester into **12-hydroxystearic acid**, [$C_{18}H_{36}O_3$,(M_w 300,4)] side chains, as shown in Figure B.30.

This process is to be considered as a chemical modification of the Castor Oil, Virgin into Hydrogenated Castor Oil. 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.30.

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.

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B.8.3.4 Castor Oil, Ethoxylated

Castor Oil, Ethoxylated is the synonym for Macrogolglycerol Ricinoleate (Ph.Eur.). It is defined in the Ph.Eur. as 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

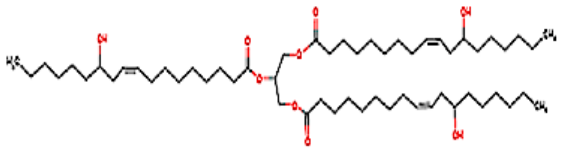
One of the major properties for the identification of this substance material is the viscosity. This property is a predominant property for the chemical Substance Type: “Polymer”. In Figure B.30/figure A, an illustrative representation is presented for Macrogolglycerol Ricinoleate. In Figure B.30, an illustrative representation is presented for the polymer when the polymeric reaction between Castor Oil and ethylene oxide 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.

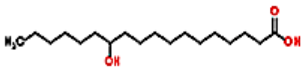
Figure B.31 shows the specifications for Castor Oil, Virgin and Castor Oil, Hydrogenated.

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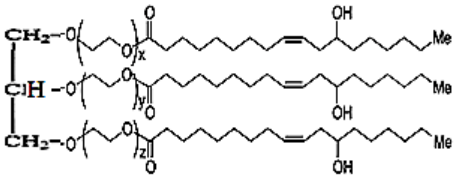


Castor Oil, Main constituent: UNII: D5340Y219G
Glycerol tri-Recinoleic acid ester. :
Mol. formula: $C_{57}H_{104}O_9$; Mol. weight: 933.4;
Side chain: (9*Z*,12*R*)-12-Hydroxyoctadec-9-enoic acid, (synomym: 12-Hydroxyoleic acid); $C_{18}H_{34}O_3$; (M_w 298.5).

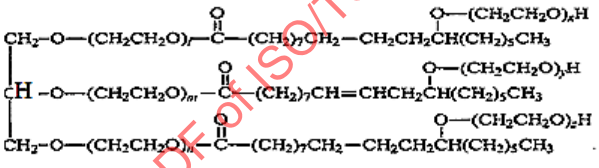


Castor Oil, Hydrogenated, Main Constituent : UNII: ZF94P8MEY
Glycerol tri-12-hydroxystearic acid ester;
Mol. formula: $C_{57}H_{110}O_9$, Mol. weight: 939.4:
Side chain: 12-Hydroxyoctadecanoic acid.
(synomym: 2-hydroxystearic acid, $C_{18}H_{36}O_3$ (M_w 300,4)

Macrogolglycerol Ricinoleate (synonym: Castor Oil , Ethoxylated), contains 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.



Castor Oil, Ethoxylated: figure A



Different polymerisation process: figure B

Figure B.30 — Structures of the major components of Castor Oil, Virgin, Castor Oil, Hydrogenated and Macrogolglycerol Ricinoleate (synonym Castor Oil, Ethoxylated)

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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.31 — Specifications for Castor Oil, Virgin and Castor Oil, Hydrogenated (Ph.Eur.)

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B.8.4 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 per cent 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 6.1.13 Physical Form and in 6.1.13.1 Physical State.

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Table B.3 — Tabular format of the Elements captured at the Substance and Specified Substance Levels

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance Type	Chemical	CD	
Substance ID	NGHD56234L (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Nitrous oxide	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	EU	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	ST	1)
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	Literature	CD	
Reference Source Citation	https://www.medicinescomplete.com/mc/martindale/current/3119q.htm?q=dinitrogen%20oxide&t=search&ss=text&p=1#_hit	ST	6)
Element Group: Substance Code			
Code	10024-97-2	CD.Code	

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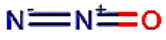
Table B.3 *(continued)*

Element Name	Value	Data Format	Note #
Code System	CAS Registry	CD.Code Sysyem Name	
Code System ID	0049	CD.Code System	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	K50XQU1029	CD.Code	
Code System	FDA Substance Registration System (UNII)	CD.Code Sysyem Name	
Code System ID	0050	CD.Code System	
Code System Status	Active	CD	
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.Code System	
Substance Classification Code	N01AX13	CD.Code	
Substance Classification Type	Other general anaesthetics	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHO Collaborating Centre for Drug Statistics methodology (WHOCC)	CD	
Reference Source Class	Literature	CD	
Reference Source Citation	http://www.whocc.no/atc_ddd_index/?code=N01AX13	ST	
Element Group: Structure			
Stereochemistry	Achiral	CD	
Optical activity	None	CD	
Molecular Formula	N_2O	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	

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Table B.3 *(continued)*

Element Name	Value	Data Format	Note #
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official name source	CD	
Reference Source Citation	European Pharmacopoeia	ST	
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment		ED	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	InChI	CD	
Structural representation	InChI=1S/N2O/c1-2-3	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Literature	CD	
Reference Source Citation	http://webbook.nist.gov/cgi/cbook.cgi?ID=C10024972&Mask=1	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	MOL	CD	
Structural Representation	See below:	ED	
-FDASRS-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	No	BL	
Reference Source Type	IND	CD	

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Element Name	Value	Data Format	Note #
Reference Source Class	Regulatory submission	CD	
Reference Source ID	222222 (Artificial ID)	ST	
Element Group: Molecular Weight			
Molecular Weight method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	44.01	PQ	
Unit	g/mol	CD	
Element Group: Stoichiometric			
Number of Moieties	1	INT	
Element Group: Moiety			
Moiety Role	Parent	CD	
Moiety ID	NGHD56234L (Artificial ID)	II	
Moiety Name	Nitrous oxide	ST	
Amount type	Exact	CD	
Element Group: Amount			
Average	1	PQ	
Element Group: Specified Substance Group 1			
Specified Substance Group 1 ID	PHJSGT785G (Artificial ID)	II	
Substance Type	Specified Substance Group 1	CD	
Specified Substance Group 1 Name	Nitrous oxide, gas	ST	
Element Group: Constituent			
Substance ID	NGHD56234L (Artificial ID)	II	
Substance Name	Nitrous oxide	ST	
Substance Role	Parent Substance	CD	
Amount type	Volume per cent	CD	
Element Group: Physical form			
Physical State	Gas	CD	

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Element Name	Value	Data Format	Note #
Physical Form Type	None	CD	
Amount Type	Volume per cent v/v of Substance	CD	
Element Group: Amount			
Low Limit	98.0	PQ	2)
Unit	per cent V/V	CD	
Element Group: Property (see figure)			
Physicochemical characterisation Solubility: 1 volume of nitrous oxide dissolves in 1.5 volumes of water • Physical characteristics: Colourless, odourless, non flammable gas • Molecular mass: 44.013 • Melting point under 101 kPa (1 atm): -90.81°C • Boiling point under 101 kPa (1 atm): -88.46°C • Critical temperature: 36.5°C • Critical pressure: 7.271 Mpa (71.99 atm) • Critical density: 452.5 Kg/m^3 • Triple point: -90.80°C sous 87.56 KPa • Density 0°C, P 31.29 bar (equilibrium: liquid: 904.0 kg/m^3 gas: 85.76 kg/m^3			
Property Type	Physical	CD	
Property Name	Melting point	CD	
Property Parameters	Measured under 101 kPa	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	-90.81	PQ	
Unit	Degree Celsius	CD	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Boiling point	CD	
Property Parameters	Measured under 101 kPa	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	-88.46	PQ	

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Element Name	Value	Data Format	Note #
Unit	Degree Celsius	CD	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Critical temperature	CD	
Property Parameters	Measured under 101 kPa	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	36.5	PQ	
Unit	Degree Celsius	CD	
Element: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Critical pressure	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	71.99	PQ	
Unit	Atm	CD	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Critical density	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	452.5	PQ	
Unit	Kg/m^3	CD	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Triple point	CD	
Property Parameters	Under 87.56 kPa	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	-90.80	PQ	

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Element Name	Value	Data Format	Note #
Unit	Degree Celsius	CD	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Density	CD	
Property Parameters	At 0˚C, 31.29 atm at equilibrium	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	904.0	PQ	
Unit	Kg/m^3	CD	
Average [Numeric Value]	85.76	PQ	
Unit	Kg/m^3	CD	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Solubility	CD	
Substance ID	059QF0KO0R (UNII)	II	
Substance Name	Water	ST	
Property Parameters	1 Volume part 20°C and at a pressure of 101 kPa	ST	
Amount Type	Number average	CD	
Element Group: Amount			
Average	1.5	PQ	
Unit	Volume Part	CD	
Element Group: Specified Substance Group 2 (Nitrous oxide)			
Specified Substance Group 2 ID	KHJTYD674R (Artificial ID)	II	
Substance Type	Specified Substance Group 2	CD	
Specified Substance Group 2 Name	Nitrous oxide-Manufacturer XX	ST	
Parent Substance ID	NGHD56234L (Artificial ID)	II	3)
Element Group: Manufacturing			
Manufacturer ID	DUNS86745HF (Artificial ID)	II	
Manufacturer Name	Company XX	ST	

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Element Name	Value	Data Format	Note #
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	
Critical Process Version Number	1	INT	4)
Element Group: Specified Substance Group 3 (Nitrous oxide)			
Specified Substance Group 3 ID	GHDRW765T (Artificial ID)	II	
Substance Type	Specified Substance Group 3	CD	
Specified Substance Group 3 Name	Nitrous oxide, Ph.Eur.	ST	
Parent Substance ID	NGHD56234L (Artificial ID)	II	5)
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name	Nitrous oxide	ST	
Grade Reference Source	Ph. Eur., 8.6th Edition	ST	
Element Group: Reference Source			
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official name source	CD	
Reference Source Citation	European Pharmacopoeia Current Edition, (Ph.Eur., monograph 01/2008:0416)	ST	

[1] European Pharmacopoeia Current Edition, (Ph.Eur., monograph 01/2008:0416).

[2] List of properties valid for Nitrous oxide, Gaseous phase sampled at -15°C.

[3] This Parent Substance ID refers to the Substance Name: Nitrous oxide.

[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 should be tied to the production system type.

[5] This Parent Substance ID refers to the Substance Name: Nitrous oxide.

[6] Access to Martindale is based on annual subscription fees

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B.9 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.

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This information shall be seen in view of the substance characteristics as discussed in B3, B4 and B5.

For the Substance Type Chemical Substances all physico-chemical properties of the Substance are placed at the Specified Substance Group 1 level, **unless** this property is essential for the defining of 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 physical 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.9.1 Example 1: Amlodipine besilate

Table B.4 — Identity of material combining the elements for Amlodipine Besilate

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance Type	Chemical	CD	
Substance ID	GHTD1234A (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Amlodipine besilate	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	EU	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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Table B.4 *(continued)*

Element Name	Value	Data Format	Note #
Reference Source Citation	European Pharmacopoeia	ST	1)
Element Group: Substance Name (Repeat)			
Substance Name	Amlodipine besylate	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name (Repeat)			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	US	CD	
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	ST	1)
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 Citation	http://chem.sis.nlm.nih.gov/chemidplus/unii/864V2Q084H	ST	
Element Group: Substance Name (Repeat)			

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Element Name	Value	Data Format	Note #
Substance Name	3-Ethyl 5-methyl (4*RS*)-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	ST	1.a)
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	
Reference Source Class	Official name source	CD	
Reference Source Citation	USP Monograph	ST	1.b)
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	IND	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source ID	111111 (Artificial ID)	ST	

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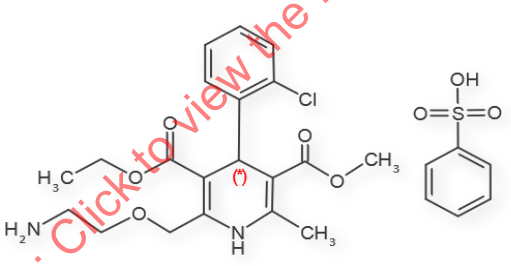
Table B.4 *(continued)*

Element Name	Value	Data Format	Note #
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 Substance Registration System (UNII)	CD.Code SystemName	
Code System ID	0050	CD.Code System	
Code System Status	Active	CD	
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.Code System	
Substance Classification Code	C08CA01	CD.Code	
Substance Classification Type	Selective Calcium channel blockers with mainly vascular effects, Dihydropyridine derivatives	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHO Collaborating Centre for Drug Statistics methodology (WHOCC)	CD	
Reference Source Class	Web	CD	
Reference Source Citation	http://www.whocc.no/atc_ddd_index/?code=C08C	ST	
Element Group: Structure			
Stereochemistry	Racemic	CD	

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Table B.4 *(continued)*

Element Name	Value	Data Format	Note #
Optical activity	(+-)	CD	
Molecular Formula	$C_{26}H_{31}ClN_2O_8S$	ST	2)
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 Pharmacopoeia Current Edition	ST	
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural representation Attachment		ED	2)
Element Group: Structure (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	
Reference Source Class	Public Database	CD	

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Table B.4 *(continued)*

Element Name	Value	Data Format	Note #
Reference Source Citation	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	
Public Domain	Yes	BL	
Reference Source Type	ChemIDplus	CD	
Reference Source Class	Public Database	CD	
Reference Source Citation	http://chem.sis.nlm.nih.gov/chemidplus/unii/864V2Q084H	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	MOL	CD	
Structural Representation Attachment	document TEXT	ED	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	IND	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	

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Table B.4 *(continued)*

Element Name	Value	Data Format	Note #

```
Symyx   06091422262D 1   1.00000    0.00000    0

     38 39  0  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
  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
```

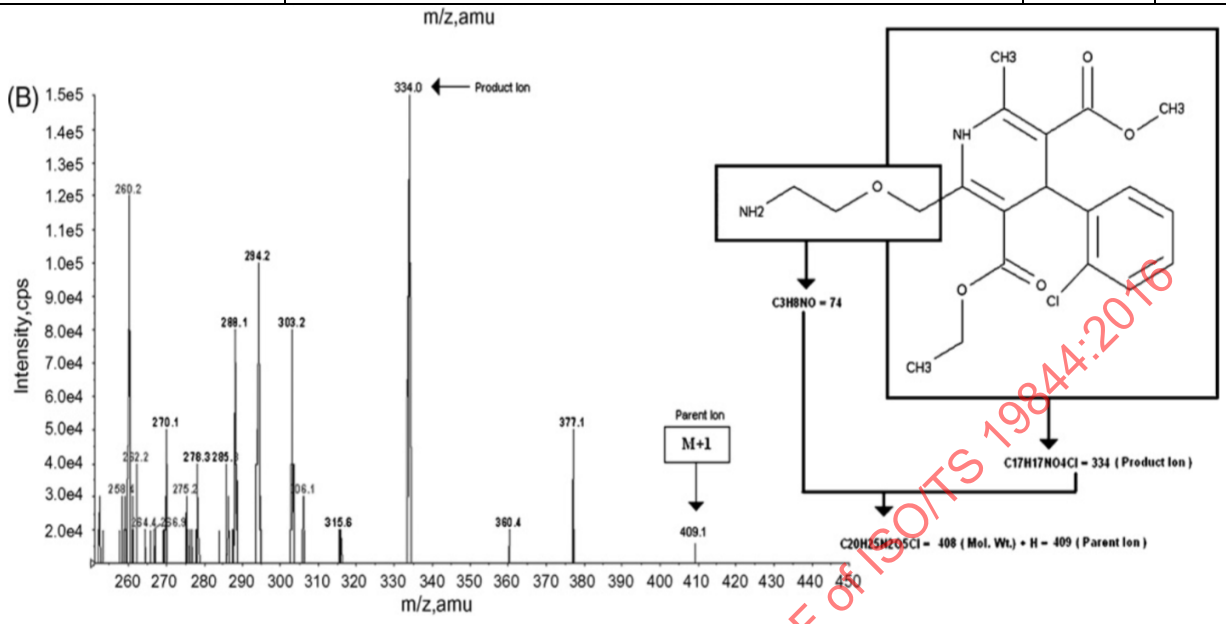
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Element Name	Value	Data Format	Note #
17.2455 -9.9824 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 16.6372 -10.3324 0.0000 C 0 0 0 0 0 0 0 0 0 0 0 0 24 20 1 0 0 0 0 25 14 1 0 0 0 0 26 19 2 0 0 0 0 27 23 1 0 0 0 0 28 26 1 0 0 0 0 4 2 2 0 0 0 0 28 21 2 0 0 0 0 2 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			
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Moelecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	567.1 [567,06 = (408.88 + 158.18); rounded at 567,1]	PQ	
Unit	g/mol	CD	
Element Group: Reference Source Document			
Reference Source Document	PDF Document, see figure below:	ED	
Amlodipine besylate mass spectrum obtained by LC-MS/MS, $[M+H]^+$ = 409,1 *m/z* Journal of Chromatography B. 873 (2008) 77-85			

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Element Name	Value	Data Format	Note #
			
Reference Source Document Type	Journal article : MS-spectra Amlodipine salts	ST	
Reference Source Classification	Mass spectra	CD	
Reference Source Document URL	https://www.researchgate.net/publication/23227282_Simultaneous_determination_of_metoprolol_succinate_and_amlodipine_besylate_in_human_plasma_by_liquid_chromatography-tandem_mass_spectrometry_method_and_its_application_in_bioequivalence_study	ST	
Element Group: Stoichiometric			
Number of Moieties	2	INT	
Element Group: Moiety			
Moiety Role	Salt	CD	
Moiety ID	685928Z18A (UNII)	II	
Moiety Name	Benzenesulphonic acid	ST	
Amount type	Mole Ratio to Amlodipine	CD	
Element group: Amount			
Average	1	PQ	
Element Group: Moiety (Repeat)			
Moiety Role	Base	CD	
Moiety ID	1J444QC288 (UNII)	II	

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Table B.4 *(continued)*

Element Name	Value	Data Format	Note #
Moiety Name	Amlodipine	ST	
Amount type	Mole Ratio to Benzenesulfonic acid	CD	
Element group: Amount			
Average	1	PQ	
Element Group: Substance Relationship			3)
Relationship	Parent to Salt	CD	
Relationship type	Ionic	CD	
Related Substance ID	PTYF75643O (Artificial ID), 1J444QC288 (UNII)	II	
Substance Name	Amlodipine	ST	
Amount Type	Weight per cent to salt	CD	
Element Group: Amount			
Average (Numeric value	72,1	PQ	
Unit	Weight per cent	CD	

[1] Comments made to the Business Rules in 4.4.2: When the substance is described in a Pharmacopoeial monograph, no reference has to be made to the version, i.e. reference is made to Ph. Eur, USP, or JP shall comply with the latest (current) and valid edition. So if reference is made to the Ph. Eur, it means automatically Ph. Eur, 2015 version 8.3 up to July 2015.

1.a) Amlodipine besilate: Ph.Eur., monograph 04/2012:1491.

1.b) Amlodipine besylate: USP Monograph, USP38–NF33 Page 2207.

[2] Comments made to the Business Rules in 4.8.4 and 4.8.5. The molecular formula 4.8.4 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 (see4.8.5)**: $C_{46}H_{64}N_{14}O_{12}S_2$. $C_2H_4O_2$. $3H_2O$.

[3] The Parent to salt is a one-way relationship. The amount as weight per cent of the Parent substance (in this case the Amlodipine base) to the Amlodipine besilate salt shall be provided.

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B.9.2 Example 2: Ponatinib hydrochloride

Ponatinib hydrochloride is not described in a Pharmacopoeia.

Table B.5 — 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 Type	Chemical	CD	
Substance ID	POYFG4531Y (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Ponatinib hydrochloride	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	USAN	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	US	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	ST	
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Journal article	CD	
Reference Source Document URL	https://www.medicinescomplete.com/mc/martindale/current/ms-28485-s.htm?q=Ponatinib%20hydrochloride&t=search&ss=text&tot=12&p=1#_hit (accessed on 2016-06-08)	ST	
Element Group: Substance Name (Repeat)			

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Table B.5 *(continued)*

Element Name	Value	Data Format	Note #
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 Citation	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 Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS	CD	
Reference Source Class	Other name source	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	Submitter Martindale	CD	

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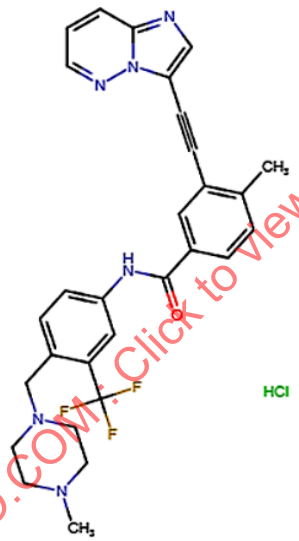
Table B.5 *(continued)*

Element Name	Value	Data Format	Note #
Reference Source Class	Regulatory submission	CD	
Reference Source ID	CBG345267C (Artificial ID)	ST	
Element Group: Substance Code			
Code	1114544-31-8	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	96R6PU3D8J	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	L01XE24	Cd.Code	
Substance Classification Type	Protein kinase inhibitors	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHO Collaborating Centre for Drug Statistics methodology (WHOCC)	CD	
Reference Source Class	Web	CD	
Reference Source Citation	http://www.whocc.no/atc_ddd_index/?code=L01XE24	ST	
Element Group: Structure			
Stereochemistry	Achiral	CD	
Optical activity	None	CD	
Molecular Formula	$C_{29}H_{28}FClN_6O$	ST	

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Table B.5 *(continued)*

Element Name	Value	Data Format	Note #
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	
Reference Source Citation	http://chem.sis.nlm.nih.gov/chemidplus/unii/96R6PU3D8J	ST	
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment		ED	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation Attachment	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	

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Table B.5 *(continued)*

Element Name	Value	Data Format	Note #
Reference Source Type	ChemID*plus*	CD	
Reference Source Class	Public Database	CD	
Reference Source Citation	http://chem.sis.nlm.nih.gov/chemidplus/unii/96R6PU3D8J	ST	
Element Group: Structural Representation(Repeat)			
Structural Representation Type	SMILES	CD	
Structural Representation Attachment	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 Citation	http://chem.sis.nlm.nih.gov/chemidplus/unii/96R6PU3D8J	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	MOL	CD	
Structural Representation Attachment	document TEXT, in attachment below	ED	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	IND	CD	
Reference Source Class	Regulatory submission	CD	
Reference Source ID	33333 (Artificial ID)	ST	
Element Group: Reference Source Document			
Reference Source Document	TEXT, in attachment	ED	
Reference Source Document Type	Text file	CD	
Symyx 06091422112D 1 1.00000 0.00000 0			

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Element Name	Value	Data Format	Note #
40 43 0 0 0 999 V2000			
-2.2340 -0.1661 0.0000 N 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			
-1.5965 0.9381 0.0000 C 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			
-2.8716 0.9381 0.0000 C 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			
-0.9048 1.1589 0.0000 N 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			
-0.9048 -0.0453 0.0000 C 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			
-0.4382 -1.4453 0.0000 C 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			
0.4952 -2.2827 0.0000 C 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			
1.4535 -3.1411 0.0000 C 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			
1.9451 -2.5994 0.0000 N 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			
2.9035 -3.4619 0.0000 C 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			
3.8368 -4.2953 0.0000 C 0 0 3 0 0 0 0 0 0			
3.3451 -4.8619 0.0000 F 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			
4.5535 -4.4703 0.0000 F 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			
4.8201 -3.2161 0.0000 C 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			
6.0493 -2.8203 0.0000 C 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			
6.2951 -1.5703 0.0000 N 0 0 3 0 0 0 0 0 0			
6.8118 -1.0286 0.0000 C 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			
5.0909 -1.9620 0.0000 C 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			
3.1493 -2.2077 0.0000 C 0 0 0 0 0 0 0 0 0			
0.2243 -3.5369 0.0000 C 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			
-0.7090 -2.6744 0.0000 C 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			
3.5313 0.2188 0.0000 Cl 0 0 0 0 0 0 0 0 0			

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Element Name	Value	Data Format	Note #
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			
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			

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Element Name	Value	Data Format	Note #
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	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	569.02	PQ	1)
Unit	g/mol	CD	
Element Group: Stoichiometric			
Number of Moieties	2	INT	
Element Group: Moiety			
Moiety Role	Salt	CD	
Moiety ID	QTT17582CB (UNII)	II	
Moiety Name	Hydrochloric acid	ST	
Amount Type	Mole Ratio to Ponatinib	ST	
Element group: Amount			
Average Number	1	PQ	
Element Group: Moiety			
Moiety Role	Base	CD	
Moiety ID	QTT17582CB (UNII)	II	
Moiety Name	Ponatinib	ST	
Amount Type	Mole Ratio to Hydrochloric acid	ST	
Element Group: Amount			
Average Number	1	PQ	
Element Group: Substance Relationship			
Relationship	Parent to salt	CD	
Relationship Type	Ionic	CD	
Related Substance ID	POFG64523B (Artificial ID), 4340891KFS	II	

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Element Name	Value	Data Format	Note #
	(UNII)		
Related Substance Name	Ponatinib	ST	
Amount Type	Weight per cent to salt	CD	
Element Group: Amount			
Average (Numeric Value	93.6	PQ	
Unit	Weight per cent	CD	
For the Specified Substance Group1 and 2 see Table B.7 **and** Table B.8			

[1] Since the Substance is not described in any Pharmacopoeia evidence of the **structure** should be **substantiated** by means of Mass spectrometry in order to give substantiate structure and molecular weight. The following information has been provided at the application, which will not be disclosed:

- Provided information: Accurate Mass Determination: A molecular ion m/z $[MH]^+$ = 533.2269 Da (corresponding to $(ponatinib + H)^+$ was observed for ponatinib HCl, consistent with the predicted molecular ion m/z $[MH]^+$ = 533.2271 Da;

- Mass Spectrometry (MS-MS Fragmentation): The Ponatinib HCl MS^n fragmentation pattern follows a well characterised pattern of bond breakage and elimination of labile chemical moieties. The ponatinib fragments observed are consistent with both known fragmentation routes and the chemical structure of ponatinib HCl.

Table B.6 — Captured elements at the Substance level for Ponatinib (base)

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance Type	Chemical	CD	
Substance ID	GHF26754YQ (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Ponatinib	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	US, EU	CD	

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Table B.6 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	INN	CD	
Reference Source Class	Official name source	CD	
Reference Source Citation	WHO Drug Information Vol. 25, no 3, 2011 Recommend INN: list 66	ST	
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Journal article	CD	
Reference Source Document URL	http://www.who.int/medicines/publications/druginformation/issues/RL_66.pdf	ST	
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 Citation	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 Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	

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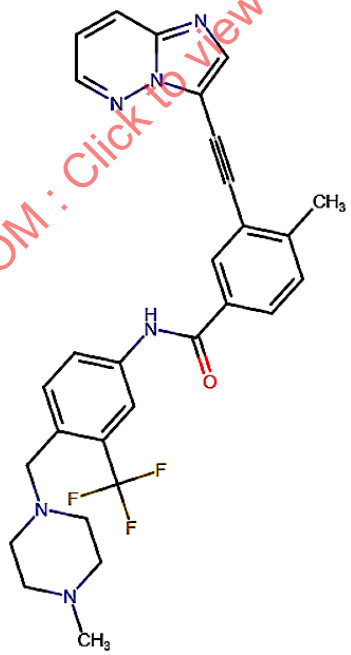
Table B.6 *(continued)*

Element Name	Value	Data Format	Note #
Reference Source Type	CAS	CD	
Reference Source Class	Other name source	CD	
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 Substance Registration System (UNII)	CD.Code SystemName	
Code System ID	0050	CD.Code System	
Code System Status	Active	CD	
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.Code System	
Substance Classification Code	L01XE24	CD.Code	
Substance Classification Type	Protein kinase inhibitors	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHO Collaborating Centre for Drug Statistics methodology (WHOCC)	CD	
Reference Source Class	Web	CD	

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Table B.6 *(continued)*

Element Name	Value	Data Format	Note #
Reference Source Citation	http://www.whocc.no/atc_ddd_index/?code=L01XE24	ST	
Element Group: Structure			
Stereochemistry	Achiral	CD	
Optical Activity	None	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	
Reference Source Citation	http://chem.sis.nlm.nih.gov/chemidplus/unii/4340891KFS	ST	
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment		ED	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	InChI	CD	

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Table B.6 *(continued)*

Element Name	Value	Data Format	Note #
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 Citation	http://chem.sis.nlm.nih.gov/chemidplus/unii/4340891KFS	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	SMILES	CD	
Structural Representation Attachment	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 Citation	http://chem.sis.nlm.nih.gov/chemidplus/unii/4340891KFS	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	MOL	CD	
Structural Representation Attachment	document TEXT	ED	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	IND	CD	
Reference Source Class	Regulatory submission	CD	
Reference Source ID	4444 (Artificial ID)	ST	

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Table B.6 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Reference Source Document			
Reference Source Document	TEXT, in attachment	ED	
Reference Source Document Type	Text file	CD	

```
 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
```

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Element Name	Value	Data Format	Note #
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			
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			

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Element Name	Value	Data Format	Note #
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 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	
Moelecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	532.56	PQ	
Unit	g/mol	CD	
Element Group: Stoichiometric			
Number of Moieties	1	INT	1)
Element Group: Substance Relationship			
Relationship	Parent to salt	CD	
Relationship Type	Parent	CD	
Related Substance ID	POYFG4531Y (Artificial ID), 96R6PU3D8J (UNII)	II	
Related Substance Name	Ponatinib hydrochloride	ST	

[1] Element Group Moiety

When the substance is stoichiometric and contains only one moiety the attribute 'Number of Moieties' to be calculated is equal to 1. If the numeric value is equal to 1, the moiety class shall not be used (see 5.1.5.1).

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Discussion on the Specified Substance Information level

Table B.7 — Captured elements at the Specified Substance Group 1 level for Ponatinib hydrochloride

Element Type	Value	Data Format	Note #
Element Group: Specified Substance Group 1 (Properties to be described Ponatinib hydrochloride)			
Specified Substance Group 1 ID	PHIT2345RA (Artificial ID)	II	
Substance Type	Specified Substance Group 1	CD	
Specified Substance Group 1 Name	Ponatinib hydrochloride, crystalline, form 1	ST	
Element Group: Constituent			
Substance ID	POYFG4531Y (Artificial ID)	II	
Substance Name	Ponatinib hydrochloride	ST	
Substance Role	Parent Substance	CD	
Amount Type	Non-numeric value	ST	
Element Group: Physical form			
Physical State	Solid	CD	
Physical Form Type	Anhydrous crystalline form 1	CD	1)
Amount Type	Non-numeric value	ST	
Element Group: Property			
Property Type	Physical	CD	
Property Name	Solubility	CD	
Property Parameters	Measured at 20°C	ST	
Substance ID	YOW8V9698H (UNII)	II	
Substance Name	Dimethyl Sulfoxide	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average (Numeric Value)	80	PQ	
High Limit	90	PQ	
Low Limit	70	PQ	
Unit	mg/ml	CD	
Element Group: Property (Repeat)			
Property Type	Physical	CD	

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Table B.7 *(continued)*

Element Type	Value	Data Format	Note #
Property Name	Solubility	CD	
Property Parameters	Measured at 20°C	ST	
Substance ID	Y4S76JWI15 (UNII)	II	
Substance Name	Methanol	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average (Numeric Value)	30	PQ	
Unit	mg/ml	CD	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	Melting point	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average (Numeric Value)	263	PQ	
High Limit	262	PQ	
Low Limit	264	PQ	
Unit	Degree Celsius	CD	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	pK_a	CD	
Property Parameters	Measured at pH range of 2.5 -10.5	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average (Numeric Value)	7.80	PQ	2)
Unit	None	CD	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	pK_a	CD	
Property Parameters	Measured at pH range of 2.5 -10.5	ST	
Amount Type	Exact	CD	

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Table B.7 *(continued)*

Element Type	Value	Data Format	Note #
Element Group: Amount			
Average (Numeric Value)	2.77	PQ	
Unit	None	CD	
Element: Property (Repeat)			
Property Type	Physical	CD	
Property Name	UV absorption maxima	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	258	PQ	
Unit	Nanometer	CD	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	pK_a	CD	
Property Parameters	Measured at pH range of 2.5 -10.5	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	301	PQ	
Unit	Nanometer	CD	
Element Group: Property (Repeat)			
Property Type	Physical	CD	
Property Name	pK_a	CD	
Property Parameters	Measured at pH range of 2.5 -10.5	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	321	PQ	
Unit	Nanometer	CD	

[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].

[2] There are instances that the pKa has two values depended on the electrochemical potential difference within a pH range of 2.5-10.5

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Table B.8 — 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	
Substance Type	Specified Substance Group 2	CD	
Specified Substance Group 2 Name	Ponatinib hydrochloride, crystalline form 1-Manufacturer YY	ST	
Parent Substance ID	PHIT2345RA (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturer ID	DUNS543210 (Artificial ID)	II	
Manufacturer Name	Company YY	ST	
Manufacturing Type	Manufacturer	CD	
Production Method Type	Synthetic	CD	
Production Method Description	Chemical synthesis from starting materials, purification steps and recrystallisation to obtain crystalline form 1	ST	
Production System Type	Chemical synthesis	CD	
Critical Process Version Number	1	INT	2)

NOTE Since Ponatinib hydrochloride is not described in any pharmacopoeia the Specified Substance Group 3 information is not applicable.

[1] This Parent Substance ID refers to the Specified Substance Group 1 Name: Ponatinib hydrochloride, crystalline form 1.

[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 is not applicable

B.9.3 Example 3: Benzathine Benzylpenicillin tetrahydrate, sterilised.

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.9 — Tabular format of the captured elements at the Substance level for Benzathine, Benzylpenicillin tetrahydrate sterilised USP

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance Type	Chemical	CD	
Substance ID	GHFTE5643B (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Penicillin G Benzathine	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	US	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 Pharmacopoeia	ST	

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Table B.9 *(continued)*

Element Name	Value	Data Format	Note #
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	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS	CD	
Reference Source Class	Other name source	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	MAA	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.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	RIT82F58GK	CD.Code	

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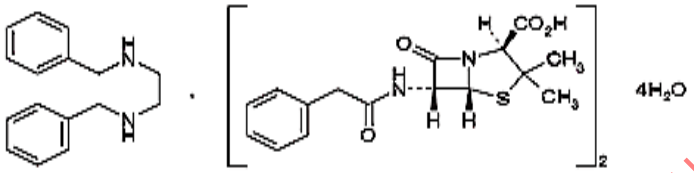
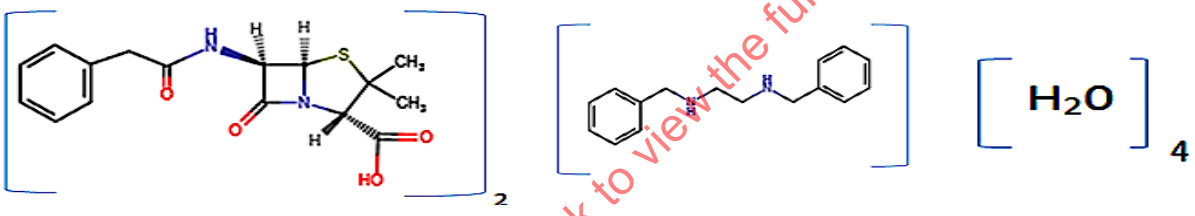
Table B.9 *(continued)*

Element Name	Value	Data Format	Note #
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	J01CE08	CD.Code	
Substance Classification Type	Beta-lactamase sensitive penicillins	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHO Collaborating Centre for Drug Statistics methodology (WHOCC)	CD	
Reference Source Class	Web	CD	
Reference Source Citation	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-SRS	CD	
Reference Source Class	Web	CD	
Reference Source Citation	http://fdasis.nlm.nih.gov/srs/auto/rit82f58gk	ST	

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Table B.9 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment	In image 1 below	ED	
	 **Image 1** **Structural Representation in accordance with 4.8.1**  **Image 2**		
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 Citation	http://chem.sis.nlm.nih.gov/chemidplus/rn/41372-02-5	ST	
Element Group: Structural Representation (Repeat)			

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Table B.9 *(continued)*

Element Name	Value	Data Format	Note #
Structural Representation Type	MOL	CD	
Structural Representation Attachment	document TEXT	ED	
Element Group: Reference Source			
Public Domain	No	BL	
Reference Source Type	IND	CD	
Reference Source Class	Regulatory submission	CD	
Reference Source ID	44444 (Artificial ID)	ST	
Element Group: Reference Source Document			
Reference Source Document	TEXT, in attachment	ED	
Reference Source Document Type	Regulatory submission	CD	

```
-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
    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
```

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Element Name	Value	Data Format	Note #
-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 21 20 2 0 0 0 0			

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Element Name	Value	Data Format	Note #
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			

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Element Name	Value	Data Format	Note #
M SMT 2 4 M END			
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Moelecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average (Numeric Value)	981.20	PQ	
Unit	g/mol	CD	
Element Group: Stoichiometric			
Number of Moieties	3	INT	
Element Group: Moiety			
Moiety Role	Salt	CD	
Moiety ID	C659VZ7P7T (UNII)	II	
Moiety Name	Benzanthine	ST	
Amount Type	Mole Ratio to 2 molecules Penicillin G	CD	
Element Group: Amount			
Average Number	1	PQ	
Element Group: Moiety (Repeat)			
Moiety Role	Hydrate	CD	
Moiety ID	059QF0KO0R (UNII)	II	
Moiety Name	Water	ST	
Amount Type	Mole Ratio to Penicillin G	CD	
Element Group: Amount			
Average Number	2	PQ	
Element Group: Moiety (Repeat)			
Moiety Role	Acid	CD	
Moiety ID	PENC56432TY (Artificial ID), Q42T66VG0C (UNII)	II	
Moiety Name	Penicillin G	ST	
Amount Type	Mole Ratio to salt Benzanthine	CD	

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Table B.9 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Amount			
Average	0.5	PQ	
Element Group: Substance Relationship			
Relationship	Parent to salt-hydrate	CD	
Relationship Type	Ionic	CD	
Related Substance ID	PENC56432TY (Artificial ID), Q42T66VG0C (UNII)	II	
Related Substance Name	Penicillin G	ST	
Amount Type	Weight per cent to salt	CD	
Element Group: Amount			
Average (Numeric Value	68.2	PQ	
Unit	Weight per cent	CD	

Specified Substance Group 2 information level

The following table shows the elements captured at the Specified **Substance Group 2 level** for Benzathine, Benzylpenicillin tetrahydrate, sterilised (USP).

Table B.10 — Tabular format of the captured elements at the Specified Substance Group 2 level for Benzathine, Benzylpenicillin tetrahydrate, sterilised (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	
Substance Type	Specified Substance Group 2	CD	
Specified Substance Group 2 Name	Benzathine Benzylpenicillin tetrahydrate - Manufacturer ZZ	ST	
Parent Substance ID	GHFTE5643B (Artificial ID)	II	1)
Element Group: Manufacturing			
Manufacturer ID	DUNS543210 (Artificial ID)	II	
Manufacturer Name	Company ZZ	ST	
Manufacturing Type	Manufacturer	CD	
Production Method Type	Fermentation and Chemical synthesis	CD	
Production Method Description	Fermentation, Chemical synthesis from starting	ST	

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	materials, purification steps and recrystallisation to obtain crystalline form.		
Production System Type	Chemical synthesis	CD	
Critical Process Version Number	1	INT	2)

[1] This Parent Substance ID refers to the Substance Name: Penicillin G Benzathine.

[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, sterilised (USP):

Table B.11 — Tabular format of the captured elements at the Specified Substance Group 3 level for Benzathine, Benzylpenicillin tetrahydrate, sterilised (USP)

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 3 (Benzathine Benzylpenicillin tetrahydrate, sterilised (USP)			
Specified Substance Group 3 ID	JKHYR7865P (Artificial ID)	II	
Substance Type	Specified Substance Group 3	CD	
Specified Substance Group 3 Name	Benzathine Benzylpenicillin tetrahydrate, sterilised-USP	ST	
Parent Substance ID	GHFTE5643B (Artificial ID)	II	1)
Element Group: Grade			
Grade Type	USP	CD	
Grade Name	Benzathine Benzylpenicillin tetrahydrate sterilised-USP	ST	
Grade Reference Source	USP, Monograph *USP38–NF33* Page 4781	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	USP	CD	
Reference Source Class	Official name source	CD	
Reference Source Citation	http://www.uspnf.com/uspnf/pub/index?usp=38&nf=33&s=1&officialOn=August 1, 2015	ST	

[1] This Parent Substance ID refers to the Substance Name: Penicillin G Benzathine.

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B.10 Radiopharmaceutical substance

B.10.1 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 17.

The registration of parent and daughter nuclides and registration of energy emission will be a following issue of consideration probably to be discussed in a separate Annex for Radiofarmaceutical substance/preparations and radio nuclide 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 Chemical ANNEX 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.

