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SCIENCE MEDICINES HEALTH

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Information Management

## EMA Substance names best practice

Procedure and principles to handle substance name in the substance management system

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<sup>1</sup> MDMS contact point was replaced with EMA Service Desk.

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# 1. Introduction

As part of the efforts to provide high quality of Article 57(2) data, one important activity is focusing on the quality assurance of substances in the Extended EudraVigilance Medicinal Product Dictionary (XEVMPPD), which is the key reference terminology required for the description of medicines.

As part the overall Article 57(2) data quality assurance (QA), the Agency carried out a de-duplication activity on the XEVMPPD (Art.57) substance names.

The result of this activity has been the development and implementation of a comprehensive and consistent reference terminology of unique substance names and identifiers (EV CODEs) in the XEVMPPD/Article 57(2) database. The methodology for this phase has been:

- Identification of clusters of potentially duplicated substance names;
- Identification of a 'master substance' EV CODE = 'master substance';
- Reviewing and relinking of all duplicated substance names and associated EV CODEs to the 'master substance' EV CODE.

The final outcome of the de-duplication activity and the table with the full list of substance names has been published on the Agency's website.

The principles to assess whether a substance name is a duplicate is based on the substance definitions and classes as described in the ISO 11238:2012 IDMP standard on substances (see *0General definitions and principles*).

This paper is aiming to provide practical guidance to handle additional substance name requests to be included in the XEVMPPD database in a consistent manner.

This best practice guidance is based on the experience gained during the substance de-duplication exercise.

The different chapters of the document are organised in line with the substance classes described in the ISO 11238:2012 IDMP standards. For each substance class, examples are provided where applicable based on real experience identified during the de-duplication activity. These examples are used to highlight common errors and/or the best approach to handle particular cases in XEVMPPD. Due to the complexity of some substance types it was deemed necessary to focus and provide more detailed guidance on how to handle more complicated substances such as herbals, insulins and vaccines (refer to *4.3.2.5. Protein practical example - Insulin*; *4.5.1. SDS- Vaccine*; *4.5.3. SDS-Herbals*).

## 2. General definitions and principles

### 2.1. Definitions applicable for Article 57(2) database

**EVMPD:** The EudraVigilance Medicinal Product Dictionary was developed by the European Medicines Agency in collaboration with the EudraVigilance implementation fora. The main objective of the EVMPD was to assist the pharmacovigilance activities in the European Economic Area (EEA). As such, the EVMPD was designed to support the collection, reporting, coding and evaluation of authorised and investigational medicinal product and substance information in a standardised and structured way.

**XEVMPD:** In December 2010 new pharmacovigilance legislation amending existing legislation was adopted in the European Union (EU) resulting in the need to update the EVMPD in accordance with the format for the electronic submission of information on medicines published by the Agency on 1 July 2011. Based on the new format, the EVMPD has been re-named as eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD). The Agency plans to use this information for the following purposes:

- performing data analysis, including:
  - analysis of data in EudraVigilance and signal management,
  - reporting and coding of individual case safety reports,
  - data analytics and business intelligence;
- facilitating medicines regulation and fulfilling regulatory actions and legal obligations, such as:
  - coordination of regulatory actions to safeguard public health, including referral procedures, establishment of a repository of periodic safety update reports (PSURs) and literature monitoring,
  - supporting the calculation of fees for pharmacovigilance;
- strengthening communication with stakeholders by means of:
  - establishing the European medicines web portal,
  - granting proactive and reactive access to EudraVigilance data,
  - exchanging data within the EU and internationally,
  - supporting communication between the Pharmacovigilance Risk Assessment Committee (PRAC) and marketing-authorisation holders.

**XEVPRM:** eXtended EudraVigilance Product Report Message; format to electronically submit to the Agency information on all medicinal products for human use authorised in the European Union as referred into the Article 57 (2) of the regulation 726/2004.

**ACKNOWLEDGEMENT MESSAGE (XEVPRM\_ACK):** a message generated upon receipt of an XEVPRM; it contains the result of the processing of the XEVPRM. If errors are identified, the XEVPRM\_ACK will also report the description of each error identified.

**EV CODE** (EudraVigilance code) is a unique code assigned to any entity (e.g. substance, product etc.) entered in the XEVMPD. An EV Code is generated after the substance has been inserted successfully in the XEVMPD; the EV Code is included in the XEVPRM\_ACK.

**MASTER EV CODE** corresponds to the EV Code of the 'master substance' name in a selected cluster of potentially duplicated names. It is the EV Code to which all the duplicates of the 'master substance' must be associated. Following the implementation of the de-duplication exercise in XEVMPD the 'master substance' name will be the preferred name of the associated EV Code.

**SUBSTANCE PREFERRED NAME** is the preferred name of the substance associated with an EV Code and it is selected based on the review of reference sources. E.g. Paracetamol (INN).

**DUPLICATE SUBSTANCE** is a name that refers to the same substance and reference information as the 'master substance' name or example synonym according to an official reference source or name presented differently or spelled differently, with its own EV Code, that must be re-linked to the 'master substance' EV Code.

**SYNONYM/ALIAS** is a valid alternative term, according to the official reference sources, that may be used to refer to the substance preferred name. E.g. Acetaminophen (USAN) synonym of Paracetamol (INN).

**TRANSLATION** is a valid alternative term of the preferred name in another European language, according to an official reference source, e.g. Paracetamolo is the Italian translation for Paracetamol.

**SUBSTANCE CLASS:** substances shall be defined using one or more of the following groups of elements (classes):

- chemical,
- protein,
- nucleic acid,
- polymer,
- structurally diverse (i.e. allergen, blood, cell therapy, herbal, immunoglobulin, vaccine, other),
- mixture substance,
- specified substance (group 1, 2, 3).

**REFERENCE SOURCES** are bibliographic sources and documents against which a substance name must be validated, e.g. INN (International Non-proprietary Name), European Pharmacopoeia, etc. (see 5. *Annex 1: Bibliographic reference sources* and published [CV of Reference Sources](#)).

**CONTROLLED VOCABULARY** is an established list of standardised terminology for use in indexing and retrieval of information. A complete list of Controlled Vocabularies is published in the EMA's [Guidance documents](#) webpage and includes the XEVMPD list of substances, classes and reference sources.

## ***2.2. General definition on substance classification***

**Substance** refers to any matter of defined composition that has discrete existence, whose origin may be biological, mineral or chemical.

NOTE 1: Substances can be single substances, mixture substances or one of a group of specified substances. Single substances are defined using a minimally sufficient set of data elements divided into five types: chemical, protein, nucleic acid, polymer and structurally diverse. Substances may be salts, solvates, free acids, free bases or mixtures of related compounds that are either isolated or

synthesized together. Pharmacopoeial terminology and defining characteristics will be used when available and appropriate. Defining elements are dependent on the type of substance.

NOTE 2: The term moiety is used to define the entity within the substance that has a complete and continuous molecular structure and it shall be used in the context of non-stoichiometric chemical substances and in modification of nucleic acid, proteins, polymers and structurally diverse substances.

NOTE 3: Discrete existence refers to the ability of a substance to exist independently of any other substance. Substances can either be well-defined entities containing definite chemical structures, synthetic (i.e. isomeric mixtures) or naturally-occurring (i.e. conjugated oestrogens) mixtures of chemicals containing definite molecular structures, or materials derived from plants, animals, microorganisms or inorganic matrices for which the chemical structure may be unknown or difficult to define.

*EXAMPLE: Salbutamol, Senna leaves*

**Single substance:** substance that can be described by a single representation or set of descriptive elements.

NOTE 1: A single substance can be described using one or more of the five following types of elements: chemical, protein, nucleic acid, polymer and structurally diverse substances.

NOTE 2: Racemates and substances with unknown, epimeric or mixed chirality can be defined as single substances because a single structural representation may be generated and the stereochemistry indicated as descriptive text.

**Chemical substance:** type of substance defined by a single molecular structure that is not a protein or nucleic acid substance.

**Protein substance:** type of substance with a defined sequence of alpha-amino-acids connected through peptide bonds.

NOTE 1: Synthetic peptides and proteins with defined sequences, recombinant proteins and highly purified proteins extracted from biological matrices are described as protein substances. Sites of glycosylation, disulfide linkages and glycosylation type (e.g. fungal, plant, arthropod, avian, mammalian, human) are defining elements of protein substances, when known. A graphical molecular structure is also included in the definition of all peptides of 15 amino acid residues or less.

NOTE 2: Monoclonal immunoglobulins are described as proteins. Somatropin, a non-glycosylated protein that can be produced in *E. coli*, yeast or mammalian cells, is defined as the same single substance regardless of the cell line it was produced in.

NOTE 3: The current glycosylation types include fungal, plant, arthropod, avian, mammalian and human.

NOTE 4: Differences in even a single amino acid would result in two distinct substances. For example, interferon alfa-2a and interferon alfa-2b will be defined as separate substances because the sequences differ by a single amino acid. Aggregated human serum albumin, which is formed by irreversible partial physical denaturation, would be defined as a separate substance from human serum albumin.

**Polymer substance:** type of polydisperse substance that contains structural repeating units linked by covalent bonds.

NOTE 1: Monodisperse proteins and nucleic acids with defined sequences shall not be defined using the polymer substance elements.

Polymers shall refer to material that is inherently heterogeneous and contains structural repeating units.

Polymers shall be defined using a combination of the molecular structure of the structural repeating units, substituents that are attached to the structural repeating unit, which are described as either fragment or moiety modifications, molecular weight or the polydispersity of the material. The degree of polymerization, monomers used to synthesize synthetic polymers or copolymers, the source material for naturally derived polymers, polymeric end groups, and physical or biological properties shall also be captured when known and needed to distinguish material. Polymers shall be defined to the level of specificity needed to distinguish materials, and broad polymeric definitions shall be discouraged.

The polymer type shall be defined by the number of structural repeating units and the connectivity between them. A controlled vocabulary shall be developed as required to describe the polymer class, polymer geometry and copolymer sequence type.

Physical and biological properties shall only be a defining element if they are necessary to distinguish polymeric substances from one another and are related to the underlying molecular structures of the polymeric ensemble.