B.10.2 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 18F 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 synthesised 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 radiosynthesiser. In the synthesiser the ^{18}F-radiolabeling reaction takes place on the Florbetapir precursor and replacement

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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 finally 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.12 — Identity of material, combining the elements for Florbetapir 18F, Substance and Specified Substance information level

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance Type	Chemical	CD	
Substance ID	FLOR67453S (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Florbetapir (^{18}F)	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Source			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	EU, US	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Recommended INN list 65	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	INN, WHO Drug information, Vol. 25, No. 1, 2011	ST	

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Table B.12 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Web page	CD	
Reference Source Document URL	http://www.who.int/medicines/publications/druginformation/innlists/PL103.pdf?ua=1	ST	
Element Group: Substance Name (Repeat)			
Substance Name	(4-[(1*E*)-2-(6-{2-[2-(2-[^{18}F]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	Literature	CD	
Reference Source Citation	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-[(1*E*)-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	MAA	CD	
Reference Source Class	Regulatory Submission	CD	
Reference Source Citation	A123456 (Artificial ID)	ST	
Element Group: Substance Code			
Code	956103-76-7	CD.Code	

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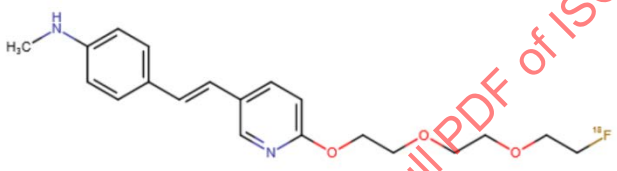
Table B.12 *(continued)*

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 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	V09AX05	CD.Code	
Substance Classification Type	Radiopharmaceuticals for diagnostic	ST	1)
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHO Collaborating Centre for Drug Statistics methodology (WHOCC)	CD	
Reference Source Class	Literature	CD	
Reference Source Citation	http://www.whocc.no/atc_ddd_index/?code=V09AX05&showdescription=yes	ST	
Element Group: Structure			
Stereochemistry	Achiral	CD	2)
Optical activity	None	CD	
Molecular Formula	$C_{20}H_{25}{}^{18}FN_2O_3$	ST	

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Table B.12 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Recommended INN List 65	CD	
Reference Source Class	Official name source	CD	
Reference Source Citation	http://www.whocc.no/atc_ddd_index/?code=V09AX05	ST	
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment		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 Citation	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: Reference Source			

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Table B.12 *(continued)*

Element Name	Value	Data Format	Note #
Public Domain	YES	BL	
Reference Source Type	ChemID *plus*	CD	
Reference Source Class	Public databse	CD	
Reference Source Citation	http://chem.sis.nlm.nih.gov/chemidplus/unii/6W15Z5R0RU	ST	
Element Group: Reference Source Document			
Reference Source Document	TEXT, in attachment	ED	
Reference Source Document Type	Regulatory submission	CD	

```
 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
  17.6255  -11.5734    0.0000 C  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
  16.8468  -10.2244    0.0000 C  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
  16.0679  -11.5734    0.0000 C  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
  18.4044  -12.0230    0.0000 N  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
  13.7315  -10.2244    0.0000 C  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
  12.9527   -8.8755    0.0000 C  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
  12.1739  -10.2244    0.0000 N  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
  19.1832  -11.5734    0.0000 C  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
  10.6162   -9.3252    0.0000 C  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
   9.0586   -9.3251    0.0000 O  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
   7.5009   -9.3251    0.0000 C  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
   5.9433   -9.3251    0.0000 C  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
```

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Element Name	Value	Data Format	Note #
4.3857 -9.3251 0.0000 F -1 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 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: Isotope			
Nuclide ID	JKHTF18784 4M4WE5N2GE (UNII)	II	
Nuclide Name	^{18}F-Fluoride	CD	
Substitution Type	Specific	CD	
Nuclide Half-life	109.77	PQ	
Amount Type	Exact	CD	
Element Group: Amount			
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	
Amount Type	Exact	CD	
Element Group: Amount			
Average (Numeric Value)	359.18	PQ	
Unit	g/mol	CD	
Element Group: Stoichiometric			
Number of Moieties	1	INT	

[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 (^{99m}Tc) exametazime (V09AA01) and technetium (^{99m}Tc) exametazime labelled cells (V09HA02).

[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.13 — Specified Substance Group 2 level for Florbetapir (18F)

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2 [Florbetapir (^{18}F)]			
Specified Substance Group 2 ID	HJFTE2345F (Artificial ID)	II	
Substance Type	Specified Substance Group 2	CD	
Specified Substance Group 2 Name	Florbetapir (^{18}F)-- Company Cyclotron ZZ	ST	
Parent Substance ID	FLOR67453S (Artificial ID)	II	1)
Element Group: Manufacturing			

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Manufacturer ID	DUNSNUCL78 (Artificial ID)	II	
Manufacturer Name	Company Cyclotron ZZ	ST	
Manufacturing Type	Manufacturer	CD	
Production Method Type	Synthetic	CD	
Production Method Description	Nuclide production by bombardment of [18O] 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 synthesiser. The substance is not isolated during manufacturing.	ST	
Production System Type	Nuclide production by bombardment of a parent substance followed by radiolabelling.	CD	
Critical Process Version Number	1`	INT	2)

[1] This Parent Substance ID refers to the Substance Name: Florbetapir (^{18}F).

[2] The Critical Process Number Version Number would change if a substantial change in the manufacturing process occurred. The change in a version number should be tied to the production system type.

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Annex C
(normative)

Protein substance

C.1 Scope

This Annex provides guidance to define elements that describe peptides and proteins in order to generate ISO 11238 Substance Identifiers in view of ISO 11238 standard (hereafter ISO 11238) by providing examples.

C.2 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 50 amino acid residues. Chains longer than fifty 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 biosynthesised 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 full 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.

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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. UNIIs will be used for Substance IDs; at the Specified Substance level the IDs are artificially created. It should be noted that in addition to the formats presented below for structural representation of 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 mol format, which is not indicated below, may be the preferred format for transmitting structural information on small peptidic molecules.

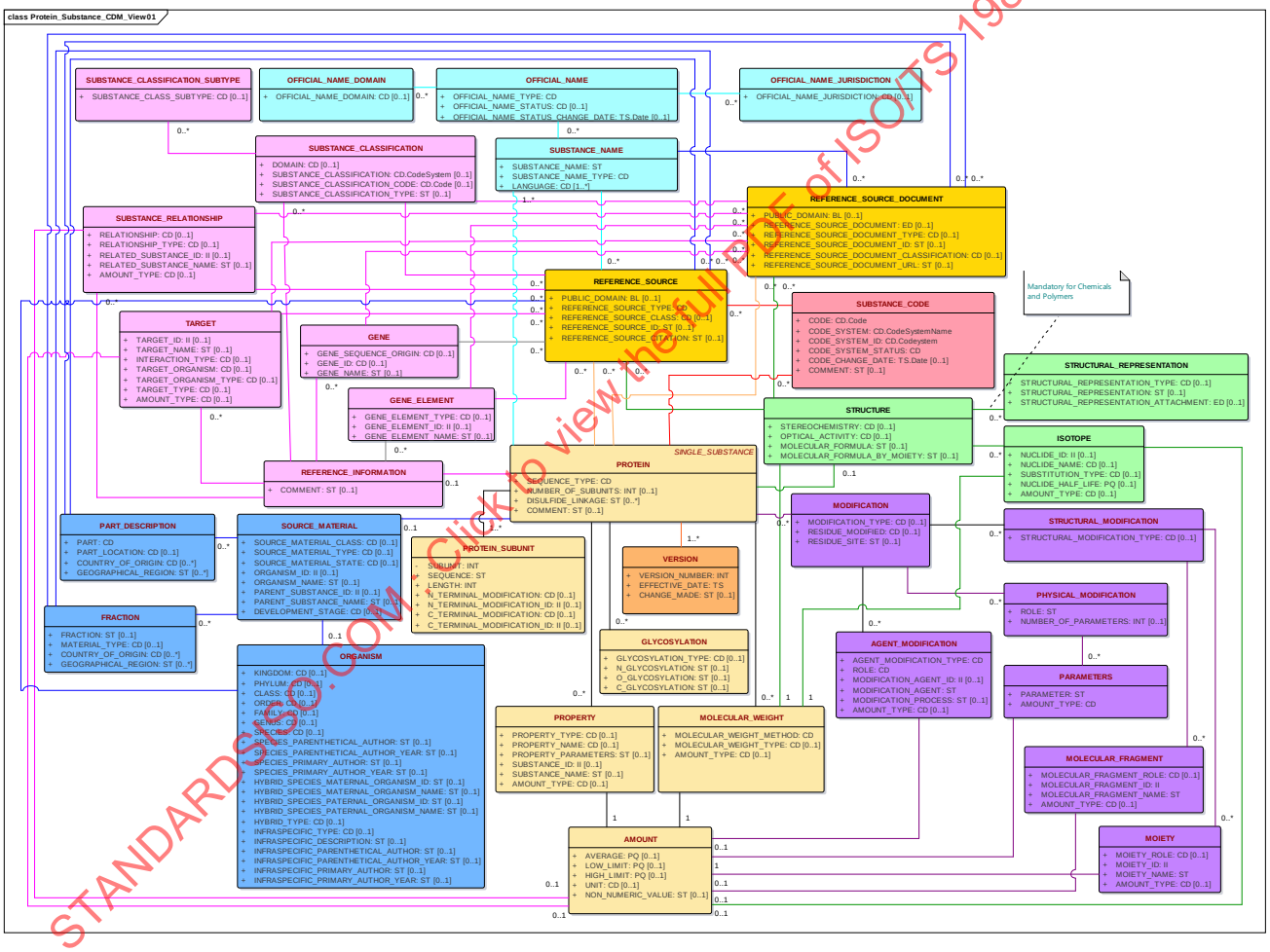


Figure C.1 — Conceptual data model view of Protein

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C.3 Peptide Substances

C.3.1 Example IIIa: 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.

It should be noted that the maintenance organisation should maintain lists of official names linked to the appropriate Substance or Specified Substance. A submitter or requestor should only need to submit an official name for the jurisdiction for which the substance is to be marketed.

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 Type	Protein	CD	
Substance ID	BDTDG7856V (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Vasopressin	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	US	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	Argipressin	ST	
Substance Name Type	Other Name (represents a synonym)	CD	

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Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Martindale: The complete Drug Reference	ST	
Reference Source Class	Literature	CD	
Reference Source Citation	Martindale: The complete Drug Reference, monograph Argipressin, last modification: 14-jan-2014.	ST	
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	
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	
Element Group: Substance Code			
Code	113-79-1	CD.Code	
Code System	CAS Registry	CD.CodeSystemName	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	

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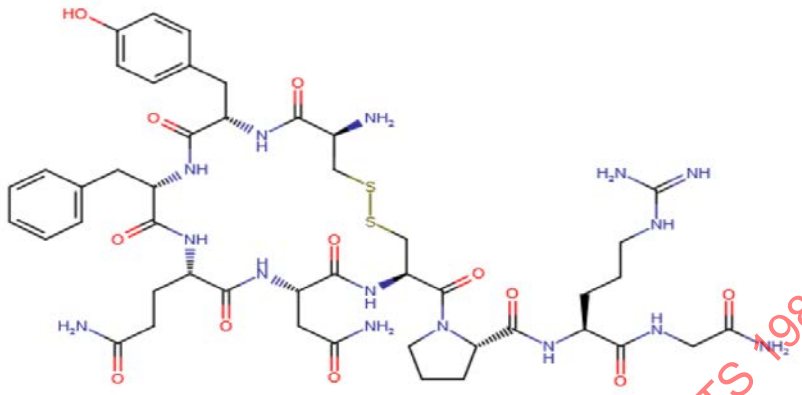
Table C.1 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Substance Code (Repeat)			
Code	Y490706MFD	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	H01BA01	CD.Code	
Substance Classification Type	Pituitary and hypothalamic hormones and analogues	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC (WHO Collaborating Centre for Drug Statistics Methodology)	CD	
Reference Source Class	Web	CD	
Reference Source Citation	http://www.whocc.no/atc_ddd_index/?code=H01BA01	ST	
Element Group: Structure			
Structural Representation Type	Full	CD	
Structural Representation Attachment	See image below.	ED	

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Table C.1 *(continued)*

Element Name	Value	Data Format	Note #
			
Element Group: Structure (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 Citation	http://www.chemspider.com/Chemical-Structure.17216149.html	ST	
Element Group: Structure (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			

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Table C.1 *(continued)*

Element Name	Value	Data Format	Note #
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Literature	CD	
Reference Source Citation	http://www.chemspider.com/Chemical-Structure.17216149.html	ST	
Element Group: Structure			
Stereochemistry	Absolute	CD	
Optical Activity	(-)	CD	
Molecular Formula	$C_{46}H_{65}N_{15}O_{12}S_2$	ST	1)
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	2)
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average Non-numeric Value)	1084.24	PQ	
Unit	g/mol	CD	
Element Group: Gene (Not applicable)			
Element Group: Protein			
Sequence Type	Complete	CD	
Number of Subunits	1	INT	
Element Group: Protein Subunit			
Subunit	1	INT	
Sequence	CYFQNCPRG	ST	
Length	9	INT	
Element Group: Protein (Part of Group)			
Disulfide linkage	1_1-1_6	ST	3)
Element Group: Protein Subunit (Part of Group); C-terminal modification of Glycine shall be captured as a modification within the Structural modification group			
Element Group: Protein Subunit (Repeat)			
C-Terminal Modification	Glycine	CD	

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Table C.1 *(continued)*

Element Name	Value	Data Format	Note #
C-Terminal Modification ID	TE7660XO1C (UNII)	II	
Element Group: Protein Subunit (Part of Group); 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 Sites	1_9	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Role	C-Terminal Modification	CD	
Molecular Fragment ID	4JDT453NWO (UNII)	II	
Molecular Fragment Name	Glycinamide	ST	
Amount Type	Non-numeric value	ST	
Element Group: Amount			
Non-numeric value	Complete	ST	

[1] The molecular formula, as defined in 4.8.4 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 [1] Monoacetate Trihydrate: **Molecular formula by moiety** (see 4.8.5): $C_{46}H_{64}N_{14}O_{12}S_2 . C_2 H_4 O_2 . 3H_2O$ and by Molecular formula, 4.8.4, following the Hill system: $C_{48}H_{74}N_{14}O_{17}S_2$.

[2] The molecular weight was implied as part of the Chemical Substance class in the ISO 11238 Standard.

[3] This indicates there is a disulfide bond between residues 1 and 6; each subunit is numbered even is there is only one.

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C.3.2 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.

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Table C.2 — Protein Substance: Desmopressin

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance Type	Protein	CD	
Substance ID	HJTFH3452D (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Desmopressin	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	US, EU	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	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	
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Journal	CD	
Reference Source Document URL	https://mednet-communities.net/inn/db/media/docs/p-innlist33.pdf	ST	
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	ST	
Element Group: Substance Name (Repeat)			

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Table C.2 *(continued)*

Element Name	Value	Data Format	Note #
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	
Substance Name Type	Systematic Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	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	IUPAC Name	CD	
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	
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.	CD	
Element Group: Substance Code			
Code	16679-58-6	CD.Code	

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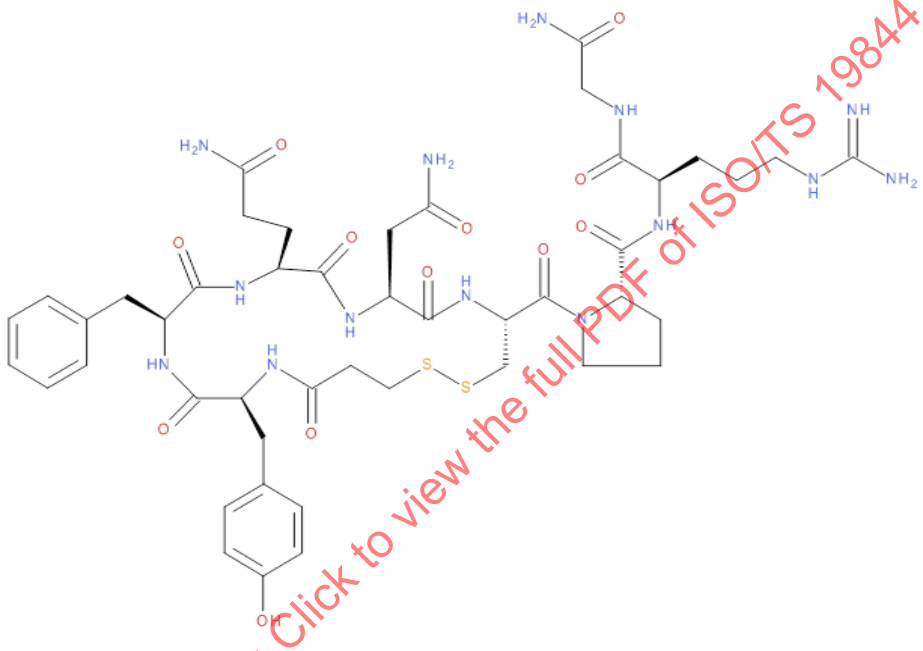
Table C.2 *(continued)*

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	ENR1LLB0FP	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	H01BA02	CD.Code	
Substance Classification Type	Pituitary and hypothalamic hormones and analogues	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC (WHO Collaborating Centre for Drug Statistics Methodology)	CD	
Reference Source Class	Web	CD	
Reference Source Citation	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	

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Table C.2 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment	See image below.	ED	
			
Element Group: Structure Represenation (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation	IInChI=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	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	

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Table C.2 *(continued)*

Element Name	Value	Data Format	Note #
Reference Source Class	Web	CD	
Reference Source Citation	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	ED	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web Page	CD	
Reference Source Class	Web	CD	
Reference Source Citation	http://www.chemspider.com/Chemical-Structure.10481973.html	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average (Non-numeric Value)	1069.22	PQ	
Unit	g/mol	CD	
Element Group: Gene (Not applicable)			
Element Group: Protein			
Number of Moieties	1	INT	
Sequence Type	Complete	CD	
Number of Subunits	1	INT	
Element Group: Protein Subunit			
Subunit	1	INT	

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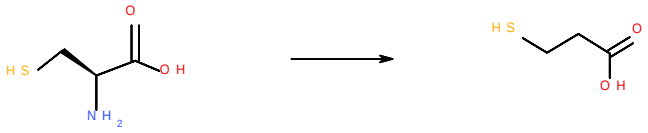
Table C.2 *(continued)*

Element Name	Value	Data Format	Note #
Sequence	CYFQNCPrG (D-Arginine is represented by the smaller letter r)	ST	
Length	9	INT	
Element Group: Protein (Part of Group)			
Disulfide linkage	1_1-1_6 (Disulfide linkage is still between residue 1 and 6; Cysteine is replaced with a structural modification capable of forming a disulfide linkage)	ST	
Element Group: Protein Subunit (Part of Group); 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: Protein subunit (Part of Group)			
N-Terminal Modification	Cysteine	CD	
N-Terminal Modification ID	K848JZ4886 (UNII)	II	
C-Terminal Modification	Glycine	CD	
C-Terminal Modification ID	TE7660XO1C (UNII)	II	
Element Group: Modification (N-Terminal Modification)			
Modification Type	Structural Modification	CD	
Residue Modified	Cysteine	CD	
Residue Sites	1_1	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Role	N-Terminal Modification	CD	
Molecular Fragment ID	B03TJ3QU9M (UNII)	II	
Molecular Fragment Name	3-Mercaptopropionic acid (The amino acid is replaced by thiol acid)	ST	
Amount Type	Non-numeric value	ST	

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Table C.2 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Amount			
Average (Non-numeric Value)	Complete	CD	
Element Group: Structure			
Structural Representation Type	Full	CD	
Structural Representation Attachment		ED	
Element Group: Modification (Repeat)(C-Terminal Modification)			
Modification Type	Structural Modification	CD	
Residue Modified	Glycine	CD	
Residue Sites	1_9	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Role	C-Terminal Modification	CD	
Molecular Fragment ID	4JDT453NWQ (UNII)	II	
Molecular Fragment Name	Glycinamide	ST	
Amount Type	Non-numeric value	ST	
Element Group: Amount			
Non-numeric value	Complete	ST	

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C.3.3 Example IIIc: 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.

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Table C.3 — Protein Substance: Desmopressin Acetate (USAN); Desmopressin Acetate Hydrate (JAN)

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance Type	Protein	CD	
Substance ID	GFTDSR765T (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Desmopressin Acetate	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	US	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 (Synonym)	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	

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Table C.3 *(continued)*

Element Name	Value	Data Format	Note #
Language	en	CD	
Element Group: Official Name			
Official name Type	JAN (Japanese Accepted Name); JP (Japanese Pharmacopoeia)	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	JP	CD	
Element Group: Reference Source			
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	
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	

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Table C.3 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Substance Name (Repeat)			
Substance Name	(S)-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-pentaazacycloicosane-4-carbonyl)-N-((R)-1-((2-amino-2-oxoethyl)amino)-5-guanidino-1-oxopentan-2-yl)pyrrolidine-2-carboxamide acetate trihydrate	ST	
Substance Name Type	Systematic Name	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	IUPAC Name	CD	
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	XB13HYU18U	CD.Code	
Code System	FDA Substance Registration System (UNII)	CD.Code SystemName	
Code System ID	0050	CD.Code System	
Code System Status	Active	CD	
Element Group: Substance Classification			
Domain	Human Pharmaceutical	CD	
Substance Classification	ATC	CD.Code System	

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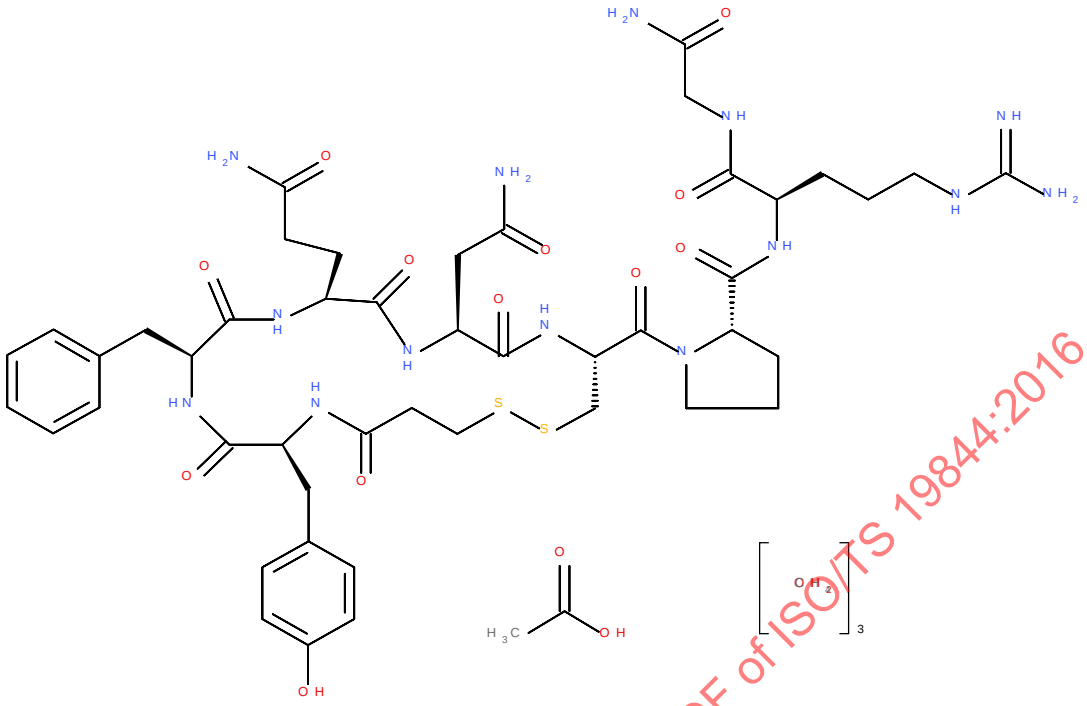
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Table C.3 *(continued)*

Element Name	Value	Data Format	Note #
Substance Classification Code	H01BA02	CD.Code	
Substance Classification Type	Pituitary and hypothalamic hormones and analogues	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC (WHO Collaborating Centre for Drug Statistics Methodology)	CD	
Reference Source Class	Literature	CD	
Reference Source Citation	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	$C_{46}H_{64}N_{14}O_{12}S_2.\ C_2H_4O_2.\ 3\ H_2O$	ST	
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	

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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)15-24-29-40(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	
Reference Source Citation	http://www.chemspider.com/Chemical-Structure.19969319.html	ST	
Element Group: Structural Representation (Repeat)			

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Table C.3 *(continued)*

Element Name	Value	Data Format	Note #
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]	ED	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Web	CD	
Reference Source Class	Literature	CD	
Reference Source Citation	http://www.chemspider.com/Chemical-Structure.19969319.html	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average (Numeric Value)	1183.24	PQ	
Unit	g/mol	CD	
Element Group: Modification			1)
Modification Type	Structural modification	CD	
Element Group: Moiety			
Moiety Role	Salt	CD	
Moiety ID	Q40Q9N063P (UNII)	II	
Moiety Name	Acetic Acid	ST	
Amount Type	Mole Ratio to Parent Substance	CD	
Element Group: Amount			
Average	1	PQ	
Element Group: Moiety (Repeat)			
Moiety Role	Solvate	CD	

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Table C.3 *(continued)*

Element Name	Value	Data Format	Note #
Moiety ID	059QF0KO0R (UNII)	II	
Moiety Name	Water	ST	
Amount Type	Mole Ratio to Parent Substance	ST	
Element Group: Amount			
Average	3	PQ	
Element Group: Moiety (Repeat)			
Moiety Role	Parent	CD	
Moiety ID	HJTFH3452D (Artificial ID)	II	
Moiety Name	Desmopressin	ST	
Amount Type	Mole Ratio to Salt Hydrate	CD	
Element Group: Amount			
Average	1	PQ	
Element Group: Substance Relationship			
Relationship	Parent	CD	
Relationship Type	Ionic	CD	
Related Substance ID	HJTFH3452D (Artificial ID) 1J444QC288 (UNII)	II	
Substance Name	Desmopressin	ST	
Amount Type	Weight per cent to salt	CD	
Element Group: Amount			
Average (Numeric value)	90,4	PQ	
Unit	Weight per cent	CD	
Element Group: Gene (Not applicable)			
Element Group: Protein (Part of Group)1)			
Sequence Type	Complete	CD	
Number of Subunits	1	INT	
Element Group: Protein Subunit			
Subunit	1	INT	
Sequence	CYFQNCPrG (D-Arginine is represented by the smaller letter r)	ST	
Length	9	INT	

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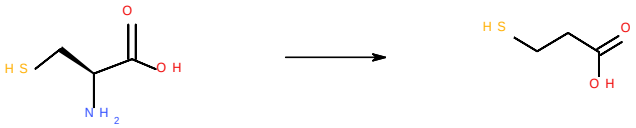
Table C.3 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Protein (Part of Group)			
Disulfide linkage	1_1-1_6 (Disulfide linkage is still between residue 1 and 6; cysteine is replaced with a structural modification capable of forming a disulfide linkage)	ST	
Element Group: Protein Subunit (Part of Group); 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: Protein subunit (Part of Group)			
N-Terminal Modification	Cysteine	CD	
N-Terminal Modification ID	K848JZ4886 (UNII)	II	
C-Terminal Modification	Glycine	CD	
C-Terminal Modification ID	TE7660XO1C (UNII)	II	
Element Group: Modification (N-Terminal modification)			
Modification Type	Structural modification	CD	
Residue Modified	Cysteine	CD	
Residue Sites	1_1	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Role	N-Terminal Modification	CD	
Molecular Fragment ID	B03TJ3QU9M (UNII)	II	
Molecular Fragment Name	3-Mercaptopropionic acid (The amino acid is replaced by thiol acid)	ST	
Amount Type	Non-numeric value	ST	
Element Group: Amount			
Average (Non-numeric value)	Complete	CD	
Element Group: Structure Representation			
Structural Representation Type	Full	CD	

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Table C.3 *(continued)*

Element Name	Value	Data Format	Note #
Structural Representation Attachment		ED	
Element Group: Modification (Repeat) (C-Terminal Modification)			
Modification Type	Structural modification	CD	
Residue Modified	Glycine	CD	
Residue Sites	1_9	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment (Repeat)			
Modification Type	C-rewTerminal Modification	CD	
Molecular Fragment ID	4JDT453NWO (UNII)	II	
Molecular Fragment Name	Glycinamide	ST	
Amount Type	Non-numeric value	ST	
Element Group: Amount			
Non-numeric value	Complete	ST	

[1] For a protein substance all other molecular entities that are not covalently attached to the protein shall be captured as a moiety.

C.3.4 Example IIId: 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.

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Table C.4 — Protein Substance: Calcitonin Salmon

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance Type	Protein	CD	
Substance ID	CHJT8360JS (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Calcitonin Salmon	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	US	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	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	EU	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	

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Table C.4 *(continued)*

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	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Calcitonin (Salmon)	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	INN	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	
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Journal	CD	
Reference Source Document URL	http://whqlibdoc.who.int/druginfo/INN_1999_list41.pdf	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Calcitonin (Salmon)	ST	
Substance Name Type	Official Name	CD	
Language	en	CD	
Element Group: Official Name			
Official name Type	BAN	CD	

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Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	GB	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	BAN	CD	
Reference Source Class	Official name source	CD	
Reference Source Citation	BAN monograph	ST	
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	
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	
Element Group: Substance Code			
Code	47931-85-1	CD.Code	

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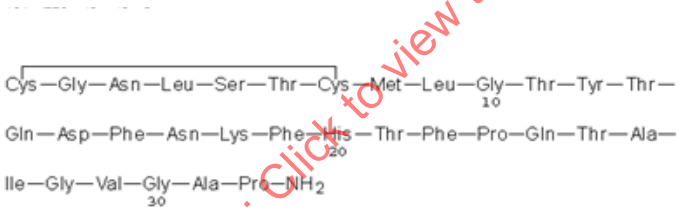
Table C.4 *(continued)*

Element Name	Value	Data Format	Note #
Code System	CAS Registry	CD.CodeSystem Name	
Code System ID	0049	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Substance Code (Repeat)			
Code	7SFC6U2VI5	CD.Code	
Code System	FDA Substance Registration System (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	H05BA01	CD.Code	
Substance Classification Type	Calcitonin (salmon synthetic)	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	WHOCC (WHO Collaborating Centre for Drug Statistics Methodology)	CD	
Reference Source Class	Web	CD	
Reference Source Citation	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: Reference Source			
Public Docmain	Yes	BL	
Reference Source Type	Journal	CD	

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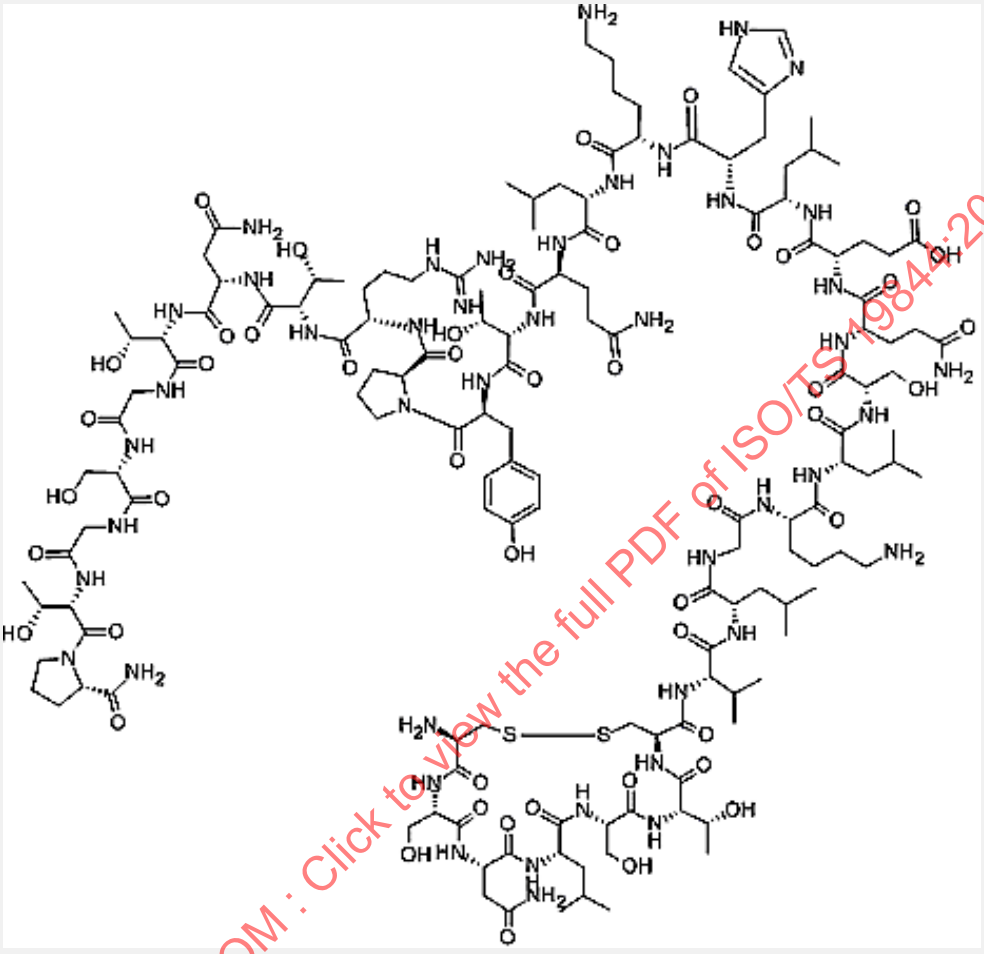
Table C.4 *(continued)*

Element Name	Value	Data Format	Note #
Reference Source Citation	WHO Drug Information, Vol. 13, No. 1, 1999 RECOMMENDED INN: List 41	ST	
Element Group: Reference Source Document			
Public Docmain	Yes	BL	
Reference Source Document	PDF	ED	
Reference Source Document Type	Regulatory submission	CD	
Reference Source Document URL	http://whqlibdoc.who.int/druginfo/INN_1999_list41.pdf	ST	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	See image below.	ED	
			
Element Group: Structural Representation(Repeat)			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	See image below.	ED	

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Table C.4 *(continued)*

Element Name	Value	Data Format	Note #
Calcitonin salmon 			
Element Group: Reference Source (Repeat)			
Public Domain	Yes	BL	
Reference Source Type	Chemical Book	CD	
Reference Source Class	Public Database	CD	
Reference Source Citation	http://www.chemicalbook.com/ChemicalProductProperty_EN_CB2127316.htm	ST	
Element Group: Reference Source Document (Repeat)			
Public Domain	Yes	BL	
Reference Source Document	Image above (Calcitonin salmon), Pdf	ED	
Reference Source Document Type	Regulatory submission	CD	

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Table C.4 *(continued)*

Element Name	Value	Data Format	Note #
Reference Source Document Classification	Chemical structure	CD	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	InChI	CD	
Structural Representation Attachment	See attachment below	ED	
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)			
Reference Source Type	PubChem	CD	
Reference Source Class	Public Database	CD	
Reference Source Citation	http://pubchem.ncbi.nlm.nih.gov/compound/Salmon_calcitonin#section=Computed-Descriptors;	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	SMILES	CD	

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Table C.4 *(continued)*

Element Name	Value	Data Format	Note #
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 Citation	http://pubchem.ncbi.nlm.nih.gov/compound/Salmon_calcitonin#section=Canonical-SMILES	ST	
Element Group: Structural Representation (Repeat)			
Structural Representation Type	HELM	CD	
Structural Representation	PEPTIDE1{C.S.N.L.S.T.C.V.L.G.K.L.S.Q.E.L.H.K.L.Q.T.Y.P.R.T.N.T.G.S.G.T.P.[am]}$PEPTIDE1,PEPTIDE1,1:R3-7:R3$$$	ST	
Element Group: Reference Source (Repeat)			
Public Domain	Yes	BL	
Reference Source Type	JAVA APPLICATION	CD	
Reference Source Citation	HELM Editor V1.2	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average (Numeric Value)	3431.85	PQ	
Unit	g/mol	CD	

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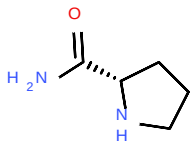
Table C.4 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Gene (Not applicable)			
Element Group: Protein			
Sequence Type	Complete	CD	
Number of Subunits	1	INT	
Element Group: Protein Subunit			
Subunit	1	INT	
Sequence	CSNLSTCVLGKLSQELHKLQTYPRTNTGSGTP	ST	
Length	32	INT	
Element Group: Protein (Part of Group)			
Disulfide linkage	1_1-1_7	ST	
Element Group: Protein Subunit (Part of Group); There is one structural modification: The C-terminal modification of Proline shall be captured as a modification within the Structural modification group;			
Element Group: Protein Subunit (Part of Group)			
C-Terminal Modification	Proline	CD	
C-Terminal Modification ID	9DLQ4CIU6V (UNII)	II	
Element Group: Modification			
Modification Type	Structural Modification Amino Acid Substitution	CD	
Residue Modified	Proline	CD	
Residue Sites	1_32	ST	
Element Group: Structural Modification			
Structural Modification Type	Structural Modification	CD	
Element Group: Molecular Fragment			
Role	C-Terminal Modification	CD	
Molecular Fragment ID	VD6PQK9DHG (UNII)	II	
Molecular Fragment Name	Prolinamide	ST	
Amount Type	Non-numeric value	ST	

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Table C.4 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Amount			
Average (Non-numeric value)	Complete	CD	
Element Group: Structural Representation (Repeat)			
Structural Representation [Molecular Fragment]	Full	ST	
Structural Representation Attachment		ED	

C.3.5 Example IIIe: 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 Type	Protein	CD	
Substance ID	HUI53427HT (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Insulin Human	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	US, JP	CD	

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Table C.5 *(continued)*

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	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	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	US, JP	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	
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Journal article	CD	
Reference Source Citation	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	

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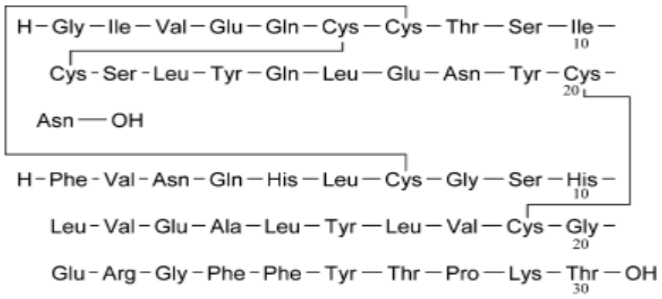
Table C.5 *(continued)*

Element Name	Value	Data Format	Note #
Language	en	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	EU	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, 01/2011:0838	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: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	INN	CD	
Reference Source Class	Official name source	CD	
Reference Source Citation	WHO Drug Information Vol, 37, No.6, 1983, Recommended INN List 23	ST	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	

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Table C.5 *(continued)*

Element Name	Value	Data Format	Note #
Structural Representation Attachment		ED	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average (Numeric Value)	5807.57	PQ	
Unit	g/mol	CD	.
Element Group: Gene (Not applicable)			
Element Group: Protein			
Sequence Type	Complete	CD	
Number of Subunits	2	INT	
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	

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Table C.5 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Protein (Part of Group)			
Disulfide linkage	1_7-2_7; 1_19-2_20; 2_6-2_11 (Each disulfide linkage listed in a single field separated by semi-colons)	ST	

C.4 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.

C.4.1 Example IVa: 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)

Element Group: Protein, Specified Substance Group 1			
Specified Substance Group 1 ID	HJGTD875G1 (Artificial ID)	II	
Specified Substance Group1 Name	Insulin Human Zinc Injectable Suspension (Amorphous)	ST	1)
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	EU	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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Table C.6 *(continued)*

Reference Source Citation	Ph.Eur. monograph	ST	
Element Group: Constituent			
Substance ID	1Y17CTI5SR (UNII)	II	
Substance Name	Insulin Human	ST	
Substance Role	Parent	CD	
Amount Type	Substance Units	CD	2)
Element Group: Amount			
Average	100	PQ	
Unit:	Insulin Units	CD	
Element Group: Constituent (Repeat)			
Substance ID	13S1S8SF37 (UNII)	II	
Substance Name	Zinc Cation	ST	
Substance Role	Stabilizing ion	CD	
Amount Type	Weight average	CD	
Element Group: Amount (Zinc Cation)			
Average	0.19	PQ	
Low Limit	0.12	PQ	
High Limit	0.25	PQ	
Unit	mg/100 Insulin Units	CD	
Element Group: Physical Form (Insulin human)			
Physical State	Solid	CD	
Physical Form Type	Amorphous Powder	CD	
Element Group: Property (Insulin human)			
Property Type	Physical	CD	
Property Name	Particle Size	CD	
Amount Type	Dimension along any axis	CD	
Element Group: Amount			
High Limit	2	INT	
Unit	Micrometre	CD	

[1] The **SSG1-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

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water. The SSG3-Name and Pharmacopoeial Grade-Name will be discussed in C.4.3.

[2] **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.4.2 Example IVb: 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: Substance			
Substance Type	Protein	CD	
Substance ID	HUI53427HT (Artificial ID)	II	
Element Group: Substance Name			
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	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	EU	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	ST	
Element Group: Protein, Specified Substance Group 1			
Specified Substance Group1 ID	JFGER7453P (Artificial ID)	II	
Specified Substance Group1 Name	Insulin Human Zinc Injectable Suspension (Crystalline)	ST	1)
Substance Name Type	Official	CD	

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Language	en	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	EU	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	ST	
Element Group: Constituent			
Substance ID	1Y17CTI5SR (UNII)	II	
Substance Name	Insulin Human	ST	
Substance Role	Parent	CD	
Amount Type	Substance Units	CD	
Element Group: Amount			
Average	100	PQ	
Unit:	Insulin Units	CD	
Element Group: Constituent (Repeat)			
Substance ID	13S1S8SF37 (UNII)	II	
Substance Name	Zinc Cation	ST	
Substance Role	Stabilizing ion	ST	
Amount Type	Weight average	CD	
Element Group: Amount (Zinc Cation)			
Average	0.19	PQ	
Low Limit	0.12	PQ	
High Limit	0.25	PQ	
Unit	mg/100 Insulin Units	CD	
Element Group: Physical Form (Insulin human)			
Physical State	Solid	CD	

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Physical Form Type	Crystalline	CD	
Element Group: Property (Insulin human)			
Property Type	Physical	CD	
Property Name	Particle Size	CD	
Amount Type	Dimension along any axis	CD	
Element Group: Amount			
High Limit	40	PQ	
Low Limit	10	PQ	
Unit	Micrometre	CD	

[1] The **SSG1-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 SSG3-Name and Pharmacopoeial Grade-Name will be discussed in example C.4.3.

C.4.3 Example IVc: Insulin Human Zinc Suspension taken from Ph.Eur./USP Monographs for Zinc Suspensions, including discussion for Specified Substance Group 3 information

This example will discuss a mixture of Zinc Insulin, amorphous (30 IU/ml) and Zinc Insulin, crystalline (70 IU/ml).

Table C.8 — Insulin Human Zinc Suspension

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance Type	Protein	CD	
Substance ID	HUI53427HT (Artificial ID)	II	
Element Group: Substance Name			
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	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	EU	CD	
Element Group: Reference Source			

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Public Domain	Yes	BL	
Reference Source Type	Ph.Eur.	CD	
Reference Source Class	Official name source	CD	
Reference Source Citation	Ph.Eur. monograph	ST	
Element Group: Protein, Specified Substance Group 1			
Specified Substance Group 1 ID	HJGYD4532M (Artificial ID)	II	
Specified Substance Group1 Name	Insulin Human Zinc Injectable Suspension	ST	1)
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	Ph.Eur.	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	EU	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	ST	
Element Group: Protein, Specified Substance Group1 (Repeat)			
Specified Substance Group1 Name	Insulin Human Zinc Injectable Suspension	ST	1)
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	USP	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name	US	CD	

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Jurisdiction			
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			
Substance ID	JFGER7453P (Artificial ID)	II	2)
Substance Name	Insulin Human Zinc Injectable Suspension (Crystalline)	ST	
Substance Role	Active Specified Substance	CD	
Amount Type	Weight Per cent of Total Insulin	CD	
Element Group: Amount			
Average	70	PQ	
Element Group: Constituent (Repeat)			
Substance ID	HJGTD875G1 (Artificial ID)	II	2)
Substance Name	Insulin Human Zinc Injectable Suspension (Amorphous)	ST	
Substance Role	Active Specified Substance	CD	
Amount Type	Weight Per cent of Total Insulin	CD	
Element Group: Amount			
Average	30	PQ	

[1] The **SSG1-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.

[2] The Substance ID and name refers to a Specified Substance Group 1.

Element Group: Protein Specified Substance Group 3			
Specified Substance Group 3 ID	KHJTYE563P (Artificial ID)	II	
Specified Substance Group 3 Name	Insulin Human Zinc Injectable Suspension Ph.Eur.	ST	
Parent Substance ID	HJGYD4532M (Artificial ID)	II	3)
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name	Insulin Zinc Injectable Suspension	ST	
Grade Reference Source	European Pharmacopoeia	ST	

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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 8.0, pg 2501	ST	
Element Group: Reference Source Document			
Public domain	Yes	BL	
Reference Source Document Type	Pharmacopoeial monograph	CD	
Reference Source Document URL	http://online6.edqm.eu/ep805/	ST	
Element Group: Protein Specified Substance Group 3 (Repeat)			
Specified Substance Group 3 ID	ASTEY6794F (Artificial ID)	II	
Specified Substance Group 3 Name	Insulin Human Zinc Injectable Suspension USP	ST	
Parent Substance ID	HJGYD4532M (Artificial ID)	II	3)
Element Group: Grade			
Grade Type	USP	CD	
Grade Name	Insulin Zinc Suspension	ST	
Grade Reference Source	USP37-NF32 pg.3349	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	

[1] The **SSG1-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.

[2] The Substance ID and name refers to a Specified Substance Group 1.

[3] The Substance ID and name refers to a Specified Substance Group 1.

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C.5 Element Group Protein, Specified Substance Group 2

The ISO 11238:2012 Substance Standard provides for the possibility to go from the Substance information level directly to the Specified Substance Group 2 information level (see Figure 1).

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

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process a separate M3 regulatory dossier shall be submitted and separate SSG2 IDs will be generated. In the Pharmacopoeial monograph Calcitonin Salmon, 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.

C.5.1 Example Va: 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 Type	Protein	CD	
Substance ID	CHJT8360JS (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Acme Calcitonin Salmon	ST	
Substance Name Type	Brand	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Element Group: Substance Classification			
Further Element Groups: See example IIId			
Element Group: Protein, Specified Substance Group 2			
Specified Substance Group 2 ID	KHJR98675T (Artificial ID)	II	
Specified Substance Group 2 Name	Synthetic Calcitonin Salmon — Acme, site xxxx	ST	
Parent Substance ID	CHJT8360JS (Artificial ID)	II	
Element Group: Manufacturing			
Manufacturer ID	DUNS78654A (Artificial ID)	II	
Manufacturer Name	Acme, site xxxx	ST	
Manufacturing Type	Manufacturer	CD	
Production Method Type	Synthetic	CD	
Production System Type	Solid Phase Chemistry	CD	
Production System	FMOC Chemistry	CD	

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Critical Process Version Number	1	INT	1)
(See Specified Substance Group 3 for further information below)			
[1] 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.			

C.5.2 Example Vb: Recombinant Calcitonin Sal— 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 Sal— Company Acme

Element Name	Value	Data Format	Note #
Element Group: Substance			
Further Element Groups: See example IIId			
Element Group: Protein, Specified Substance Group 2			
Specified Substance Group 2 ID	RDFS2341HL (Artificial ID)	II	
Specified Substance Group 2 Name	Recombinant Calcitonin Salmon — Acme, site yyyy	ST	
Parent Substance ID	CHJT8360JS (Artificial ID)	II	
Element Group: Manufacturing			
Manufacturer ID	DUNS37245R (Artificial ID)	II	
Manufacturer Name	Acme, site yyyy	ST	
Manufacturer Type	Manufacturer	CD	
Production Method Type	Recombinant Protein Production	CD	
Production Method Description	See, Document enclosed at 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	

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

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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.

The Version should 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.6 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.

C.6.1 Example: Calcitonin Salmon (Synthetic) Specified Substance Group 3

Table C.11 — Calcitonin Salmon (Synthetic) SSG3

Element Group: Protein Specified Substance Group 3			
Specified Substance Group 3 ID	8SJUTVDF89 (Artificial ID)	II	
Specified Substance Group 3 Name	Calcitonin Salmon USP (Synthetic)	ST	
Parent Substance ID	CHJT8360JS (Artificial ID)	II	
Element Group: Grade			
Grade Type	USP	CD	
Grade Name	Calcitonin Salmon	ST	
Grade Reference Source	USP 38-NF-33; page 2525-2526	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: Protein Specified Substance Group 3 (Repeat)			
Specified Substance	8RKHJT345P (Artificial ID)	II	

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Group 3 ID			
Specified Substance Group 3 Name	Synthetic Calcitonin Salmon Ph.Eur.	ST	
Parent Substance ID	CHJT8360JS (Artificial ID)	II	
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name	Calcitonin (Salmon)	ST	
Grade Reference Source	European Pharmacopoeia 8.5	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 8.5 p. 1726-1727	ST	
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Pharmacopoeial monograph	CD	
Reference Source Document URL	http://online6.edqm.eu/ep805/#	ST	

C.6.2 Example: Calcitonin Salmon (Recombinant) Specified Substance Group 3

Table C.12 — Calcitonin Salmon (Synthetic) SSG3

Element Group: Protein Specified Substance Group 3			
Specified Substance Group 3 ID	GHHJGD6745 (Artificial ID)	II	
Specified Substance Group 3 Name	Recombinant Calcitonin Salmon USP	ST	
Parent Substance ID	CHJT8360JS (Artificial ID)	II	
Element Group: Grade			
Grade Type	USP	CD	
Grade Name	Calcitonin Salmon	ST	
Grade Reference source	USP 38-NF-33; p. 2525-2526	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	

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Reference Source Type	USP	ST	
Reference Source Class	Official name source	CD	
Reference Source Citation	USP 38-NF-33; p. 2525-2526	ST	
Element Group: Protein Specified Substance Group 3 (Repeat)			
Specified Substance Group 3 ID	HGDFR67453 (Artificial ID)	II	
Specified Substance Group 3 Name	Recombinant Calcitonin Salmon Ph.Eur.	ST	
Parent Substance ID	CHJT8360JS (Artificial ID)	II	
Element Group: Grade			
Grade Type	Ph.Eur.	CD	
Grade Name	Calcitonin (Salmon)	ST	
Grade Reference Source	Ph.Eur. monograph, 01/2008:0471	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	

C.7 Example Protein Substance Example of a 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 targeted 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.2**,** 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.3.

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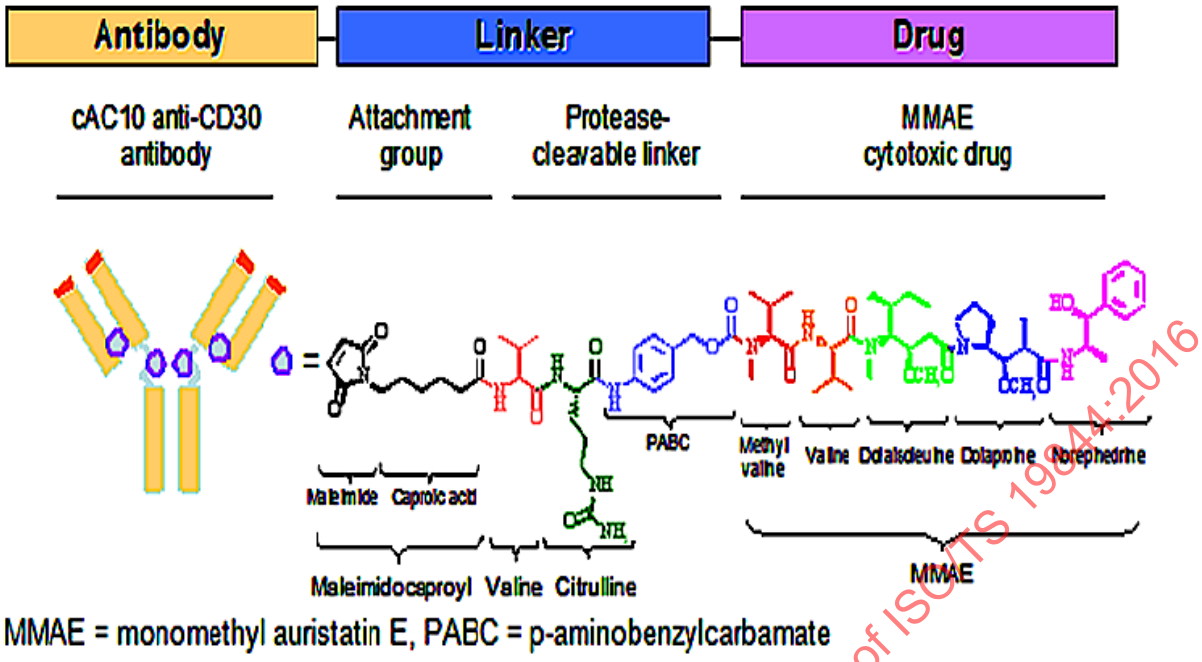
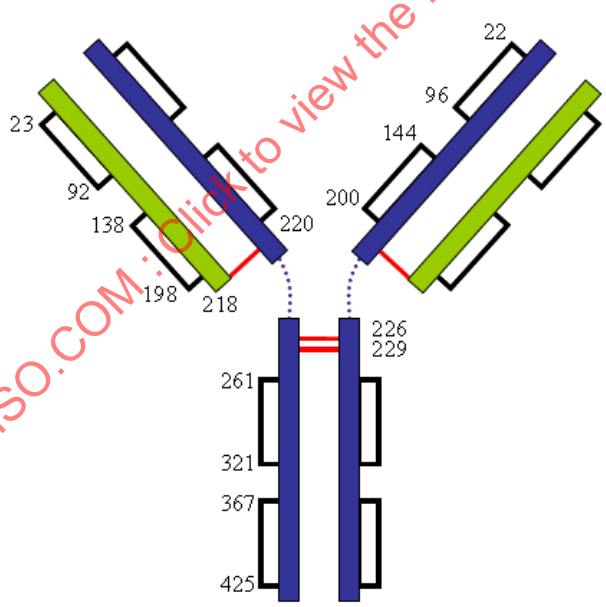


Figure C.2 — Structural representation of Brentuximab Vedotin



Green bars denote light chain. Blue bars represent heavy chain. Dashed blue line represents hinge region. Black lines represent intra-chain disulfide bonds. Red lines represent inter-chain disulfide bonds. Numbers indicate cysteine residue associated with disulfide bonds.

Figure C.3 — Schematic depiction of disulfide bridges in Brentuximab

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Table C.13 — Brentuximab Vedotin

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance Type	Protein	CD	
Substance ID	JKHGYD6453 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Brentuximab Vedotin	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	USAN, INN	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	US, EU	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)
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Journal article	CD	
Reference Source Document 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	
Element Group: Official Name			
Official Name Type	JP	CD	

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Table C.13 *(continued)*

Element Name	Value	Data Format	Note #
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	JP	CD	
Element Group: Reference Source			
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 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 Substance Registration System (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	3)
Molecular Formula by Moiety	$C_{6588}H_{10108}N_{1696}O_{2108}S_{40}.4[C_{68}H_{106}N_{11}O_{15}]$	ST	

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Table C.13 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	Brentuximab Vedotin structure.pdf\ (see Figure C.2)	ED	2)
Element Group: Structural Representation (Repeat)			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	Brentuximab Vedotin disulphide linkage.pdf (see Figure C.3)	ED	2)
Element Group: Reference Information			
Element Group: Gene			
Gene Sequence Origin	Mouse-Human Chimeric	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)	CD	4)
Gene ID	ID ghdftwu123	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')	CD	4)
Gene ID	ID glertwu456	CD	
Element Group: Substance Classification			
Substance Classification Type	Monoclonal Antibody	ST	
Element Group: Substance Classification Subtype			
Substance Class Subtype	IgG1	ST	
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	

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Table C.13 *(continued)*

Element Name	Value	Data Format	Note #
Target Organism	Human	CD	
Target Organism Type	Human Receptor	CD	
Element Group: Protein			
Sequence Type	Complete	CD	
Number of Subunits	4	INT	
Element Group: Protein Subunit			
Subunit	1	INT	
Sequence	QIQLQQSGPEVVKPGASVKISCKASGYTFTDYYITWVKQ KPGQGLEWIGWIYPGSGNTKYNEKFKGKATLTVDTSSS TAFMQLSSLTSEDTAVYFCANYGNYWFAYWGQGTQVT VSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK	ST	
Length	446	INT	
Element Group: Protein Subunit (Repeat)			
Subunit	2	INT	
Sequence	QIQLQQSGPEVVKPGASVKISCKASGYTFTDYYITWVKQ KPGQGLEWIGWIYPGSGNTKYNEKFKGKATLTVDTSSS TAFMQLSSLTSEDTAVYFCANYGNYWFAYWGQGTQVT VSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK	ST	
Length	446	INT	
Element Group: Protein Subunit (Repeat)			
Subunit	3	INT	

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Table C.13 *(continued)*

Element Name	Value	Data Format	Note #
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	
Element Group: Protein (Part of Group)			
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: Glycosylation			
Glycosylation Type	Mammalian	CD	
N-Glycosylation	1_297; 2_297	ST	
Element Group: Protein subunit (Part of Group)			
Element Group: Modification (N-Terminal Modification)			
N-Terminal Modification	Glutamine (Q)	CD	
N-Terminal Modification ID	0RH81L854J (UNII)	II	
C-Terminal Modification	Lysine (K)	CD	
C-Terminal Modification ID	K3Z4F929H6 (UNII)	II	
Element Group: Modification			
Modification Type	Structural Modification	CD	

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Table C.13 *(continued)*

Element Name	Value	Data Format	Note #
Residue Modified	Glutamine (Q)	CD	
Residue Sites	1_1; 2-1	ST	
Element Group: Structural Modification			
Structural Modification Type	Amino Acid Substitution	CD	
Element Group: Molecular Fragment			
Role	N-Terminal Pyroglu Formation	CD	
Molecular Fragment 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 Sites	1-447; 2-447	ST	
Element Group: Structural Modification (Repeat)			
Structural Modification Type	Amino Acid Removal	CD	4)
Element Group: Molecular Fragment			
Role	C-Terminal Lysine removal	CD	
Molecular Fragment ID	K3Z4F929H6 (UNII)	II	
Molecular Fragment Name	Lysine (K)	ST	
Amount Type	Per cent removed	CD	
Element Group: Amount			
High Limit	90	PQ	
Low Limit	70	PQ	
Non-numeric Value	Incomplete	ST	
Element Group: Modification (Repeat)			
Modification Type	Structural modification	CD	
Residue Modified	Cysteine (C)	CD	
Residue Sites	Variable	ST	7)

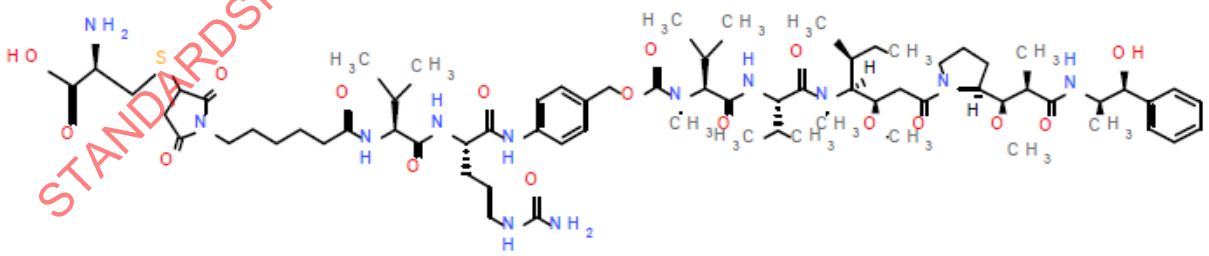
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Table C.13 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Structural Modification (Repeat)			
Structural Modification Type	Amino Acid Substitution	CD	6)
Element Group: Molecular Fragment			
Role	Toxin Conjugation	CD	
Molecular Fragment ID	6603L01WUR (UNII)	II	
Molecular Fragment Name	Cysteine-VC-MMAE	ST	8)
Amount Type	Average Mole Ratio Toxin to Antibody	CD	
Element Group: Amount			
Average	4.0	PQ	
Low Limit	3	PQ	
High Limit	5	PQ	
Element Group: Structure			
Element Group: Structural Representation			
Structural Representation (Molecular Fragment)	Full	CD	
Molecular Fragment Attachment	See image below	ED	

Cysteine-VC-MMAE Structure



[1] It is not required that both a Reference Source Citation and a Reference Source Document URL are transmitted but both are included here as an example.

[2] Provision of a structural representation for proteins is not required, but they can be very useful for the understanding structure, so it may be provided. The structure in Figure C.2 can be provided as either a PDF or other supported image file formats, likewise with a representation of the disulphide linkage in Figure C.3 (also, see 4.8.1).

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Element Name	Value	Data Format	Note #
[3] 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. [4] In initial implementations of ISO 11238 a controlled vocabulary for these elements and therefore provision of information as text will also be supported. [5] 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. [6] 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. [7] The value “variable” is provided since modification is not site specific. [8] The molecular fragment may also need to be registered if it is not already defined and has a Substance ID.			

C.8 Addendum: Microheterogeneity

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.

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Annex D
(normative)

Nucleic acid substance

D.1 Scope

This Annex provides guidance to define elements that describe nucleic acids in order to generate ISO 11238 Substance Identifiers in view of ISO 11238 and ISO/TS 19844 by providing examples.

D.2 General

Nucleic acids are one of the five types of single substances described in ISO 11238. The fundamental property of nucleic acids is that they consist of strands of bases attached to sugars or sugar-like rings and 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.

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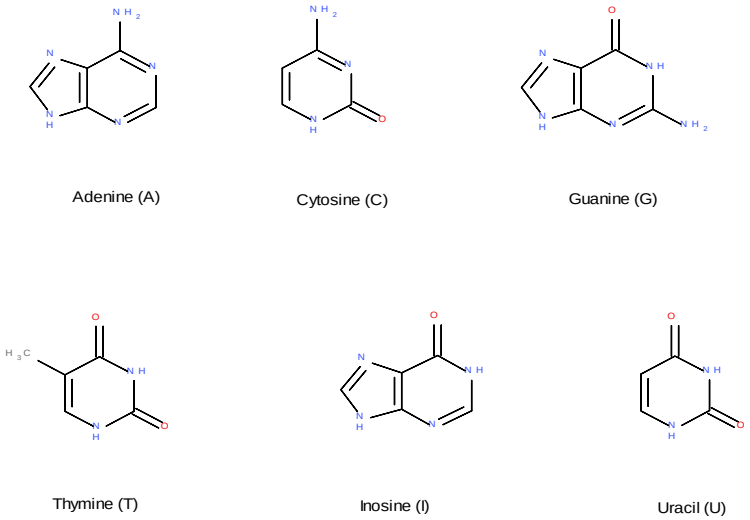


Figure D.1 — Nucleic acid bases

A conceptual data model view for nucleic acids is shown in Figure D.2 below:

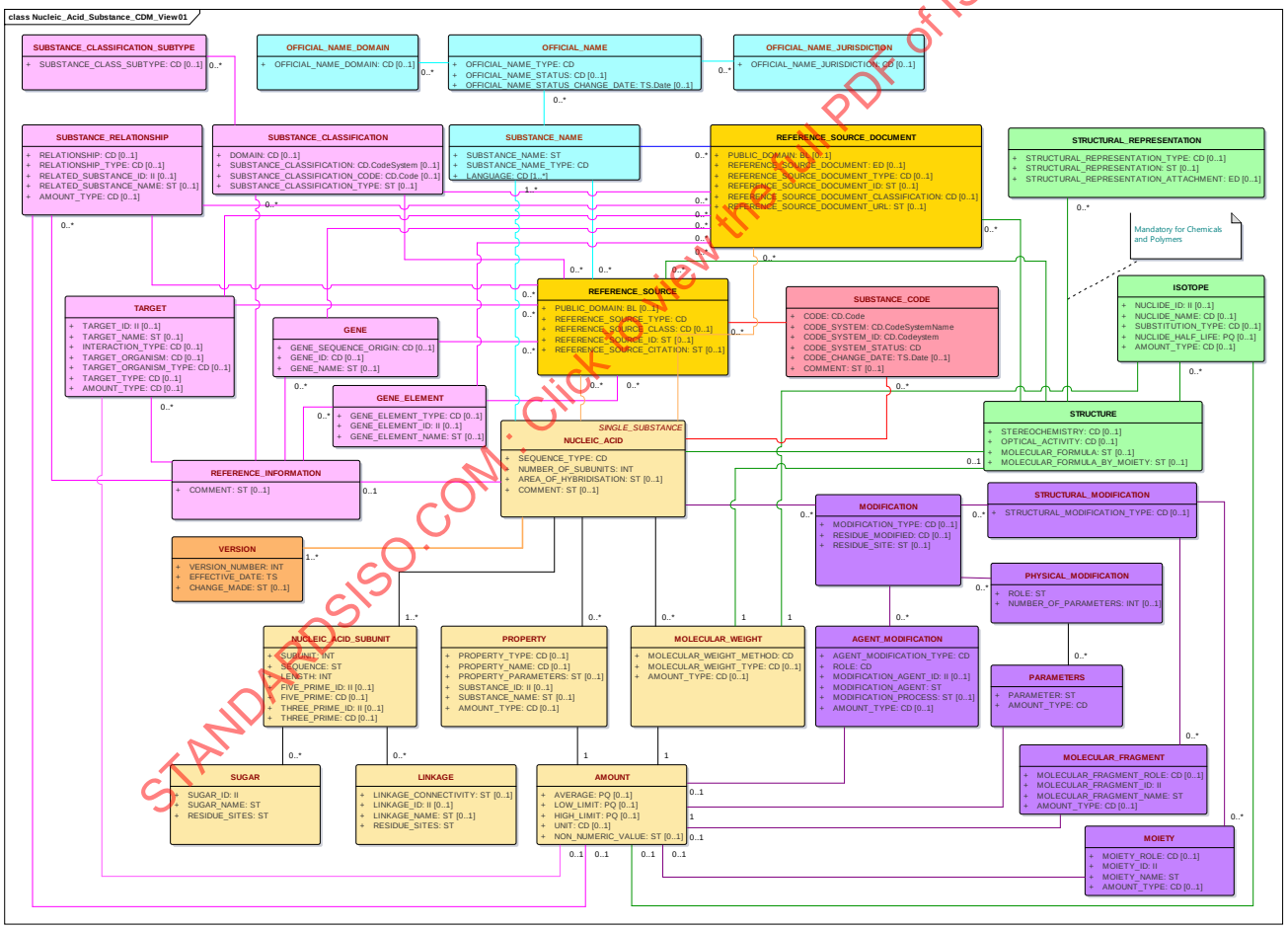


Figure D.2 — Information Model for Nucleic Acids

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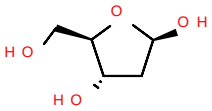
D.3 Examples

D.3.1 Example: 5-Methylcytosine

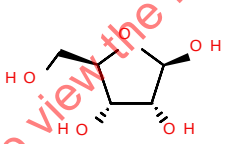
5-Methylcytosine is a commonly observed modified base present in both oligonucleotides and the regulatory regions of many genes. The actual base sequence would still use C but there would a site specific base-substitution at every site where 5-methylcytidine is present.

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. Fragments with connection points will be used if bases are connected to a position other that 1' position. Common sugars are listed below:

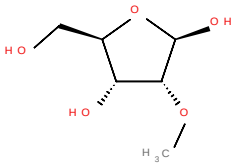
Sugar ID: Z9I45OZ8PJ
Sugar Name: .beta.-D-2-Deoxyribose



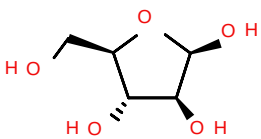
Sugar ID: IVV837V11N
Sugar Name: .beta.-D-2-Ribose



Sugar ID: AW90983458
Sugar Name: 2-O-Methyl-.beta.-D-ribofuranose



Sugar ID: 0K9V1SR8T9
Sugar Name: .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.

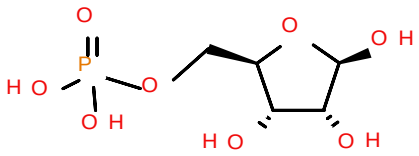
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D.3.2 Example: A 5'-phosphate ribonucleotide

A 5'-phosphate ribonucleotide end group can be captured through a sugar residue at position 1.

Sugar ID: BVJ0IQF3T8
Sugar Name: .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.

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'.

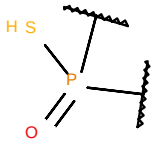
Each linkage fragment shall have a name and ID and will be registered as a substance.

Example:

Linkage ID: 7Z7BK2GWOA

Linkage Name: PHOSPHOTHIOATE LINKAGE

Stereochemistry: Racemic



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D.4 Substances

D.4.1 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.3 which is an attachment to the tabulated format information shown below.

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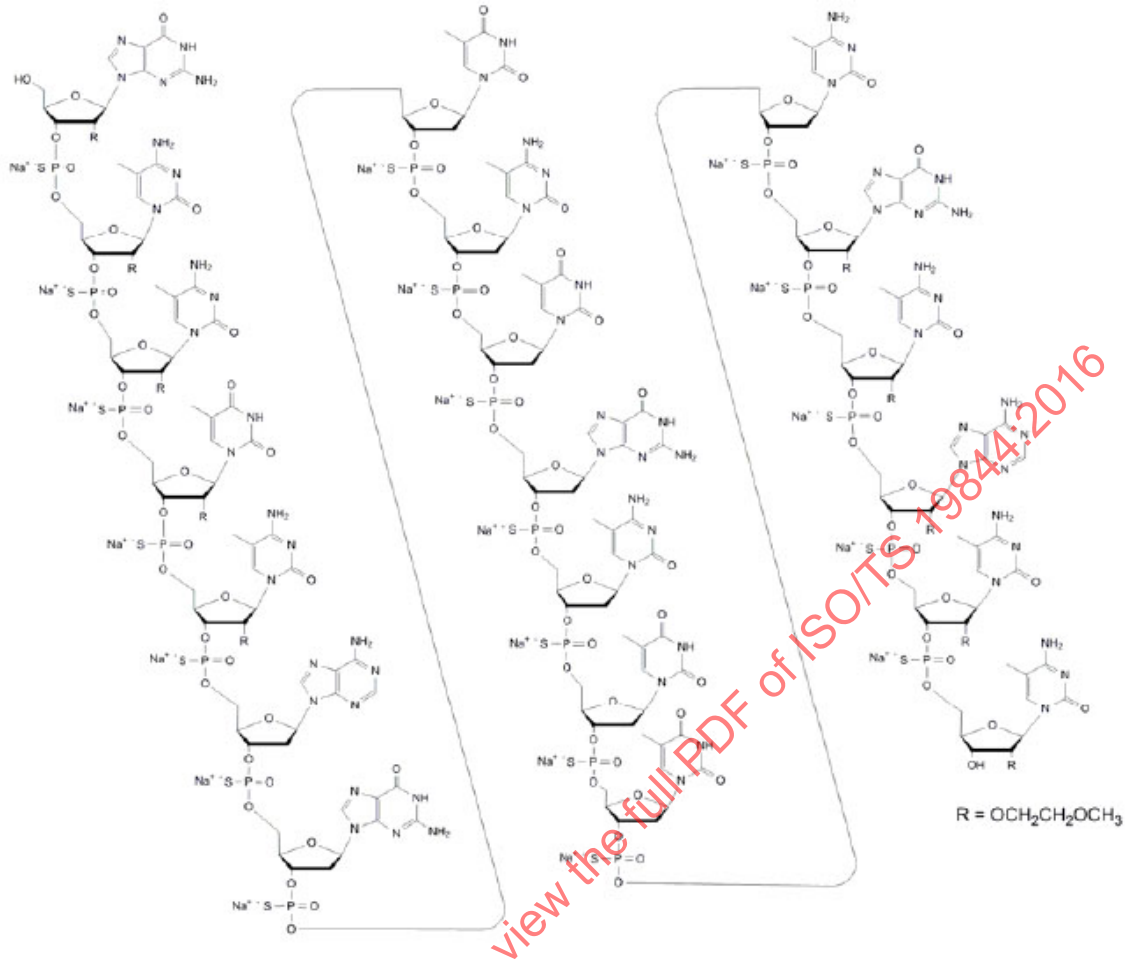


Figure D.3 — Structure of Mipomersen Sodium

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D.4.2 Example: Oligonucleotide Elements

Mipomersen sodium is a synthetic second-generation 2′-methoxyethyl antisense oligonucleotide inhibitor of the molecular target, apolipoprotein B-100.

D.4.2.1 Example Nucleic Acid Substance: Mipomersen sodium

Table D.1 — Mipomersen sodium

Element Name	Value	Data Format	Note #
Element Group: Substance			
Substance Type	Nucleic Acid	CD	
Substance ID	MIPO78654S (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Mipomersen Sodium	ST	

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Table D.1 *(continued)*

Element Name	Value	Data Format	Note #
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Offical Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Official Name Jurisdiction	US, EU	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	INN	CD	
Reference Source Class	Official name source	CD	
Reference Source Citation	WHO Drug Information Vol. 22, No 2, 2008	ST	1)
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Document Type	Journal article	CD	
Reference Source Document URL	http://www.who.int/medicines/publications/druginformation/innlists/PL99.pdf?ua=1	ST	

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Table D.1 *(continued)*

Element Name	Value	Data Format	Note #
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	WHO Drug Information Vol. 22, No 2, 2008	CD	
Reference Source Class	Web	CD	
Reference Source Citation	http://www.who.int/medicines/publications/druginformation/innlists/PL99.pdf?ua=1	ST	
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	

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Table D.1 *(continued)*

Element Name	Value	Data Format	Note #
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS	CD	
Reference Source Class	Other name source	CD	
Reference Source Citation	CAS Registry Name	ST	
Element Group: Substance Code (Repeat)			
Code	629167-92-6	CD.Code	
Code System	CAS Registry	CD.Code SystemName	
Code System ID	0049	CD.Code System	
Code System Status	Active	CD	
Element Group: Structure			
Stereochemistry	Chiral	CD	
Optical activity	Not applicable	CD	
Molecular Formula	C_{230} H_{305} N_{67} Na_{19} O_{122} P_{19} S_{19}	ST	
Molecular Formula by moiety	C_{230} H_{305} N_{67} O_{122} P_{19} S_{19}. Na_{19}	ST	
Element Group: Structural Representation			
Structural Representation Type	Representative	CD	
Structural Representation Attachment	See Figure D.3	ED	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			

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Table D.1 *(continued)*

Element Name	Value	Data Format	Note #
Average (Numeric Value)	7594.9	PQ	
Unit	g/mol	CD	
Element Group: Nucleic Acid			
Sequence Type	Complete	CD	
Number of Subunits	1	INT	
Element Group: Modification			
Modification Type	Structural modification	CD	
Element Group: Moiety			
Moiety Role	Salt	CD	
Moiety ID	YYY (Artificial ID)	II	
Moiety Name	Sodium	ST	
Amount Type	Mole Ratio to Parent Substance	CD	
Element Group: Amount			
Average	19	PQ	
Element Group: Moiety (Repeat)			
Moiety Role	Parent	CD	
Moiety ID	MEPO0564352 (Artificial ID)	II	
Moiety Name	Mipomersen	ST	
Amount type	Mole Ratio to Salt	CD	
Element group: Amount			
Average	1	PQ	
Element Group: Substance Relationship			
Relationship	Parent	CD	
Relationship Type	Ionic	CD	
Related Substance ID	MEPO0564352 (Artificial ID)	II	
Substance Name	Mipomersen	ST	
Amount Type	Weight per cent to salt	CD	

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Table D.1 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Amount			
Average [Numeric Value]	94.2	PQ	
Unit	Weight per cent	CD	
Element Group: Nucleic Acid Subunit (Part of group)			
Subunit	1	INT	
Sequence	GCCUCAGTCTGCTTCGCACC	ST	1)
Length	20	INT	
Five Prime	Guanine (G)	CD	
Three Prime	Cytosine (C)	CD	
Element Group: Modification			
Modification Type	Structural modification	CD	
Residue Modified	Cytosine	CD	
Residue Sites	1_2; 1_3; 1_5; 1_6; 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: Fragment			
Molecular Fragment Role	Nucleotide base modification	CD	
Molecular Fragment ID	6R795COT4H (UNII)	II	
Molecular Fragment Name	5-Methylcytosine	ST	
Element Group: Amount			
Non-numeric Value	Complete	ST	
Element Group: Sugar			
Sugar ID	Z9I45OZ8PJ (UNII)	II	
Sugar Name	.beta.-D-2-Deoxyribose	ST	
Residue	1_6-1_14	ST	
Element Group: Sugar (Repeat)			
Sugar ID	FY7FL6G6HT (UNII)	II	

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Table D.1 *(continued)*

Element Name	Value	Data Format	Note #
Sugar Name	.beta.-D-2′-O-(2-methoxyethyl)ribose	ST	
Residue Sites	1_1-1_5; 1_16-1_20	ST	
Element Group: Linkage			
Linkage Connectivity	3->5	ST	
Linkage ID	1ST100S00F (UNII)_	II	
Linkage Name	Phosphothioate sodium linkage	ST	
Residue Sites	1_2-1_20	ST	
NOTE The underlined residues are 2′-*O*-(2-methoxyethyl) nucleosides, all other residues are 2′-deoxynucleosides.			

D.4.2.2 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: Nucleic Acid Substance			
Substance Type	Nucleic Acid	CD	
Substance ID	PYTRS34526 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	Litenimod	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Official Name			
Official Name Type	INN	CD	
Official Name Status	Current	CD	
Official Name Domain	Drug	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	INN	CD	
Reference Source Class	Official name source	CD	

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Table D.2 *(continued)*

Element Name	Value	Data Format	Note #
Reference Source Citation	WHO Drug Information, Vol. 21, No. 3, 2007 Recommended INN: List 58	ST	
Element Group: Reference Source Document			
Public Domain	Yes	BL	
Reference Source Type	Journal	CD	
Reference Source Document 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-(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	ST	
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)		
Substance Name Type	Other		
Language	en		
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	CAS Registry	CD	
Reference Source Class	Other name source	ST	

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Table D.2 *(continued)*

Element Name	Value	Data Format	Note #
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 Substance Registration System (UNII)	CD.CodeSystemName	
Code System ID	0050	CD.CodeSystem	
Code System Status	Active	CD	
Element Group: Structure			
Stereochemistry	Chiral	CD	
Optical Activity	N/A		
Molecular Formula	$C_{256}H_{322}O_{129}P_{25}S_{25}$	ST	
Element Group: Structural Representation			
Structural Representation Type	HELM	CD	
Structural Representation	DNA1{[DR](T)SP.[DR](A)SP.[DR](A)SP.[DR](A)SP.[DR](C)SP.[DR](G)SP.[DR](T)SP.[DR](T)SP.[DR](A)SP.[DR](T)SP.[DR](A)SP.[DR](A)SP.[DR](C)SP.[DR](G)SP.[DR](T)SP.[DR](T)SP.[DR](A)SP.[DR](T)SP.[DR](G)SP.[DR](A)SP.[DR](C)SP.[DR](G)SP.[DR](T)SP.[DR](C)SP.[DR](A)SP.[DR](T)}$$$$	ST	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	FDA_SRS	CD	
Element Group: Molecular Weight			

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Table D.2 *(continued)*

Element Name	Value	Data Format	Note #
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	8369.20	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	JKUHT76541 (Artificial ID)	II	
Five Prime	Tymidine (T)	CD	
Three Prime ID	JKUHT76541 (Artificial ID)	II	
Three Prime	Tymidine (T)	CD	
Element Group: Sugar			
Sugar ID	Z9I45OZ8PJ (UNII)	II	
Sugar Name	.beta.-D-2-Deoxyribose	ST	
Residue Sites	1_1-1_26	ST	
Element Group: Linkage			
Linkage Connectivity	3->5	ST	
Linkage ID	7Z7BK2GWOA (UNII)	II	
Linkage Name	Phosphothioate linkage	ST	

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D.4.3 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 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: Nucleic Acid Substance			
Substance Type	Nucleic Acid	CD	
Substance ID	ANRNA67543 (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	TGF.beta.-2 Anti-sense RNA (6-935)	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Element Group: Reference Source			
Reference Source Class	FDA_SRS	CD	
Element Group: Substance Code			
Code	FUA17JE46Y	CD.Code	
Code System	FDA Substance Registration System (UNII)	CD.Code SystemName	
Code System ID	0050	CD.Code System	
Code System Status	Active	CD	
Element Group: Structure			
Element Group: Structural Representation			
Structural Representation Type	HELM	CD	
Structural Representation	RNA1{R(C)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(C)P.R(A)P.R(A)P.R(A)P.R(C)P.R(U)P.R(G)P.R(C)P.R(U)P.R(C)P.R(U)P.R(G)P.R(A)P.R(A)P.R(G)P.R(U)P.R(G)P.R(U)P.R(U)P.R(C)P.R(U)P.R(G)P.R(C)P.R(U)P.R(U)P.R(C)P.R(A)P.R(G)P.R(C)P.R(U)P.R(U)P.R(G)P.R(G)P.R(C)P.R(C)P.R(U)P.R(U)P.R(A)P.	ST	