NOTE 2: Values for polymer class would include homopolymer and copolymer; values for polymer geometry would include linear, branched and network; values for copolymer sequence type would include random, block and alternating. Polydispersity is usually determined from the ratio of the weight average molecular weight to the number average molecular weight. Properties such as viscosity, light scattering or sedimentation velocity, which are indicative of molecular weight, and biological properties such as enzymatic inhibition can also be distinguishing properties.

**Nucleic Acid substance:** type of substance that can be defined by a linear sequence of nucleosides typically linked through phosphate esters.

NOTE 1: The type of nucleic acid substance (RNA, DNA) is also identified. Oligonucleotides and gene elements (i.e. promoters, enhancers, coding sequences and silencers) are defined as nucleic acid substances.

The sequence of the nucleic acid, the type (RNA, DNA, mixed), together with any modifications that affect the molecular structure, shall be the defining elements for nucleic acid substances.

Genes, plasmids and the nucleic acid portion of viral vectors used in gene therapy shall also be described as nucleic acid substances.

Individual gene elements shall be described and defined as substances.

Irreversible modifications, either physical or chemical, that irreversibly modify the underlying molecular structure shall be described using modification elements.

For gene therapy, the entire sequence of the transforming/transducing vector shall be used as the defining element. Each gene element shall also be captured and defined as a substance.

NOTE 2: Gene elements would include promoters, enhancers, silencers, etc. For nucleic acids used in gene therapy, the entire sequence of the transforming/transducing entity would be captured along with each gene element.

**Structurally Diverse Substance:** type of polydisperse substance isolated from a single source that is a complex mixture which cannot be described as a mixture of a limited number of single substances.

NOTE 1: Structurally diverse substances are defined based on immutable properties of a given material. Modifications that irreversibly alter the structure of the material, distinctive physical properties or components subsumed into the material, e.g. a gene in gene therapy substances, are defining elements for structurally diverse substances. Fractions derived from source material (oils and juices) are also captured in the definition. Protein mixtures containing a large number of diverse sequences such as polyclonal immunoglobulins are defined as structurally diverse substances.

NOTE 2: Within the XEVMPD, Structurally Diverse Substance may refer to one of the following types:

- Vaccine – non protein;
- Immunoglobulin;
- Blood derived;
- Herbal Allergen;
- Cell therapy;
- Other.

Substances that cannot be defined as a limited number of related single substances (mixture substances) shall be defined as structurally diverse.

Structurally diverse substances shall be defined by the source material from which the substance is derived, modifications that result in irreversible changes in the underlying material and/or physical or biological properties related to underlying molecular composition of the material.

Physical or biological properties shall only be used when they are essential to defining and distinguishing the material.

NOTE 3: The majority of structurally diverse substances are derived from biological organisms. They might also be complex natural materials such as coal tar or mineral oil.

*EXAMPLE: Light mineral oil is distinguished from mineral oil on the basis of the viscosity and specific gravity.*

For organism-based polydisperse substances, the parent organism from which the source material was derived is essential to the definition of the substance. Parent organisms shall be defined from the kingdom to at least the species level to which it belongs. Varieties, cultivars, strains or sub-strains of biological material shall be defining information if intraspecific differences are distinct and reflect consistent differences in functionality or composition.

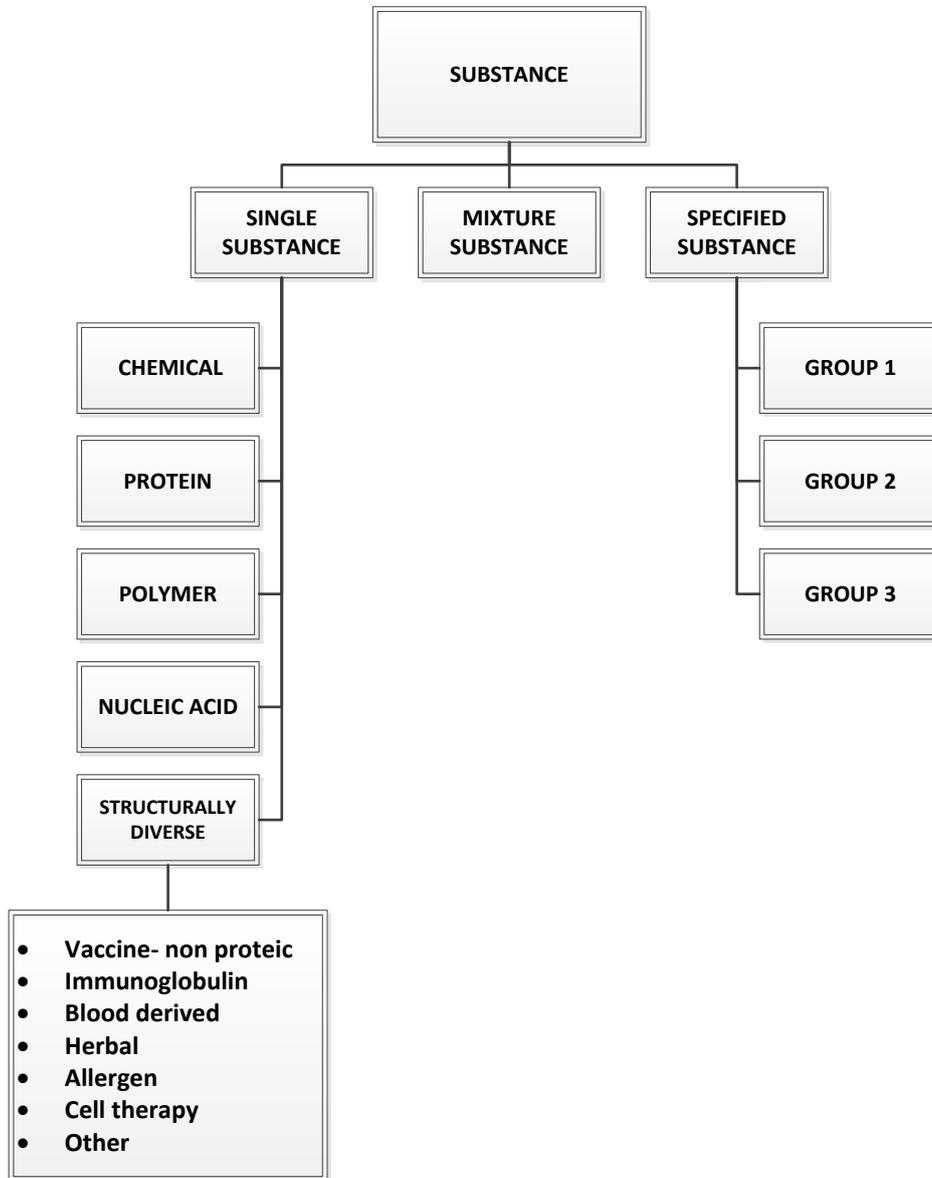
**Mixture substance:** type of polydisperse substance that is a combination of single substances isolated together or produced in the same synthetic process.

**Specified Substance:** group of elements which describe multi-substance materials and specify further information on substances and multi-substance materials relevant to the description of medicinal products

*EXAMPLE: grade, units of measure, physical form, constituents, manufacturer, critical manufacturing processes (i.e. extraction, synthetic, recombinant processes), specification and the analytical methods used to determine that a substance is in compliance with a specification.*

NOTE: There are three different groups of elements that can be used to define a given specified substance and specific relationships between each group of elements.

**Figure 1.** Substance classification

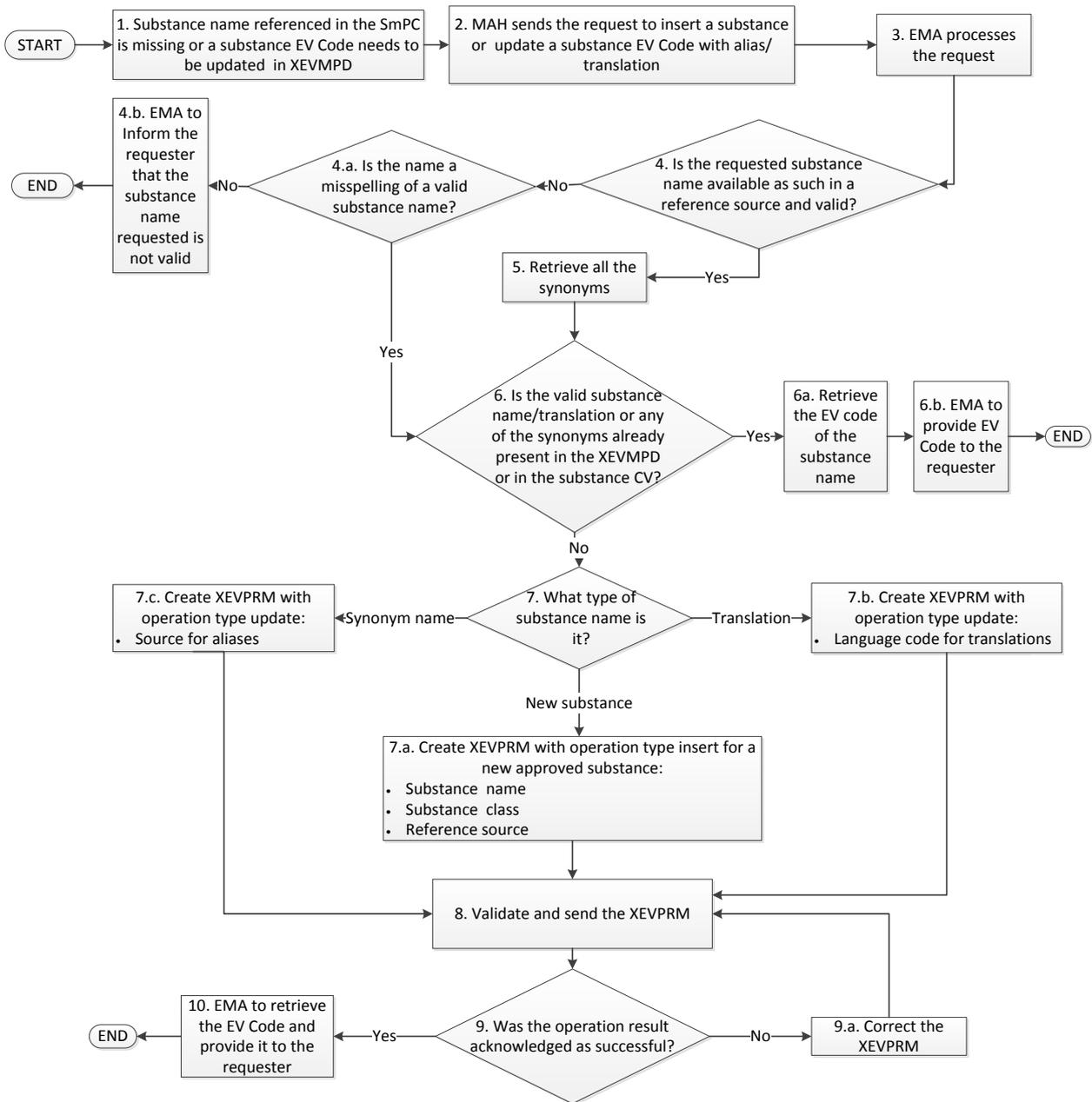


### 3. Overall business process to handle approved substance name in the XEVMPD

The following flow chart outlines the process on how approved substance names are handled when a request is received via [MDMS@ema.europa.eu](mailto:MDMS@ema.europa.eu) the EMA Service Desk (<https://servicedesk.ema.europa.eu/>).