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Element Name	Value	Data Format	Note #
	R(U)P.R(A)P.R(G)P.R(A)P.R(C)P.R(C)P.R(U)P.R(C)P.R(A)P.R(G)P.R(C)P.R(A)P.R(A)P.R(A)P.R(G)P.R(C)P.R(G)P.R(A)P.R(C)P.R(C)P.R(U)P.R(U)P.R(U)P.R(C)P.R(C)P.R(C)P.R(C)P.R(A)P.R(C)P.R(C)P.R(A)P.R(G)P.R(G)P.R(G)P.R(U)P.R(G)P.R(U)P.R(C)P.R(C)P.R(A)P.R(G)P.R(C)P.R(U)P.R(C)P.R(A)P.R(A)P.R(U)P.R(G)P.R(G)P.R(G)P.R(C)P.R(A)P.R(G)P.R(C)P.R(A)P.R(G)P.R(C)P.R(U)P.R(C)P.R(U)P.R(G)P.R(U)P.R(G)P.R(U)P.R(U)P.R(G)P.R(U)P.R(G)P.R(G)P.R(U)P.R(U)P.R(G)P.R(A)P.R(U)P.R(G)P.R(U)P.R(U)P.R(G)P.R(U)P.R(U)P.R(G)P.R(G)P.R(C)P.R(A)P.R(C)P.R(A)P.R(C)P.R(G)P.R(U)P.R(G)P.R(G)P.R(A)P.R(G)P.R(C)P.R(U)P.R(G)P.R(A)P.R(U)P.R(G)P.R(U)P.R(C)P.R(A)P.R(G)P.R(A)P.R(G)P.R(C)P.R(G)P.R(G)P.R(U)P.R(C)P.R(A)P.R(C)P.R(A)P.R(G)P.R(C)P.R(U)P.R(U)P.R(C)P.R(C)P.R(A)P.R(G)P.R(G)P.R(A)P.R(U)P.R(G)P.R(A)P.R(A)P.R(C)P.R(U)P.R(C)P.R(G)P.R(C)P.R(U)P.R(G)P.R(C)P.R(U)P.R(G)P.R(A)P.R(U)P.R(C)P.R(G)P.R(U)P.R(C)P.R(G)P.R(C)P.R(U)P.R(G)P.R(A)P.R(A)P.R(C)P.R(U)P.R(C)P.R(C)P.R(A)P.R(U)P.R(G)P.R(G)P.R(A)P.R(U)P.R(G)P.R(C)P.R(A)P.R(C)P.R(A)P.R(G)P.R(U)P.R(C)P.R(G)P.R(C)P.R(U)P.R(G)P.R(A)P.R(A)P.R(C)P.R(U)P.R(C)P.R(C)P.R(A)P.R(G)P.R(G)P.R(A)P.R(U)P.R(G)P.R(A)P.R(U)P.R(C)P.R(A)P.R(G)P.R(G)P.R(U)P.R(U)P.R(C)P.R(U)P.R(U)P.R(G)P.R(U)P.R(U)P.R(G)P.R(A)P.R(U)P.R(G)P.R(U)P.R(U)P.R(G)P.R(G)P.R(C)P.R(A)P.R(C)P.R(A)P.R(C)P.R(G)P.R(U)P.R(C)P.R(G)P.R(C)P.R(U)P.R(G)P.R(A)P.R(A)P.R(C)P.R(U)P.R(C)P.R(C)P.R(A)P.R(U)P.R(G)P.R(G)P.R(A)P.R(U)P.R(A)P.R(C)P.R(U)P.R(C)P.R(G)P.R(G)P.R(U)P.R(U)P.R(A)P.R(A)P.R(C)P.R(G)P.R(C)P.R(G)P.R(G)P.R(U)P.R(A)P.R(G)P.R(C)P.R(A)P.R(G)P.R(U)P.R(A)P.R(G)P.R(A)P.R(A)P.R(G)P.R(A)P.R(U)P.R(G)P.R(A)P.R(U)P.R(G)P.R(A)P.R(U)P.R(G)P.R(A)P.R(C)P.R(A)P.R(G)P.R(A)P.R(U)P.R(A)P.R(G)P.R(A)P.R(U)P.R(G)P.R(G)P.R(C)P.R(A)P.R(A)P.R(C)P.R(U)P.R(C)P.R(C)P.R(C)P.R(A)P.R(G)P.R(U)P.R(G)P.R(G)P.R(U)P.R(G)P.R(G)P.R(G)P.R(C)P.R(A)P.R(G)P.R(G)P.R(A)P.R(G)P.R(G)P.R(C)P.R(U)P.R(G)P.R(A)P.R(U)P.R(G)P.R(C)P.R(C)P.R(U)P.R(G)P.R(U)P.R(C)P.R(U)P.R(C)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(A)P.R(A)P.R(A)P.R(U)P.R(U)P.R(G)P.R(U)P.R(U)P.R(A)P.R(U)P.R(A)P.R(U)P.R(U)P.R(C)P.R(U)P.R(U)P.R(G)P.R(A)P.R(G)P.R(A)P.R(A)P.R(G)P.R(A)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(U)P.R(G)P.R(U)P.R(G)P.R(A)P.R(U)P.R(C)P.R(G)P.R(U)P.R(U)P.R(C)P.R(U)P.R(G)P.R(C)P.R(A)P.R(U)P.R(C)P.R(A)P.R(G)P.R(A)P.R(C)P.R(U)P.R(A)P.R(G)P.R(C)P.R(A)P.R(U)P.R(C)P.R(U)P.R(U)P.R(G)P.R(A)P.R(U)P.R(A)P.R(U)P.R(U)P.R(C)P.R(U)P.R(U)P.R(G)P.R(A)P.R(G)P.R(A)P.R(A)P.R(G)P.R(A)P.R(U)P.R(G)P.R(C)P.R(A)P.R(G)P.R(C)P.R(A)P.R(U)P.R(C)P.R(U)P.R(C)P.R(A)P.R(U)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(A)P.R(G)P.R(U)P.R(C)P.R(A)P.R(G)P.R(G)P.R(A)P.R(U)P.R(U)P.R(G)P.R(C)P.R(U)P.R(G)P.R(G)P.R(U)P.R(G)P.R(U)P.R(U)P.R(A)P.R(U)P.R(A)P.R(U)P.R(U)P.R(U)P.R(C)P.R(U)P.R(U)P.R(C)P.R(U)P.R(G)P.R(A)P.R(G)P.R(A)P.R(A)P.R(G)P.R(A)P.R(U)P.R(A)P.R(U)P.R(G)P.R(A)P.R(U)P.R(G)P.R(U)P.R(U)P.R(C)P.R(U)P.R(G)P.R(A)P.R(C)P.R(U)P.R(C)P.R(A)P.R(U)P.R(C)P.R(A)P.R(G)P.R(A)P.R(G)P.R(C)P.R(U)P.R(C)P.R(A)P.R(C)P.R(G)P.R(A)P.R(C)P.R(A)P.R(G)P.R(G)P.R(A)P.R(A)P.R(C)P.R(A)P.R(C)P.R(A)P.R(U)P.R(G)P.R(A)P.R(A)P.R(G)P.R(U)P.R(C)P.R(A)P.R(C)P.R(U)P.R(C)P.R(A)P.R(G)P.R(C)P.R(G)P.R(G)P.R(U)P.R(U)P.R(U)P.R(U)P.R(U)P.R(U)P.R(C)P.R(C)P.R(U)P.R(U)P.R(C)P.R(A)P.R(U)P.R(A)P.R(A)P.R(U)P.R(G)P.R(U)P.R(C)P.R(A)P.R(C)P.R(U)P.R(U)P.R(G)P.R(C)P.R(A)P.R(U)P.R(U)P.R(G)P.R(G)P.R(A)P.R(G)P.R(A)P.R(C)P.R(A)P.R(G)P.R(C)P.R(A)P.R(U)P.R(C)P.R(U)P.R(U)P.R		

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Element Name	Value	Data Format	Note #
	(C)P.R(C)P.R(A)P.R(G)P.R(A)P.R(A)P.R(U)P.R(A)P.R(A)P.R(A)P.R(G)P.R(U)P.R(C)P.R(A)P.R(U)P.R(G)P.R(G)P.R(U)P.R(A)P.R(G)P.R(G)P.R(G)P.R(G)P.R(A)P.R(G)P.R(C)P.R(U)P.R(U)P.R(G)P.R(G)P.R(G)P.R(G)P.R(U)P.R(C)P.R(A)P.R(U)P.R(G)P.R(G)P.R(C)P.R(A)P.R(A)P.R(A)P.R(C)P.R(U)P.R(G)P.R(U)P.R(C)P.R(U)P.R(C)P.R(U)P.R(A)P.R(G)P.R(U)P.R(G)P.R(U)P.R(U)P.R(A)P.R(U)P.R(G)P.R(U)P.R(U)P.R(C)P.R(U)P.R(C)P.R(G)P.R(U)P.R(C)P.R(A)P.R(U)P.R(U)P.R(C)P.R(U)P.R(U)P.R(U)P.R(C)P.R(U)P.R(C)P.R(C)P.R(A)P.R(U)P.R(A)P.R(C)P.R(A)P.R(G)P.R(C)P.R(C)P.R(A)P.R(C)P.R(A)P.R(C)P.R(A)P.R(G)P.R(C)P.R(C)P.R(U)P.R(U)P.R(C)P.R(C)P.R(U)P.R(G)P.R(U)P.R(G)P.R(G)P.R(C)P.R(U)P.R(U)P.R(C)P.R(U)P.R(C)P.R(A)P.R(C)P.R(A)P.R(G)P.R(A)P.R(U)P.R(G)P.R(G)P.R(A)P.R(G)P.R(G)P.R(U)P.R(G)P.R(A)P.R(U)P.R(G)P.R(C)P.R(U)P.R(G)P.R(C)P.R(A)P.R(G)P.R(U)P.R(U)P.R(G)P.R(C)P.R(U)P.R(C)P.R(A)P.R(U)P.R(G)P.R(C)P.R(U)P.R(U)P.R(U)P.R(C)P.R(U)P.R(G)P.R(G)P.R(A)P.R(U)P.R(C)P.R(A)P.R(A)P.R(A)P.R(C)P.R(U)P.R(G)P.R(A)P.R(C)P.R(U)P.R(G)P.R(C)P.R(A)P.R(C)P.R(C)P.R(U)P.R(U)P.R(G)P.R(U)P.R(U)P.R(G)P.R(U)P.R(U)P.R(G)P.R(U)P.R(C)P.R(A)P.R(G)P.R(U)P.R(G)P.R(A)P.R(C)P.R(U)P.R(A)P.R(U)P.R(C)P.R(A)P.R(U)P.R(G)P.R(U)P.R(C)P.R(G)P.R(U)P.R(U)P.R(A)P.R(U)P.R(U)P.R(A)P.R(A)P.R(U)P.R(C)P.R(A)P.R(U)P.R(U)P.R(G)P.R(U)P.R(C)P.R(U)P.R(C)P.R(A)P.R(G)P.R(U)P.R(G)P.R(G)P.R(A)P.R(U)P.R(G)P.R(C)P.R(U)P.R(C)P.R(U)P.R(C)P.R(A)P.R(G)P.R(C)P.R(C)P.R(U)P.R(C)P.R(C)P.R(A)P.R(U)P.R(U)P.R(U)P.R(C)P.R(A)P.R(C)P.R(A)P.R(G)P.R(C)P.R(U)P.R(G)P.R(C)P.R(A)P.R(G)P.R(A)P.R(U)P.R(G)P.R(A)P.R(U)P.R(U)P.R(A)P.R(U)P.R(C)P.R(U)P.R(C)P.R(A)P.R(G)P.R(U)P.R(G)P.R(G)P.R(G)P.R(C)P.R(A)P.R(C)P.R(U)P.R(C)P.R(C)P.R(U)P.R(A)P.R(U)P.R(C)P.R(C)P.R(A)P.R(C)P.R(A)P.R(C)P.R(C)P.R(G)P.R(U)P.R(C)P.R(A)P.R(G)P.R(A)P.R(U)P.R(G)P.R(A)P.R(U)P.R(U)P.R(U)P.R(C)P.R(A)P.R(U)P.R(C)P.R(U)P.R(C)P.R(U)P.R(G)P.R(G)P.R(G)P.R(C)P.R(C)P.R(U)P.R(C)P.R(C)P.R(A)P.R(U)P.R(U)P.R(U)P.R(U)P.R(C)P.R(C)P.R(A)P.R(C)P.R(A)P.R(U)P.R(C)P.R(C)P.R(G)P.R(A)P.R(C)P.R(U)P.R(U)P.R(C)P.R(U)P.R(G)P.R(A)P.R(A)P.R(C)P.R(G)P.R(U)P.R(G)P.R(C)P.R(G)P.R(G)P.R(U)P.R(G)P.R(G)P.R(G)P.R(A)P.R(U)P.R(C)P.R(G)P.R(U)P.R(G)P.R(C)P.R(U)P.R(G)P.R(C)P.R(A)P.R(G)P.R(U)P.R(C)P.R(C)P.R(U)P.R(C)P.R(C)P.R(A)P.R(C)P.R(A)P.R(G)P.R(G)P.R(A)P.R(C)P.R(G)P.R(U)P.R(C)P.R(G)P.R(U)P.R(G)P.R(C)P.R(U)P.R(G)P.R(G)P.R(C)P.R(G)P.R(A)P.R(U)P.R(G)P.R(C)P.R(U)P.R(C)P.R(C)P.R(A)P.R(C)P.R(A)P.R(G)P.R(C)P.R(G)P.R(U)P.R(C)P.R(C)P.R(U)P.R(G)P.R(C)P.R(C)P.R(A)P.R(G)P.R(C)P.R(C)P.R(C)P.R(C)P.R(U)P.R(G)P.R(A)P.R(G)P.R(C)P.R(A)P.R(G)P.R(C)P.R(C)P.R(C)P.R(C)P.R(C)P.R(G)P.R(A)}$$$$		
Element Group: Reference Source			

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Element Name	Value	Data Format	Note #
Public Domain	Yes	BL	
Reference Source Type	FDA_SRS	CD	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average	298892.36	CD	
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	CAAGAGGCAUACUCCUCAUAGGGAAAGAUCUUGACUGCCACUG UCUCAAACUGCUCUGAAGUGUUCUGCUUCAGCUUGGCCUUAUA GACCUCAGCAAAGCGACCUUUCCCCACCAGGGUGUCCAGCUCAA UGGGCAGCAGCUCUGUGUUGUGGUUGAUGUUGUUGGCACACG UGGAGCUGAUGUCAGAGCGGUCAUCUUCCAGGAUGAUGGCACA GUGCUCGCUGAACUCCAUGAGCUUCCGCGUCUUGCCGGUUUCC CAGGUUGAACUCAGCUUCUGCUGCCGGUUAACGCGGUAGCAGU AGAAGAUGAUGAUGACAGAUAUGGCAACUCCCAGUGGUGGCAG GAGGCUGAUGCCUGUCACUUGAAAUAUGACUAGCAACAAGUCA GGAUUGGCUGGUGUUAUAUUCUUCUGAGAAGAUGAUGUUGUCA UUGCACUCAUCAGAGCUACAGGAACACAUGAAGAAAGUCUCAC CAGGCUUUUUUUUUUCCUUCAUAAUGCACUUUGGAGAAGCAG CAUCUUCCAGAAUAAAGUCAUGGUAGGGGAGCUUGGGGUCAUG GCAAACUGUCUCUAGUGUUAUGUUCUCGUCAUUCUUUCUCCA UACAGCCACACAGACUUCCUGUGGCUUCUCACAGAUGGAGGUG AUGCUGCAGUUGCUCAUGCAGGAUUUCUGGUUGUCACAGGUG GAAAAUCUCACAUCACAAAAUUUACACAGUUGUGGAAACUUG ACUGCACCGUUGUUGUCAGUGACUAUCAUGUCGUUAUUAAUA UGUCUCAGUGGAUGGGCAGUCCUAUUACAGCUGGGGCAGAUGA UUUCAUCUUUCUGGGCCUCCAUUUCCACAUCCGACUUCUGAAC GUGCGGUGGGAUCGUGCUGGCGAUACGCGUCCACAGGACGAUG UGCAGCGGCCACAGGCCCCUGAGCAGCCCCCGA	ST	
Length	930	INT	

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Element Name	Value	Data Format	Note #
Element Group: Sugar			
Sugar ID	Z9I45OZ8PJ (UNII)	II	
Sugar Name	.beta.-D-Ribose	ST	
Residue SItes	1_1-1_930	ST	
Element Group: Linkage			
Linkage Connectivity	3->5	ST	
Linkage ID	SSG1RX859B (UNII)	II	
Linkage Name	PHOSPHORYL LINKAGE	ST	

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Annex E
(normative)

Structurally Diverse Substance – Herbal Substance/Herbal Specified Substance

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 EN ISO 11238 standard (hereafter 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.1 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 preparations:	- 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

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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.

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 substances 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 Annex, 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.2.

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 infraspecies (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 4.2.1), and Herbals are defined using the elements for a Structurally Diverse Substance (see Figure E.2 and 5.5 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 class (Figure E.3). 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 standardised 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 Name and further specifications

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described at the Specified Substance Group1 (SSG1) level, such as the mass ratio Herbal Substance/Herbal extract (DER) and the extraction solvent composition(s).

Note, in this context, 'Herbal Substance' can be either a Substance (fresh) or a Herbal Drug.

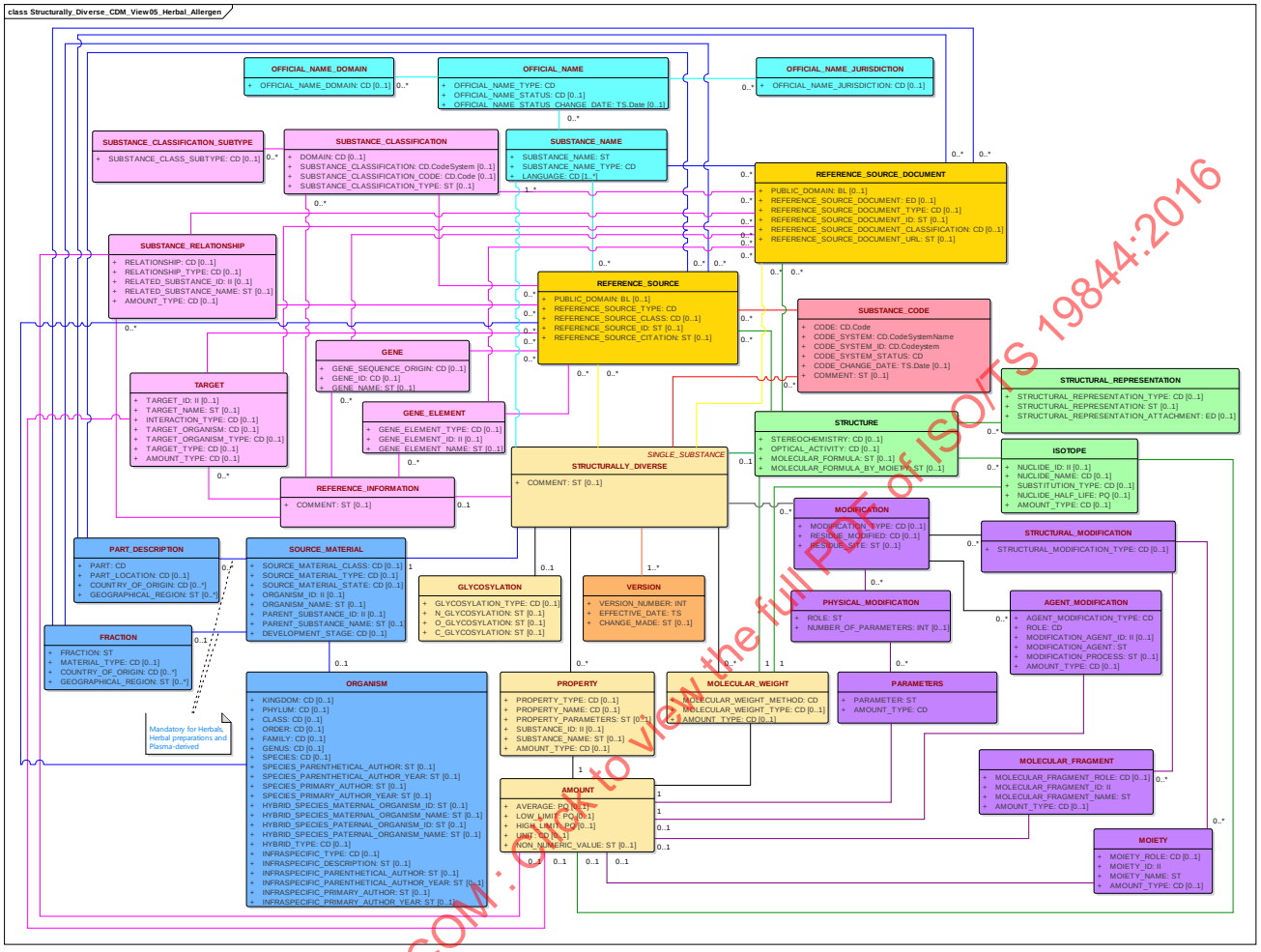


Figure E.2 — Information Model for Structurally-Diverse Substance (Herbal)

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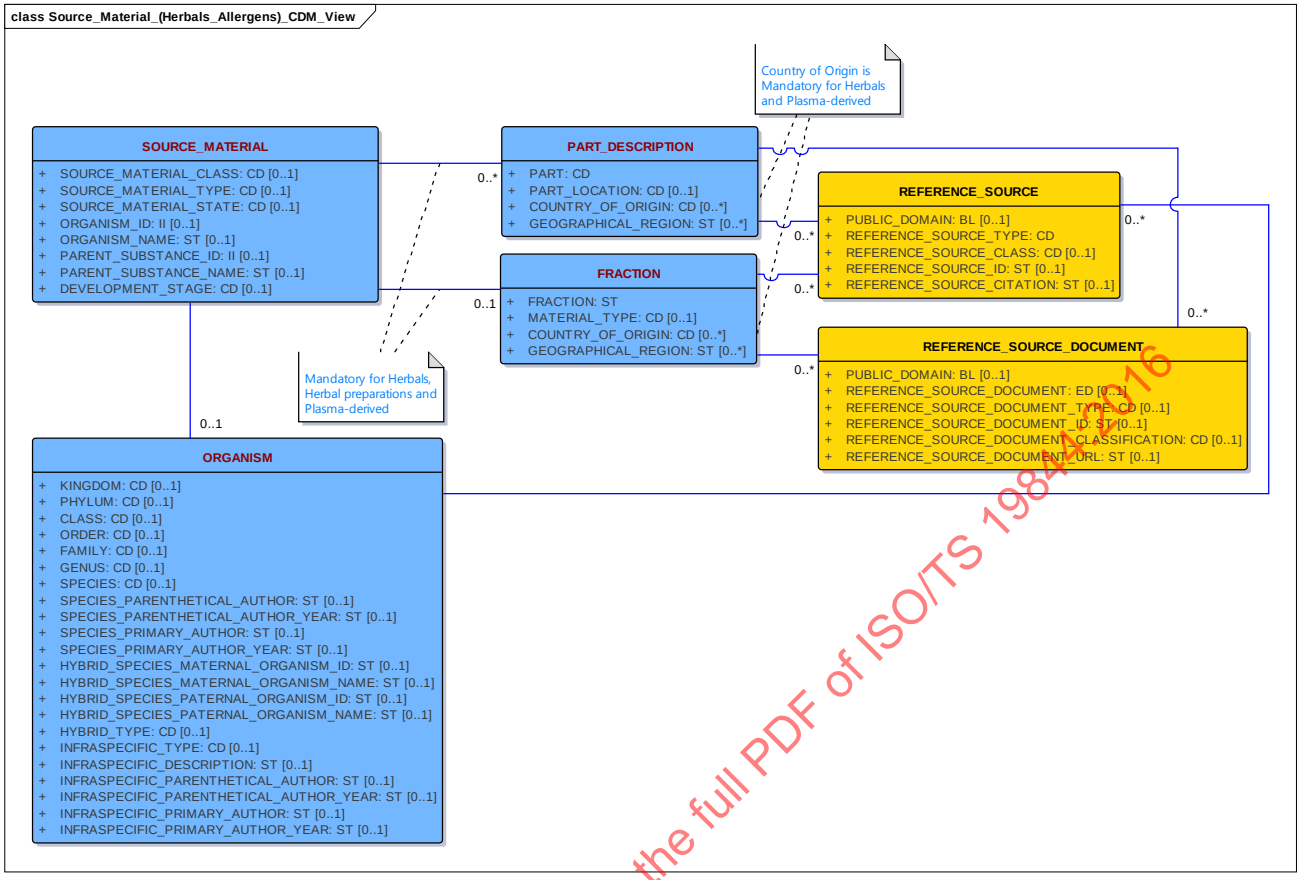


Figure E.3 — Information Model for Source Material (Herbal)

For the Substance (fresh), Herbal Drug and Herbal preparation the information model shown above will be addressed as explained in Figure E.4.

The extended Fraction's particulars, that is, the 'Herbal preparation property particulars' class is not required at the Substance level but will be a defining element at the Specified Substance Group 1 information level (see Figure E.5).

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.1.1 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 E.3 above.

This implementation guide 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

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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.

E.1.2 Organism Taxonomy

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 herbs 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.

Taxonomic information for fungi is available through 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+ organisms, 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 an organism is the combination of genus and species together with the describing author and family in that order providing validation. Infraspecific 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.1.3 Substance Names

This subclause 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.1.3.1 Substance (fresh) Name

A Substance (fresh) is always a single species, or infraspecies, or is occasionally a single genus. It will have a Name which is composed of:

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[<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 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 (Example 2).

E.1.3.2 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.1.3.3 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 is used in the element 'Extraction Solvent Composition'.

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E.1.4 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
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 of the Organism Type:

Kingdom: Plantae
Phylum: Tracheophyta
Class: Ginkgoopsida
Order: Ginkgoales
Family: Ginkgoaceae
Genus: Ginkgo
Species: biloba
Species Primary Author: L.

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

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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:

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. 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
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 Substance Group 3 because the definitions in the BP and USP are slightly different.

Example 4: (for further explanation see B.8.2.1 - B.8.2.7).

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.)

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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.

E.1.5 Specified Substance Group 1,2, and 3 information

Figure E.4 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.1.5.1 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 can be restricted using Official Name Status.

Example 1 (cont.):

Specified Substance Group 1 ID (Herbal Drug): AAAAAAAAAA (Artificial ID)
Specified Substance Group 1 Name (Herbal Drug): *Ginkgo biloba*, Leaf, Dry
Parent Substance (Herbal Drug): *Ginkgo biloba*, Leaf
Parent Substance (Herbal Drug) ID: [45SPM3HJ6Q]

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.

Specified Substance Group 1 Name (Herbal Drug): *Harpagophytum procumbens*, Root, Dry
Parent Substance (Herbal Drug): *Harpagophytum procumbens*, Root

Specified Substance Group 1 Name (Herbal Drug): *Harpagophytum zeyheri*, Root, Dry
Parent Substance (Herbal Drug): *Harpagophytum zeyheri*, Root

E.1.5.2 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 parent substance:
- Parent Specified Substance Group 1 ID (Herbal Drug): AAAAAAAAAA (Artificial ID)

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Manufacturing details:

- Manufacturer (Supplier) of the Herbal Drug (ID, Name/address/etc.) as per the Organisation class defined in ISO11615).

Other elements are detailed in Figure E.9.

- Specified Substance Group 2 Name (Herbal Drug): *Ginkgo biloba*, Leaf, Dry – Company Aa.
- Specified Substance Group 2 ID (Herbal Drug): MANER7654M (Artificial ID)

E.1.5.3 Specified Substance Group 3 Name:

For Herbal Drugs which have been defined at the Specified Substance Group 1 level by reference to a pharmacopoeia monograph, the information about the grade of the substance will have already been captured and there is no need to repeat the information at the Specified Substance Group 3 level.

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 Substance Group 3. These are official names, and their language and jurisdiction should be captured.

There are 3 types of extracts described in the Ph.Eur.. Standardised, Quantified and Other.

The Standardised, and Quantified extracts will be distinguished by name from the other extracts.

Example 1 (cont.):

Specified Substance Group 3 ID (Herbal Drug): JJJJJJJJJ (Artificial ID)
Specified Substance Group 3 Name (Herbal Drug): *Ginkgo biloba*, Leaf, Dry, [Standardised/Quantified]
Grade type: Ph.Eur.
Grade Name: Ginkgo Leaf
Parent Specified Substance Group 1 (Herbal Drug): *Ginkgo biloba*, Leaf, Dry
Parent Specified Substance Group 1 (Herbal Drug) ID: AAAAAAAAAA (Artificial ID)

Example 2 (cont.):

Where the Specified Substance is a multi-substance material, the name will be composed of the scientific name for each substance, up to a maximum of four scientific names. 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.

Specified Substance Group 3 Name (Herbal Drug): *Harpagophytum procumbens and_or Harpagophytum zeyheri,* Root, Dry, [Standardised/Quantified]
Grade type: Ph.Eur.
Grade Name: Devil's Claw Root
Parent Specified Substance Group 1 Name (Herbal Drug): *Harpagophytum procumbens*, Root, Dry
Parent Specified Substance Group 1 Name (Herbal Drug): *Harpagophytum zeyheri*, Root, Dry

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E.1.5.4 Overview of the Naming connections of the Botanical Material for the Substance and Specified Substance Group 1,2,3 Levels.

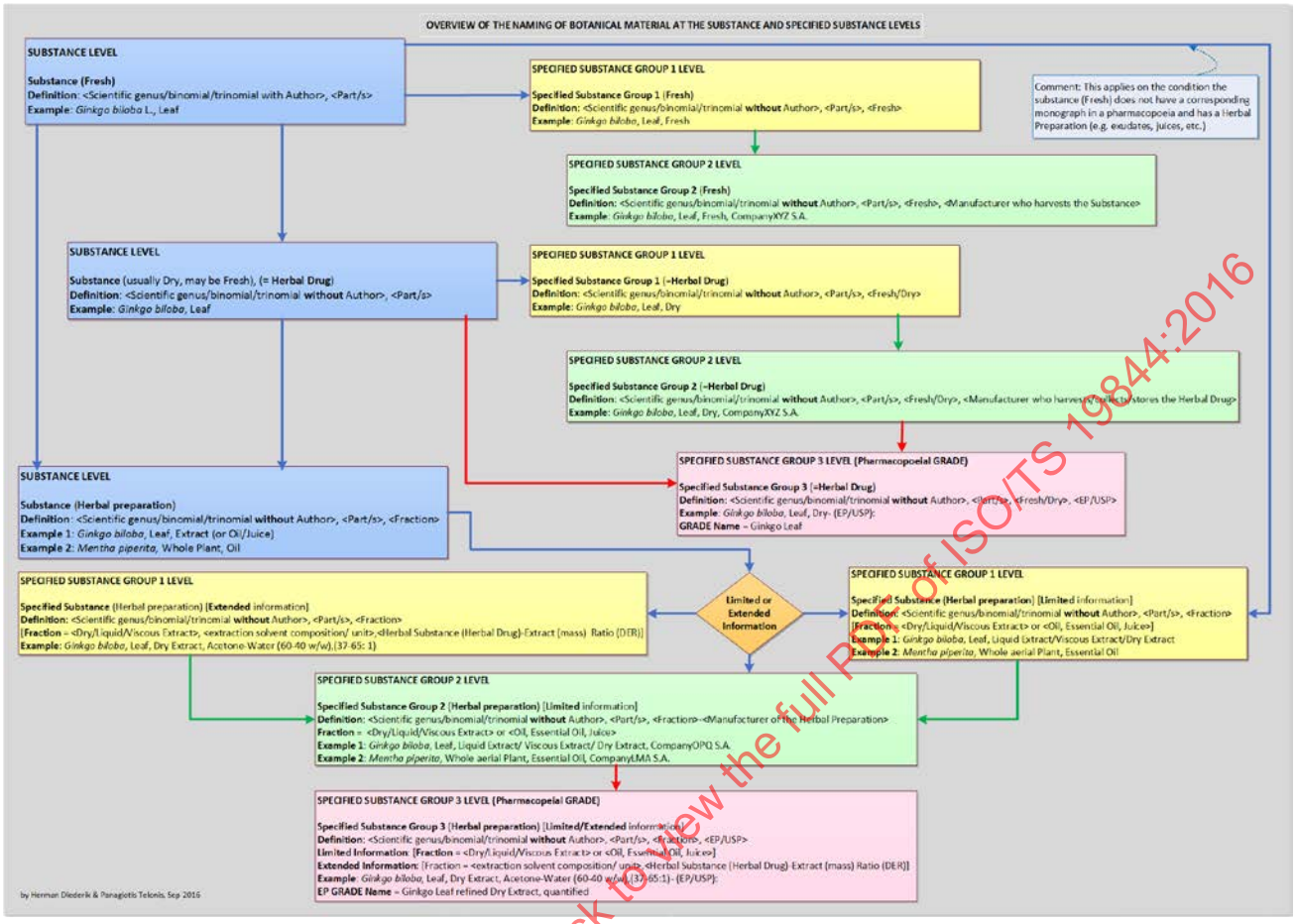


Figure E.4 — Overview of the Naming for Herbal Substance, Herbal Drug and Herbal preparation in relation to the Information levels

E.1.6 Specified Substance Group 1 Information

The Specified Substance Group 1 (SSG1), (see 6.1) 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 properties essential to the description of the material, see Figure E.5. The defining and distinguishing elements for herbal **extracts** include the primary extraction solvent(s), amounts of major or specific constituents or properties that may relate to the amount of 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 Amount Group. By doing so, the requirements for a standardised or quantified extract can be laid down.

NOTE The class 'Herbal Substance Particulars' is 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 E.5. The attributes to be captured by the class 'Herbal Substance Particulars' are: Wild/Cultivated; Degree

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of comminution; Process state; Growth state; Harvesting condition; Decontamination process; Country of origin, Geographical region, Storage time and Storage conditions.

NOTE The Element Group 'Herbal preparation Property Particulars' will enable to capture further information about the fraction (Herbal preparation) <Extract> such as, the Extraction solvent composition(s) 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. In this context, 'Herbal Substance' can be either a Substance (fresh) or a Herbal Drug.

NOTE The Specified Substance Group 1 Fraction class contains the attribute 'Country of Origin'. This attribute is 'optional' in case of the Herbal substance since the information is already been captured by the element class 'Herbal Substance Particulars', see Figure E.5 and note above).

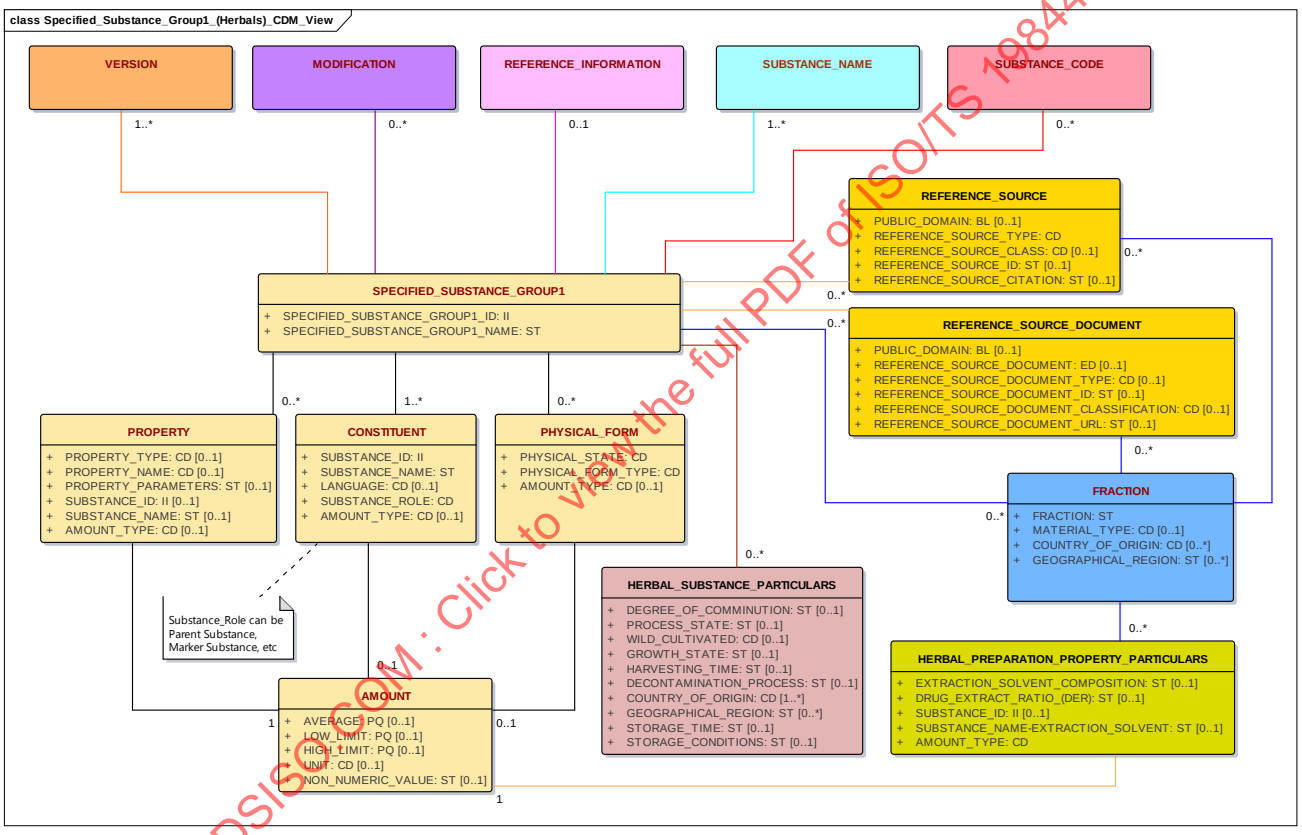


Figure E.5 — Information model for the Specified Substance Group 1 expanding the Herbal Substance Particulars and the Herbal preparation Property Particulars

In Figure E.6 and Figure E.7 a rationale will be provided for the use of the Element Group 'Herbal preparation Property Particulars' showing the use of the defining attributes Extraction Solvent Composition and 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 E.5. Depending on the composition and the polarity of the extraction solvent, in the range from water – up to water-ethanol

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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.7 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.7 the optimal yield for the constituent Oleuropein is obtained by a solvent composition of ethanol 65% - 96% (v/v). Up to 90% ethanol the DER is about 3.2 – 3.6 parts to 1part extract. When 96% 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 case of standardized, quantified or other herbal extract. These specifictions can also be provided as an 'In house' specification document enclosed as a reference source document at Specified Substance Group 2 or at Specified Substance Group 3 information level.

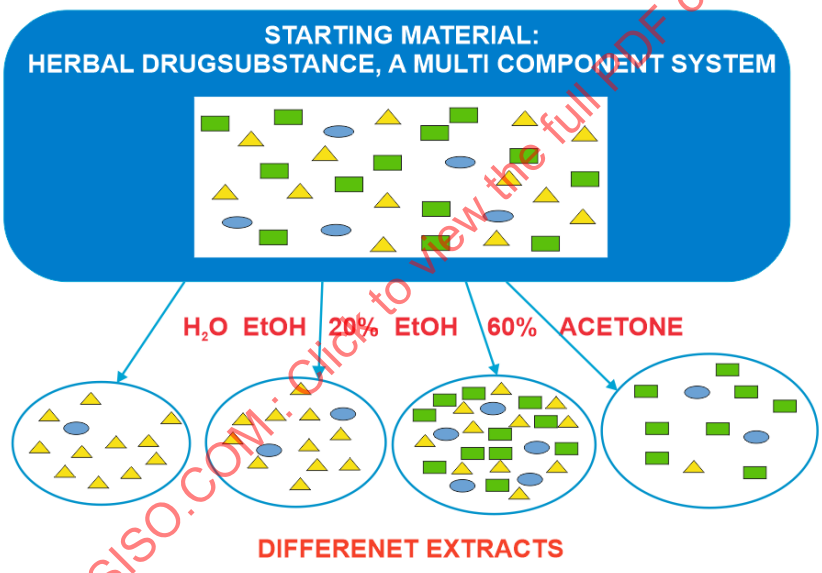


Figure E.6 — Difference of constituent content dependency on the extraction solvent composition. Herbal Substance in this figure can be either fresh plant material or a Herbal Drug

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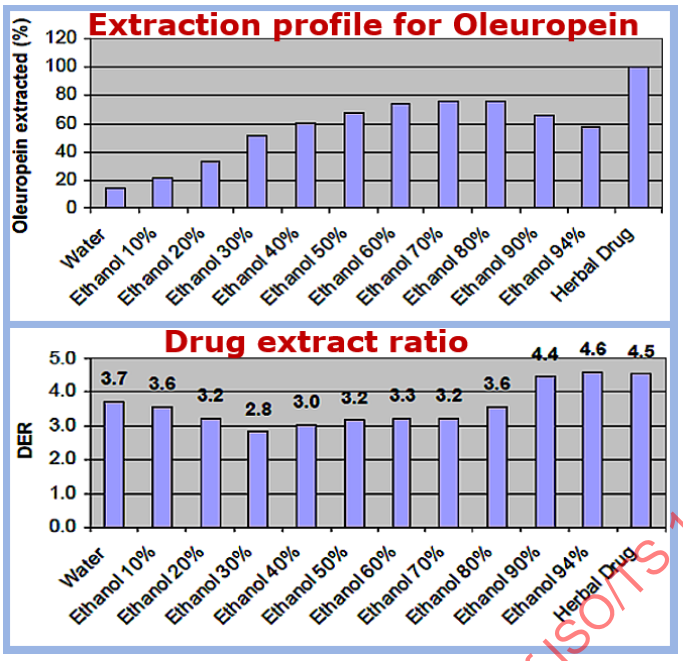


Figure E.7 — Extraction solvent composition range used to obtain the optimal constituent yield of Oleuropein in comparison with the minimum required amount of Herbal Substance (=Substance (fresh) or Herbal Drug)

In Figure E.8 an example is presented illustrating the content information for the Element Group Herbal preparation Property Particulars for a Soft (semi-solid) Extract of the Herbal Drug Salvia miltiorrhiza, Rhizome and Root in which the primary extraction solvent composition is Ethanol (90)–Water (10). Note that in the second extraction step the residue of the first extraction step is taken and extracted with water (100) 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).

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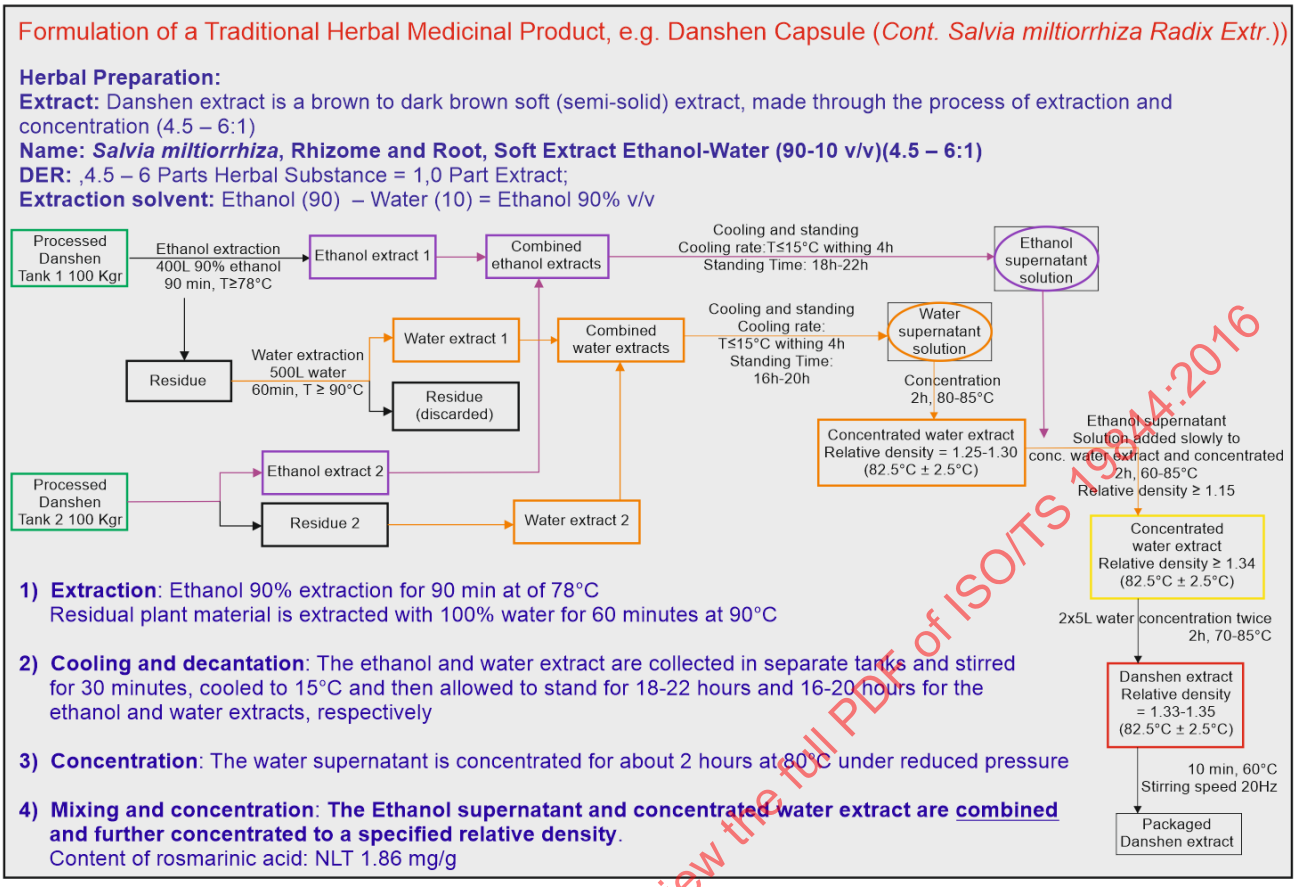


Figure E.8 — Example of Herbal preparation with two extraction solvent compositions

E.1.7 Specified Substance Group 2 Information

Specified Substance Group 2 (SSG2) shall capture manufacturer information, see Figure E.9. 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.

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.

The manufacturer is not necessarily the entity that holds the market authorisation, but the entity that manufactures, collects, processes and stores the material.

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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 version number and in some cases in a new SSG2 ID. The version number should be tied to the production system (see 6.2.6.7).

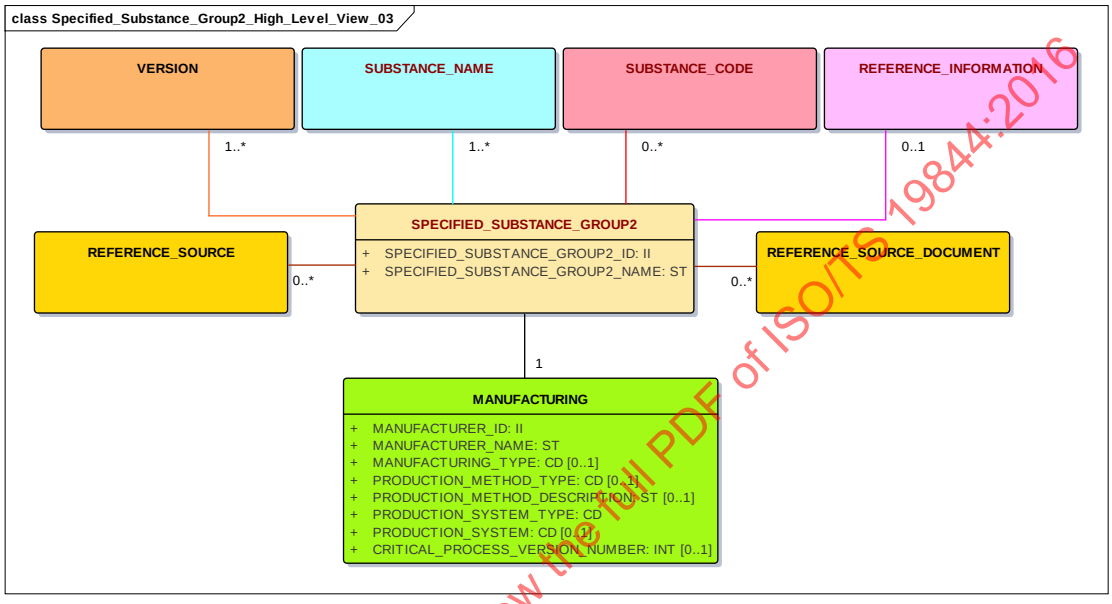


Figure E.9: Information model for SSG2 (high level view)

Figure 29 provides the information model for the Element Group Manufacturing. As mentioned in the main body of this TS, only the elements of the Manufacturing Class (in green colour) will currently be implemented in connection with Figure E.9.

Figure E.10 provides a high level simplified view of the Manufacturing Class for the Herbal preparation(s) (Extracts) since more information is needed to describe Standardised and Quantified Herbal preparations.

The Herbal Drug or Herbal Substance (fresh) is equivalent to the term 'Starting Material'. 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 Group.

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.8. The final extract is obtained by combining several intermediate extraction steps and is called the 'Resultant Substance(s)' (see relevant comment in Figure E.10.

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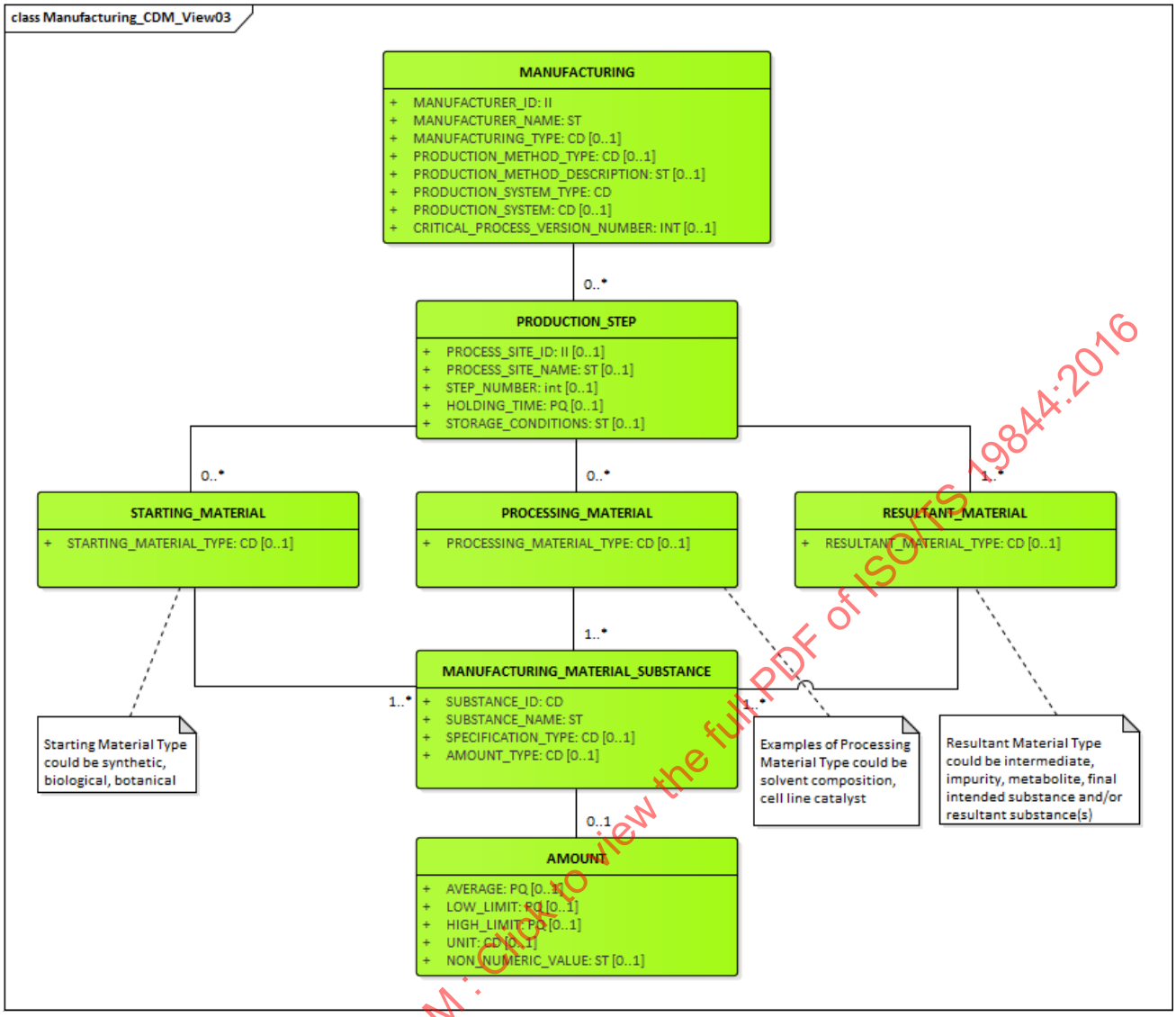


Figure E.10 — Manufacturing Information model with 'limited' extended information

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E.1.8 Substance and Specified Substance information for Iberis amara L, Whole Plant and of the liquid extract. (Simplified example)

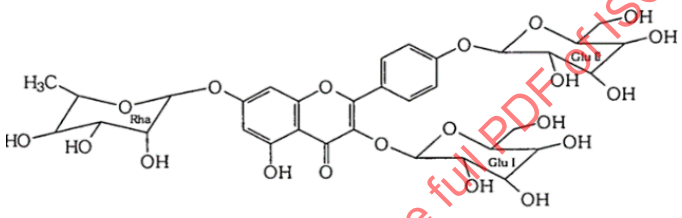
Table E.1 — Tabular format of the Substance and Specified Substance information for Iberis amara L, Whole Plant and of the liquid extract

Element Name	Value	Data Format	Note #
Substance (fresh) information of Iberis amara L, Whole Plant			
Substance ID	HERBS78654 (Artificial ID)	II	
Substance (fresh) Name	*Iberis amara* L., Whole Plant 	ST	
Herbal Substance (fresh) information captured at the Specified Substance Group 1			
Specified Substance Group 1 ID	HERB78654G1 (Artificial ID)	II	
Specified Substance Group 1 (fresh) Name	*Iberis amara,* Whole Plant, Fresh	ST	
Element Group: Constituent			
Substance ID	HERBS78654 (Artificial ID)	II	
Parent Substance (fresh) Name	*Iberis amara* L., Whole Plant	ST	
Language	LA	CD	
Substance Role	Parent Substance	CD	
Element Group: Herbal Substance Particulars			
Harvest Time	June-August	ST	
Country of Origin	Germany	CD	
Storage Conditions	Shock frozen directly after harvesting, stored protected from light at -20°C to -24°C for maximum 24 months	ST	
Element Group: Constituent			
Substance ID	KAEM56231L (Artificial ID)	II	
Substance Name	Kaempferol-3,4’ –O-β-diglucopyranoside-7-O-α-rhamnopyranoside	ST	

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Table E.1 *(continued)*

Element Name	Value	Data Format	Note #
Substance Role	Marker	CD	
Amount Type	Non-numeric value	CD	
Element Group: Structure			
Stereochemistry	Geometric Isomerism (Glycosidic bonds)	CD	
Optical Activity	(+/-)	CD	
Molecular Formula	$C_{33}H_{44}O_{20}$	ST	
Element Group: Structural Representation			
Structural Representation Type	Full	CD	
Structural Representation Attachment		ED	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric value]	756.38	PQ	
Unit	g/mol	CD	
Herbal preparation information of the fraction: at the Substance information level: (Limited information)			
Substance ID (Herbal preparation)	EXTRA89765 (Artificial ID)	II	
Substance Name (Herbal preparation)	*Iberis amara*, Whole Plant, Extract	ST	
Element Group: Source Material			
Parent Substance ID	HERBS78654 (Artificial ID)	II	
Parent Substance Name	*Iberis amara* L., Whole Plant	ST	

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Table E.1 *(continued)*

Element Name	Value	Data Format	Note #
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	
Specified Substance Group 1 Name	*Iberis amara*, Whole Plant, Liquid Extract	ST	
Element Group: Constituent			
Substance ID	EXTRA89765 (Artificial ID)	II	
Substance Name	*Iberis amara* L., Whole Plant	ST	
Language	la	CD	
Substance Role	Parent	CD	
Element Group: Fraction			
Material Type	Herbal, Liquid Extract	CD	
Fraction	Liquid Extract	CD	
Country of Origin	Germany	ST	1)
Element Group: Constituent (Repeat)			
Substance ID	KAEM56231L (Artificial ID)	II	
Substance Name	Kaempferol-3,4' –O-β-diglucopyranoside-7-O-α-rhamnopyranoside	ST	
Substance Role	Active Marker	CD	
Amount Type	Average	CD	
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	
Specified Substance Group 1 Name	*Iberis amara*, Whole Plant, Ethanol-Water Liquid Extract (50 – 50 v,v) (1:1.5 -2.5)	ST	
Parent Substance ID	EXTRA89765 (Artificial ID)	II	
Parent Substance Name	*Iberis amara*, Whole Plant, Extract	ST	
Element Group: Fraction			
Material Type	Herbal, Liquid Extract	CD	
Fraction	Liquid Extract	CD	

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Table E.1 *(continued)*

Element Name	Value	Data Format	Note #
Country of Origin	Germany	ST	1)
Element Group: Herbal preparation Property Particulars			
Extraction Solvent Composition	Ethanol 50% v/v	ST	
Substance ID	ETHAN98765	II	
Substance Name	Ethanol	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average (Numeric value)	50	PQ	
Unit	Volume per cent	CD	
Element Group: Herbal preparation Property Particulars (Repeat)			
Substance ID	WATEP67543	II	
Substance Name	Water	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average (Numeric value)	50	PQ	
Unit	Volume per cent	CD	
Element Group: Herbal preparation Property Particulars (Repeat)			
Drug Extract Ratio (DER)	1 part Herbal substance = 1.5 – 2.5 parts extract	ST	
Element Group: Constituent			
Substance ID	KAEM56231L (Artificial ID)	II	
Substance Name	Kaempferol-3,4' –O-β-diglucopyranoside-7-O-α-rhamnopyranoside	ST	
Substance Role	Active Marker	CD	
Amount Type	Average	CD	
Element Group: Amount			
Average (Numeric value)	0.10	PQ	
Low Limit	0.05	PQ	
High Limit	0.15	PQ	
Unit	mg/ml	CD	

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Table E.1 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Structure			
Structural Representation Type	Full	CD	
Structural Representation Attachment	See figure above in this Table	ED	
Molecular Formula	$C_{33}H_{44}O_{20}$	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average (Numeric value)	756.38	PQ	
Unit	g/mol	CD	

[1] This information is optional since it is captured at the Element Group 'Herbal Substance Particulars'.

[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.

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E.1.9 Specified Substance Group 2 Information for *Iberis amara*, Whole Plant, liquid extract (Extended Information).

Table E.2 — Tabular format of the Specified Substance Group 2 Information for Iberis amara, Whole Plant, liquid extract (Extended Information).

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 2			
Substance Type	Specified Substance Group 2	CD	
Specified Substance Group 2 ID	JKHYR86461 (Artificial ID)	II	
Specified Substance Group 2 Name	*Iberis amara*, Whole Plant, Ethanol-Water Extract (50 – 50 v,v) (1:1.5 -2.5)—Company ST GmbH	ST	
Parent Substance ID	SPHERP2341 (Artificial ID)	II	
Element Group: Manufacturing			
Manufacturer ID	DUNS86745HF (Artificial ID)	II	

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Manufacturer Name	Company ST GmbH, (Address, GPS code)	ST	1)
Manufacturing Type	Manufacturer	CD	
Production Method Type	Extraction, Percolation	CD	
Production Method Description	for example, the text written in Figure E.11	ST	
Critical Process Version Number	1	INT	2), 3)
Element Group: Reference Source			
Reference source documentation type:	Release specification.	CD	

[1] Manufacturer identification is defined with reference to Organisations in ISO 11615 and ISO/TS 20443

[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 shall be submitted along with a variation and shall be tied to the Production System Type.

[3] Change/additional remark to the ISO 19844 Implementation Guide (see 6.2.6.6) Business rule: **The versioning shall be tied to the Element Group Production System Type**.

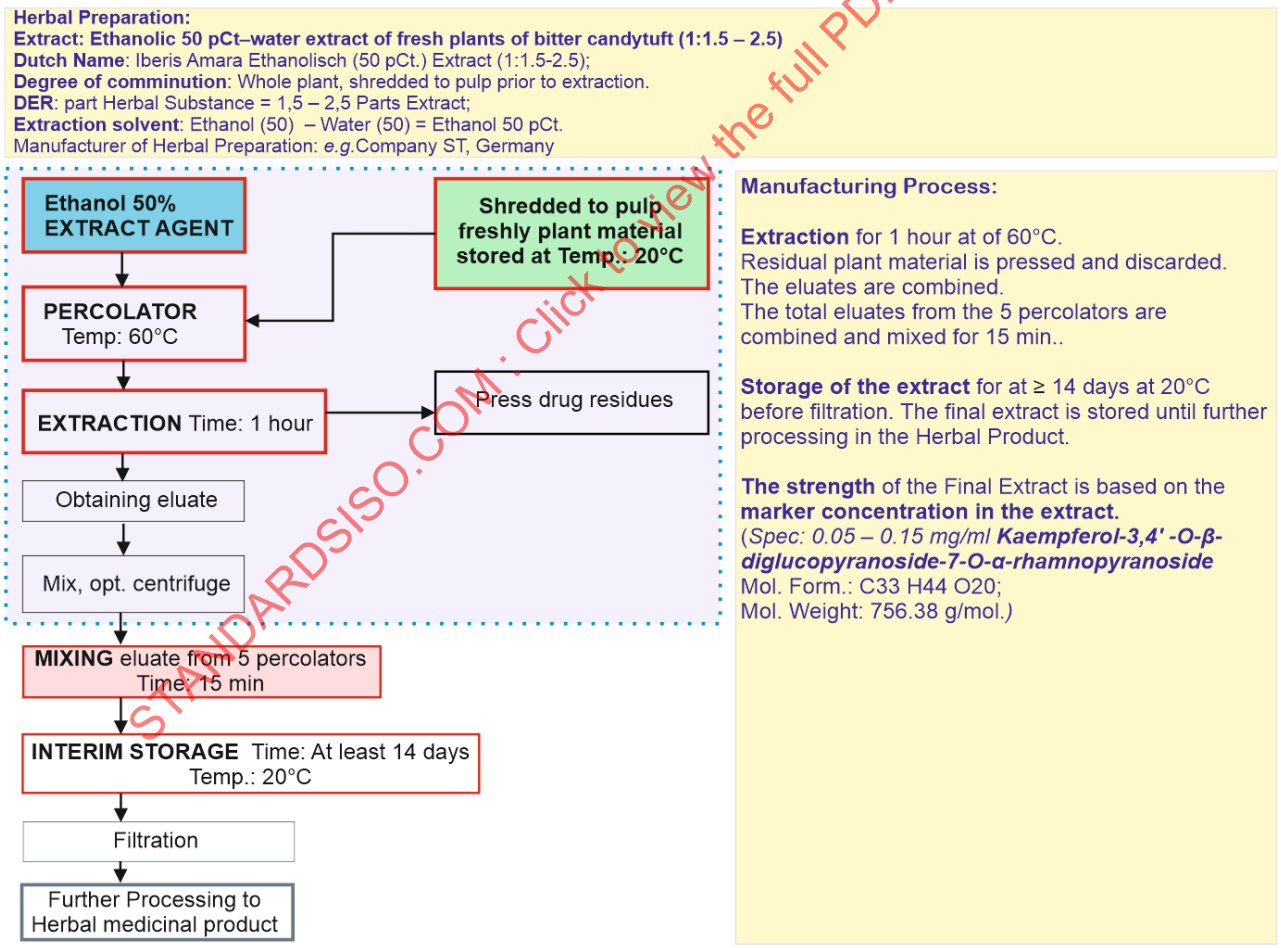


Figure E.11 —Manufacturing information of the Iberis Amara Ethanolic Extract

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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.

E.1.10 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. recognises three types of Herbal Drugs/Herbal preparations Standardised, Quantified, and Other. Each will require the appropriate defining information. Standardised and quantified grades not covered in a pharmacopoeia, and also organic grades of material, would also be distinguished at this level, see Figure E.12.

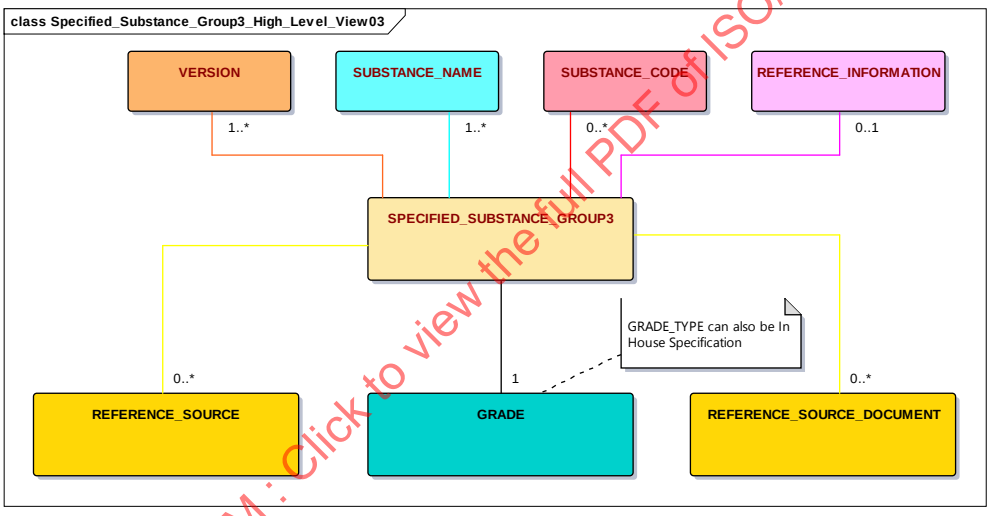


Figure E.12 — Specified Substance Group 3 High Level View.

In this ANNEX we will walk through each example at the substance and Specified Substance levels.

E.2 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/DTS 18062, Health informatics, Categorical structure for representation of herbal medicaments in terminological systems.

E.2.1 Definitions according to Directive 2001/83/EC and Directive 2004/24/EC, Title 1, Definitions

Article 30: Herbal medicinal product:

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"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 comminuted or powdered Herbal Substances (= Herbal Drugs), tinctures, extracts, essential oils, expressed juices and processed exudates."

NOTE 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 Herbal preparations such as oils and juices may be obtained from fresh plant material which has been captured at the Substance level as a Substance (fresh).

E.2.2 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).

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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.

Herbal teas comply with the monograph Herbal teas (1435)

NOTE 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 E.1.5.4 and Figure E.4).

NOTE 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>].

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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[6]).

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) 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.

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

[6] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/09/WC500113209.pdf

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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.

Standardisation: 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 either by adding excipients or by blending batches of the Herbal Substance (= Herbal Drug) and/or Herbal preparation (e.g. standardised 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.

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NOTE In accordance with the Ph.Eur. and the Herbal Guidelines Herbal Substances (= Herbal Drugs) are described as:

- **Standardised 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.
  Standardisation 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.'[7]

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[8].

'Guidance for Industry: Botanical Drug Products', U.S. Department of Health and Human Services, FDA, Centre for Drug Evaluation and Research (CDER), June 2004[9].

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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[7] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003272.pdf

[8] http://hmc.usp.org

[9] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf

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E.3 Documentation and Explanation of Example 1

E.3.1 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.3 — Tabular Format Herbal Substance Ginkgo biloba: Description of the elements at the Substance information level and at the Specified Substance Group 1,2,3.

Element Name	Value	Data Format	Note #
Element Group: Substance (Herbal Drug)			
Substance Type	Structurally Diverse Herbal Substance	CD	
Substance ID	45SPM3HJ6Q (Artificial ID)	II	
Element Group: Substance Name			
Substance Name (Herbal Drug)	*Ginkgo biloba*, Leaf	ST	
Substance Name Type	Official	CD	
Language	LA	CD	1)
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: Substance Name (Repeat)			
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	LH6754329O (Artificial ID)	II	
Organism Name	*Ginkgo biloba* L.	ST	2)
Parent Substance ID	19FUJ2C58T (Artificial ID)	II	

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Table E.3 *(continued)*

Element Name	Value	Data Format	Note #
Parent Substance Name (fresh)	*Ginkgo biloba* L., Leaf	ST	
Development stage	Mature plant stage	CD	
Element Organism			
Kingdom	Plantae	CD	
Phylum	Tracheophyta	CD	
Class	Ginkgoopsida	CD	
Order	Ginkgoales	CD	
Family	Ginkgoaceae	CD	
Genus	Ginkgo	CD	
Species	biloba	CD	3)
Species Primary Author	L.	ST	
Element Group: Part Description			
Part	Leaf	CD	
Part location	N/A		
Element Group: Reference Source Document			
Reference Source Document	 **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	
Specified Substance Group 1 Information level for the Herbal Drug			
Specified Substance Group 1 ID	GINKSP1HD0 (Artificial ID)	II	

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Table E.3 *(continued)*

Element Name	Value	Data Format	Note #
Substance Type	Specified Substance Group 1	CD	
Specified Substance Group 1 Name	*Ginkgo biloba*, Leaf, Dry	ST	
Element Group: Constituent			
Substance ID	45SPM3HJ6Q (Artificial ID)	II	
Substance Name	*Ginkgo biloba*, Leaf	ST	
Language	la	CD	
Substance Role	Parent Substance	CD	
Element Group: Herbal Substance Particulars			
Degree of Comminution	Cut, Fragmented, Sliced and Sifted leaves	ST	
Process State	Natural dried at 20°C for 6 hours	ST	
Wild/Cultivated	Cultivated	CD	
Growth State	Before leaves turn yellow	ST	
Harvesting Time	June – October	ST	
Country of Origin	China	CD	
Geographical Region	Provinces Shandong, Jiangsu, Sichuan	ST	
Storage Time	NMT 6 month	ST	
Storage Conditions	Stored protected from light at 0°C, until processed	ST	
Element Group: Constituent			
Substance ID	KAEM56231L (Artificial ID)	II	
Substance Name	Kaempferol-3,4' –O-β-diglucopyranoside-7-O-α-rhamnopyranoside (see Structure above in table 1)	ST	4)
Substance Role	Active Marker	CD	
Amount Type	Average	CD	
Element Group: Amount			
Average (Numeric value)	0.5	PQ	
Low Limit	0.5	PQ	
Unit	Mass per cent	CD	
Element Group: Specified Substance Group 2 (Manufacturer who harvests/collects/stores the Herbal Drug)			
Substance Type	Specified Substance Group 2	CD	

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Table E.3 *(continued)*

Element Name	Value	Data Format	Note #
Specified Substance Group 2 ID	GHRC786543 (Artificial ID)	II	
Specified Substance Group 2 Name	*Ginkgo biloba*, Leaf, Dry—Company HARV, China	ST	
Parent Substance ID	45SPM3HJ6Q (Artificial ID)	II	
Element Group: Manufacturing			
Manufacturer ID	DUNS1234HF (Artificial ID)	II	
Manufacturer Name	Company HARV, (Address, GPS code)	ST	
Manufacturing Type	Harvester	CD	
Production Method Type	Harvesting	CD	
Production Method Description	Cutting, fragmenting	ST	
Critical Process Version Number	1	INT	
Element Group: Reference Source			
Reference Source Documentation Type:	Storage conditions description	CD	

[1] The Scientific name has the language value LA; see 4.3.3.

[2] The Organism ID and Name should be provided by The Kew Gardens Medicinal Plant Names Services (MPNS).

[3] Species: biloba [Only the specific epithet part of the name is captured here].

[4] 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).

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E.3.2 Herbal preparation Ginkgo biloba extract, Limited information: Description of the elements at the Substance information level

Table E.4 — 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 Type	Structurally Diverse, (Herbal preparation)	CD	
Substance ID	HPR852369P (Artificial ID)	II	
Element Group: Substance Name			
Substance Name	*Ginkgo biloba*, Leaf, Extract	ST	
Substance Name Type	Other	CD	
Language	la	CD	
Element Group: Substance Name (Repeat)			
Substance Name (Synonym)	Maidenhair tree leaf, extract	ST	
Substance Name Type	Other	CD	
Language	en	CD	
Official Name Jurisdiction	EU, US	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Journal	CD	
Reference Source Class	Web	CD	
Reference Source Citation	http://europepmc.org/abstract/med/19702174	ST	
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			
Material Type	Herbal, Extract	CD	
Fraction	Extract	CD	
Country of Origin	China	CD	

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Table E.4 *(continued)*

Element Name	Value	Data Format	Note #
Geographical Region	Provinces Shandong, Jiangsu, Sichuan	ST	
Element Group: Property			
Property Type	Physical	CD	
Property Name	Solubility	CD	
Property Parameters	1 mass part at 20° C	ST	
Substance ID	ETHAN60987	II	
Substance Name	Ethanol 60% (v/v)	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	10	PQ	
Unit	g	CD	

E.3.2.1 Herbal preparation Ginkgo biloba extract, Limited information: Description of the elements at the Specified Substance Group 1,2,3.

Table E.5 — Tabular Format Herbal preparation Ginkgo biloba extract, Limited information: Description of the elements at the Specified Substance Group 1,2,3

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	
Substance Type	Specified Substance Group 1	CD	
Element Group: Constituent			
Substance ID	HPR852369P (Artificial ID)	II	
Substance Name	*Ginkgo biloba*, Leaf, Dry Extract	ST	
Language	la	CD	
Substance Role	Parent Substance	CD	
Element Group: Fraction			
Material Type	Herbal, Dry Ethanolic	CD	
Fraction	Dry Ethanolic Extract	CD	
Country of Origin	China	CD	

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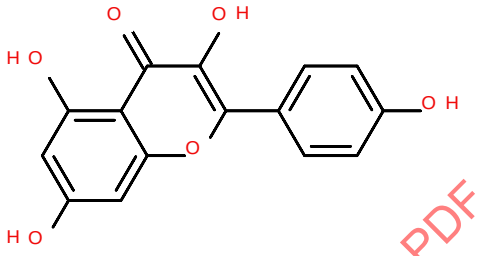
Table E.5 *(continued)*

Element Name	Value	Data Format	Note #
Geographical Region	Provinces Shandong, Jiangsu, Sichuan	ST	
Element Group: Herbal preparation Property Particulars			
Extraction Solvent Composition	Ethanol 60% v/v	ST	
Substance ID	ETHAN98765 (Artificial ID)	II	
Substance Name Extraction Solvent	Ethanol	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	60	PQ	
Unit	Volume per cent	CD	
Element Group: Herbal preparation Property Particulars (Repeat)			
Extraction Solvent	Ethanol 60% v/v	ST	
Substance ID	WATERP67543 (Artificial ID)	II	
Substance Name Extraction Solvent	Water	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	40	PQ	
Unit	Volume per cent	CD	
Element Group: Constituent			
Substance ID	FKLAV98765 (Artificial ID)	II	
Substance Name	Flavone Glycoside	ST	1)
Substance Role	Active Marker	CD	
Amount Type	Average	CD	
Element Group: Amount			
Average (Numeric value)	25	PQ	
Low Limit	22	PQ	
High Limit	27	PQ	
Unit	Mass per cent	CD	
Element Group: Constituent (Repeat)			

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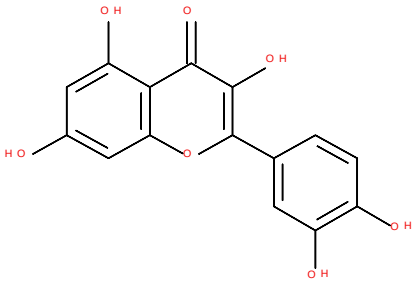
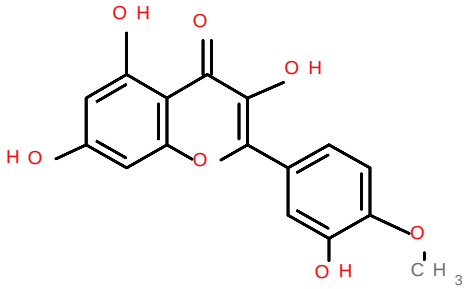
Table E.5 *(continued)*

Element Name	Value	Data Format	Note #
Substance ID	731P2LE49E (UNII)	II	
Substance Name	Kaempferol	ST	1)
Substance Role	Active Marker	CD	
Amount Type	Non-numeric value	CD	
Element Group: Structure			
Structural Representation Type	Full	CD	
Structural Representation Attachment		ED	
Molecular Formula	$C_{15}H_{10}O_6$	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average value	286.23	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Substance ID	9IKM0I5T1E (UNII)	II	
Substance Name	Quercetin	ST	1)
Substance Role	Active Marker	CD	
Amount Type	Non-numeric value	CD	
Element Group: Structure			
Structural Representation Type	Full	CD	

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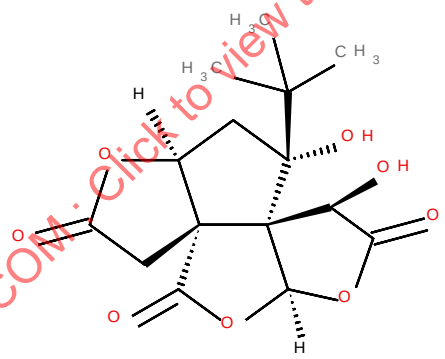
Table E.5 *(continued)*

Element Name	Value	Data Format	Note #
Structural Representation Attachment		ED	
Molecular Formula	$C_{15}H_{10}O_7$	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average Value	302.23	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Substance ID	73WRA8Z8M8 (UNII)	II	
Substance Name	Isorhamnetin	ST	1)
Substance Role	Active Marker	CD	
Amount Type	Non-numeric value	CD	
Element Group: Structure			
Structural Rrepresentation Type	Full	CD	
Structural Representation Attachment		ED	
Molecular Formula	$C_{16}H_{12}O_7$	ST	
Element Group: Molecular Weight			

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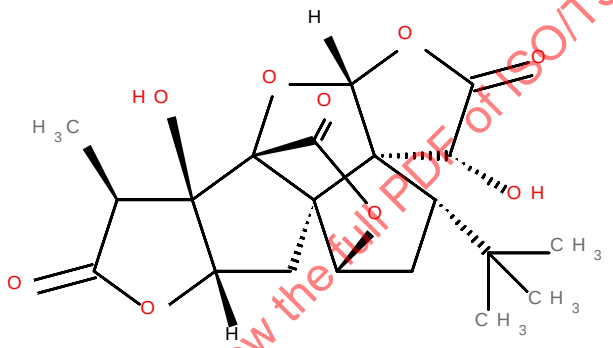
Table E.5 *(continued)*

Element Name	Value	Data Format	Note #
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average Value	316.26	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Substance ID	M81D2O8H7U (UNII)	II	
Substance Name	Bilobalide	ST	1)
Substance Role	Active Marker	CD	
Amount Type	Non-numeric value	CD	
Element Group: Structure			
Structural Representation Type	Full	CD	
Structural Representation Attachment		ED	
Molecular Formula	$C_{15}H_{18}O_8$	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average value	326.29	PQ	
Unit	g/mol	CD	

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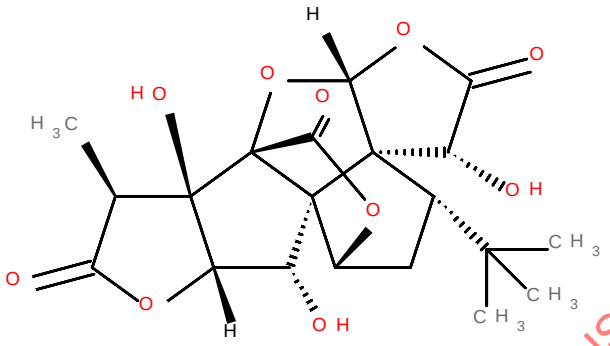
Table E.5 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Constituent (Repeat)			
Substance ID	TAZ2DPR77B (UNII)	II	
Substance Name	Ginkgolide A	ST	1)
Substance Role	Active Marker	CD	
Amount Type	Non-numeric value	CD	
Element Group: Structure			
Structural Representation Type	Full	CD	
Structural Representation Attachment		ED	
Molecular Formula	$C_{20}H_{24}O_9$	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average Value	408.40	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Substance ID	DF149B946O (UNII)	II	
Substance Name	Ginkgolide B	ST	1)
Substance Role	Active Marker	CD	
Amount Type	Non-numeric value	CD	

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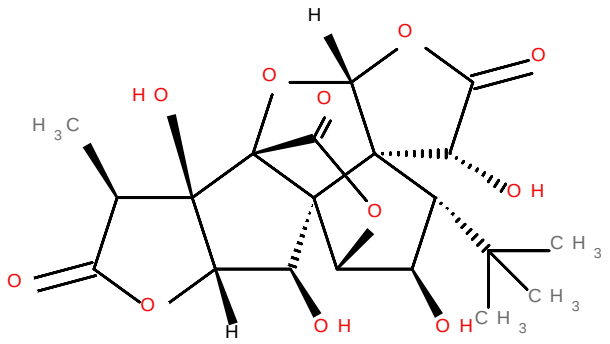
Table E.5 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Structure			
Structural Representation Type	Full	CD	
Structural Representation Attachment		ED	
Molecular Formula	$C_{20}H_{24}O_{10}$	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average Value	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	
Amount Type	Non-numeric value	CD	
Element Group: Structure			
Structural Representation Type	Full	CD	

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Table E.5 *(continued)*

Element Name	Value	Data Format	Note #
Structural Representation Attachment		ED	
Molecular Formula	$C_{20}H_{24}O_{11}$	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average Value	440.40	PQ	
Unit	g/mol	CD	
Element Group: Specified Substance Group 2 (Manufacturer of the Herbal preparation) Extract Limited information			
Substance Type	Specified Substance Group 2	CD	
Specified Substance Group 2 ID	GHTW12345 (Artificial ID)	II	
Specified Substance Group 2 Name	*Ginkgo biloba*, Leaf, Dry Extract—Company RGHS, Netherlands	ST	
Parent Substance ID	HPR852369P (Artificial ID)	II	
Element Group: Manufacturing			
Manufacturer ID	DUNS78544HP (Artificial ID)	II	
Manufacturer Name	Company RGHS, (Address, GPS location)	ST	
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	

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Table E.5 *(continued)*

Element Name	Value	Data Format	Note #
Critical Process Version Number	1	INT	
Element Group: Specified Substance Group 3, Herbal preparation (Ph.Eur., Limited information)			
Specified Substance Group 3 ID	GHDMK123EP (Artificial ID)	II	
Substance Type	Specified Substance Group 3	CD	
Specified Substance Group 3 Name	*Ginkgo biloba*, Leaf, Dry Extract-Ph.Eur.	ST	
Parent Substance ID	HPR852369P (Artificial ID)	II	
Element Group: Specified Substance Group 3 Grade			
Grade Type	Ph.Eur.	CD	
Grade Name (= Name of the Ph.Eur. monograph)	Ginkgo dry extract, refined and quantified	ST	
Grade Reference Source	Ph.Eur., Monograph 04/2008:1827	ST	
[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).			

E.3.2.2 Herbal preparation Ginkgo biloba extract, Extended information: Description of the elements at the Specified Substance Group 1,2,3.

Table E.6 — Tabular Format Herbal preparation Ginkgo biloba extract, Extended information: Description of the elements at the Specified Substance Group 1,2,3.