The frameworks of the submission of the approved substance names are outlined in [Chapter 3.II: Extended EudraVigilance product report message \(XEVPRM\) user guidance](#) available at the [EMA's Guidance documents webpage](#).

Process map/flow chart:



## Procedure:

STEP	ACTION
1.	An approved substance name referenced in the SmPC is missing or an information within an approved substance EV Code needs to be updated in the XEVMPD.
2.	<p>MAH sends a request to insert an approved substance or to update an existing approved substance EV Code with alias/ translation to <a href="mailto:MDMS@ema.europa.eu">MDMS@ema.europa.eu</a> the EMA Service Desk (<a href="https://servicedesk.ema.europa.eu/">https://servicedesk.ema.europa.eu/</a>).</p> <p>See <a href="#">Changes to some business rules of the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD): Submission of substance information</a> for related information.</p> <p>The information may refer to a new substance to be inserted in the XEVMPD (step 7.a) or to additional information to be added to an existing substance (i.e. update with alias(es)/translation(s) (step 7.b./7.c.).</p> <p>Before sending the request the MAH should check the list of names that have been validated during the de-duplication exercise in the published Excel file <a href="http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142231.xlsx">http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142231.xlsx</a> available in section 'Controlled vocabularies: quality control' of the <a href="#">EMA's Guidance documents webpage</a>.</p>
3.	EMA will process the request.
4.	<p>Is the requested substance name available in a reference source and valid?</p> <p>If no, go to step 4.a</p> <p>If yes, go to step 5.</p> <p>Note: To define if a substance is a synonym of an existing name or needs to be inserted as new, refer to 4.2. General naming convention and 4.3. Substance class rules (for the unique identifiers of each class of substances e.g. molecular structure for chemical, aminoacidic sequence for proteins and in general level of granularity of the information).</p>
4.a	<p>Is the name a misspelling of a valid substance name?</p> <p>If no, go to step 4.b</p> <p>If yes, go to step 6.</p>
4.b	EMA to inform the requester that the substance name requested is not valid.
5.	Retrieve all synonyms.
6.	<p>Is the valid substance name/ translation or any of the synonyms already present in the XEVMPD or in the substance CV?</p> <p>If yes, go to step 6.a</p> <p>If no, go to step 7.</p>
6.a	Retrieve the EV Code of the substance name.

- 
- 6.b EMA to provide the EV Code to the requester.
- 
7. What type of substance/name is it?
- If 'New substance', go to step 7.a
- If 'Translation' go to step 7.b
- If 'Synonym name', go to step 7.c
- 
- 7.a The EMA creates an XEVPRM with operation type 'Insert (1)' for a new approved.
- For each substance name select an appropriate substance class based on the definition provided in section *0General definition and principles* and *4.3. Substance class rules* and in accordance with the [Published list of Controlled Vocabulary of Substance Classes](#).
- A valid reference source must be specified in accordance with the [published CV of Reference Sources](#).
- 
- 7.c Create an XEVPRM with operation type 'Update (2)' for a synonym.
- For each alias specify a valid reference source in accordance with the [published CV of Reference Sources](#).
- 
- 7.b Create an XEVPRM with operation type 'Update (2)' for a translation.
- For each translation specify the language code.
- 
8. Validate and send the XEVPRM using the 'Validate' and 'Send' buttons in the 'Create and Send product reports' in EVWEB.
- 
9. Was the entity inserted successfully?
- If yes go to step 10.
- If no go to step 8.a.
- 
- 8.a. Correct the XEVPRM.
- Go back to 8.
- 
10. EMA to retrieve the EV Code and provide it to the requester.
-

## 4. Best practice to handle substances in the XEVMPD

### 4.1. General principles in line with ISO 11238:2012 IDMP standards on substances

The concepts required for the unique identification and description of substances are described in the ISO 11238:2012 IDMP standard on substances as summarised below.

Substances shall be single substances, mixture substances or specified substances.

NOTE: The term 'substance' as used below generally refers to a single substance or mixture substance. A specified substance is generally a further specification of a substance that captures information on manufacture, specifications, physical form and multi-substance materials that are components of a medicinal product formulation.

The ISO IDMP defines the concepts required for the unique identification of substances based on the following principles:

- a substance shall generally be defined based on what something is and not on how it is made or used;
- a substance shall be defined based on immutable properties independent of physical form, grade or level of purity;
- substances can be single molecular entities or mixtures of single molecular entities either synthesized or isolated together;
- to avoid ambiguity and facilitate implementation, a mixture shall be defined as a combination of single substances;
- substances shall not be diverse materials brought together to form a medicinal product or multi-substance material.

Substances shall be defined using one of the following groups of elements:

- chemical;
- protein;
- nucleic acid;
- polymer;
- structurally diverse;
- mixture substance.

All types of substances shall have the ability to capture official names, synonyms, isotopic information and reference information.

The information related to the substance class shall be specified in accordance with the terms of the [\[Substance classes\] Controlled Vocabulary](#) published at the [EMA's Guidance documents webpage](#).

Specified substances shall include further information for substances and multi-substance materials. A specified substance shall capture more detailed characteristics of single substances or the composition of a material that contains multiple substances or multiple physical forms.

The elements necessary to define specified substances shall be divided into three groups to facilitate implementation.

These groups shall be delineated as follows:

**Group 1:** constituents (including components for material containing multiple substances, marker substance and extraction solvents for herbals and allergenic extracts), physical form and any physical property that is essential for defining the specified substance;

**Group 2:** limited manufacturing information, parent substance or Group 1 specified substance, manufacturer, high-level production method, overall production method type (e.g. synthetic, extractive, recombinant) production system type (i.e. cell line, plant or animal tissue), production system (specific cell line).

**Group 3:** parent substance or Group 1 specified substance, grade and source of grade (pharmacopoeia, technical).

## 4.2. General naming Conventions

The provision of substance names within the XEVMPD relies on the reference sources as available in the [XEVMPPD Controlled Vocabulary of reference sources](#) published on the [EMA's Guidance documents webpage](#) and based on conventions for the naming as follows:

- every substance will have a name in English.
- synonyms and translations of English names into other languages can be associated with a substance language.

As a general rule, the substance preferred name should be specified according to the following priority:

1. INN (International Non-proprietary Name) from Martindale or INN website;
2. Ph. Eur. (European Pharmacopoeia);
3. BAN (British Approved name) from Martindale;
4. USAN (United States Adopted Name) from National library of medicines Unites States or United States Pharmacopoeia;
5. JAN (Japan Approved Name) from Genome or Japanese Pharmacopoeia;
6. International Union of Pure and Applied Chemistry (IUPAC) name;
7. ATC code.

Other valid names should be referenced as synonyms or translations of the preferred term. The principles to identify synonyms are described below.

The substance name is a **synonym** when:

- it is cited as such in an official reference source;  
EXAMPLE: Ascorbic acid= Vitamin C
- The substance name is presented differently based on order of the words or when there is a comma or hyphen or brackets in the substance name;  
EXAMPLE: fluoxetine hydrochloride= hydrochloride fluoxetine  
EXAMPLE: CALCITONIN (HUMAN) = CALCITONIN, HUMAN

- The substance name is spelled differently e.g. British and American English;  
EXAMPLE: Sulphate= Sulfate.

#### 4.2.1. Invalid substance names

Naming conventions as described in the paragraph 4.2. *General naming convention* apply. Any substance name that is not synonym/alias as described in paragraph 4.2. and that is not available in any official reference source is considered invalid.

Not acceptable names include:

- product Names;  
Product names should not be inserted in XEVMPD as substance names. This applies also in cases where in official reference sources they are reported as a synonym of the substance.
- pharmaceutical product characteristics as part of the substance name;  
Pharmaceutical product characteristics reported as part of the substance name e.g. 'For Injection', 'For Solution For Infusion' are acceptable in the dictionary only if these are referring in a specific Pharmacopoeia monograph. Otherwise, the term is not considered to be valid.  
EXAMPLE 1: 'CALCIUM GLUCONATE FOR INJECTION': This substance name classified as specified substance group 1 with Ph. Eur. as reference source is retained as valid. However, such a name should be more correctly inserted as 'CALCIUM GLUCONATE FOR INJECTION, Ph. Eur.' and be classified as Specified Substance Group 3.  
EXAMPLE 2: 'CALCIUM GLUCONATE 50 mg/ml' is not a valid substance name. The strength should be expressed in the context of the product information submission, as part of the pharmaceutical product information in the field relevant to the active ingredient or excipient strength.  
NOTE: The expression of the strength is different from the concentration of a substance; in this case the information can be included in the name according to the definition of Specified Substance Group 1. e.g.: HCl 1N (Reference to paragraph 4.7.1.
- substance names in the form 'SUBSTANCE NAME (AS SOLVATED/SALT/PRODRUG)';  
EXAMPLE 1: 'CLOPIDOGREL (AS HYDROCHLORIDE)' or 'ABACAVIR (AS ABACAVIR SULFATE)' are not valid substance names. Instead, for CLOPIDOGREL (AS HYDROCHLORIDE) the name 'CLOPIDOGREL' or 'CLOPIDOGREL HYDROCHLORIDE' should be used. This applies to terms in English and translations.  
EXAMPLE 2: 'MACROGOL (PEG 400)' or 'MACROGOL 400 (PEG 400)' are not valid names. The substance name should be 'PEG 400' or 'MACROGOL 400'.  
EXAMPLE 3: 'Solid hemi synthetic glycerides (Witepsol W25)' is not a valid substance name. The trade name in brackets must be inserted as the separate substance 'WITEPSOL W25' (if not already present in XEVMPD) because it may refer to a different type of solid hemi synthetic glycerides.  
NOTE: in case the name in brackets is a generic trade name without any specification of the molecular weight or viscosity (e.g. W25 in the example) it is considered a synonym. This means that for 'Solid hemi synthetic glycerides (Witepsol)' there will be no need to insert 'Witepsol' as a separate substance. However the submission of a name with information in brackets should be avoided, especially when it is not clear if the specific information refers to another type of substance (see also 4.4.2. *Polymer naming convention*, as these substances are often polymers/excipients).

- Multiple substance names or substance class;  
A substance is considered not valid when the name refers to a class of substances or when more substances are listed (e.g. separated with commas, pluses).

EXAMPLE 1:

'ANTIHYPERTENSIVES' is referring to a substance class and is not a valid substance name;

'ANTIASTHMATICS' is referring to a substance class and is not a valid substance name;

'HERBALS+ VITAMINS+ MINERALS' Is a multiple name also referring to substance classes and is not a valid substance name;

'Vitamin C, Acerola, Propolis' is referring to a list of substances.

EXAMPLE 2: CAMEL 150 is considered not valid. This excipient should be further specified as CAMEL 150A, CAMEL 150B or CAMEL 150C according to the reference sources.

EXAMPLE 3: Substance names like VITAMINS NOS and LYPIDS NOS (NOS= not otherwise specified) are not valid for the reason explained above.

EXAMPLE 4: Codes that refers to more than one substance like acronym describing chemotherapy (ALL BMF-86).

**EXCEPTIONS:** names referring to substance class but that are reported in individual case safety reports (ICSRs) must be retained in XEVMPD due to safety monitoring and public health purposes.

EXAMPLE: IMMUNOGLOBULINS and PANCREATIC ENZYMES.

### 4.3. Substance class rules

#### 4.3.1. Chemicals

Chemical is the type of substance that can be described as a stoichiometric or non-stoichiometric single molecular entity and is not a protein or nucleic acid substance.

##### 4.3.1.1. Bibliographic reference

The bibliographic reference sources used for chemical substance validation are listed below:

- Martindale (<http://www.medicinescomplete.com/mc/martindale/current/>);
- INN (International Non-proprietary Name) from Martindale or INN website;
- SRS (Substance Registration System) (<http://fdasis.nlm.nih.gov/srs/srs.jsp>);
- National Library of Medicine (US) (<http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp>);
- NCBI – PubChem for IUPAC name;
- DailyMed;
- Ph. Eur. (European Pharmacopoeia);
- Merck Index;
- Handbook of Pharmaceutical Excipients;
- Chem industry (<http://www.chemindustry.com/apps/chemicals>);
- For other countries (<http://www.vifapharm.de/pmn.htm>);
- Summary of product characteristics (SmPC);
- Any other national sources or monographs.

#### 4.3.1.2. Chemical naming convention

The preferred name of a chemical substance should be selected according to the priority ranking of the following reference sources:

- International Non-Proprietary Name (INN);
- Ph. Eur. (European Pharmacopoeia);
- British Approved Name (BAN);
- United States Pharmacopoeia (USP);
- United States Approved Name (USAN);
- Japanese Approved Name (JAN);
- International Union of Pure and Applied Chemistry (IUPAC) name;
- Summary Product Characteristics (SmPC);
- ATC code.

Where there is no INN available and the chemical substance name refers to a Ph. Eur. Monograph, the Ph. Eur. Monograph title should be provided. Any other name should be provided in the XEVPRM as substance alias.

#### 4.3.1.3. Chemical rules

1. In cases where the source is part of the name e.g. 'Sodium Hydrogen Carbonate (Eu. Ph.)' the term is classified as Specified Substance group 3 and not as a Single chemical substance. This substance name should have a distinct identifier (EV Code) from 'Sodium Hydrogen Carbonate'.
2. The IUPAC name should not be selected as substance preferred name, unless there is no other common name in English available.
3. Molecular formulas are not acceptable to be provided as such or as part of the name and the full English name should be retained as preferred name.  
EXAMPLE: TOLYCAINE HYDRICHLORIDE is preferred to TOLYCAINE HCL.
4. The order of the information on chemical substances is to state first the name of the active molecule followed by any additional information (hydration, salt ester). However this should be checked against the reference sources on a case-by-case basis.  
EXAMPLE 1: LUFENURON ANHYDROUS is preferred to ANHYDROUS LUFENURON  
EXAMPLE 2: PHENETICILLIN POTASSIUM is preferred to POTASSIUM PHENETICILLIN.
5. The name of the active moiety should have a distinct EV Code from the substance name of the different salts, esters or hydration forms.  
EXAMPLE:  
IRON SULFATE → EV Code 1  
IRON MONOHYDRATE → EV Code 2  
IRON TETRAHYDRATE → EV Code 3  
IRON → EV Code 4
6. Enantiomer molecules should be entered in XEVMPD as separate substances, after checking for each case the terminology in the reference sources.  
EXAMPLE:

VERBENONE -> EV Code 1  
D - VERBENONE → EV Code 2  
L - VERBENONE → EV Code 3  
DL - VERBENONE → EV Code 4

7. E-Numbers are acceptable as alias/synonyms of an approved substance name. They should be associated with the preferred substance name they refer to which can be identified in the reference sources.

EXAMPLE: 'TITANIUM DIOXIDE' is the preferred name and 'TITANIUM DIOXIDE (E 171)' should be associated as a synonym. 'E 171' is a synonym of 'TITANIUM DIOXIDE (E 171)'.

8. According to the ISO 11238 irreversible changes in the underlying molecular structure of a substance are described as a modification of the antecedent material and the modification will typically result in a new chemical substance. Modifications of chemical substances are inherently captured in the structural representation. The representation is essential to the development of a controlled vocabulary for simple chemical structures. The system of representation should be both unambiguous and unique, only one single representation will be allowed for a given structure. The structural representation is important in order to determine if a substance name can be considered a synonym of another substance or not.

#### **4.3.1.4. Radiopharmaceuticals naming convention**

The following naming convention should be used for radiopharmaceuticals, based on the INN:

##### **Radionuclide being the Isotope number - the Element symbol - Carrier agent name**

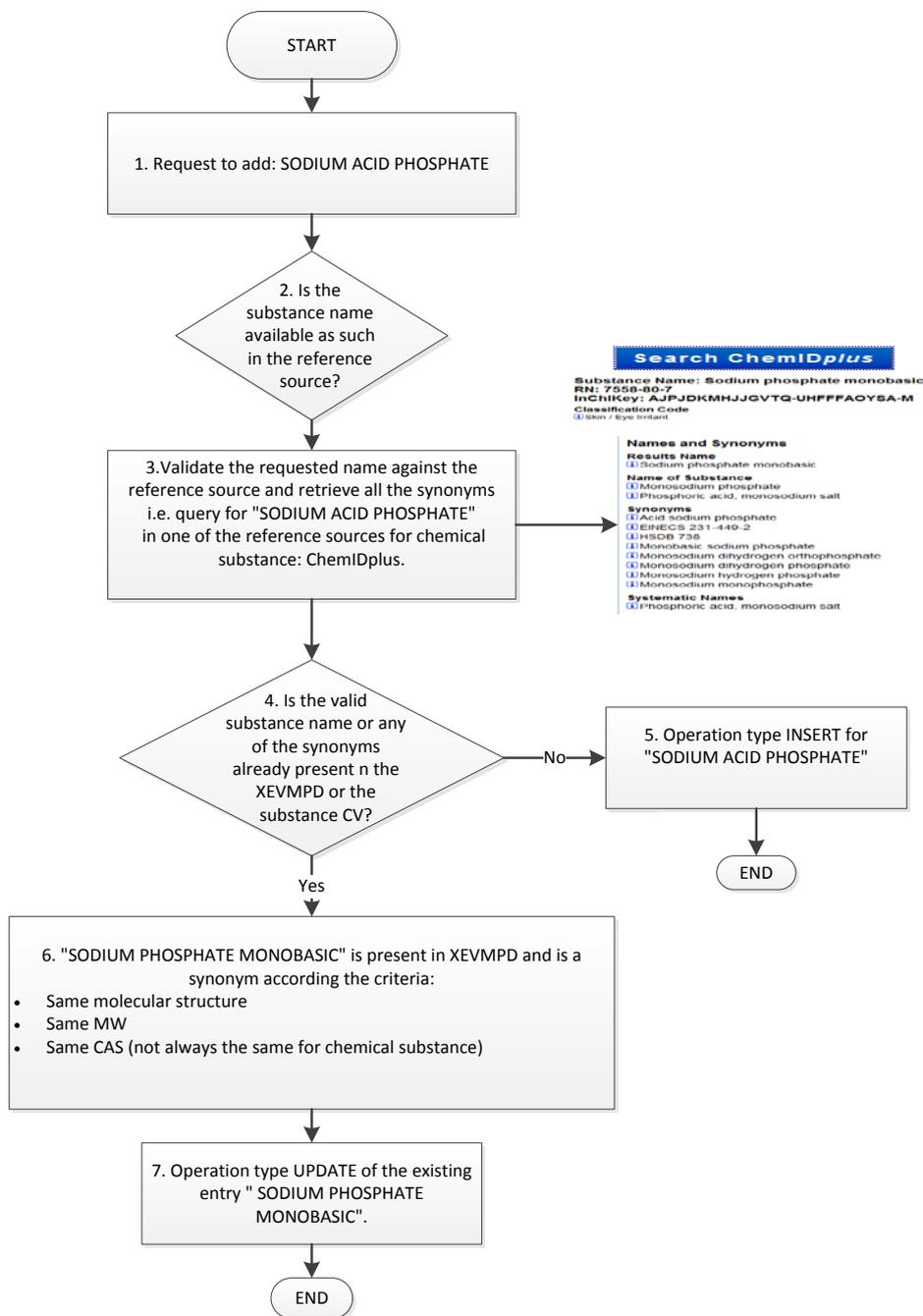
The radionuclide applies to the full name of the radioactive isotope whereas the isotope number and element symbol may vary from one isotope to another (e.g. Cobalt (56Co) or Cobalt (60Co)). The carrier agent name relates to any additional element linked to the radionuclide.