Element Name	Value	Data Format	Note #
Element Group: Specified Substance Group 1, (Herbal preparation Extended information)			
Substance Type	Specified Substance Group 1	CD	
Specified Substance Group 1 ID	HERBP12345 (Artificial ID)	II	
Specified Substance Group 1 Name	*Ginkgo biloba*, Leaf, Dry Extract, Acetone-Water (60-40 w/w),(37-65:1)	ST	
Element Group: Constituent			
Substance ID	HPR852369P (Artificial ID)	II	
Substance Name	*Ginkgo biloba*, Leaf, Dry Extract	ST	
Language	la	CD	

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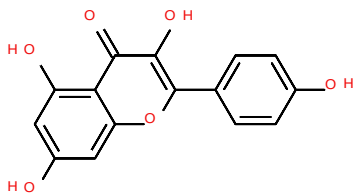
Table E.6 *(continued)*

Element Name	Value	Data Format	Note #
Substance Role	Parent Substance	CD	
Element Group: Fraction			
Material Type	Herbal, Leaf	CD	
Fraction	Extract, Dry, Acetone-Water	CD	
Country of Origin	China	CD	
Geographical Region	Provinces Shandong, Jiangsu, Sichuan	ST	
Element Group: Herbal preparation Property Particulars			
Extraction Solvent Composition	Acetone-Water (60-40 w/w)	ST	
Substance ID	ACETO98765 (Artificial ID)	II	
Substance Name Extraction Solvent	Acetone	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	60	PQ	
Unit	Weight per cent	CD	
Element Group: Herbal preparation Property Particulars (Repeat)			
Extraction Solvent Composition	Acetone-Water (60-40 w/w)	ST	
Substance ID	WATEP67543 (Artificial ID)	II	
Substance Name Extraction Solvent	Water	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Average [Numeric Value]	40	PQ	
Unit	Weight per cent	CD	
Element Group: Herbal preparation Property Particulars (Repeat)			
Drug Extract Ratio (DER)	37 – 65 parts Herbal Substance = 1part Herbal Extract	ST	
Amount Type	Numeric value	CD	
Element Group: Amount			
Average Value	51	PQ	
Low Limit	37	PQ	

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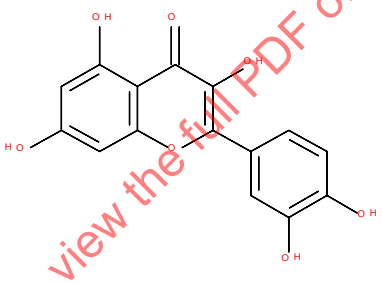
Table E.6 *(continued)*

Element Name	Value	Data Format	Note #
High Limit	65	PQ	
Unit	g	CD	
Element Group: Constituent (Repeat)			
Substance ID	FKLAV98765 (Artificial ID)	II	
Substance Name	Flavone Glycoside	ST	1)
Substance Role	Active Marker	CD	
Amount Type	Average	CD	
Element Group: Amount			
Average (Numeric value)	25	PQ	
Low Limit	22	PQ	
High Limit	27	PQ	
Unit	Mass per cent	CD	
Element Group: Constituent (Repeat)			
Substance ID	731P2LE49E (UNII)	II	
Substance Name	Kaempferol	ST	1)
Substance Role	Active Marker	CD	
Amount Type	Non-numeric value	CD	
Element Group: Structure			
Structural Representation Type	Full	CD	
Structural Representation Attachment		ED	
Molecular Formula	$C_{15}H_{10}O_6$	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	

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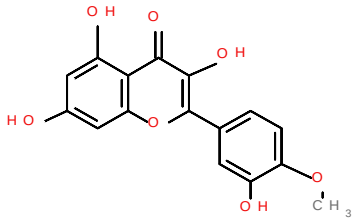
Table E.6 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Amount			
Average Value	286.23	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Substance ID	9IKM0I5T1E (UNII)	II	
Substance Name	Quercetin	ST	1)
Substance Role	Active Marker	CD	
Amount Type	Non-numeric value	CD	
Element Group: Structure			
Structural Representation Type	Full	CD	
Structural Representation Attachment		ED	
Molecular Formula	$C_{15}H_{10}O_7$	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average Value	302.23	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Substance ID	73WRA8Z8M8 (UNII)	II	
Substance Name	Isorhamnetin	ST	1)
Substance Role	Active Marker	CD	
Amount Type	Non-numeric value	CD	

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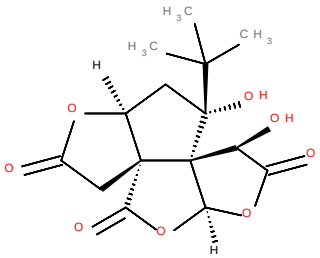
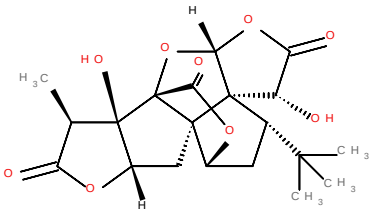
Table E.6 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Structure			
Structural Representation Type	Full	CD	
Structural Representation Attachment		ED	
Molecular Formula	$C_{16}H_{12}O_7$	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average Value	316.26	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Substance ID	M81D2O8H7U (UNII)	II	
Substance Name	Bilobalide	ST	1)
Substance Role	Active Marker	CD	
Amount Type	Non-numeric value	CD	
Element Group: Amount			
Average (Numeric value)	2.9	PQ	
Low Limit	2.6	PQ	
High Limit	3.2	PQ	
Unit	Mass per cent	CD	
Element Group: Structure			
Structural Representation Type	Full	CD	

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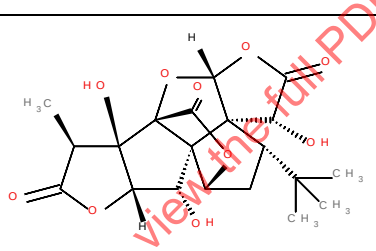
Table E.6 *(continued)*

Element Name	Value	Data Format	Note #
Structural Representation Attachment			
Molecular Formula	$C_{15}H_{18}O_8$	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average Value	326.29	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Substance ID	TAZ2DPR77B (UNII)	II	
Substance Name	Ginkgolide A	ST	1)
Substance Role	Active Marker	CD	
Amount Type	Non-numeric value	CD	
Element Group: Structure			
Structural Representation Type	Full	CD	
Structural Representation Attachment			
Molecular Formula	$C_{20}H_{24}O_9$	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	

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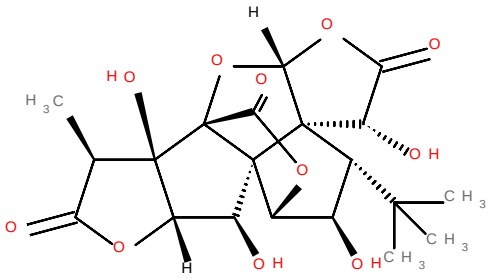
Table E.6 *(continued)*

Element Name	Value	Data Format	Note #
Amount Type	Exact	CD	
Element Group: Amount			
Average Value	408.40	PQ	
Unit	g/mol	CD	
Element Group: Constituent (Repeat)			
Substance ID	DF149B946O (UNII)	II	
Substance Name	Ginkgolide B	ST	1)
Substance Role	Active Marker	CD	
Amount Type	Non-numeric value	CD	
Element Group: Structure			
Structural Representation Type	Full	CD	
Structural Representation Attachment			
Molecular Formula	$C_{20}H_{24}O_{10}$	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average Value	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	
Amount Type	Non-numeric value	CD	
Element Group: Structure			

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Table E.6 *(continued)*

Element Name	Value	Data Format	Note #
Structural Representation Type	Full	CD	
Structural Representation Attachment			
Molecular Formula	$C_{20}H_{24}O_{11}$	ST	
Element Group: Molecular Weight			
Molecular Weight Method	Calculated	CD	
Molecular Weight Type	Number average	CD	
Amount Type	Exact	CD	
Element Group: Amount			
Average Value	440.40	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	
Amount Type	Non-numeric value	CD	
Element Group: Amount (Constituents Ginkgolide A, B, C)			
Average (Numeric value)	3.1	PQ	
Low Limit	2.8	PQ	
High Limit	3.4	PQ	
Unit	Mass per cent	CD	
Element Group: Constituent (Repeat)			
Substance ID	32ZQ957R4A (UNII)	II	
Substance Name	Ginkgolic acid	ST	1)
Substance Role	Toxic Ingredient	CD	2)
Amount Type	Numeric value	CD	

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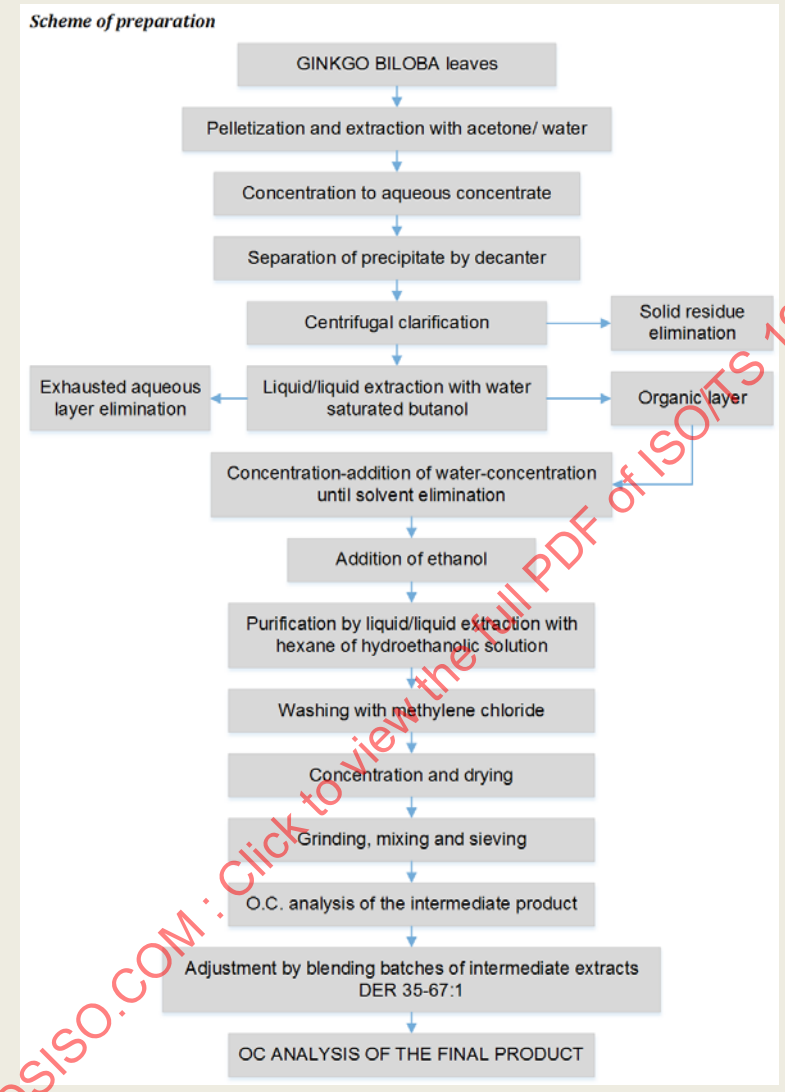
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Table E.6 *(continued)*

Element Name	Value	Data Format	Note #
Element Group: Amount (Constituent**)**			
Average (Numeric value)	5	PQ	
High Limit	5	PQ	
Unit	ppm	CD	
Element Group: Reference Source Document			
Reference Source Document	Pdf. Document	ED	
Reference Source Document Type	Journal article: MS-spectra Ginkgo acids in microsomes	ST	
Reference Source Document URL	http://onlinelibrary.wiley.com/enhanced/doi/10.1002/rcm.4086	ST	2)
Element Group: Specified Substance Group 2 (Manufacturer of the Herbal preparation) Extract Extended information			
Substance Type	Specified Substance Group 2	CD	
Specified Substance Group 2 ID	FGDWE56341 (Artificial ID)	II	
Specified Substance Group 2 Name	*Ginkgo biloba*, Leaf, Dry Extract, Acetone-Water (60-40 w/w),(37-65:1)—Company XYZ, Netherlands	ST	
Parent Substance ID	HPR852369P (Artificial ID)	II	
Element Group: Manufacturing			
Manufacturer ID	DUNS6753HP (Artificial ID)	II	
Manufacturer Name	Company XYZ, (Address, GPS code)	ST	
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 Document			
Reference Source Document	Pdf. Document, Manufacturing flow overview	ED	
Reference Source Document Type	Regulatory Submission	CD	
Reference Source Document URL	N/A		

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Element Name	Value	Data Format	Note #
Manufacturing overview, Herbal preparation, Dry Extract: 			
Element Group: Specified Substance Group 3, Herbal preparation (Ph.Eur., Extended information)			
Substance Type	Specified Substance Group 3	CD	
Specified Substance Group 3 ID	HJFGERA897 (Artificial ID)	II	
Specified Substance Group 3 Name	*Ginkgo biloba*, Leaf, Dry Extract, Acetone-Water (60-40 w/w),(37-65:1)-Ph.Eur.	ST	
Parent Substance ID	HPR852369P (Artificial ID)	II	
Element Group: Specified Substance Group 3 Grade			
Grade Type	Ph.Eur.	CD	
Grade Name (= Name of the	Ginkgo dry extract, refined and quantified	ST	

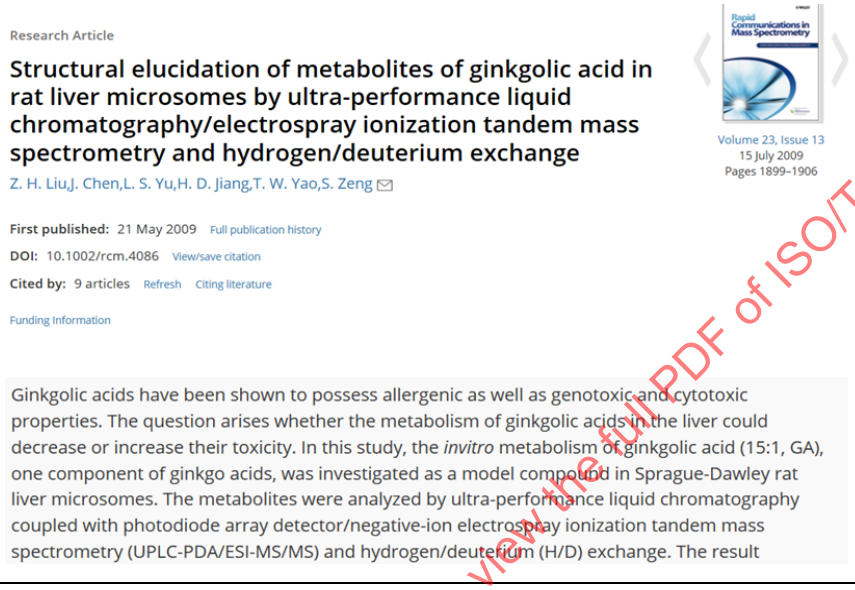
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Element Name	Value	Data Format	Note #
Ph.Eur. monograph)			
Grade Reference Source	Ph.Eur., Monograph 04/2008:1827	ST	

[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).

[2] Reference for the Toxicity and allergenic activity of Ginkgo acids, in particular Ginkgolic acid. URL: http://onlinelibrary.wiley.com/enhanced/doi/10.1002/rcm.4086



Research Article

Structural elucidation of metabolites of ginkgolic acid in rat liver microsomes by ultra-performance liquid chromatography/electrospray ionization tandem mass spectrometry and hydrogen/deuterium exchange

Z. H. Liu,J. Chen,L. S. Yu,H. D. Jiang,T. W. Yao,S. Zeng

Volume 23, Issue 13
15 July 2009
Pages 1899–1906

First published: 21 May 2009 Full publication history

DOI: 10.1002/rcm.4086 View/save citation

Cited by: 9 articles Refresh Citing literature

Funding Information

Ginkgolic acids have been shown to possess allergenic as well as genotoxic and cytotoxic properties. The question arises whether the metabolism of ginkgolic acids in the liver could decrease or increase their toxicity. In this study, the *invitro* metabolism of ginkgolic acid (15:1, GA), one component of ginkgo acids, was investigated as a model compound in Sprague-Dawley rat liver microsomes. The metabolites were analyzed by ultra-performance liquid chromatography coupled with photodiode array detector/negative-ion electrospray ionization tandem mass spectrometry (UPLC-PDA/ESI-MS/MS) and hydrogen/deuterium (H/D) exchange. The result

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E.3.3 Example 2: Devil's Claw Root (Ph.Eur.), continued

This example is a submission for an 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.

Information provided within the regulatory submission:

E.3.3.1 General Information Herbal Drug

Table E.7 — Devil's Claw Root

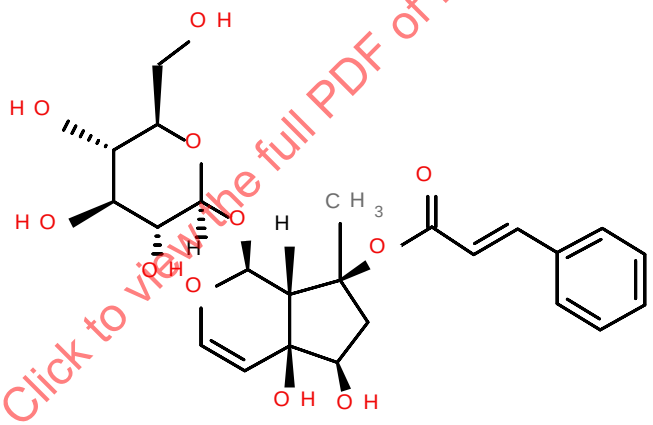
Provided information	Description
Description:	Devil's claw root consists of the cut and dried tuberous secondary roots of *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne. Note: Only one species is used. Content: minimum 1.2 per cent of harpagoside ($C_{24}H_{30}O_{11}$; Mr 494.5)

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Provided information	Description
Reference: Source: Plant, Part Dry Extract:	(dried drug). European Pharmacopoeia ed. 8.6 Ph.Eur. monograph 01/2011:1095 Ph.Eur. monograph 01/2008:1871
Process State, Wild/cultivated, Growth State Harvesting Conditions Decontamination Process Storage Conditions:	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.) Crop-grown plants are harvested during the whole year after they have been cultivated for at least two growth periods. 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. 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. The well-dried drug is stored in dry bags. No post-harvesting treatment with ethylene oxide or other fumigant against pests is applied. The well-dried drug is stored in dry bags indoors, protected from light.
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.

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Provided information	Description
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 Characterisation: Molecular Formula: Molecular Weight:	CAS: 19210-12-9 (Harpagoside) UNII: 8KGS1DC5ZU $C_{24}H_{30}O_{11}$ 494.5 g/mol.
Structural Information	see below 
Systematic Name:	*1S-(1α,4aα,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)
CharacteriSation Macroscopic, Microscopic Examination	Characterisation 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

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Provided information	Description
Primary Process	Harvesting, cutting, drying

E.3.3.2 General Information Herbal preparation

Table E.8 — 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
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, GPS location
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 ulfra-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 – 2.5 per cent NMT 5.0 per cent NMT 0.5 per cent ethanol
NOTE NMT equals to: Not More Than NOTE NLT equals to: Not Less Than	

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E.3.4 Organisation of the information according to ISO 11238 and ISO/TS 19844.

E.3.4.1 Information at the Substance level

The example is not organised in tabular format but the specific organisation of the information for this Substance class is discussed. In addition, a tabular summary is provided in Table E.8.

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E.3.4.1.1 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

Element Group: Substance Name (Repeat)
Substance Name: *Harpagophytum procumbens* (Burch.) DC. ex Meisn.
Substance Name Type: Scientific

Element Group: Source Material
Organism ID: DSERW78654 (Artificial ID)
Organism Name: *Harpagophytum procumbens* (Burch.) DC. ex Meisn.

Element Group: Organism
Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Lamiales
Family: Pedaliaceae
Genus: Harpagophytum
Species: procumbens
Species Parenthetical Author: Burch.
Species Primary Author: DC. ex Meisn.

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

Element Group: Substance Name (Repeat)
Substance Name: *Harpagophytum zeyheri* Decne.

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Substance Name Type: Scientific

Element Group: Source Material
Organism ID: YTREW8654Z (Artificial ID)
Organism Name: *Harpagophytum zeyheri* Decne.

Element Group: Organism
Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Lamiales
Family: Pedaliaceae
Genus: Harpagophytum
Species: zeyheri
Species Primary Author: Decne.

Element Group: Part Description
Part: Tuberous root

E.3.4.1.2 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: la

Element Group: Official Name
Official Name Type: Ph.Eur.
Official Name Status: Current
Official Name Domain: Drug
Official Name Jurisdiction: EU

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: LA

Element Group: Official Name
Official Name Type: Ph.Eur.
Official Name Status: Current
Official Name Domain: Drug
Official Name Jurisdiction: EU

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.3.4.1.3 Substance, Herbal preparation

Element Group: Substance
Substance ID (Herbal preparation): EEEEEEEEEE (Artificial ID)

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Substance Type: Structurally Diverse (Herbal Substance)

Element Group: Substance Name
Substance Name (Herbal preparation): *Harpagophytum procumbens*, 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: CCCCCCCCCC (Artificial ID)
Parent Substance Name (Herbal Drug): *Harpagophytum procumbens*, Root

Element Group: Part Description
Part: Tuberous root

Element Group: Fraction
Material Type: Herbal
Fraction: Extract

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
Material Type: Herbal
Fraction: Extract

E.3.4.2 Specified Substance Group 1 information level for the Herbal Drug

Element Group: Specified Substance Group 1
Substance Type: Specified Substance Group 1
Specified Substance Group 1 ID (Herbal Drug): GHTDR6435H (Artificial ID)
Specified Substance Group 1 Name (Herbal Drug): *Harpagophytum procumbens*, Root, Dry

Element Group: Substance Name
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
Substance ID (Herbal Drug): CCCCCCCCCC (Artificial ID)
Substance Name (Herbal Drug): *Harpagophytum procumbens*, Root
Language: la
Substance Role: Parent
(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)

Element Group: Specified Substance Group1
Substance Type: Specified Substance Group 1
Specified Substance Group 1 ID (Herbal Drug): TE84K152PR (Artificial ID)
Specified Substance Group 1 Name (Herbal Drug): *Harpagophytum zeyheri*, Root, Dry

Element Group: Substance Name
Official Name: Devil's Claw Root, Dry
Substance Name Type: Official
Language, en

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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 01/2011:1095

Element Group: Constituent
Substance ID (Herbal Drug): DDDDDDDDDD (Artificial ID)
Substance Name (Herbal Drug): *Harpagophytum zeyheri*, Root
Substance Role: Parent
(which in turn has the Parent Substance (fresh): *Harpagophytum zeyheri* Decne., Root, with the Parent Substance ID: FGTE56432H (Artificial ID)

Element Group: Herbal Substance Particulars for the Herbal Drug:
Degree of Comminution: cut into slices of 2-4 cm.
Process State: Dried indoors, well ventilated.
Wild_Cultivated: Cultivated
Growth State: Mature plant
Harvesting Time: Plants are harvested during the whole year after they have been cultivated for at least two growth periods
Countries of Origin: South Africa and Namibia
Storage Time: 2 years.
Storage Conditions: Undamaged tubers and stored under dry conditions.

Element Group: Constituent
Substace ID: 8KGS1DC5ZU (Artificial ID)
Substance Name: Harpagoside ($C_{24}H_{30}O_{11}$; Mr. 494.5; Mr. 494.5), see Table E.7
Substance Role: Marker
Amount Type: Exact

Element Group: Amount
Avarage (Numeric Value): 1.2
Low Limit: 1.2
Unit: Mass per cent

NOTE: 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.

E.3.4.3 Specified Substance Group 2 information level for the Herbal Drug

Element Group: Specified Substance Group 2

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Substance Type: Specified Substance Group 2
Specified Substance Group 2 ID (Herbal Drug): TYFGS7654M (Artificial ID)
Specified Substance Group 2 Name (Herbal Drug): *Harpagophytum procumbens*, Root, Dry – Manufacturer AA.
Parent Substance Group 1 ID (Herbal Drug): GHTDR6435H (Artificial ID)

Element Group Manufacturing
Manufacturer ID: MANDUNS452 (Artificial ID)
Manufacturer Name: Name, address, town, country (South Africa), GPS location
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

Elemenet Group: Specified Substance Group 2
Substance Type: Specified Substance Group 2
Specified Substance Group 2 ID (Herbal Drug): GJURT4523K (Artificial ID)
Specified Substance Group 2 Name (Herbal Drug): *Harpagophytum zeyheri*, Root, Dry – Manufacturer AA.
Parent Substance Group 1 ID (Herbal Drug): [TE84K152PR]

Element Group Manufacturing
Manufacturer ID: MANDUNS452 (Artificial ID)
Manufacturer Name: Name, address, town, country (South Africa), GPS location
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

E.3.4.4 Specified Substance Group 3 information level for the Herbal Drug

Element Group: Specified Substance Group 3
Substance Type: Specified Substance Group 3
Specified Substance Group 3 ID (Herbal Drug): GGGGGGGGGG (Artificial ID)
Specified Substance Group 3 Name (Herbal Drug): *Harpagophytum procumbens and_or Harpagophytum zeyheri*, Root, Dry, Standardised
Parent Substance Group 1 ID (Herbal Drug): GHTDR6435H (Artificial ID)
(corresponding to the Specified Substance Group 1 Name (Herbal Drug): *Harpagophytum procumbens*, Root, Dry)

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Parent Substance Group 1 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
Grade Reference Source: Ph.Eur. monograph 01/2008:1095

E.3.4.5 Elements captured at the Specified Substance Group 1 level for the Herbal preparation (Extract, extended information)

Substance Type: Specified Substance Group 1
Specified Substance Group 1 ID (Herbal preparation): EXCTER654E (Artificial ID)
Specified Substance Group 1 Name (Herbal preparation):
Harpagophytum procumbens, Root, Dry Extract, Ethanol-Water (60-40 v/v) (1.5–3.0:1)

Element Group: Constituent
Substance ID: EEEEEEEEEE (Artificial ID
Substance Name: *Harpagophytum procumbens*, Root
Language: la
Substance Role: Parent

Element Group: Fraction
Material Type: Herbal
Fraction: Dry Extract
Country of Origin: South Africa, Namibia

Element Group: Herbal preparation Property Particulars
Extraction Solvent Composition: Ethanol 60% v/v
Substance ID: ETHAN98765 (Artificial ID)
Substance Name: Ethanol
Amount Type: Exact

Element Group: Amount
Average [Numeric Value]: 60
Unit: Volume per cent

Element Group: Herbal preparation Property Particulars (Repeat)
Extraction Solvent Composition: Ethanol 60% v/v
Substance ID: WATER67543 (Artificial ID)
Substance Name: Water
Amount Type: Exact

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Element Group: Amount
Average [Numeric Value]: 40
Unit: Volume per cent

Element Group: Herbal preparation Property Particulars (Repeat)
Drug Extract Ratio (DER): 1.5 – 3.0:1
Amount Type: Exact

Element Group: Amount
Average [Numeric Value]: 2.2
Low Limit: 1.5
High Limit: 3.0
Unit: g

Element Group: Constituent
Substance ID: 8KGS1DC5ZU (Artificial ID)
Substance Name: Harpagoside, ($C_{24}H_{30}O_{11}$; Mr. 494.5)
Language: en
Substance Role: Marker
Amount Type: Exact

Element Group: Amount
Average [Numeric Value]: 1.5
Low Limit: 1.5
Unit: Mass per cent m/m

NOTE Marker specification: Minimum 1.5 per cent dried extract
Final Blending: Lactose monohydrate, Silicium Dioxide
Standardisation: concentration of 2.5% Harpagoside relative to the finished extract preparation.

An extract made from the Harpagophytum zeyheri would require a separate Specified Substance Group1:

Substance Type: Specified Substance Group 1
Specified Substance Group 1 ID (Herbal preparation): UFR78E231Y (Artificial ID)
Specified Substance Group 1 Name (Herbal preparation): *Harpagophytum zeyheri*, Root, Dry Extract, Ethanol-Water (60-40 v/v) (1.5–3.0:1)

Element Group: Constituent
Substance ID: FFFFFFFFFF (Artificial ID)
Substance Name: *Harpagophytum zeyheri*, Root
Language: la
Substance Role: Parent

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Element Group: Fraction
Material Type: Herbal
Fraction: Dry Extract
Country of Origin: South Africa, Namibia

Element Group: Herbal preparation Property Particulars
Extraction Solvent Composition: Ethanol 60% v/v
Substance ID: ETHAN98765 (Artificial ID)
Substance Name: Ethanol
Amount Type: Exact

Element Group: Amount
Average [Numeric Value]: 60
Unit: Volume per cent

Element Group: Herbal preparation Property Particulars (Repeat)
Extraction Solvent Composition: Ethanol 60% v/v
Substance ID: WATER67543 (Artificial ID)
Substance Name: Water
Amount Type: Exact

Element Group: Amount
Average [Numeric Value]: 40
Unit: Volume per cent

Element Group: Herbal preparation Property Particulars (Repeat)
Drug Extract Ratio (DER): 1.5 – 3.0:1
Amount Type: Exact

Element Group: Amount
Average [Numeric Value]: 2.2
Low Limit: 1.5
High Limit: 3.0
Unit: g

Element Group: Constituent
Substance ID: 8KGS1DC5ZU (Artificial ID)
Substance Name: Harpagoside, ($C_{24}H_{30}O_{11}$; Mr. 494.5)
Language: en
Substance Role: Marker
Amount Type: Exact

Element Group: Amount
Average [Numeric Value]: 1.5

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Low Limit: 1.5
Unit: Mass per cent m/m

E.3.4.6 Elements captured at the Specified Substance Group 2 level for the Herbal preparation (Extract, extended information)

Substance Type: Specified Substance Group 2
Specified Substance Group 2 ID (Herbal preparation): AGHFT4352E (Artificial ID)
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.
Parent Substance Group 1 ID (Herbal preparation): EXCTER654E (Artificial ID)

Substance Type: Specified Substance Group 2
Specified Substance Group 2 ID (Herbal preparation): MZFTH564E (Artificial ID)
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.
Parent Substance Group 1 ID (Herbal preparation): TE84K152PR (Artificial ID)

Element Group: Manufacturing

Manufacturer ID: DUNS674521
Manufacturer Name: Name, address, town, country (South Africa), GPS location
Manufacturing Type: Manufacturer
Production Method Type: Extraction
Production Method Description[10]: Maceration with ethanol 60%, ultr-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

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.

E.3.4.7 Elements captured at the Specified Substance Group 3 level for the Herbal preparation (Extract, extended information)

Substance Type: Specified Substance Group 3
Specified Substance Group 3 ID (Herbal preparation): YUTDR4267E (Artificial ID)

[10] 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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Specified Substance Group 3 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., Standardised.

Parent Specified Substance Group 1 (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 Specified Substance Group 1 (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: Grade
Grade Type: Ph.Eur.
Grade Name: Devil's Claw Dry Extract
Grade Reference Source: Ph.Eur., 8th edition, monograph 01/2008:1871

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

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E.3.4.8 Summary of the Organisation of the information for Devil's Claw

Structurally Diverse Substance, Substance (fresh) and Herbal Drug			
Substance information level A Substance (fresh) is always a single species, or infraspecies, or is occasionally a single genus. It will have a Name which is composed of: [<Scientific genus/binomial/trinomial with Author>,<Part(s)>]			
Substance Type	Structurally Diverse (Herbal Substance)	Substance Type	Structurally Diverse (Herbal Substance)
Substance ID	DEVTYS543H (Artificial ID)	Substance ID	FGTE56432H (Artificial ID)
Substance Name	*Harpagophytum procumbens* (Burch.) DC. ex Meisn., Root [a)]	Substance Name	*Harpagophytum zeyheri* Decne., Root [b)]
Part	Tuberous root	Part	Tuberous root
Element Group Organism from which the Source Material is derived:		Element Group Organism from which the Source Material is derived:	
Genus	Harpagophytum	Genus	Harpagophytum
Species	procumbens	Species	zeyheri
Species Parenthetical Author	Burch.	Species Parenthetical Author	
Species Primary Author	DC. ex Meisn.	Species Primary Author	Decne.
Parent Substance Name	N/A	Parent Substance Name	N/A
Substance information level Information in accordance to a Pharmacopoeia (Ph.Eur.) for the Herbal Substance for which the ANNEX uses 'Herbal Drug'. It will have a Name which is composed of: [<Scientific genus/binomial/trinomial without 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)
Substance Name	*Harpagophytum procumbens*, Root	Substance Name	*Harpagophytum zeyheri*, Root
Part	Tuberous root	Part	Tuberous root
Parent Substance Name	*Harpagophytum procumbens* (Burch.) DC. ex Meisn., Root	Parent Substance Name	*Harpagophytum zeyheri* Decne., Root
Parent Substance ID	DEVTYS543H (Artificial ID)	Parent Substance ID	FGTE56432H (Artificial ID)
NOTE [a)] The scientific part of the name is: *Harpagophytum procumbens* (Burch.) DC. Ex Meisn.		NOTE [b)] The scientific part of the name is: *Harpagophytum zeyheri* Decne.	

Figure E.13 — Substance and Specified Substance Information Devil's Claw Root, Part I.

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Specified Substance Group 1 information level Information in accordance to a Pharmacopoeia (Ph.Eur.) for the 'Herbal Drug'. It will have a SSG1-Name which is composed of: [<Scientific genus/binomial/trinomial without Author>,<Part(s)><Fresh/Dry]			
Substance Type	Specified Substance Group 1	Substance Type	Specified Substance Group 1
Specified Substance Group 1 ID	GHTDR6435H (Artificial ID)	Specified Substance Group 1 ID	TE84K152PR (Artificial ID)
Specified Substance Group 1 Name	*Harpagophytum procumbens*, Root, Dry	Specified Substance Group 1 Name	*Harpagophytum zeyheri*, Root, Dry
Substance Name (Herbal Drug)	Devil's Claw Root	Substance Name (Herbal Drug)	Devil's Claw Root
Substance Name Type	Official	Substance Name Type	Official
Substance Name (Repeat) (Synonym)	Harpagophyti radix	Substance Name (Repeat) (Synonym)	Harpagophyti radix
Substance Name Type	Other	Substance Name Type	Other
Parent Substance Name	*Harpagophytum procumbens*, Root	Parent Substance Name	*Harpagophytum zeyheri*, Root
Parent Substance ID	CCCCCCCCCC (Artificial ID)	Parent Substance ID	DDDDDDDDDD (Artificial ID)
Elements Captured at the Specified Substance Group 1 Information level for the Herbal Drug - **See Element Group: Herbal Substance Particulars:** Degree of Comminution; Process State; Wild/Cultivated; Growth State; Harvesting Time; Decontamination Process; Country of Origin; Storage Time; Storage Condition - **See Element Group: Constituents:** Substance ID; Substance Name; Language; Substance Role (Markers); Amount Type and the element group Amount. Structural information of the constituents is inherited from the Element Group: Structure.			

Figure E.14 —Substance and Specified substance information Devil's Claw Root, Part II.

Specified Substance Group 2 information level for the Herbal Drug The SSG2-Name is composed of: SSG1-Name extended with the Manufacturer (Supplier) Name			
Substance Type	Specified Substance Group 2	Substance Type	Specified Substance Group 2
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	Substance Name	*Harpagophytum zeyheri*, Root, Dry – Manufacturer AA
Element Group Manufacturing			
Manufacturer ID	MANDUNS452 (Artificial ID)	Manufacturer ID	MANDUNS452 (Artificial ID)
Manufacturer Name	Company AA	Manufacturer Name	Company AA
Manufacturing Type	Harvester	Manufacturer Type	Harvester
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
Parent (Specified) Substance Group 1 Name	*Harpagophytum procumbens*, Root, Dry	Parent (Specified) Substance Name	*Harpagophytum zeyheri*, Root, Dry
Parent Substance ID	GHTDR6435H (Artificial ID)	Parent Substance ID	TE84K152PR (Artificial ID)
Specified Substance Group 3 information level for the Herbal Drug The SSG3-Name is composed of: SSG1-Name extended with the Pharmacopoeial Name			
Substance Type	Specified Substance Group 3		
Specified Substance Group 3 ID	GGGGGGGGGG (Artificial ID)		
Specified Substance Group 3 Name	*Harpagophytum procumbens and_or Harpagophytum zeyheri*, Root, Dry-Ph.Eur.		
Parent (Specified) Substance Group 1 Name	*Harpagophytum procumbens*, Root, Dry; *Harpagophytum zeyheri*, Root, Dry		
Parent (Specified) Substance Group 1 ID	GHTDR6435H (Artificial ID); TE84K152PR (Artificial ID)		
Element Group: Grade			
Grade Type	Ph.Eur.		
Grade name	Devil's Claw Root		
Grade Reference Source	Ph.Eur. monograph 01/2008:1095		

Figure E.15 — Substance and Specified substance information Devil's Claw Root, Part III.

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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 Type	Structurally Diverse (Herbal preparation)	Substance Type	Structurally Diverse (Herbal preparation)
Substance ID	EEEEEEEEEE (Artificial ID)	Substance ID	FFFFFFFFFF (Artificial ID)
Substance Name	*Harpagophytum procumbens*, Root, Extract	Substance Name	*Harpagophytum zeyheri*, Root, Extract
Parent Substance Name (Herbal Drug)	*Harpagophytum procumbens*, Root	Parent Substance Name (Herbal Drug)	*Harpagophytum zeyheri*, Root
Parent Substance ID	CCCCCCCCCC (Artificial ID)	Parent Substance ID	DDDDDDDDDD (Artificial ID)
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 Name which is composed of: **[<Scientific genus/binomial/trinomial without Author>,<Part(s)>,<Fraction>,<Dry/Liquid/Viscous>]**			
Substance Type	Structurally Diverse (Herbal Drug)	Substance Type	Structurally Diverse (Herbal Drug)
Substance ID	RGFSD7865L (Artificial ID)	Substance ID	JKHGR1234L (Artificial ID)
Substance Name	*Harpagophytum procumbens*, Root, Dry Extract	Substance Name	*Harpagophytum zeyheri*, Root, Dry Extract
Parent Substance Name (Herbal Preparation)	*Harpagophytum procumbens*, Root, Extract	Parent Substance Name (Herbal Preparation)	*Harpagophytum zeyheri*, Root, Extract
Parent Substance ID	EEEEEEEEEE (Artificial ID)	Parent Substance ID	FFFFFFFFFF (Artificial ID)
Elements Captured at the Specified Substance Group 1 Information level for the Herbal preparation with **limited information** - **See Element Group: Herbal Preparation Property Particulars:** Extraction Solvent Composition (limited qualitative information) - **See Element Group: Constituents:** Substance ID; Substance Name; Language; Substance Role (Markers); Amount Type and the element group Amount. Structural information of the constituents is inherited from the Element Group: Structure.			
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)>]**			
Substance Type	Structurally Diverse (Herbal Drug)	Substance Type	Structurally Diverse (Herbal Drug)
Substance ID	EXCTER654E (Artificial ID)	Substance ID	UFR78E231Y (Artificial ID)
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)
Fraction	Dry Extract	Fraction	Dry Extract
Extraction Solvent Composition	Ethanol-Water (60-40 v/v)	Extraction Solvent Composition	Ethanol-Water (60-40 v/v)
Herbal Substance Extract Ratio (DER)	1.5-3.0:1	Herbal Substance Extract Ratio (DER)	1.5-3.0:1
Constituent: Substance Name Substance Role	Harpagoside Marker substance [a]	Constituent: Substance Name Substance Role	Harpagoside Marker substance [a]
Parent Substance Name (Herbal preparation)	*Harpagophytum procumbens*, Root, Extract	Parent Substance Name (Herbal Drug)	*Harpagophytum zeyheri*, Root, Extract
Parent Substance ID	EEEEEEEEEE (Artificial ID)	Parent Substance ID	FFFFFFFFFF (Artificial ID)
Elements captured at the Specified Substance Group 1 Information level for the Herbal preparation with **Extended information** - **See Element Group: Herbal Preparation Property Particulars:** Extraction Solvent Composition (quantitative information) - **See Element Group: Constituents:** Substance ID; Substance Name; Language; Substance Role (Markers and specification); Amount Type and the Element Group Amount. Structural information of the constituents is inherited from the Element Group: Structure. NOTE [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; Standardisation: 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 standardised extract.			

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Figure E.16 — Substance and Specified substance information Devil's Claw Root Extract, Part I.

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Specified Substance Group 2 information level for the Herbal preparation with extended information The SSG2-Name is composed of: SSG1-Name extended with the Manufacturer (Supplier) Name			
Substance Type	Specified Substance Group 2	Substance Type	Specified Substance Group 2
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
Element Group Manufacturing			
Manufacturer ID	DUNS674521 (Artificial ID)	Manufacturer ID	DUNS674521 (Artificial ID)
Manufacturer Name	Company BB	Manufacturer Name	Company BB
Manufacturing Type	Manufacturer	Manufacturer 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
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 Name	*Harpagophytum zeyheri*, Root, Dry Extract Ethanol-Water (60-40 v/v),(1.5-3.0:1)
Parent Substance ID	EXCTER654E (Artificial ID)	Parent Substance ID	TE84K152PR (Artificial ID)
Specified Substance Group 3 information level for the Herbal preparation The SSG3-Name is composed of: SSG1-Name extended with the Pharmacopoeial Name			
Substance Type	Specified Substance Group 3		
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), Standardised-Ph.Eur.		
Parent Specified) Substance Group 1 Name	*Harpagophytum procumbens*, Root, Dry Extract, Ethanol-Water (60-40 v/v),(1.5-3.0:1) *Harpagophytum zeyheri*, *Root, Dry* Extract, Ethanol-Water (60-40 v/v),(1.5-3.0:1)		
Parent (Specified) Substance Group 1 ID	EXCTER654E (Artificial ID) UFR78E231Y (Artificial ID)		
Element Group: Grade			
Grade Type	Ph.Eur.		
Grade name	Devil's Claw Root Dry Extract		

Figure E.17—Substance and Specified substance information Devil's Claw Root Extract, Part II.

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E.4 Documentation and Explanation of Example 3

E.4.1 Example 3: Salvia Miltiorrhiza Root and Rhizome (BP=Ph.Eur.) and Chinese Salvia (USP), *continued*.

E.4.1.1 Specifications according to the USP and Ph.Eur.:

Chinese Salvia is defined in the USP as:

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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.4.3.2).
- 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.4.3.2).

The specifications of the markers are slightly different and therefore there will be two different Specified Substances Group 1 and Group 3.

NOTE 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 should be defined capturing the Ph.Eur. specifications and Grade at SSG3 and a separate extraction method should be defined covering the USP specifications and Grade at SSG3. In this case two SSG1 and SSG3 ID's 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.

NOTE 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.8.

NOTE 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: Maker A, pharmacopoeia 1, specification for the extract is ≥ 2.0 mg/g extract.
Maker A, pharmacopoeia 2, specification for the extract is ≥ 2.5 mg/g extract.
In house specification is defines 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 1.33-1.35., with a specification for the marker: Rosmarinic acid: NLT (≥) 1.86 mg/g.

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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.4.1.2 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, see Figure E.18.

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.19.



Figure E.18 — Salvia miltiorrhiza



Figure E.19 — 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 – 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); NLT 3.0 %
- Tanshinone IIA (Molecular formula: C_{19} H_{18} O_3; *Mr*: 294.3); 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)-

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CAS No.: 20283-92-5; Molecular formula: C_{18} H_{16} O_8; *Mr*: 360.3 g/mol.

E.4.2 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:

Manufacturer of Herbal preparation: Manufacturer GHT.

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 1.33-1.35.