In the absence of an INN, a Ph. Eur. monograph title should be specified. When the Ph. Eur. monograph title contains additional characteristics (e.g. TECHNETIUM (99mTc) BICISATE INJECTION) the full monograph title should be provided as the official name of the substance.

If INN and Ph. Eur. Monograph are not available the USAN name can be specified as a substance preferred name.

EXAMPLE: TECHNETIUM (99MTC) EXAMETAZINE (INN) is the substance preferred name; TECHNETIUM TC 99M EXAMETAZINE (USAN) is associated as synonym.

#### 4.3.1.5. Chemical- Practical examples



As outlined in the previous paragraph, the structural representation is important in order to determine if a substance name can be considered a synonym of another substance or not. Taking this and also the current usage of XEVMPD in safety monitoring into account, the practice to follow in some particular scenarios is presented below:

**SCENARIO 1:** How to handle substance names indicating the general term 'HYDRATE' as the grade of hydration? Are these names synonyms to a particular grade of hydration or should they have distinct EV Codes?

The reference sources should be consulted in order to verify whether a particular substance has only one grade of hydration.

EXAMPLE: HALOMETASONE HYDRATE  
HALOMETASONE MONOHYDRATE

In this example, the only form of hydration is the mono hydration; therefore 'HALOMETASONE MONOHYDRATE' can be linked as synonym to 'HALOMETASONE HYDRATE'. In this example the preferred name will be 'HALOMETASONE MONOHYDRATE' because it includes the highest level of information.

**SCENARIO 2:** What to do in case the concentration (e.g. molarity or normality) is part of the name?

EXAMPLE: SODIUM HYDROXIDE 1N.

Where the concentration is part of the substance name the substance name is classified as Specified Substance Group 1. For further details on how to handle this case, refer to 4.7.1. Specified substance Group 1.

**SCENARIO 3:** A common data quality issue observed for the chemical substances was the failure to identify synonyms due to the different denomination of the same compound. This has been observed for example in the case of sodium, potassium, calcium salts.

With regards to this scenario it is important to define some correlations and the example below for 'SODIUM PHOSPHATE' is applicable also to other types of salts.

Table: SODIUM PHOSPHATE and synonyms for MONOSODIUM, DISODIUM, TRISODIUM PHOSPHATE

Preferred term	Synonyms	EV Code
MONOSODIUM PHOSPHATE	SODIUM <b>DIHYDROGEN</b> PHOSPHATE	EV Code 1
	SODIUM <b>PHOSPHATE</b>	
	<b>MONOBASIC</b> SODIUM PHOSPHATE	
	SODIUM <b>ACID PHOSPHATE</b>	
DISODIUM PHOSPHATE	SODIUM <b>DIHYDROGEN ORTHOPHOSPHATE</b>	EV Code 2
	<b>DIBASIC</b> SODIUM PHOSPHATE	
TRISODIUM PHOSPHATE	SODIUM PHOSPHATE <b>TRIBASIC</b>	EV Code 3

This has been retrieved from a reference source (ChemIDplus), where the chemical structure is clearly associated with the salt (monosodium/disodium) and all the synonyms are correctly linked. The preferred term in this case shall be 'DISODIUM' or 'MONOSODIUM PHOSPHATE'.

## 4.3.2. Proteins and peptides

### 4.3.2.1. Bibliographic reference

The bibliographic reference sources used for the validation of proteins and peptides are listed below.

- INN (Recommended International Non-Proprietary Name);
- Ph. Eur. (European Pharmacopoeia);
- Martindale;
- SRS (Substance Registration System);
- National Library of Medicine (US);
- Summary of product characteristics (SmPC).

### 4.3.2.2. Protein naming convention

The INN experts have adopted the following general scheme for the naming of peptides/ proteins, available at <http://apps.who.int/medicinedocs/pdf/h1806e/h1806e.pdf>:

1. Selection of *stem* for the main compound, e.g. *-poetin* (for erythropoietin derivatives);
2. Designation of *subgroup* by expanding the stem, e.g. *-eptacog*, *-octacog*;

Examples of naming convention of protein are the ones applying for recombinant blood coagulation factors and for all colony stimulating factors.

The following stems have been selected up to date for blood coagulation factors:

- Blood coagulation factor: *-cog*
  - factor VII: *(-)eptacog*,
  - factor VII: *(-)ocotcog*,
  - factor IX: *(-)nonacog*.

A general stem for all colony stimulating factors was selected and substems for the various categories were designated:

- colony stimulating factors: *-stim*;
- combination of two different types of colony stimulating factors: *-distim*;
- granulocyte colony stimulating factor type substances: *-grastim*.

Enzymes are also included in the 'Protein' class and the common stem is *-ase*. Substems are referring to the origin of the substances, e.g. tissue plasminogen activator.

The general rules applying for protein naming convention are listed below:

1. The most recommended name is a word that ends with 'in';  
EXAMPLE: 'zyxin', 'insulin', 'hemoglobin', 'caveolin', 'desmoglein', 'secretin', etc.
2. Names ending in 'ine' should be treated as synonyms;  
EXAMPLE: 'maurocalcine' alias of 'maurocalcin'.

3. Wherever appropriate, the recommended name should use British spelling conventions (as opposed to American spelling), e.g. 'haemoglobin' instead of 'hemoglobin';
4. A recommended name should not contain a Roman numeral;  
 EXAMPLE: 'caveolin-2' instead of 'caveolin-II'.  
 EXCEPTION: historical cases. e.g. 'coagulation factor IX', 'casein kinase II', 'HLA class I', etc.
5. Abbreviations should not be built using the molecular weight;  
 EXAMPLE: Abbreviations such as p123, Gp62, p34 are not suitable.  
 EXCEPTION: cases where historically the molecular weight has been consistently and generally applied as part of the accepted name, e.g. 'p53'.
6. For proteins that belong to a multigene family, it is recommended to choose a coherent nomenclature with numbers to specify the different members of the family;
7. When naming proteins which can be grouped into a family based on homology or according to a notion of shared function (like the interleukins), the different members should be enumerated with a dash '-' followed by an Arabic number;  
 EXAMPLE: 'desmoglein-1', 'desmoglein-2', etc.

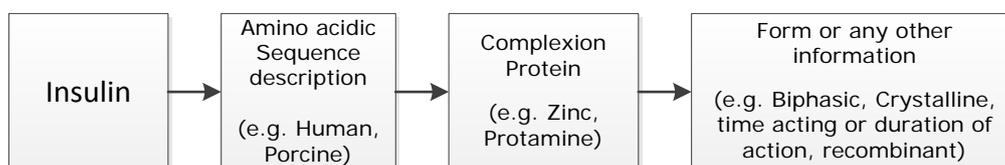
#### 4.3.2.3. *Insulin naming convention*

In order to insert an insulin substance in XEVMPD, an initial assessment is to be performed using this list of reference sources. (Refer to 4.3.2. Bibliographic reference source for proteins).

The assessment is aimed to evaluate:

- if the insulin term is a synonym of an existing entry in the XEVMPD;
- if the insulin term to be entered contains additional information which is not included in any of the existing XEVMPD insulin standard term.

If the insulin term to be entered contains additional information which is not included in any of the existing XEVMPD insulin standard terms, the preferred term must be entered in the XEVMPD adding information in the following order:



As presented in the schema above, in order to describe insulins, several levels of information may be required to be part of the substance name. Depending on the information specified, the substance class may vary.

See the following notes to be taken into account in order to identify synonym terms:

- to describe insulin information, the term 'Regular' is a synonym of 'Dissolved' and 'Soluble';
- to describe 'Insulin zinc injectable suspension':

- the term 'Lente' is a synonym of 'zinc injectable suspension',
- the term 'Semilente' is a synonym of 'zinc injectable suspension amorphous',
- the term 'Ultralente' is a synonym of 'zinc injectable suspension crystalline';
- 'highly purified insulins' and 'monocomponent insulins' are terms which sometimes apply to insulins that have undergone both gel filtration and ion-exchange chromatography and they are synonyms. The U.S. Food and Drug Administration (FDA) has designated the term 'purified insulins' for preparations similarly prepared and containing less than 10 ppm of proinsulin;
- according to the general principles, the product names are not valid, even if in some sources they are reported as synonyms;
- The term 'Isophane' is a synonym of 'Neutral' or 'NPH' (neutral protamine Hagedorn);
- The abbreviation 'NPL' stands for 'Insulin Lispro Protamine'.

#### **4.3.2.4. Protein rules**

1. Proteins that differ in protein sequence, type of glycosylation, disulphide linkages or glycosylation site shall be defined as two separate substances. They shall be defined by the final expressed sequence; pre-pro-proteins shall not be described.  
In XEVMPD single protein substances are further classified as 'Protein – Vaccine' or 'Protein – Other'.  
Vaccines that contain protein subunits or recombinant proteins can be classified as 'protein – Vaccine'.  
EXAMPLE: DIPHTHERIA TOXOID
2. When information about the manufacturing process (e.g. recombinant, synthetic) is included in the substance name, this will have a distinct EV CODE, different from the single protein substance, and will be classified as Specified substance Group 2.  
EXAMPLE 1: 'CALCITONIN SALMON RECOMBINANT' is a Specified substance Group 2 with a distinct EV Code from 'CALCITONIN SALMON'.  
EXAMPLE 2: In vaccine substances the same approach applies. 'CHOLERA TOXIN B SUBUNIT' should not be a synonym of 'CHOLERA TOXIN B SUBUNIT RECOMBINANT (RCTB)'
3. In the substance naming conventions of the Japanese Pharmacopeia the term 'GENETICAL RECOMBINATION' is the common part of the substance name for all recombinant substances.  
EXAMPLE 1: 'Pamiteplase (genetical recombination)' (JAN) is also known as 'Palmitelplase' (INN). Palmitelplase is defined as a recombinant modified human tissue plasminogen activator; therefore the recombination is an integral part of the INN. In this case 'Pamiteplase (genetical recombination)' should be considered as a synonym of 'Palmitelplase' sharing the same EV Code.  
EXAMPLE 2: The INN 'NONACOG ALFA' is defined as 'Recombinant human coagulation Factor IX' therefore 'NONACOG ALFA (GENETICAL RECOMBINATION)' (JAN) is a synonym of NONACOG ALFA.
4. Monoclonal Immunoglobulins are described as proteins, polyclonal immunoglobulins shall be described as structurally diverse materials (refer to 4.5.2. SDS- Polyclonal immunoglobulin).

#### **4.3.2.5. Protein practical example- Insulin**

Insulins are classified as single protein substances and in XEVMPD the classification 'Protein – Other' applies. Insulins may also refer to specified substance groups where applicable.

#### 4.3.2.5.1. Insulin rules and practical examples

- Specification of the Origin:

Distinct Substance Name	Substance class	EV CODE
Insulin	Single Substance - Protein	EV Code 1
Insulin Human	Single Substance - Protein	EV Code 2
Insulin Animal	Single Substance - Protein	EV Code 3
Insulin Bovine	Single Substance - Protein	EV Code 4
Insulin Porcine	Single Substance - Protein	EV Code 5

- Specification of type:

Distinct Substance Name	Substance class	EV CODE
Insulin Zinc	Single Substance - Protein	EV Code 1
Insulin Isophane	Single Substance - Protein	EV Code 2
Insulin Protamine	Single Substance - Protein	EV Code 3

- Specification of the form (e.g. biphasic or crystalline) or any information about the time acting or duration of action (e.g. long acting). We consider the Pharmacopoeia's monographs as a source.

Distinct Substance Name	Substance class	EV CODE
Insulin shot-acting	Specified substance Group 1	EV Code 1
Insulin rapid-acting	Specified substance Group 1	EV Code 2
Insulin intermediate-acting	Specified substance Group 1	EV Code 3
Insulin long-acting	Specified substance Group 1	EV Code 4

NOTE 1: Insulin biphasic is an injectable form of insulin as described in Ph. Eur. The same applies for insulin soluble, regular or dissolved. Therefore the following applies the following substance names are considered synonyms and the preferred term is chosen to be the one defined in the monograph:

Distinct Substance Name	Substance class	EV CODE
Insulin Injection Biphasic	Specified substance Group 1,2 or 3	Master-EV Code 1
Insulin Biphasic		Synonym-EV Code 1
Insulin Biphasic preparation injectable		Translation-EV Code 1
Insulin Injection Soluble	Specified substance Group 1,2 or 3	Master-EV Code 2
Insulin Regular		Synonym-EV Code 2
Insulin Dissolved		Synonym-EV Code 2

NOTE 2: In the case of INSULIN ZINC, we have to maintain the 'injectable' and the 'suspension' separate, because they refer to different monograph and therefore different proprieties:

Distinct Substance Name	Substance class	EV CODE
Insulin Zinc	Single substance- Protein	EV Code 1
Insulin Zinc for injection	Specified substance Group 3	EV Code 2
Insulin zinc injectable suspension	Specified substance Group 3	EV Code 3
Insulin zinc injectable suspension amorphous	Specified substance Group 3	EV Code 4
Insulin zinc injectable suspension crystalline	Specified substance Group 3	EV Code 5

NOTE 3: The substance class 'INSULIN ANALOGUES' contains insulins similar to human insulin, laboratory created by growing insulin proteins within E-coli bacteria (*Escherichia coli*).

This type of process is known as undergoing 'recombinant DNA' technology.

Officially, the FDA refers to these as 'insulin receptor ligands', although they are more commonly referred to as insulin analogues.

In some case we have information about the production (GENETICAL RECOMBINATION). In this scenario, we follow these rules:

1. The following terms are synonyms since they describe the same way of production of RDNA:  
RDNA ORIGIN  
GENETICAL RECOMBINATION  
RECOMBINANT  
RECOMBINANT DNA  
BIOSYNTHETIC
2. The following terms are not synonyms since they describe different types of modification of insulin:  
EMP  
CRB  
PRB

The term 'EMP' describes an enzymatic modification of insulin obtained from the porcine pancreas and is a synonym of 'Semisynthetic'.

The term 'CRB' describes insulin produced by chemical combination of A and B chains that have been duly obtained from bacteria genetically modified by recombinant DNA technology.

The term 'PRB' describes insulin produced by proinsulin obtained from bacteria genetically modified by recombinant DNA technology.

3. As it is for the protein class, when the term 'GENETICAL RECOMBINATION' refers to an insulin analogue, it can be a synonym, because they are always produced by recombinant DNA technology.

The information 'GENETICAL RECOMBINATION' comes from the Japanese Pharmacopoeia.

*EXAMPLE:* INSULIN DETEMIR and INSULIN DETEMIR (GENETICAL RECOMBINATION) are synonyms.

When the term 'RECOMBINANT DNA' or 'RDNA ORIGIN' is an additional information for insulin human or porcine or bovine, it can't be considered as a synonym.

*EXAMPLE:*

Distinct Substance Name	Substance class	EV CODE
Insulin Human	Single substance-Protein	EV Code 1
Insulin Human RDNA	Specified substance Group 2	EV Code 2
Insulin Human (PRB)	Specified substance Group 2	EV Code 3
Insulin Human Semisynthetic	Specified substance Group 2	EV Code 4

## 4.4. Polymers

### 4.4.1. Bibliographic reference

The bibliographic reference sources for polymer validation are listed below.

- Ph. Eur. (European Pharmacopoeia);
- SRS (Substance Registration System);
- Handbook of Pharmaceutical Excipients;
- Merck Index.

#### 4.4.2. Polymers naming convention

The naming convention and the selection of the preferred term as presented in the European and British Pharmacopoeia are often preferable to the USP- NF.

A substance name that can be taken as an example to understand how to handle polymers is Polyethylene Glycol. A non-proprietary name for this polymer is Macrogol, universally recognised as a synonym. Since the Ph. Eur. has priority (after INN) we chose 'Macrogol' as preferred term. An INN is not available for this substance name.

There are many different denominations that can be assigned to the polymer, not only different ways to define the same structural formula, but also 'trade names', which are used as synonym as well. In the example of Polyethylene Glycol, the Handbook of excipient states as 'synonyms': Carbowax, Lipoxol, Lutrol E, PEG, Pluriol E and polyoxyethylene glycol.

In XEVMPD, the trade name can be considered as an acceptable synonym of the substance name unless there is a specification that leads to an additional characteristic of the polymer (e.g. a number that refers to the molecular weight); in this case the entries must be separate.

EXAMPLE:

Macrogol → EV Code 1

Carbowax → EV Code 1

Macrogol 4000 → EV Code 2

Macrogol 4000 should have a distinct EV Code as the molecular weight is specified in the name.

The following terms, are not valid (in line with paragraph 4.2.1. Invalid substance names):

Macrogol (PEG 4000);

Macrogol 4000 (PEG 4000);

Solid hemisynthetic glycerides (Witepsol W25);

Povidone (Kollidon).

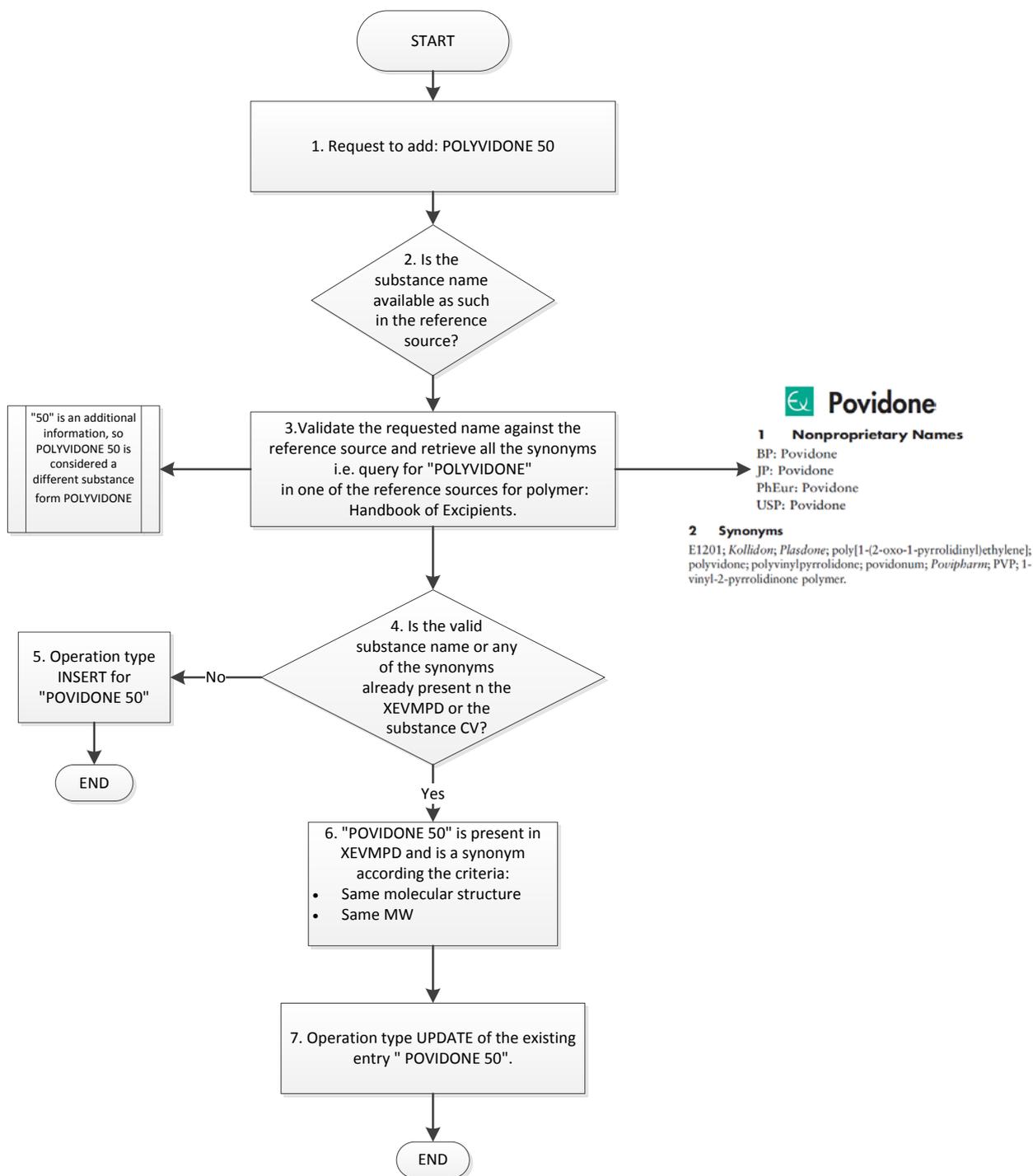
#### 4.4.3. Polymer rules

In line with the ISO definitions, polymers are described based on the representation of the molecular structure of the structural repeating units, molecular weight or the polydispersity of the material. They shall be defined to the level of specificity needed to distinguish materials, and broad polymeric definitions shall be discouraged.