Specification: Analytical marker: Rosmarinic acid: NLT 1.86 mg/g

E.4.3 Organisation of the information according to ISO 11238 and ISO/TS 19844

E.4.3.1 Substance information level

E.4.3.1.1 Substance (fresh)

Substance Type: Structurally Diverse (Herbal Substance)
Substance ID: SALV7356YS (Artificial ID)

Element Group: Substance Name
Substance (fresh) Name: *Salvia miltiorrhiza* Bunge, Rhizome and Root
Substance Name Type: Other
Language: la

Element Group: Substance Name (Repeat)
Substance Name: *Salvia miltiorrhiza* Bunge
Substance Name Type: Scientific
Language: la

Element Group: Source Material:

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Organism ID: SALVI765432 (Artificial ID)
Organism Name: *Salvia miltiorrhiza* Bunge

Element Group: Organism
Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Lamiales
Family: Lamiaceae
Genus: Salvia
Species: miltiorrhiza
Species Primary Author: Bunge

Element Group: Part Description
Part: Rhizome; Root

E.4.3.1.2 Substance (Herbal Drug)

Substance Type: Structurally Diverse (Herbal Drug)
Substance (Herbal Drug) ID: HHHHHHHHHH (Artificial ID)

Element Group: Substance Name
Substance (Herbal Drug) Name: *Salvia miltiorrhiza*, Rhizome and Root
Substance Name Type: Official
Language: la

Element Group: Reference Source
Public Domain: Yes
Reference Source Type: Ph.Eur.
Reference Source Class: Official name souce
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 souce

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

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Substance Name Type: Other
Language: cn

Element Group: Source Material:
Parent Substance ID: SALV7356YS (Artificial ID)
Parent Substance 9fresh) Name: *Salvia miltiorrhiza* Bunge, Rhizome and Root

Element Group: Part Description
Part: Rhizome and Root

E.4.3.1.3 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
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
Material Type: Herbal
Fraction: Extract
Geographical Region: Shaanxi Province of China

E.4.3.2 Specified Substance Group 1 information level (Herbal Drug)

Substance Type: Specified Substance Group 1
Specified Substance Group 1 ID: HJYTRE876S (Artificial ID)
Specified Substance Group 1 Name: *Salvia miltiorrhiza*, Rhizome and Root, Dry

Element Group: Substance Name
Substance Name: Salvia miltiorrhiza Root and Rhizome
Substance Name Type: Official
Language: en

Element Group: Reference Source
Public Domain: Yes

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Reference Source Type: Ph.Eur.
Reference Source Class: Official name souce
Reference Source Citation: Ph.Eur.: 04/2013:2663

Element Group: Substance Name (repeat)
Substance Name: Chinese Salvia
Substance Name Type: Official
Language: en

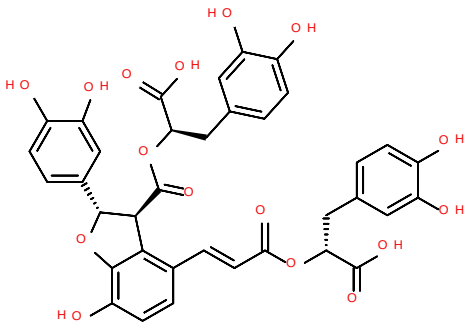
Element Group: Reference Source (Repeat)
Public Domain: Yes
Reference Source Type: USP, Dietary Supplements
Reference Source Class: Official name souce

Element Group: Constituent
Substance ID (Herbal Drug): HHHHHHHHHH (Artificial ID)
Substance Name (Herbal Drug): *Salvia miltiorrhiza*, Rhizome and Root
Substance Role: Parent Substance

Element Group: Herbal Particulars
Degree of Comminution: Dried, fragmented rhizome and root, 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
Geographical Region: Shaanxi Province of China
Storage Time: N/A
Storage Conditions: The harvested material is dried at 50°C – 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):

Substance ID: C1GQ844199 (Artificial ID)
Substance Name: Salvianolic acid B (Mol. Form.: $C_{36}H_{30}O_{16}$; Mr: 718.6)
Substance Role: Marker

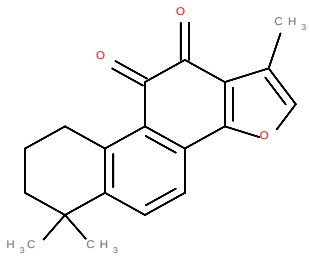


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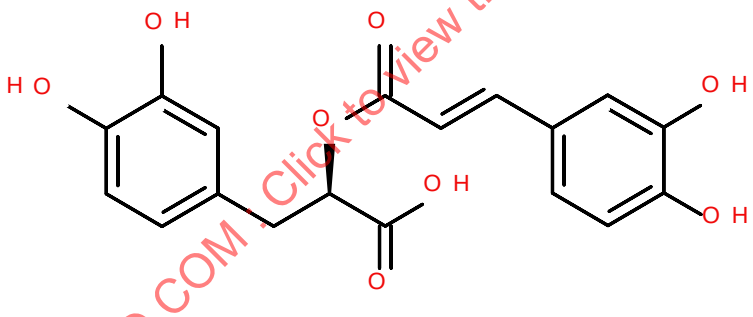
Element Group: Amount
Low Limit: NLT 3%

Element Group: Constituent
Substance ID: 4GPC9FQG6L (UNII)
Substance Name: Tanshinone IIA (Mol. Form.: C_{19} H_{18} O_3; Mr: 294.3)
Substance Role: Marker



Element Group: Amount
Low Limit: NLT 0.12%

Element Group: Constituent (Repeat)
Substance ID: MQE6XG29YI (UNII)
Substance Name: Rosmarinic acid, Mol. Form.: C_{18} H_{16} O_8; Mr: 360.3 g/mol.
Substance Role: Marker Substance



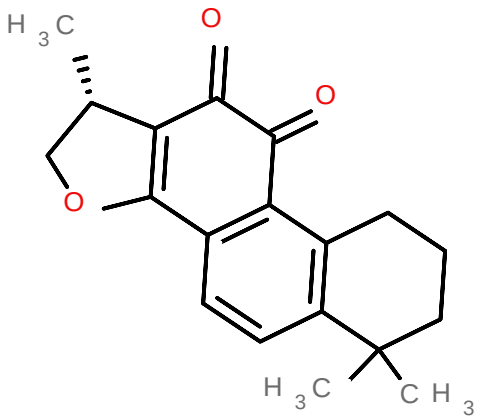
Systematic Name: Benzenepropanoic acid,.alpha. [[(2E)-3-(3.4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]-3,4-dihydroxy-, (.alpha.R)-

Element Group: Amount
Low Limit: NLT 0.17%
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.

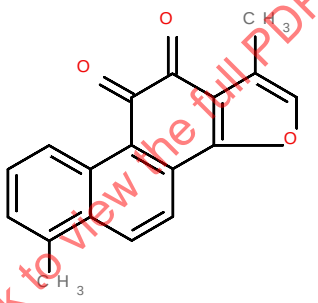
Element Group: Constituent (Repeat)
Substance ID: 5E9SXT166N (UNII)
Substance Name: Cryptotanshinone
Substance Role: Marker

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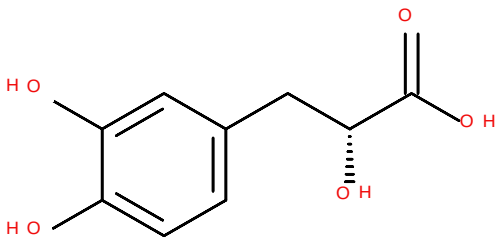
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Element Group: Constituent (Repeat)
Substance ID: 03UUH3J385 (UNII)
Substance Name: Tanshinone I
Substance Role: Marker



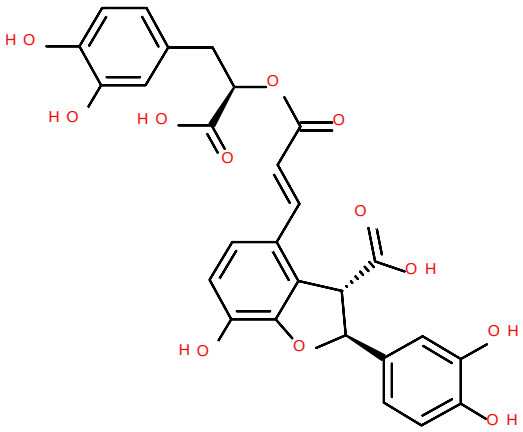
Element Group: Constituent (Repeat)
Substance ID: 4GF33A5PAJ (UNII)
Substance Name: Danshensu
Substance Role: Marker



Element Group: Constituent (Repeat)
Substance ID: 100IP83JAC (UNII)
Substance Name: Lithospermic acid
Substance Role: Marker

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E.4.3.3 Specified Substance Group 2 information level (Herbal Drug)

Substance Type: Specified Substance Group 2
Specified Substance Group 2 (Herbal Drug) ID: TYGD6754UY (Artificial ID)
Specified Substance Group 2 (Herbal Drug) Name: *Salvia miltiorrhiza*, Rhizome and Root, Dry---Manufacturer GHT
Parent Substance ID: HJYTRE876S (Artificial ID), (Herbal Drug, SSG1)

Element Group: Manufacturer
Manufacturer ID: DUNS654321 (Artificial ID)
Manufacturer Name: Name, address, town, Country (China), GPS location
Manufacturing Type: Harvester
Production Method Type: Harvesting
Production Method Description: Collecting and Harvesting, drying and storing of the Herbal Drug

E.4.3.4 Specified Substance Group 3 information level (Herbal Drug)

Substance Type: Specified Substance Group 3
Specified Substance Group 3 ID (Herbal Drug): HJGFDT67EP (Artificial ID)
Specified Substance Group 3 Name: *Salvia miltiorrhiza*, Rhizome and Root, Dry, Quantified-Ph.Eur.
Parent Substance ID: HJYTRE876S (Artificial ID), (Herbal Drug, SSG1)

Element Group: Grade
Grade Type: Ph.Eur.
Grade Name: *Salvia Miltiorrhiza* Root and Rhizome
Grade Reference Source: Ph.Eur. monograph 04/2013:2663

Substance Type: Specified Substance Group 3
Specified Substance Group 3 ID (Herbal Drug): GHFTE653US (Artificial ID)
Specified Substance Group 3 Name (Herbal Drug): *Salvia miltiorrhiza*, Rhizome and Root, Dry, Quantified–USP
Parent Substance ID: HJYTRE876S (Artificial ID), (Herbal Drug, SSG1)

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Element Group: Grade
Grade Type: USP
Grade Name: Chinese Salvia
Grade Reference Source: 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.4.4 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)
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 TS in the Specified Substance Group 1 Name of the Herbal preparation.

Element Group: Constituent
Substance ID: KKKKKKKKKK (Artificial ID)
Substnace Name: *Salvia miltiorrhiza*, Rhizome and Root, Soft Extract
Language: en
Substance Role: Parent
Amount Type: N/A

Element Group: Fraction
Material Type: Herbal
Fraction: Soft Extract
Geographical Region: Shaanxi Province China

Element Group: Herbal preparation Particulars
Extraction Solvent Composition: Ethanol 90% v/v
Substance ID: ETHAN98765 (Artificial ID)
Substance Name: Ethanol
Amount Type: Exact

Element Group: Amount
Average [Numeric Value]: 90
Unit: Volume per cent

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Element Group: Herbal preparation Particulars (Repeat)
Extraction Solvent Composition: Ethanol 90% v/v
Substance ID: WATER67543 (Artificial ID)
Substance Name: Water
Amount Type: Exact

Element Group: Amount
Average [Numeric Value]: 10
Unit: Volume per cent

Element Group: Herbal preparation Particulars (Repeat)
Drug Extract Ratio (DER): 4.5-6.0:1
Amount Type: Average

Element Group: Amount
Average [Numeric Value]: 5.2
Low Limit: 4.5
High Limit: 6.0
Unit: g

Element Group: Constituent
Substance ID: C1GQ844199 (UNII)
Substance Name: Salvianolic acid B ($C_{36}H_{30}O_{16}$; Mr 719)
Language: en
Substance Role: Marker Substance
Amount Type: Exact

Element Group: Amount
Average: 1.5
Low Limit: 3.0
Unit: Mass per cent

Element Group: Constituent (Repeat)
Substance ID: 4GPC9FQG6L (UNII)
Substance Name: Tanshinone IIA ($C_{19}H_{18}O_3$; Mr 294.3)
Language: en
Substance Role: Marker Substance
Amount Type: Exact

Element Group: Amount

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Average: 0.12
Low Limit: 0.12
Unit: Mass per cent

Element Group: Constituent (Repeat)

Substance ID: MQE6XG29YI (UNII)
Substance Name: Rosmarinic acid BP-spec.: NLT 0.17 %

Language: en
Substance Role: Analytical marker
Amount Type: Exact

Element Group: Amount
Average: 0.17
Low Limit: 0.17
Unit: Mass per cent

E.4.4.1 Specified Substance Group 2 information level of the Herbal preparation (Extract, extended information)

Specified Substance: Specified Substance Group 2
Specified Substance Group 2 ID (Herbal preparation): SALTU2345M (Artificial ID)
Specified Substance Group 2 (Herbal preparation) Name: *Salvia miltiorrhiza*, Rhizome and Root, Soft Extract, Ethanol-Water (90-10 v/v) (4.5–6.0:1)---Manufacturer FDG
Parent Substance Group 1 (Herbal preparation) ID: [SAJT6754DS (Artificial ID)

Element Group: Manufacturing
Manufacturer ID: D.U.N.S.89765M (Artificial ID)
Manufacturer Name: Name, address, town, Country (China), GPS code
Manufacturing Type: Soft Extract
Production Method Type: Extraction
Production Method Description[11]: (see Figure E.8).

NOTE A flow chart of the extraction method used in for the Herbal preparation is provided in Figure E.8.

[11] 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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E.4.4.2 Specified Substance Group 3 information level (Herbal preparation)

Substance Type: Specified Substance Group 3
Specified Substance Group 3 ID (Herbal preparation): LLLLLLLLLL (Artificial ID)
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
Parent Substance Group 1 ID (Herbal preparation): SAJT6754DS (Artificial ID)

Element Group: Grade
Grade type: In House
Grade Reference Source: Regulatory Submission
Grade Name: Salvia Miltiorrhiza Extract

E.5 Documentation and Explanation of Example 4

E.5.1 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.5.1.1 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).

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.5.1.2 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 ID (Herbal preparation): HJFTE78543 (Artificial ID)
Substance (Herbal preparation) Name: *Olea europaea*, Fruit, Oil
Substance Name Type: Other

Substance Name: Olive Oil, Virgin

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Substance Name Type: Official

NOTE For further elements see B.8.2.7.

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
Material Type: Herbal
Fraction: Oil

NOTE The value Oil is appropriate here. The fraction (Herbal preparation) is valid for: Oil, Exudate, Juice (see also Figure E.20).

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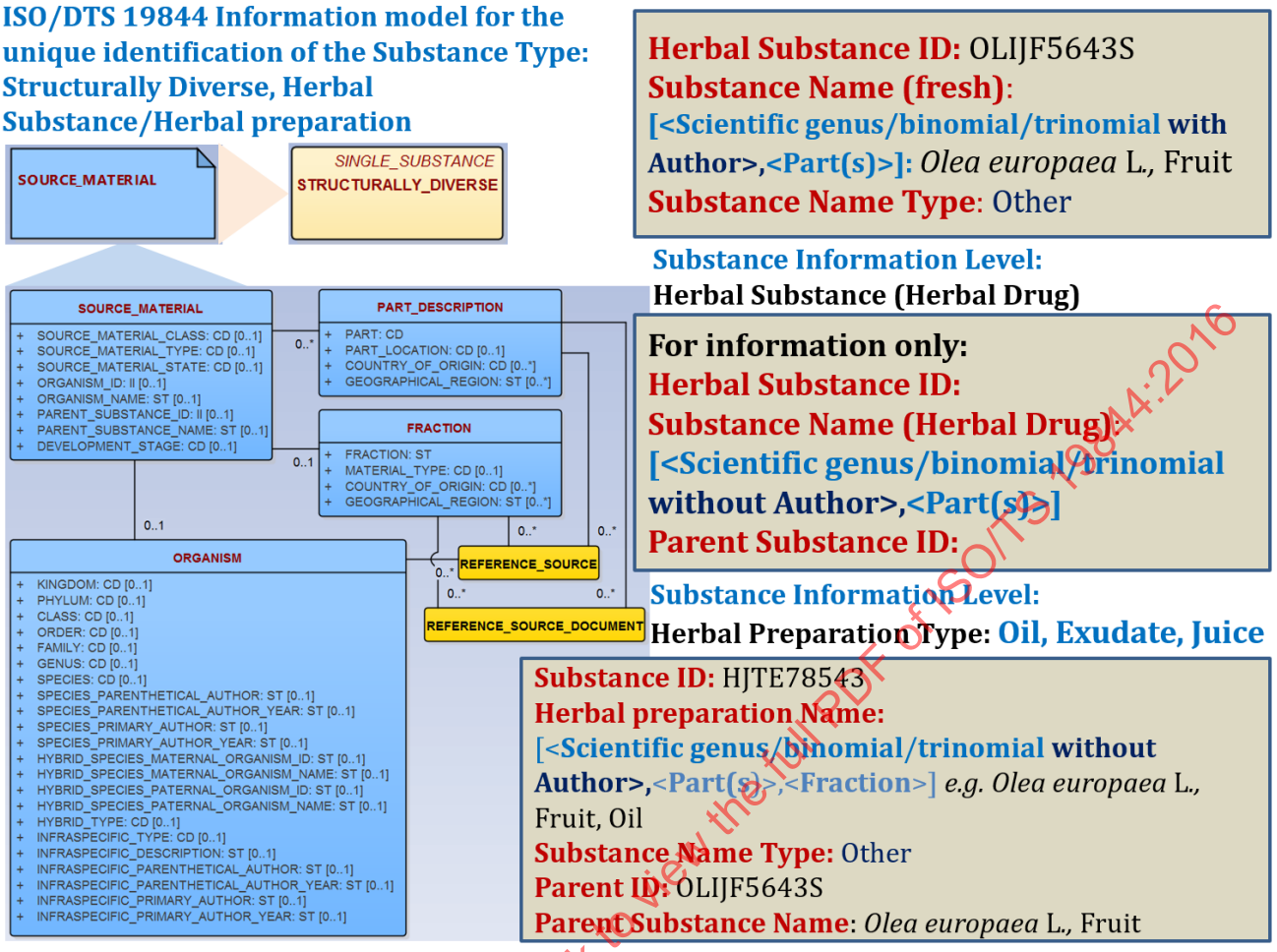


Figure E.20: The relationships between the ISO 11238, ISO/TS 19844 Structurally diverse description and the Substance (fresh) and Substance (Herbal preparation) for Olive Oil, Virgin.

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 in the ISO 11238 can be found in the Figure B.28 and Figure B.29 of the Annex B/Chemical Substances.

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E.5.1.3 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.

Substance Type: Specified Substance Group 3
Specified Substance Group 3 ID (Herbal preparation): JFGDRW4526 (Artificial ID)
Specified Substance Group 3 Name (Herbal preparation): Olive Oil, Virgin-Ph.Eur.
Parent Substance ID (Herbal preparation): HJFTE78543 (Artificial ID)

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
Grade Reference Source: 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.8.2.

E.6 Documentation and Explanation of Example 5

E.6.1 JP XVI monograph Shakuyakukanzoto Extract, see Figure E.21.

It consists of the two Herbal Drugs Peony Root (JP) and Glycyrrhiza (JP).

The Extract is prepared from 5 – 6 g of both the “Crude” Drugs and is finally quantified to 50 mg – 150 mg Peoniflorin ($C_{23}H_{28}O_{11}$, Mr 480.5) and 50 – 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.21.

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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 150 mg of peoniflorin ($C_{23}H_{28}O_{11}$: 480.46), and not less than 50 mg and not more than 150 mg 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 or 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 odor, and a sweet taste.

Figure E.21: Display of the Shakuyakukanzoto Extract with reference to the Japanese pharmacopoeia XVI.

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E.6.2 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, pulverised 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, pulverised to suitable sizes, according to the prescription and heat for a certain period of time after adding 10 - 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

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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.6.3 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- 20 cm in length, 1 - 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.

Identification: (1) Shake 0.5 g of pulverised Peony Root with 30 mL of ethanol (95) for 15 minutes, 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 ($C_{42}H_{62}O_{16}$: 822.93), calculated on the basis of dried material.

Description: Nearly cylindrical pieces, 0.5- 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

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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 pulverised Glycyrrhiza add 10 mL of a mixture of ethanol (95) and water (7:3), heat by shaking in a water bath for 5 minutes, cool, filter, and use the filtrate as the sample solution. Separately, dissolve 5 mg of Glycyrrhizinic 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.6.4 Organisation 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 class Herbal Substance Particulars and Herbal preparation Property Particulars). In addition, the JP "Kampo Code" is always mandatory in the JP jurisdiction.

E.6.4.1 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:

E.6.4.1.1 Substance (Fresh)

Element Group: Substance
Substance Type: Structurally Diverse (Herbal Substance)
Substance ID: HGTDE7634F (Artificial Code)

Element Group: Substance Name
Substance (fresh) Name: *Glycyrrhiza glabra* L., Root and Stolon

Element Group: Substance Name (Repeat)
Substance name: *Glycyrrhiza glabra* L.
Substance Name Type: Scientific
Language: en

Element Group: Source Material
Organism ID: GLYZ897650 (Artificial ID)
Organism Name: *Glycyrrhiza glabra* L.

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Element Group: Organism
Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Fabales
Family: Fabaceae (*Leguminosae*)
Genus: Glycyrrhiza
Species: glabra
Species Primary Author: L.

Element Group: Part Description
Part: Root and Stolon[12]

E.6.4.1.2 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

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
Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Fabales
Family: Fabaceae (*Leguminosae*)
Genus: Glycyrrhiza
Species: uralensis
Species Primary Author: Fisch. ex DC.

[12] NOTE Root and Stolon with (unpeeled) or without (peeled) periderm

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E.6.4.1.2.1 Substance (Herbal Drug)

Element Group: Substance

Substance Type: Structurally Diverse (Herbal Substance)
Substance ID: MMMMMMMMMM (Artificial ID)

Element Group: Substance Name
Substance (Herbal Drug) name: *Glycyrrhiza glabra*, Root and Stolon
Substance Name Type: Official
Language: la

Element Group: Official Name
Official Name Type: JP
Official Name Status: Current
Official Name Domain: Drug
Official Name Jurisdiction: JP

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[13]

Element Group: Code
Code: TRE3 (Artificial code)

[13] NOTE Root and Stolon with (unpeeled) or without (peeled) periderm

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Code System: Kampo Code
Code ID: 0051
Code System Status: Active

E.6.4.2 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.

Substance Type: Specified Substance Group 1
Specified Substance ID: GAKYT5643S (Artificial ID)
Specified Substance Group 1 Name (Herbal Drug): Glycyrrhiza *glabra*, Root and Stolon, Dry

Element Group: Substance Name
Substance Name: Glycyrrhiza radix
Substance Name Type: Official
Language: la

Element Group: Official Name
Official Name Type: JP
Official Name Status: Current
Official Name Jurisdiction: JP

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
Substance ID: MMMMMMMMMM (Artificial ID)
Substance Name: *Glycyrrhiza glabra*., Root and Stolon
Language: LA
Substance Role: Parent Substance

Element Group: Code
Code: TRE4 (Artificial code)
Code System: Kampo Code
Code ID: 0051
Code System Status: Active

Element Group: Herbal Substance Particulars[14]
Process State: (dry or fresh, processed peeled or unpeeled Roots and Stolons

[14] NOTE This class is conditional based on Jurisdictional regulation. For example, this class is optional in the JP jurisdiction.

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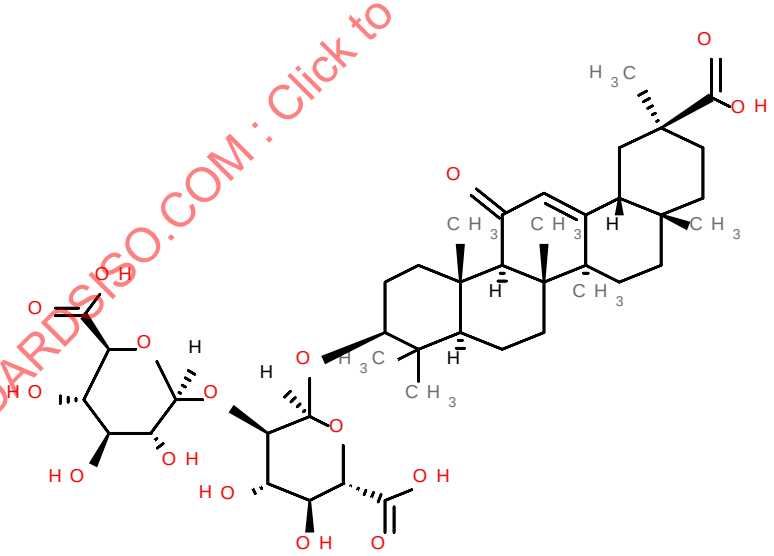
Wild/cultivated: N/A
Countries of origin: N/A
Growth state: N/A
Harvesting time: N/A

Capturing a marker specification of NLT 2.5%, calculated on basis of the dried material of Glycyrrhizic acid is shown below:

Element Group: Constituent (Repeat
Substance ID: 6FO62043WK (UNII)
Substance Name: Glycyrrhizic acid [$C_{42}H_{62}O_{16}$; Mw = 822.9]
Language: en
Substance Role: Marker
Amount Type: Numeric Value

Element Group: Amount
Average (Numeric value): 2.5
Low Limit: 2.5
High Limit: N/A
Unit: Mass per cent

Element Group: Structure
Structural Representation Type: Full
Structural representation attachment: See image below:



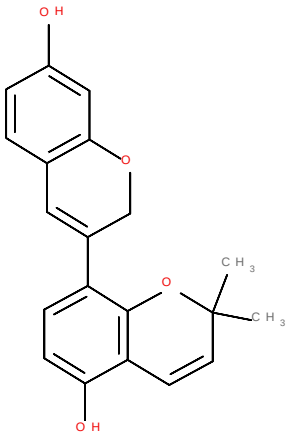
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In addition to marker substances additional constituents of each herbal extract should be captured and linked to the extract if significant biological activity has been attributed to them. The two substances below are substances from liquorice root shown to have estrogenic activity.

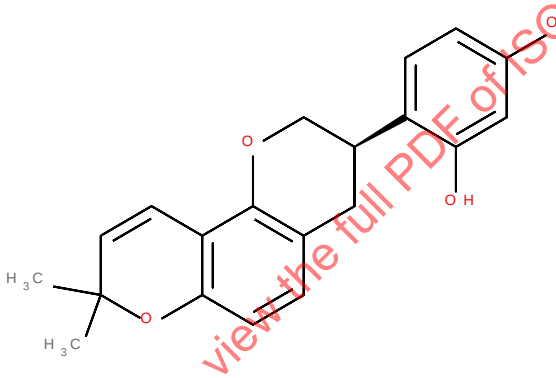
- Substance ID: C6Y321Q75O (Artificial ID)

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- Constituent: Glabrene



- Substance ID: HOC5567T41 (Artificial ID)
- Constituent: Glabridin



E.6.4.3 Information captured at the Substance level for Peony Root (JP)

Substance (fresh)
Substance Type: Structurally Diverse (Herbal Substance)
Substance ID: PEOGHDR78S (Artificial ID)

Element Group: Substance Name
Substance (fresh) name: *Paeonia lactiflora* Pall., Root

Element Group: Substance Name (Repeat)
Substance Name: *Paeonia lactiflora* Pall.
Substance Name Type: Scientific

Element Group: Source Material
Organism ID: KLJIR78634 (Artificial ID)
Organism Name: *Paeonia lactiflora* Pall.

Element Group: Organism
Kingdom: Plantae

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Phylum: Tracheophyta
Class: Magnoliopsida
Order: Saxifragales
Family: Paeoniaceae
Genus: Paeonia
Species: lactiflora
Species Primary Author: Pall.

Element Group: Part Description
Part: Root

Substance (Herbal Drug)
Substance Type: Structurally Diverse (Herbal Drug)
Substance ID: PPPPPPPPPP (Artificial ID)

Element Group: Substance Name
Substance name (Herbal Drug): *Paeonia lactiflora*, Root

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
Official Name Domain: Drug
Official Name Jurisdiction: JP

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

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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)
Parent Substance (fresh) Name: *Paeonia lactiflora* Pall., Root

Element Group: Code
Code: PAE1 (Artificial code)
Code System: Kampo Code
Code ID: 0051
Code System Status: Active

E.6.4.4 Information captured at the Group 1 Specified Substance level for the Herbal Drug Peony Root (JP)

Substance Type: Specified Substance Group 1
Specified Substance ID: YUTD65489P (Artificial ID)

Element Group: Specified Substance Name
Specified Substance Group 1 Name (Herbal Drug): *Paeonia lactiflora*, Root, Dry

Element Group: Constituent
Substance ID: PPPPPPPPPP (Artificial ID)
Substance Name: Parent Substance Name (Herbal Drug): *Paeonia lactiflora*, Root
Language: la
Substance Role: Parent

Element Group: Code
Code: YTRW2 (Artificial code)
Code System: Kampo Code
Code ID: 0051
Code System Status: Active

Element Group: Herbal Substance Particulars[15]

- Process State: (dry or fresh, processed peeled or unpeeled Roots and Stolons
- Wild/cultivated: N/A
- Countries of origin: N/A
- Growth state: N/A

[15] This class is conditional based on Jurisdictional regulations. For example, this class will be optional in the JP jurisdiction.

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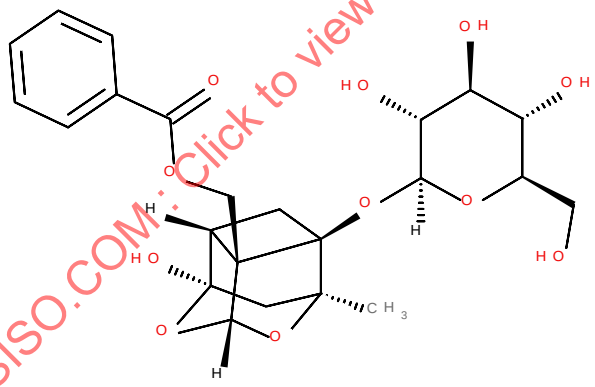
- Harvesting time: N/A

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
Substance ID: 21AIQ4EV64 (Artificial ID)
Substance Name: Peoniflorin ($C_{23}H_{28}O_{11}$, Mr 480.46)
Language: en
Substance Role: Marker
Amount Type: Numeric Value

Element Group: Amount
Average (Numeric value): 2.0
Low Limit: 2.0
High Limit: N/A
Unit: Mass per cent

Element Group: Structure
Structural Representation Type: Full
Structural Representation Attachment: See image below:



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E.6.4.5 Information captured at the Substance level for the Herbal preparation Shakuyakukanzoto Extract

Substance (Herbal preparation)
Substance Type: Structurally Diverse (Herbal Substance)
Substance ID: RRRRRRRRRR (Artificial ID)

Element Group: Substance Name
Substance Name (Herbal preparation): Shakuyakukanzoto Extract

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Substance Type: Official
Language: en

Element Group: Official Name
Official Name Type: JP
Official Name Status: Current
Official Name Domain: Drug
Official Name Jurisdiction: JP

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: Code
Code: SHE3 (Artificial code)
Code System: Kampo Code
Code ID: 0051
Code System Status: Active

E.6.4.6 Information captured at the Group 1 Specified Substance level for Shakuyakukanzoto Extract (JP)

Substance Type: Specified Substance Group 1
Specified Substance ID: EUYTS6725C (Artificial ID)
Specified Substance Group 1 Name: Shakuyakukanzoto Dry or Viscous Aqueous Extract[16]

Element Group: Constituent
Substance ID: RRRRRRRRRR (Artificial ID)
Substance Name (Herbal preparation): Shakuyakukanzoto Extract
Substance Role: Parent
Amount: N/A

Element Group: Fraction

[16] In the EU and US jurisdictions, the Specified Substance Group 1 Name should read: Shakuyakukanzoto, Dry or Viscous Aqueous Extract corresponding to 50 mg – 150 mg Peoniflorin and Glycyrrhizic Acid per 5-6 g Peony Root and 5-6 g Glycyrrhiza. In this example only Glycyrrhiza glabra, root and stolon is supposed to be used.

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Material Type: Herbal
Fraction: Extract
Country: JP

Element Group: Herbal preparation Property Particulars
Extraction Solvent Composition Composition: Water
Substance ID: WATER67543 (Artificial ID)
Substance Name: Water
Amount: N/A

Element Group: Herbal preparation Property Particulars (Repeat)
Drug Extract Ratio (DER): N/A (Optional)[17]

Element Group: Constituent[18]
Substance ID: 21AIQ4EV64 (Artificial ID)
Substance Name: Peoniflorin ($C_{23}H_{28}O_{11}$, Mr 480.46)
Language: en
Substance Role: Marker
Amount Type: Numeric Value

Element Group: Amount
Average (Numeric value): 2.0
Low Limit: 8.3
High Limit: 30
Unit: g

Element Group: Constituent (Repeat)[19]
Substance ID: 21AIQ4EV64 (Artificial ID)
Substance Name: Peoniflorin ($C_{23}H_{28}O_{11}$, Mr 480.46)
Language: en
Substance Role: Marker
Amount Type: Numeric Value

Element Group: Amount
Average (Numeric value): 2.0
Low Limit: 8.3

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[17] This element is optional for the Japanese jurisdiction

[18] 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 – 150 mg Peoniflorin per 5 – 6 g Peony Root
50 mg – 150 mg Glycyrrhizic acid per 5 – 6 g Glycyrrhiza

[19] Information on the markers: as described above

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High Limit: 30
Unit: g

Element Group: Constituent (Repeat)
Substance ID: 6FO62043WK (UNII)
Substance Name: Glycyrrhizic acid [$C_{42}H_{62}O_{16}$; Mw = 822.9]
Language: en
Substance Role: Marker
Amount Type: Numeric Value

Element Group: Amount
Average (Numeric value): 2.0
Low Limit: 8.3
High Limit: 30
Unit: g

E.6.4.7 Information captured at the Specified Substance Group 2 level for Shakuyakukanzoto Extract (JP)

Substance Type: Specified Substance Group 2
Specified Substance Group 2 ID: [HGTSIY876H]
Specified Substance Group 2 Name: Shakuyakukanzoto Dry or Viscous Aqueous Extract–Manufacturer THP
Parent Substance Group 1 ID: EUYTS6725C (Artificial ID)

NOTE Parent Substance Group 1 Name: Shakuyakukanzoto Dry or Viscous Aqueous Extract

Element Group: Manufacturing
Manufacturer ID: DUNS987654 (Artificial ID)
Manufacturer Name: Name, address, town, Country, GPS code.
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 Proces Version number: 1

E.6.4.8 Information captured at the Group 3 Specified Substance level for Shakuyakukanzoto Extract (JP)

Substance Type: Specified Substance Group 3
Specified Substance Group 3 ID: GHFTE8675G (Artificial ID)
Specified Substance Group 3 Name: Shakuyakukanzoto Dry or Viscous Aqueous Extract

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Element Group: Grade
Grade Name: Shakuyakukanzoto Extract
Grade Type: JP, ed. XVI
Grade Reference Source: Japanese Pharmacopoeia

E.7 General Information on the use of Glycyrrhiza species and their constituents

On the website of the European Medicines Agency, there is an assessment report[20] 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[21]

List of references: List of references supporting the assessment of *Glycyrrhiza glabra* L. and/or *Glycyrrhiza inflata* Bat. and/or *Glycyrrhiza uralensis* Fisch, radix[22]

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.

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

[20] Assessment report: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2012/08/WC500131285.pdf

[21] Reference: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/herbal/medicines/herbal_med_000132.jsp&mid=WC0b01ac058001fa1d)

[22] 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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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).



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_r823) (dried drug)

EP monograph no. 277

Figure E.22 — 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 (WHO 1999).

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* (Nomura et al. 2002). *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 (4–20%), mostly glycyrrhizin, a mixture of potassium and calcium salts of 18β-glycyrrhizic acid (also known as glycyrrhizic or glycyrrhizinic acid and a glycoside of glycyrrhetinic acid), which is 50 times sweeter than sugar. Other triterpenes present are liquiritic acid, glycyrretol, glabrolide, isoglaborlide and liquorice acid (Isbrucker & Burdock 2006).

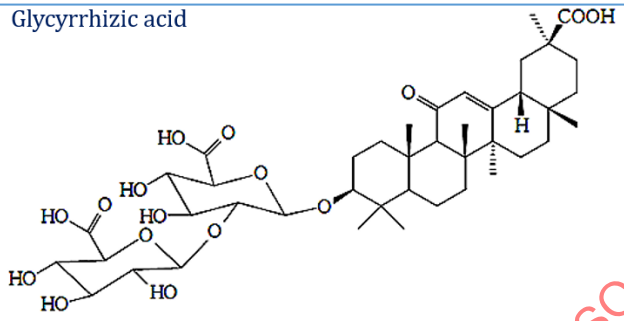
18β-glycyrrhizic acid (3-O-(2-O-β-d-glucopyranuronosyl–α-d-glucopyranurosyl)-3-β-hydroxy-11-oxo-18β,20β-olean-12-en-29-oic acid) was isolated for the first from the roots of *Glycyrrhiza glabra* by Ronbiquet (1809) who called it glycyrrhizin. The name of glycyrrhizic acid was given later by Roussin (1876) (Benigni et al. 1964). It is a monodesmoside, which on hydrolysis releases two molecules of D-glucuronic acid and the aglycone 18β-glycyrrhetic (glycyrrhetinic) acid (enoxolone) (WHO 1999). 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 (Benigni et al. 1964).

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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 cyclisation 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 (Seki et al. 2008).

Glycyrrhizic acid



IUPAC-name: 20β-Carboxy-11-oxo-30-norolean-12-en-3β-yl-2-O-β-D-glucopyranuronosyl-α-D-glucopyranosiduronic acid

Figure E.23 — Representative Structure of Glycyrrhizinic 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 (Zhang & Ye 2009).

Flavonoids are responsible for the yellow colour of liquorice. They include liquiritin, liquiritigenin, rhamnoliquiritin, neoliquiritin, chalcones, isoliquiritin, isoliquiritigenin, neoisoliquiritin, licuraside, glabrolide and licoflavonol (Williamson, 2003). 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 (Li et al. 2005).

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 (Kinoshita et al. 2005).

Coumarins

Coumarins include liqcoumarin, glabrocoumarone A and B, herniarin, umbelliferone, glycyrin, glycocoumarin, licofuranocoumarin, licopyranocoumarin and glabrocoumarin (Kinoshita et al. 2005).

Other compounds

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Minor components occur in amounts that vary depending on the species and geographical location (WHO 1999). 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 (Sultana et al. 2010). 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 (Näf & Jaquier 2006).

E.7.1 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 (Isbrucker & Burdock 2006).

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 (Asl & Hosseinzadeh 2008).

The European Pharmacopoeia reports the following liquid and dry extracts:

Liquorice ethanolic liquid extract, standardised (*Liquiritiae extractum fluidum ethanolicum normatum*), which is produced from the Herbal Drug by a suitable procedure for liquid extracts using ethanol (70 per cent 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. The eluates of several percolators are combined (see Figure E.24).

Extraction solvent: Ethanol –Water (30 – 70 v/v);

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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.

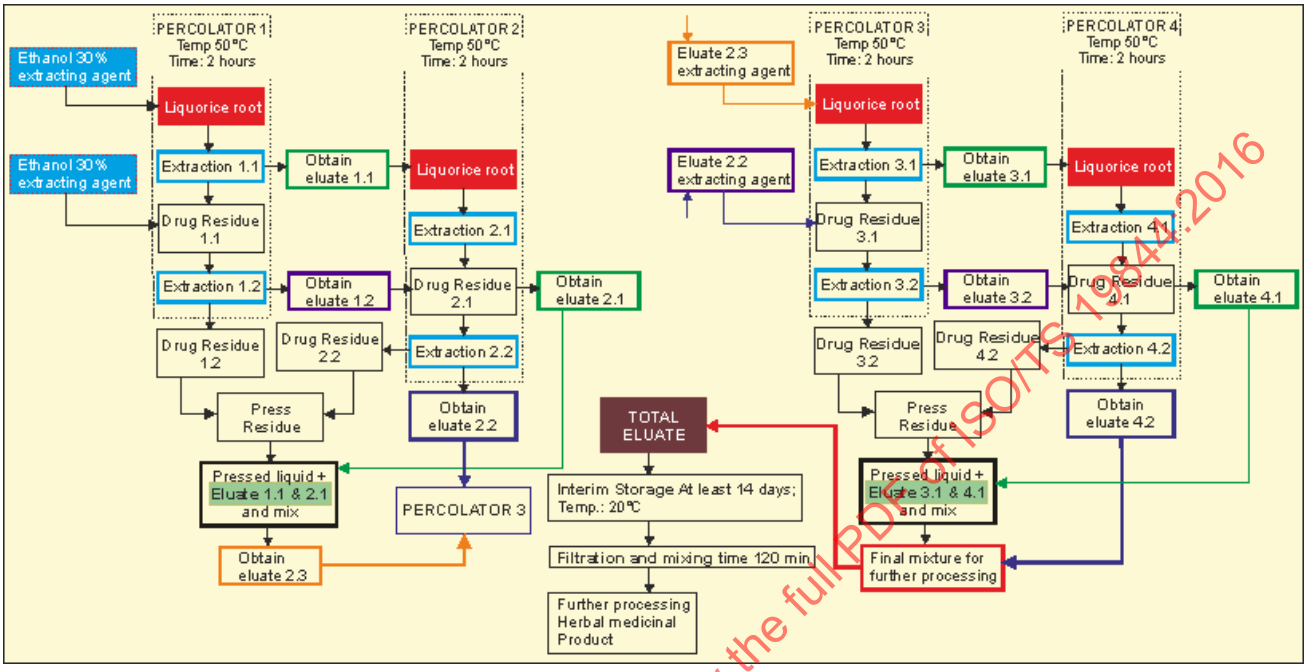


Figure E.24 — Example of multi-step extraction procedure for Liquorice root

E.8 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.