For example, polymers containing polyethylene glycol structural repeating units should always be defined based on either degree of polymerisations or molecular weight. A generic polyethylene glycol

substance should not be defined as a substance because of the wide variation in the functionality of these types of materials and safety concerns related to the degree of polymerisation.

#### 4.4.4. Polymer -practical examples



NOTE: If the substance name or any of the synonyms is not present in XEVMPD and in the reference source has been found that the preferred name is different from the name requested, it is advisable to insert the preferred name as new entry and then possibly to add the synonym. In this example 'POVIDONE 50' would be inserted as new substance and 'POLYVIDONE 50' would be added as synonym. Note that this can be done in one XEVPRM with the operation type 'Insert (1)'.

## **4.5. Structurally diverse substance**

Structurally diverse substances can't be defined as a limited number of related single substances. Within the XEVMPD, Structurally Diverse Substance may refer to one of the following types:

- Vaccine – non proteic;
- Immunoglobulin;
- Blood derived;
- Herbal;
- Allergen;
- Cell therapy;
- Other.

### **4.5.1. SDS - Vaccine**

Vaccines are usually classified as structurally diverse substances and the parent organism is an essential defining element. Some of them are also classified as 'Protein – Vaccine' (refer to 4.4. 'Proteins and peptides' for definition and example). In order to assign a substance ID information about the genus, species, subspecies, variety, cultivar group, modification changes to the chemical structure should be specified as applicable.

#### **4.5.1.1. Bibliographic reference**

The reference sources used to validate vaccines are listed below:

- European Pharmacopoeia (common names and vaccine antigens);
- Summary of Products Characteristics (Section 1 for common names where the Ph. Eur. monograph does not exist and Section 2 for vaccines antigens);
- EMA recommendations for seasonal and pandemic influenza vaccination plans (in line with WHO proposals);
- Martindale textbook, current edition;
- WHO recommendations;
- Others (national monographs, national pharmacopoeias, national product labelling/information);
- ATC codes for vaccines.

#### **4.5.1.2. Vaccine naming convention**

The [WIN/H/3302 EudraVigilance Medicinal Product Dictionary: Population with Approved Substances – type Vaccines](#) is providing guidance on the naming convention relevant for vaccines.

##### **Common name**

A common name refers to the title of the relevant European Pharmacopoeia (Ph. Eur.) monograph (if existing). Common vaccine names refer to a group of several substances that are brought together to form the pharmaceutical product. Therefore these are not valid substance names to be referenced in

the pharmaceutical product. However these names are reported in individual case safety reports (ICSRs) and must be retained in XEVMPD due to safety monitoring and public health purposes.

The naming convention of the vaccine common names should follow the rules below:

1. In cases where there is no Ph. Eur. monograph available, the stylistics and precedents of Ph. Eur. monograph titles should be observed, including the use of words such as 'live', 'adsorbed', or 'virosome' between brackets, if relevant.
2. For common names available in the Pharmacopeia, Ph. Eur. monographs define certain vaccine common names in terms of composition and quality.

EXAMPLES OF VACCINE COMMON NAMES:

PERTUSSIS VACCINE (ACELLULAR, 3- COMPONENT).

INFLUENZA VACCINE (SPLIT VIRION, INACTIVATED).

POLIOMYELITIS VACCINE.

HEAMOPHILUS TYPE B CONJUGATE VACCINE (DIPHTHERIA TOXOID CONJUGATE).

POLIOVIRUS TYPE 1, POLIOVIRUS TYPE 2, POLIOVIRUS TYPE 3 VACCINE (ORAL, LIVE, ATTENUATED).

PNEUMOCOCCAL 13- VALENT CONJUGATE VACCINE.

3. In case the common name of the vaccine is present in a Ph. Eur. monograph and other descriptive names are available, the monograph name should be kept separate from the descriptive name. Note that according to the WIN/H/3302 all the variants derived from a description in the Ph. Eur. should be inserted as aliases, but this is not in line with the new guidelines, as they all give a different level of information.

EXAMPLE:

TICK-BORNE ENCEPHALITIS VACCINE (INACTIVATED)

TICK-BORNE ENCEPHALITIS VACCINE

The first has to be kept separate.

YELLOW FEVER VIRUS ANTIGEN

YELLOW FEVER VIRUS LIVE ANTIGEN

The second has to be kept separate.

4. Trade names commonly used for a specific type of vaccine are valid names.

EXAMPLE: TICE®BCG (Bacillus of calmette and Guerin). TICE is a trade mark (BCG live attenuated culture preparation of BCG strain of *M. bovis*, developed by the University of Illinois, used for the treatment of carcinoma in situ), and is commonly used for this specific type of BCG vaccine.

#### **4.5.1.3. Vaccine rules**

In the high level the name of the vaccine should include information on the parent organism and the antigen as detailed below.

- Parent organism;  
A parent organism refers to any micro-organism (bacterium, virus or parasite) used for the

elaboration of an 'active substance' in a vaccine (e.g. Influenza virus). Choice of the preferred language for the Parent Organism 'Approved Substance Name' will depend on the actual language broadly used in the product labelling. Usually English or Latin language is chosen.

NOTE 1: Names of virus/ bacteria are acceptable as substance names.

EXAMPLE:

PSEUDOMONAS AEURIGINOSA

POLIOVIRUS

- Antigen;  
An antigen refers to a vaccine's active ingredient of microbiological origin prepared to induce protective antibodies. Antigens are reflected in Section 2 'Qualitative and Quantitative Composition' of the Summary of Product Characteristics (SmPC).

There are two different scenarios:

- Antigens as reflected in the SmPC
- Influenza virus antigens which need to be coded according to specific conventions in the EU SmPC.

### Antigen as reflected in the SmPC

Antigens reflected in the SmPC Section 2 'Qualitative and Quantitative Composition' should be described in the XEVMPD on the basis of the following characteristics as applicable:

1. Antigen name;
2. Serotype;
3. Strain description;
4. State/modification [e.g. inactivated, live (attenuated)];
5. Carrier protein (when antigen is conjugated);
6. Adsorbant/adjuvant;
7. Host cell (expression system).

If we have a generic Product A with different antigens stated in the section 2 of the SmPC, the schema below is followed to entry each of them.

Antigen name	Serotype	Conjugated to (e.g. CRM197)	Adsorbed on [e.g. Al(OH) <sub>3</sub> ]
--------------	----------	--------------------------------	--

When there are multiple serotypes stated in the vaccine name the term is treated as a multiple substance and is considered invalid. There are some exceptions and this is due to the strength and how it is expressed in the section 2 of the SmPC. If the strength is expressed for each antigen, the term is treated as a multiple substance, if there is only one strength the vaccine name is retained.

EXAMPLE: PNEUMOCOCCAL POLYSACCHARIDE SEROTYPE 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F

HUMAN PAPILLOMAVIRUS VACCINE (TYPE 6, 11, 16, 18) (RECOMBINANT, ADSORBED)

In XEVMPD for many vaccine names all the different levels of granularity exist. These have been created for the purpose of data analysis to support signal detection. However, the approach has been

reviewing the relevance of maintaining all the terms that currently exist. When for example the adsorbed protein is missing e.g.:

1. HUMAN PAPILLOMAVIRUS TYPE L1 PROTEIN ADSORBED ON AMORPHOUS ALUMINIUM HYDROXYPHOSPHATE SULPAHTE;
2. HUMAN PAPILLOMAVIRUS TYPE L1 PROTEIN ADSORBED;
3. HUMAN PAPILLOMAVIRUS TYPE L1 PROTEIN;

The approach is:

- The substance name 1 will be maintained as separate EV CODE;
- The substance name 2 is considered invalid since the information provided is incomplete;
- The substance name 3 should be maintained for safety reporting and signal detection purposes.

#### **4.5.1.4. Vaccine practical example- Influenza vaccine**

##### **Influenza Antigens**

Influenza antigens need to be entered in the XEVMPD based on the EU recommendations for seasonal and pandemic vaccination plans (in line with WHO proposals published on the [EMA's Biologics Working Party documents webpage](#)).

Three steps need to be followed:

Step 1: Retrieve the relevant seasonal influenza vaccine recommendation;

Step 2: Define the number of influenza antigens to be entered in the XEVMPD;

Step 3: Insert the influenza antigens in the XEVMPD.