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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)

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.8.1 Examples

E.8.1.1 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 m/m to 70.0 per cent m/m of esters, mainly benzyl benzoate and benzyl cinnamate.

CHARACTERS

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.8.1.2 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 30cm x 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 15-20 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.

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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.

A combination of these three tappings in definite proportions is a ´Raw Balsam´ that is then boiled to evaporate the residual water[23] (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 8-9 months per year. Average yields have been reported to be between 0,25 to 0,50 kg per tree per annum, with trees around 60 years of age giving maximum yields.

E.8.1.3 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 recognised 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).

CHARACTERS

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.8.1.4 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

[23] 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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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.

Because of the number of incisions per tree and the length of the collection of the gum are indefinite, data vary. Average of 8-10 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.8.2 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.9 Peru Balsam/Tolu Balsam structuring information

E.9.1 Capturing information for Peru Balsam (Ph.Eur.) at the Substance information level

E.9.1.1 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

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Substance Name Type: Official
Language: la

Element Group: Substance Name (Repeat)
Substance Name: *Myroxylon balsamum* (L.) Harms var. *pereirae* (Royle) Harms
Substance Name Type: Scientific

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.9.1.2 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: la

Element Group: Official Name
Official Name Type: Ph. Eur.
Official Name Status: Current
Official Name Domain: Drug
Official Name Jurisdiction: Ph. Eur.

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)

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Substance Name: Peru balsam

Substance Name Type: Common Name

Language: en

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

Material Type: Herbal

Fraction: Balsum

Countries of Origin: JM, SV, LK

E.9.2 Capturing information for Peru Balsam (Ph.Eur.) at the Specified Substance information level

Element Group: Specified Substance Group 1

Substance Type: Specified Substance Group 1

Specified Substance Group 1 ID: TTTTTTTTTT (Artificial ID)

Specified Substance Group 1 Name (Herbal preparation): *Myroxylon balsamum* var. *pereirae*, Trunk, Balsam, Dry

Element Group: Constituent

Substance ID: GHFTE7856B (Artificial ID)

Substance Name (Herbal preparation): *Myroxylon balsamum var. pereirae*, Trunk, Balsam

Language: la

Substance Role: Parent

Element Group: Specified Substance Group 2

Substance Type: Specified Substance Group2

Specified Substance Group 2 ID: MANUF67543 (Artificial ID)

Specified Substance Group 2 Name (Herbal preparation): *Myroxylon balsamum* var. *pereirae*, Trunk, Balsam, Dry—Manufacturer ZZ

Parent Substance Group 1 ID: TTTTTTTTTT (Artificial ID)

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Element Group: Manufacturing

Manufacturer Name: Name, address, town, country (Brazil), GPS location

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

Element Group: Specified Substance Group 3

Substance Type: Specified Substance Group3

Specified Substance Group 3 ID: DFSW9876HJ (Artificial ID)

Specified Substance Group 3 Name (Herbal preparation): *Myroxylon balsamum* var. *pereirae*, Trunk, Balsam, Dry—Ph.Eur.

Parent Substance Group 1 ID: TTTTTTTTTT (Artificial ID)

Element Group: Grade

Grade Type: Ph.Eur.

Name: Peru Balsam

Grade Reference source: Ph.Eur., monograph 01/2008:0754

E.9.3 Capturing information for Tolu Balsam (Ph.Eur.)

E.9.3.1 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: Official

Lnguage: LA

Element Group: Substance Name (Repeat)

Substance Name: *Myroxylon balsamum* var. *balsamum*

Substance Name Type: Scientific

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Element Group: Part Description

Part: Trunk

E.9.3.2 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: la

Element Group: Official Name

Official Name Type: Ph. Eur.

Official Name Status: Current

Official Name Domain: Drug

Official Name Jurisdiction: Ph. Eur.

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 01/2008:1596

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

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Element Group: Fraction

Material Type: Herbal

Fraction: Balsum

Countries of Origin: CO, PE, VE

E.9.3.3 Specified Substance information level

Element Group: Specified Substance Group 1

Substance Type: Specified Substance Group 1

Specified Substance Group 1 ID: RRRRRRRRRR (Artificial ID)

Specified Substance Group 1 Name (Herbal preparation): *Myroxylon balsamum* var. *balsamum*, Trunk, Balsam, Dry

Element Group: Constituent

Substance ID: JFGW9876UT (Artificial ID)

Substance Name (Herbal preparation): *Myroxylon balsamum* var. *balsamum*, Trunk, Balsam

Language: la

Substance Role: Parent

Element Group: Specified Substance Group 2

Substance Type: Specified Substance Group 2

Specified Substance Group 2 ID: MANUF67543 (Artificial ID)

Specified Substance Group 2 Name (Herbal preparation): *Myroxylon balsamum* var. *balsamum*, Trunk, Balsam, Dry—Manufacturer ZZ

Parent Substance Group 1 ID: RRRRRRRRRR (Artificial ID)

Element Group: Manufacturing

Manufacturer Name: Name, address, town, country (Brazil), GPS location

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

Element Group: Specified Substance Group 3

Substance Type: Specified Substance Group 3

Specified Substance Group 3 ID: HJGFD453Y (Artificial ID)

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Specified Substance Group 3 Name (Herbal preparation): *Myroxylon balsamum* var. *balsamum*, Trunk, Balsam, Dry—Ph.Eur.

Parent Substance Group 1 ID: RRRRRRRRRR (Artificial ID)

Element Group: Grade

Grade Type: Ph. Eur.

Grade Name: Tolu Balsam

Grade Reference Source: Ph.Eur., monograph 01/2008:1596

E.10 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 the ISO/TS 19844.

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	1: *Ginkgo biloba*, Leaf, Dry 2: *Ginkgo biloba*, Leaf, Dry – Company Aa	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-

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	3) *Ginkgo biloba*, Leaf, Dry Extract	3: Ginkgo Leaf (Ph.Eur.)	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.)
	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), Standardised 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.,		1: *Olea europaea*, Fruit, Oil

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	Fruit 3) *Olea europaea*, Fruit, Oil		3: Olive Oil, Virgin (Ph.Eur.) 3: Olive Oil, Refined (Ph.Eur.)

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Annex F
(normative)

Structurally Diverse Substance, Homeopathic substance

F.1Introduction

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 authorisation 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

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thereof, by the pharmacopoeias currently used officially in the Member States. A homeopathic medicinal product may contain a number of principles".

F.2 Manufacturing of homeopathic medicinal products/homeopathic references

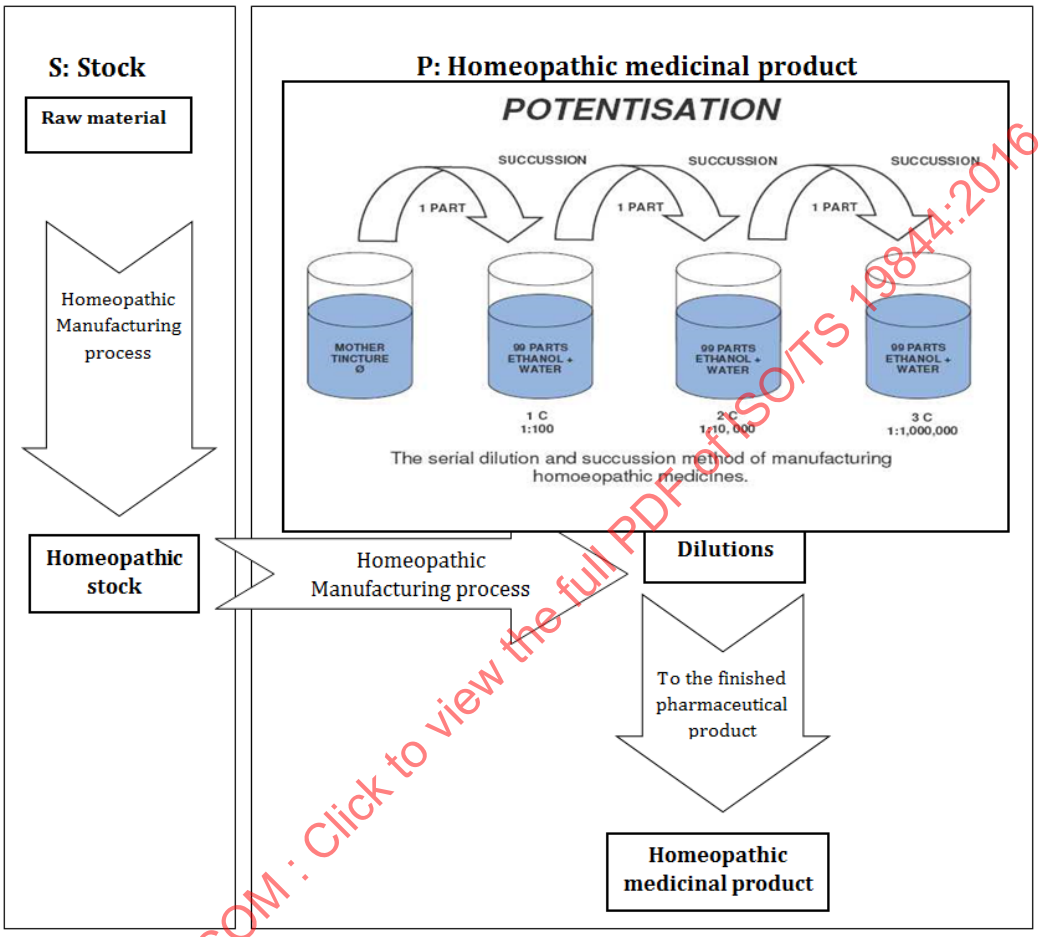


Figure F.1 — Preparation of Homeopathic medicinal product

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F.2.1 Legislation and regulatory requirements

Since some medicines in their crude state may be potentially toxic, and source materials are substantially diluted using a procedure known as potentisation or dynamisation. This process involves successive dilutions and vigorous shaking (succussion) for liquid preparations and successive grinding (trituration) for solid preparations. The potentisation 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

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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 poetised but may itself be used as a homeopathic medicine. Clean glassware (test tube and pipettes) is used for each delusional stage. Other delusional 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 potentisation 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 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

Stocks are substances, products of preparations used as starting materials for the production of homeopathic preparations. 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

Homeopathic preparations are prepared from substances, products or preparations called stocks, in accordance with a homeopathic manufacturing procedure. 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

Dilutions and triturations are obtained from stocks by a process of potentisation in accordance with a homeopathic manufacturing procedure: this means successive dilutions and successions’, or successive appropriate triturations, or a combination of these 2 processes.

The number of potentisation steps defines the degree of dilution; for example, “D3”, “3DH” or “3X” means 3 decimal potentisation steps (diluted 1:1000), and “C3” or “3CH” means 3 centesimal potentisation steps (diluted 1: 1.000.000).

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F.3.3.1 Decimal dilution/decimal potencies

The potentisation 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 (Methods of preparation of homoeopathic stocks and potentisation), and in the Homeopathic Pharmacopoeia of the United States as "Decimal scale of attenuation".

F.3.3.2 Centesimal dilution/centesimal potencies

The potentisation 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 potentisation*), 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 (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/potentisation only one container is used throughout the process. Each dilution factor corresponds to a ratio 1:100. *Symbol: K, CK*[24] The manufacturing method is described in the Homeopathic Pharmacopoeia of the United States as "*Korsakovian attenuations – Single flask method of preparation*".

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

[24] CK is described in British Homoeopathic Pharmacopoeia

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F.3.3.5 Methods of preparation of homeopathic stocks and potentisation

Definitions and description of methods of preparation of stocks and potentisation are currently described in monograph 2371 of the European Pharmacopoeia (Methods of preparation of homoeopathic stocks and potentisation) or in a pharmacopoeia currently used officially in one of the European Union Member States, e.g. the German Homeopathic Pharmacopoeia – Homöopathisches Arzneibuch (HAB), 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 potentisation are not fully harmonised.

NOTES:

There are several methods described in the Ph.Eur. monograph no 2371 under 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 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 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 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 5.1 used for preparations by co-potentising 2 or more stocks and/or dilutions thereof, where co-potentisation consists of mixing several stocks or dilutions of stocks then potentising them together in one or more potentisation 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. [European Pharmacopoeia, 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-

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organisms (according to: *Points to consider on Safety of Homeopathic medicinal products from Biological origin, and to the German Homeopathic Pharmacopoeia (HAB), Chapter H, 5-2-5*).

F.3.3.8 Potentisation

Dilutions and triturations are obtained from stocks by a process of potentisation 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 are considered as the homeopathic stock, according to the European Pharmacopoeia (*monograph Homeopathic preparations*).

F.3.3.10 Succussion

In the manufacturing of homeopathic medicinal products, the process of agitating a liquid preparation. As intermediate step in the process of serial dilution, it is part of the potentisation process.

F.3.3.11 Vehicle

Vehicles are excipients used for the preparation of certain stocks or for the potentisation process. 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, which are defined as liquid preparations obtained by the solvent action of a suitable vehicle.

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;

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Liquid preparations are solutions of the medication in water with some amount of alcohol added as a preservative.

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 1500 and 1800. 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 the 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 as 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'. This approach will be followed, for example, in the EU Jurisdiction.

F.3.6.2 Capturing Information at the Specified Substance Group1 information level

All homeopathic stocks and dilutions are further described at the Specified Substance Group 1 information level for additional information regarding the Vehicle composition and the Dilution/Potentisation.

F.3.6.3 Substance Dilution Potentisation

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 potentisation steps are: 1 part of the stock plus 9 parts of the vehicle: designated as "D", "DH" or "X" (decimal).

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Reference: Manufacturing methods are described in the European Pharmacopoeia monograph 2371 (Methods of preparation of homoeopathic stocks and potentisation) and in the Homeopathic Pharmacopoeia of the United States as “Decimal scale of attenuation”.

F.3.6.3.2 Centesimal dilution/centesimal potencies

The potentisation 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 potentisation), 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 (HAB), and in the Homeopathic Pharmacopoeia of the United States as “*Fifty millesimal scale of attenuation*”.

F.3.6.3.4 Vehicle

Definition: Vehicles are excipients used for the preparation of certain stocks or for the potentisation process.

Valid values: 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 potentisation*), and in the Homeopathic Pharmacopoeia of the United States as “Centesimal scale of attenuation”, or as described in the Homöopathisches Arzneibuch (HAB), or in the French Pharmacopoeia (Pharmacopée Française).

Homeopathic stocks examples are provided in Table F.1 classified to the origin:

Table F.1 — Examples

Homeopathic stocks [a]	Scientific name	Homeopathic name
Botanical origin (Plantae):		
Chlorophyta (Green Algae) Rhodophyta (Red Algae)	Fucus vesiculosus L.	Fucus
Trachyophyta		

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Homeopathic stocks [a]	Scientific name	Homeopathic name
Equisetopsida (Horsetails)	Equisetum arvense L.	Equisetum arvense
Ginkgoopsida	Ginkgo biloba L.	Ginkgo biloba
Pinopsida (Conifers)	Thuja occidentalis L.	Thuja
Pinus	Oleum terebintinae	Terebintina
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:		

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Homeopathic stocks [a]	Scientific name	Homeopathic name
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
Imponderabilia:		
Physical radiation	Moonlight	Luna

NOTE

[a] Reference: Angelika Bolte, Jörg Wichmann – Das natürliche System her Heilmittel/The Natural System of Remedies. Fagus-Verlag 2nd revised edition. 2006.

[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.3.6.4 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. 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 homeopathic substance material cannot be mapped to records in the MPNS. It should be noted that many common and even pharmacopoeia names of plants often map to more than one plant species, but it is important that the actual plant substance (defined as a particular species) shall be used in defining a substance.

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+ organisms, 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

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an eight kingdom model and includes infraspecifics 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 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 infraspecies, 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][25].

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.

Substance ID: 19FUJ2C58T (Artificial ID)

Substance (fresh) Name: *Ginkgo biloba* L., Leaf

Scientific Name (from the Organism Name): *Ginkgo biloba* L. [L. stands for the author Linnaeus]

Element Group: Part Description

Part: Leaf

The full taxonomy is also captured in the elements of the Organism Type:

[25] NOTE The terminology 'Herbal preparation' is not used as such in the terminology of homeopathic substances, but the description of the vehicle and the potentisation is captured in the Specified Substance Group 1 Name used for Homeopathic substances.

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Kingdom: Plantae
Phylum: Tracheophyta
Class: Ginkgoopsida
Order: Ginkgoales
Family: Ginkgoaceae
Genus: Ginkgo
Species: Biloba
Species Primary Author: L.

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.3.6.5 Capturing of the Homeopathic medicine (Stock. Dilution Grade, Dilution method)

F.3.6.5.1 Substance information level: (Homeopathic Substance)

F.3.6.5.1.1 Substance ID

- 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).

F.3.6.5.1.2 Substance 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)>

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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.3.6.5.2 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>

Name (Repeat):

(Specified) Substance Name: Botanical origin: <Scientific Name without Author>< dilution method>
< dilution>

(Specified) Substance Name Type: Specified Homeopathic Name

or:

(Specified) Substance Name: Chemical, mineral origin:

<Chemical Name, mineral><dilution method><dilution>.

Element Group Constituent:

Substance ID: [this is the ID for the Substance (Homeopathic drug) or Substance (fresh)]

Substance Name: [this is the Name for the Substance (Homeopathic drug) or Substance (fresh)]

Substance Role: [this is the role of the substance with the value 'Parent'

Amount Type: [this is attribute will not be used in the case that the Substance Role has the value 'Parent'

Element Group: Vehicle

- Element group: Amount

Element Group: Substance Dilution Potentisation

Element (Attribute): Dilution Potentisation

Element (Attribute): Dilution Grade.

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F.3.6.5.3 Specified Substance Group 2:

- Specified Substance Group 2 ID

- Specified Substance Group 2 Name (Herbal):

<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 details

- Production Method Description

F.3.6.5.4 Specified Substance Group 3:

Specified Substance Group 3 ID

Specified Substance Group 3 Name (Herbal):

<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)

Element Group: Grade

Grade Type: Pharmacopoeial specification e.g. USP/Ph.Eur.

Grade Name = Name in accordance with the Pharmacopoeia

Grade Reference Source, including method-type

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F.3.6.5.5 High Level Conceptual Data Model Structurally Diverse Substances

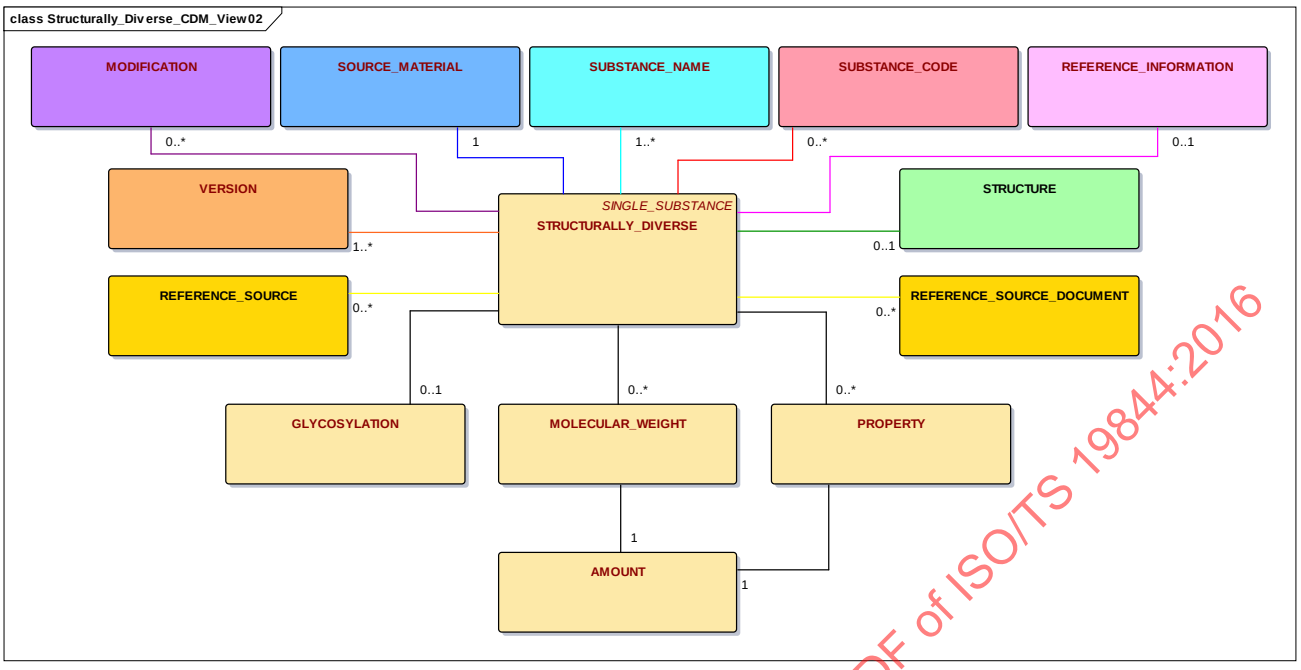


Figure F.2 — Structurally Diverse Substance High Level View

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F.3.6.5.6 High Level Information model for Source Material Homeopathic

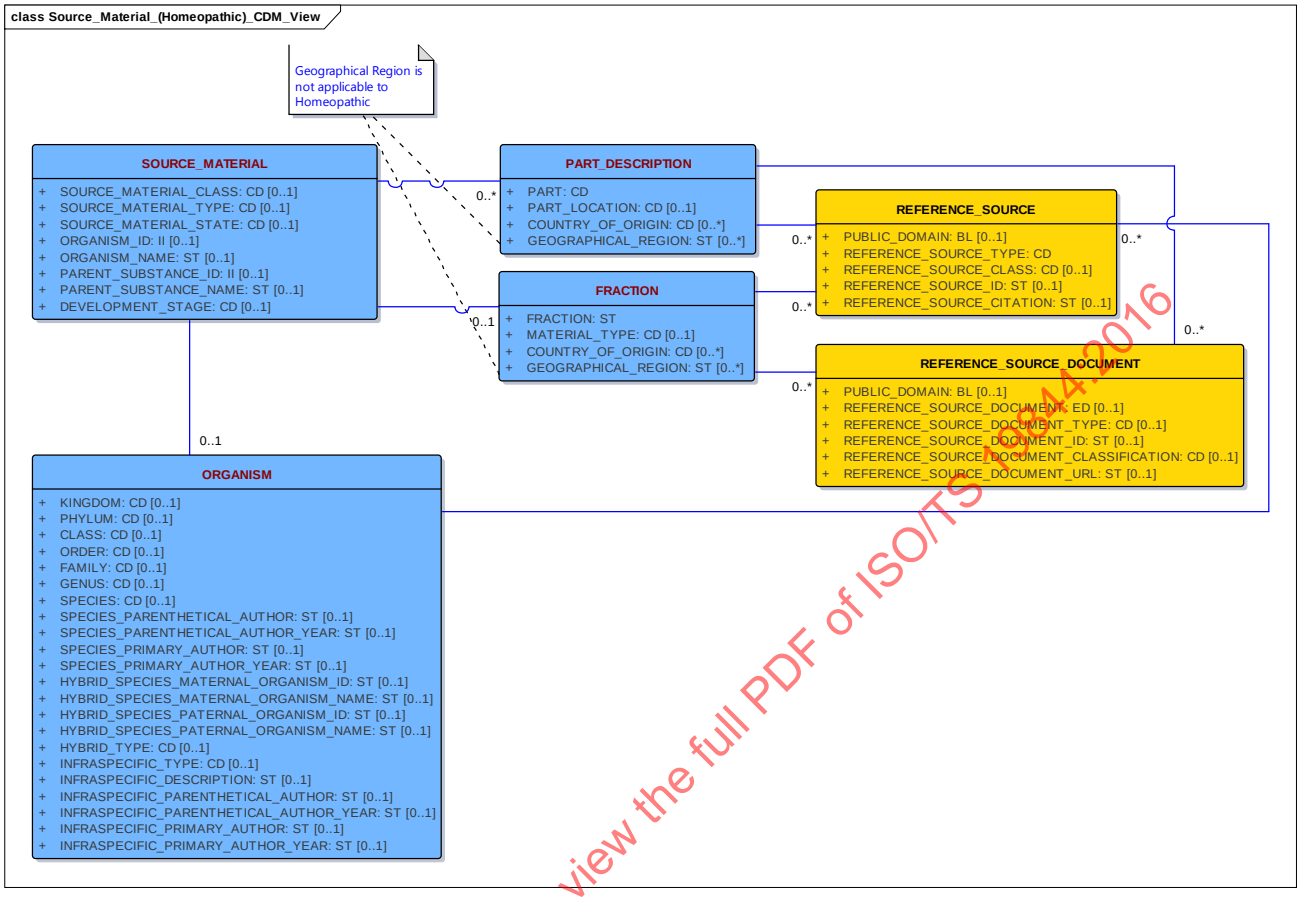


Figure F.3 — Information Model for Source Material (Homeopathic)

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F.3.6.5.7 High Level Conceptual Data Model Specified Substance Group 1 for Homeopathic use

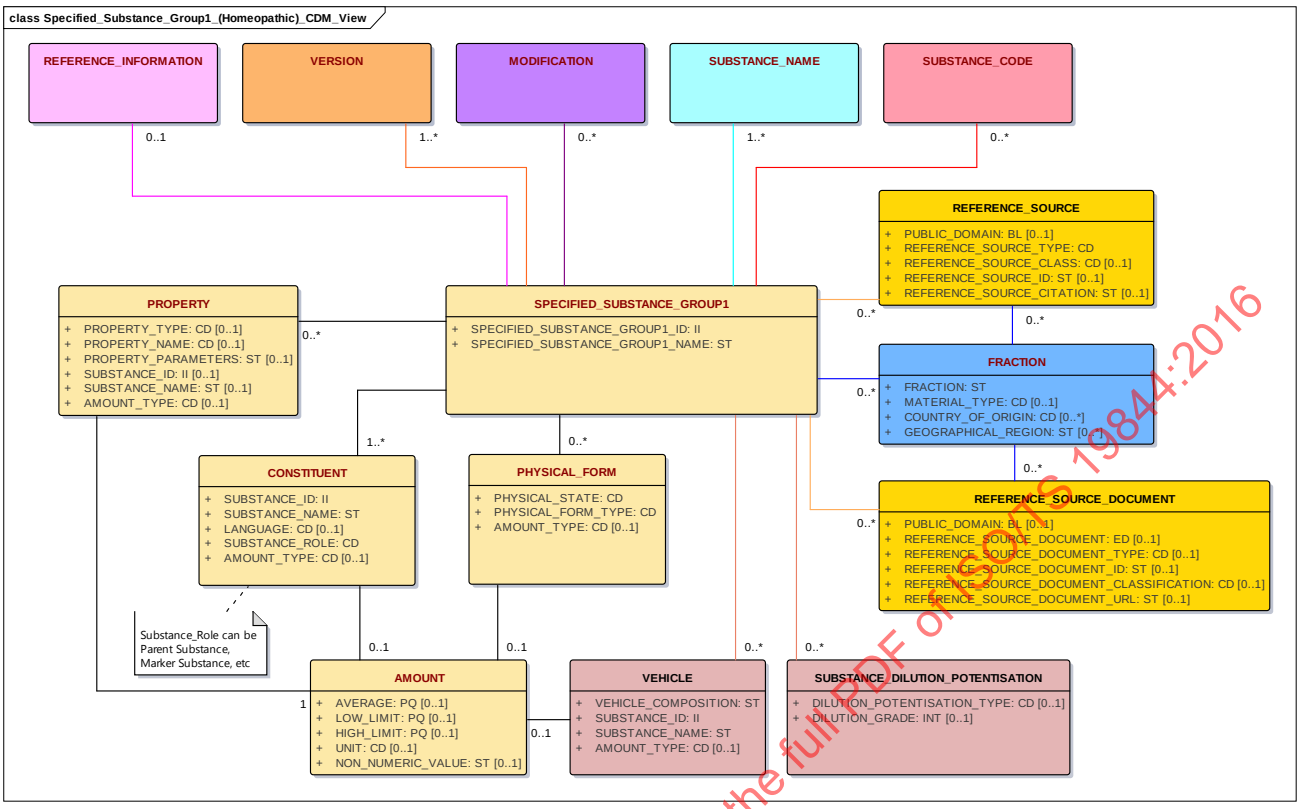


Figure F.4 — Information Model for Specified Substance Group1 Homeopathic

F.3.7 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.3.8 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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Name: Aurum metallicum; Potentisation steps: 6 Dilution method: X (decimal 1:10)



Name: Arnica montana; potentisation steps: 30: Dilution method: C (centesimal 1:100)

In Table F.2 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.

Table F.2 — The Ingredient, basis of strength and the strength are provided for a homeopathic medicinal product in accordance with the current FDA-Substance registration system

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 MACULATUM FLOWERING TOP (UNII: Q28R5GF371) (CONIUM MACULATUM FLOWERING TOP - UNII:Q28R5GF371)	CONIUM MACULATUM FLOWERING TOP	30 [hp_C] in 30 [hp_C]
IPECAC (UNII: 62I3C8233L) (IPECAC -	IPECAC	30 [hp_C]

F.3.9 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 characterised, 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 harmonised and recognised 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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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 200K	Semecarpus anacardium L.f. (syn. Anacardium orientale Steud.)	Anacardium orientale	200	K (Korsakovian)
 				

F.3.10 Nomenclature according to homeopathic tradition

Table F.3 — 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 non-proprietary 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/potentisation steps,
- The method of dilution/potentisation, related to the used symbol,

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- Reference to the (Homeopathic) Pharmacopoeia where the method of manufacturing of the stock, is described,

- Reference to the (Homeopathic) Pharmacopoeia where the method of dilution/potentisation, 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			
Substance (fresh) Name	*Arnica montana* L., Whole Plant	ST	1)
Substance Name Type	Other	CD	
Language	la	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: Source Material			
Source Material Class	Organic	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			1)
Kingdom	Plantae	CD	
Phylum	Tracheophyta	CD	
Class	Magnoliopsida	CD	

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Element Name	Value	Data Format	Note #
Order	Asterales	CD	
Family	Asteraceae	CD	
Genus	Arnica	CD	
Species	montana	CD	
Species Primary Author	L.	ST	
Element Group: Part Description			
Part	Whole Plant	CD	2)
Element Group: Substance Name (Repeat)			
Substance Name	Arnica montana	ST	
Substance Name Type	Homeopathic	CD	
Language	la	CD	
Element Group: Official Name			
Official Name Type	PhF	CD	4)
Official Name Domain	Drug	CD	
Official Name Jurisdiction	EU	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
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 Specified Substance Group 1			
Specified Substance Group 1 ID	HOMGHFTE67 (Artificial ID)	II	
Specified Substance Group 1	*Arnica montana*, Whole Plant, Fresh, Ethanol 30	ST	

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Element Name	Value	Data Format	Note #
Name	% (v/v), dil. 6DH		
Element Group: Substance Name (Repeat)			
Substance Name	Arnica montana DH 6	ST	3)
Substance Name Type	Specified Homeopathic	CD	
Language	la	CD	
Element Group: Official Name			
Official Name Type	PhF, Ph.Eur.	CD	4)
Official Name Domain	Drug	CD	
Official Name Jurisdiction	EU	CD	
Element Group: Constituent			
Substance ID	HOM1234GDA (Artificial ID)	II	
Substance Name	*Arnica montana* L., Whole Plant	ST	
Language	la	CD	
Substance Role	Parent	CD	
Element Group: Substance Dilution Potentisation			
Dilution_Potentisation Type	Decimal, DH	CD	
Dilution Grade	6	INT	
Element Group: Vehicle			
Vehicle Composition	Ethanol 30% (v/v)	ST	
Substance ID	ETHAN98765 (Artificial ID)	II	
Substance Name	Ethanol	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Amount [Numeric Value]	30	PQ	
Unit	Volume per cent	CD	
Element Group: Vehicle (Repeat)			
Vehicle Composition	Ethanol 30% (v/v)	ST	
Substance ID	WATERP67543 (Artificial ID)	II	
Substance Name	Water	ST	
Amount Type	Exact	CD	
Element Group: Amount			

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Element Name	Value	Data Format	Note #
Amount [Numeric Value]	70	PQ	
Unit	Volume per cent	CD	
Element Group: Specified Substance Group 2			
Specified Substance Group 2 ID	HOMYRT76452	II	
Specified Substance Group 2 Name	*Arnica montana,* Whole Plant, Fresh, Ethanol 30 % (v/v), dil. 6DH – COMPANY BB	ST	
Parent Substance ID	HOMGHFTE67 (Artificial ID)	II	
Element Group: Specified Substance Group 2 Manufacturing			
Manufacturer ID	LABOY87654 (Artificial ID)	II	
Manufacturer Name	COMPANY BB	ST	
Manufacturer Type	Manufacturer	CD	
Production Method Type	Extraction and Potentisation	CD	5)
Production Method Description	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).	ST	6)
Element Group: Reference Source			
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)			
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	
Specified Substance Group 3 Name	*Arnica montana*, Whole Plant, Fresh, Ethanol 30 % (v/v), dil. 6DH, for Homeopathic Preparations	ST	
Parent Substance ID	HOMGHFTE67 (Artificial ID)	II	
Element Group: Specified Substance Group 3 Grade			
Grade Type	PhF	CD	

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Element Name	Value	Data Format	Note #
Grade Name	Arnica (plante entire) pour preparations homéopathiques	ST	
Grade Reference Source	European Pharmacopoeia monograph. 2371	ST	
Element Group: Reference Source			
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 potentisation) method 1.1.10	ST	

NOTE

[1] Captured for the Substance (fresh) which is the Parent substance of this Substance (Herbal/Homeopathic drug).

[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 4.10.9.1).

[3] A) The Homeopathic Name is to be added at the Substance Name Type element (Values Allowed: Homeopathic), see 4.3.2.

B) The Homeopathic Name including the dilution/potentisation shall be added at the Specified Substance Group 1 information level with the Substance Name Type element 'Specified Homeopathic' (see 4.3.2).

[4] Official Name Type: Add with the examples PhF (Pharmacopée française), see 4.3.4.1.

[5] Production Method Type: Add with the examples 'Extraction and Potentisation' as additional value for homeopathic stock (see 6.2.6.4).

[6] The attribute Production Method Type description is to be added to the Element Group Manufacturing. This is especially the case for Homeopathic stock in which the Production Method is dependent on the type of potentisation of the Homeopathic stock.

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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	
Substance Name Type	Official	CD	
Language	la	CD	

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Element Name	Value	Data Format	Note #
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: Source material			
Source Material	Organic	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	Adult	CD	
Element Group: Organism			
Kingdom	Plantae	CD	
Phylum	Tracheophyta	CD	
Class	Magnoliopsida	CD	
Order	Asterales	CD	
Family	Asteraceae	CD	
Genus	Arnica	CD	
Species	montana	CD	
Species Primary Author	L.	ST	
Element Group: Part Description			
Part	Root	CD	1)
Element Group: Substance Name (Repeat)			
Substance Name	Arnica montana	ST	
Substance Name Type	Homeopathic	CD	
Language	la	CD	
Element Group: Official Name			
Official Name Type	PhF	CD	2)
Element Group: Official Name Domain			

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Element Name	Value	Data Format	Note #
Official Name Domain	Drug	CD	
Element Group: Official Name Jurisdiction			
Official Name Jurisdiction	EU	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.Code SystemName	
Code System ID	0050	CD.Code System	
Code System Status	Active	CD	
Element Group: Specified Substance Group 1			
Specified Substance Group 1 ID	HOMHJGT675 (Artificial ID)	II	
Specified Substance Group 1 Name	*Arnica montana*, Root, Dry, Ethanol 50 % (v/v), dil. D6	ST	
Element Group: Substance Name Repeat			
Substance Name	Arnica montana DH 6	ST	
Substance Name Type	Specified Homeopathic	CD	
Language	la	CD	
Element Group: Official Name			
Official Name Type	PhF, Ph.Eur.	CD	3)
Element Group: Official Name Domain			
Official Name Domain	Drug	CD	
Element Group: Official Jurisdiction			
Official Name Jurisdiction	EU	CD	
Element Group: Constituent			
Substance ID	HOM56432G1 (Artificial ID)	II	

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Element Name	Value	Data Format	Note #
Substance Name	*Arnica montana*, Root	ST	
Language	la	CD	
Substance Role	Parent	CD	
Element Group: Substance Dilution Potentisation			
Dilution Potentisation Type	Decimal, DH	CD	
Dilution Grade	6	INT	
Element Group: Specified Substance Group 1 Vehicle			
Vehicle Composition	Ethanol 50% (v/v)	ST	
Substance ID	ETHAN98765 (Artificial ID)	II	
Substance Name	Ethanol	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Amount [Numeric Value]	50	PQ	
Unit	Volume per cent	CD	
Element Group: Vehicle (Repeat)			
Vehicle Composition	Ethanol 50% (v/v)	ST	
Substance ID	WATERP67543 (Artificial ID)	II	
Substance Name	Water	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Amount [Numeric Value]	50	PQ	
Unit	Volume per cent	CD	
Element Group: Specified Substance Group 2			
Specified Substance Group 2 ID	HOMHJF764P (Artificial ID)	II	
Specified Substance Group 2 Name	*Arnica montana*, Root, Dry, Ethanol 50 % (v/v), dil. D6 – COMPANY CC	ST	
Parent Substance ID	HOMHJGT675 (Artificial ID)	II	
Element Group: Manufacturing			
Manufacturer ID	HJD56432VS (Artificial ID)	II	
Manufacturer Name	COMPANY CC	ST	
Manufacturer Type	Manufacturer	CD	

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Element Name	Value	Data Format	Note #
Production Method Type	Extraction and Potentisation	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	
Element Group: Reference Source			
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)			
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			
Specified Substance Group 3 ID	HOM67432US (Artificial ID)	II	
Specified Substance Group 3 Name	*Arnica montana*, Root, Dry, Ethanol 50 % (v/v), dil. D6, for Homeopathic Preparations	ST	
Parent Substance ID	HOMHJGT675 (Artificial ID)	II	
Element Group: Specified Substance Group 3 Grade			
Grade Type	HAB	CD	
Grade Name	Arnica montana	ST	
Grade Reference Source	Ph.Eur.	CD	
Element Group: Reference Source			
Reference Source Class	Official Name Source	CD	
Reference Source Citation	European Pharmacopoeia monograph 2371 (methods of preparation of homoeopathic stocks and potentisation), 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.

[2)] PhF (Pharmacopée française)

[3)] Ph.Eur. (European Farmacopeia), (Pharmacopée European)

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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	
Element Group: Substance Name			
Substance Name	Arsenic trioxide	ST	
Substance Name Type	Official	CD	
Language	en	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Official Name Type	Martindale	CD	
Official Name Status	Primary	CD	
Official Name Domain	Drug	CD	
Element Group: Reference Source			
Public Domain	Yes	BL	
Reference Source Type	Martindale	CD	
Reference Source Class	Official Name Source	CD	
Reference Source Citation	https://www.medicinescomplete.com/mc/martindale/current/12396-y.htm?q=Arsenic%20trioxide&t=search&ss=text&p=4#_hit	ST	
Element Group: Substance Name (Repeat)			
Substance Name	Arsenicum album	ST	
Substance Name Type	Homeopathic	CD	
Language	la	CD	
Element Group: Reference Source			
Reference Source Type	HAB	CD	3)
Reference Source Class	Official name source	CD	
Reference Source Citation	Homöopathisches Arzneibuch	ST	
Element Group: Substance Code			

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Element Name	Value	Data Format	Note #
Code	1327-53-3	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	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 Citation	http://www.whocc.no/atc_ddd_index/?code=L01XX27	ST	
Element Group: Structure			
Structural Representation Type	Full	CD	
Structural Representation	$[As]_2.[O]_3$	ST	
Element Group: Structure (Repeat)			

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Element Name	Value	Data Format	Note #
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 Citation	http://www.chemspider.com/Chemical-Structure.452539.html	ST	
Element Group: Structure (Repeat)			
Stereochemistry	Unknown	CD	
Molecular Formula	As_2O_3	ST	
Element Group: Reference Source			
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	
Amount Type	Exact	CD	
Element Group: Amount			
Amount [Numeric Value]	197.8	PQ	
Unit	g/mol	CD	
Element Group: Specified Substance Group 1 Name			
Specified Substance Group 1 ID	ASG5632TYE (Artificial ID)	II	
Specified Substance Group 1 Name	Arsenic trioxide dil. C30, ethanol 43% (w/w)	ST	

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Element Name	Value	Data Format	Note #
Element Group: Substance Name			
Substance Name	Arsenicum album C30	ST	
Substance Name Type	Specified Homeopathic	CD	
Language	la	CD	
Element Group: Official Name			
Official Name Type	HAB	CD	3)
Element Group: Official Name Domain			
Official Name Domain	Drug	CD	
Element Group: Official Name Jurisdiction			
Official Name Jurisdiction	EU	CD	
Element Group: Constituent			
Substance ID	ASO56432TY (Artificial ID)	II	
Substance Name	Arsenic trioxide	ST	
Substance Role	Parent	CD	
Element Group: Substance Dilution Potentisation			
Dilution Potentisation Type	Centesimal, C	CD	
Dilution Grade	30	INT	
Element Group: Vehicle			
Vehicle Composition	Ethanol 43% (v/v)	ST	
Substance ID	ETHAN98765 (Artificial ID)	II	
Substance Name	Ethanol	ST	
Amount Type	Exact	CD	
Element Group: Amount			
Amount [Numeric Value]	43	PQ	
Unit	Volume per cent	CD	
Element Group: Vehicle (Repeat)			
Vehicle Composition	Ethanol 43% (v/v)	ST	
Substance ID	WATERP67543 (Artificial ID)	II	
Substance Name	Water	ST	

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