The same influenza strain can be applicable to more than one vaccination season. Therefore the XEVMPD needs to be checked for existing strains, before a new strain is entered to avoid duplicate entries. According to the reference document the following information needs to be captured:

- A/NEW CALEDONIA/20/99 (H1N1) - LIKE STRAIN, specified as:  
A/NEW CALEDONIA/20/99 (H1N1) - LIKE STRAIN (A/NEW CALEDONIA/20/99 REASS. IVR-116);
- A/WISCONSIN/67/2005 (H3N2) - LIKE STRAIN specified as:  
A/WISCONSIN/67/2005 (H3N2) - LIKE STRAIN (A/HIROSHIMA/52/2005 REASS. IVR-142);
- A/WISCONSIN/67/2005 (H3N2) - LIKE STRAIN (A/WISCONSIN/67/2005 REASS. NYMCX-161);
- A/WISCONSIN/67/2005 (H3N2) - LIKE STRAIN (A/WISCONSIN/67/2005 REASS. NYMCX-161-B);
- B/MALAYSIA/2506/2004 - LIKE STRAIN, specified as:  
B/MALAYSIA/2506/2004 - LIKE STRAIN (B/MALAYSIA/2506/2004).

NOTE 1: To define how to treat the different nomenclature of the strains; e.g.:

1. B/MALAYSIA/2506/2004;
2. B/MALAYSIA/2506/2004-LIKE STRAIN;
3. B/MALAYSIA/2506/2004-LIKE STRAIN (B/MALAYSIA/2506/2004).

Consider that:

1. B/MALAYSIA/2506/2004-LIKE STRAIN should be kept as a separate entry;
2. B/MALAYSIA/2506/2004 and 3) B/MALAYSIA/2506/2004-LIKE STRAIN (B/MALAYSIA/2506/2004) should be linked as synonyms since they refer to the strain B/MALAYSIA/2506/2004;

NOTE 2: The expression 'LIKE STRAIN' and 'LIKE VIRUS' are considered synonyms.

#### 4.5.2. SDS- Polyclonal Immunoglobulin

Immunoglobulins (or antibodies) can be monoclonal or polyclonal.

Polyclonal immunoglobulins shall be described as structurally diverse materials and require identification of the immunoglobulin type and targeted antigen. Monoclonal immunoglobulins are described as proteins because they are derived from a single cell line. The main differences are highlighted in the table.

Monoclonal Antibody	Polyclonal Antibody
Consists of one immunoglobulin class/subclass which is selective for a single epitope on the antigen	Contains a mixture of antibodies (mainly IgGs), often recognizing multiple epitopes on the antigen
Usually generated in mice, other rodents, or isolated from a phage display library	Generated in a variety of species including rabbit, goat, sheep, and donkey
Always identical, as they are produced from the same transfected cell line (or hybridoma, or bacterial clone)	Prone to batch to batch variability
Their homogeneous nature ensures better reproducibility between tests, where conditions are kept constant. Useful for quantification experiments like flow cytometry	Their heterogeneity means they are more tolerant to slight changes to the antigen e.g. denaturation, polymorphism or differences in glycosylation state
Because of their specificity, they are less likely to cross-react with other proteins, giving lower background than polyclonal immunoglobulins	May contain non-specific immunoglobulin resulting in background staining
Specificity makes them ideal as the primary immunoglobulin in an assay, for detecting antigens in tissue, or for affinity purification of antigens	Useful as secondary immunoglobulins or for immunoprecipitation, as they target multiple epitopes providing a more robust detection

##### 4.5.2.1. Bibliographic reference

The bibliographic reference sources used for immunoglobulin validation are listed below.

- Ph. Eur. (European Pharmacopoeia);
- Martindale;
- Others (national monographs, national pharmacopoeias, national product labelling/information);
- WHO;
- Martindale textbook, current edition;
- NCBI- PubChem website.

#### 4.5.2.2. Naming convention

The [WIN/H/3302 EudraVigilance Medicinal Product Dictionary: Population with Approved Substances – type polyclonal immunoglobulin](#) is providing guidance on the naming convention relevant for this class. The Polyclonal Immunoglobulin substance names should be structured based on the order of the following elements:

#### **Extractive origin - Targeted antigen – Immunoglobulin - Intended use acronym**

The extractive origin applies to human or animal whereas the targeted antigen points to the antigen the polyclonal immunoglobulin is specific to (i.e. Varicella).

The reference to the Intended use acronym (i.e. IV) should remain optional since this element is not always available to describe the Polyclonal Immunoglobulins substances. The xEVMPD substance name field should in priority be populated with the European Pharmacopoeia monograph title, when such name is available, taking into account the element and order mentioned above.

Although some Polyclonal Immunoglobulin substances are not described in the European Pharmacopoeia (Ph. Eur.), the specific format of Polyclonal Immunoglobulin substance names entered in the xEVMPD is based on the stylistics of the European Pharmacopoeia Monograph titles.

EXAMPLE:

ANIMAL HUMAN T LYMPHOCYTE IMMUNOGLOBULIN  
HUMAN ANTIHEPATITIS B IMMUNOGLOBULIN

#### 4.5.3. SDS- Herbals

Herbals should be specified as Structurally Diverse Substances, Specified Substance Group 1, Group 2 or Group 3.

##### 4.5.3.1. Bibliographic reference

The bibliographic reference sources used for herbal substance validation are listed below:

- European Pharmacopoeia Monograph;
- Community herbal monographs;
- [Encyclopedia of life](#);
- [The plant list](#);
- [WHO Monograph on selected medicinal plants](#);
- Iplants Database;
- German Commission E Monographs;
- Hagers Handbuch der Drogen und Arzneistoffe;
- Other national Pharmacopoeias
- [World Checklist of Selected Plant Names, Kew royal botanic gardens](#);
- [Taxonomy browser](#).

#### 4.5.3.2. Naming convention

The following characteristics should be reflected accordingly in the herbal substance name:

- Plant Latin Name;
- Herbal Substance term;
- Herbal Preparation term;
- Herbal Marker.

##### **Plant Latin Name**

The plant name, from which the herbal substance and preparation is derived, should be specified using the botanical name of a plant in Latin in accordance with the International Botanical Nomenclatural Code (add cross reference).

The formal botanical name of a plant consists of the description of the following:

- Genus;
- Species;
- Infraspecies.

Those are described based on the:

- Latin name (its epithet) and the name of the author that published that name (e.g. *Tanacetum parthenium* Sch. Bip. (L.) var. *alpinum*);
- Common name refers to the plant name(s) commonly used in the region e.g. *Tanacetum parthenium* (L.) Sch. Bip. - common name e.g.: Feverfew.

According to the binomial nomenclature, the element that constitutes the plant Latin names shall be specified in the following order:

- Genus of the plant refers to the Latin epithet of the genus of the plant; it is present in names for genera, species and infraspecies. The genus is always presented with an upper case letter according to the International Botanical Nomenclatural Code/International Code of Zoological Nomenclature (e.g. *Tanacetum*);
- Species, which refers to the Latin epithet of the species of the plant; it is present in names for species and infraspecies. The species will always start with a lower case letter according to the International Botanical Nomenclatural Code/International Code of Zoological Nomenclature (e.g. *parthenium*);
- Species Primary Author, which refers to the first author, who published the plant name (of any rank) or subsequently reclassified the taxon placing it in a different genus (e.g. Sch. Bip.);
- Species Parenthetical Author, which refers to the first author, who published the plant name (of any rank). Parenthetical authors are only required for names of taxa which have been subsequently reclassified in different Genera (e.g.: (L.));
- Intraspecific Rank, which refers to the intraspecific genus of the plant, being the rank at which the Latin plant name was published: i.e. the subspecies, variety or forma. It is only indicated for infraspecific names (e.g. *Subsp.*, *Var.*) Intraspecific terms will only be used when specified in a pharmacopeia or when considered to be essential for the activity of the substance;

- Infrspecific, which refers to the Latin epithet of the infrspecific category of the plant/animal; it is only applicable for infrspecific Latin names and starts with a lower case letter according to the International Botanical Nomenclatural Code/International Code of Zoological Nomenclature (e.g. alpinum);
- Infrspecies Primary Author, which refers to the primary author (the first author) who published the infrspecific plant name (of any infrspecific rank) or subsequently reclassified the taxon placing it in a different infrspecific rank (e.g. Baker);
- Infrspecific Parenthetical Author, which refers to the first author, who published the infrspecific plant name (of any rank) (e.g. (L.)).

NOTE 1: The genus and genus + species levels are commonly available when describing a botanical name whilst other information may not be available. Therefore, the genus and genus + species levels shall always be specified for each plant name. Additional information shall be specified where available.

NOTE 2: The common rule for botanical nomenclature of hybrid plants requires the introduction of an 'x' between the genus and species element of the name. For such hybrid plants it is necessary to provide the substance name following the same rules applying to the non-hybrid plants with the addition of an 'x' between the genus and species (e.g. *Mentha x piperita*).

### **Herbal Substance Name**

Herbal substance refers to 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 subject to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).

Herbal substances should be classified as Single Structurally Diverse Substances

For herbal substances, the herbal substance name in Latin (e.g. *Valerianae radix*) should be provided. Where the herbal substance name is cited in the European Pharmacopoeia or a national pharmacopoeia monograph, the Latin name should be specified in accordance with the monograph title (e.g. *Valerianae radix*).

If no monograph is available, the herbal substance name should be provided based on the following order of elements:

### **Plant Latin Name - part of the plant**

#### **Herbal Preparation Name**

The herbal preparation name refers to treatments of herbal substances such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

Herbal preparation names may be classified as Specified Substance Group 1, Specified Substance Group 2 or Specified Substance Group 3.

The herbal preparation name should be provided based on the herbal monograph title where available. If no herbal monograph is available the name should be presented as a concatenation of the following elements:

**Plant Latin Name or Herbal Substance name – Preparation Form – Preparation Process – Solvent – Other**

**4.5.3.3. Herbal rules and practical examples**

1. Herbals are typically described by parent organism family, genus, species and part or parts. If specific parts of a plant are used, identification requires lists of individual parts such as the flower, leaf and stem. An indication of the plant life cycle segment may also be necessary, e.g. whole flowering. Because of variability in constituents due to extraction processes (solvent, temperature, time) and growing conditions (season and place of harvest, type of soil, use of fertilizer, amount of daylight and water), biological extracts shall be identified by their source unless they represent a particular fraction or class of chemicals, e.g. Sennosides (Senna alexandrina anthraquinone glycosides).

A cultivar or variety of a plant shall be defined as a different substance if differences exist in constituents or functionality.

EXAMPLE: Broccoli and cauliflower, which are different cultivar groups or varieties of Brassica oleracea, are defined as different substances even though they share the same genus and species because there are considerable differences in appearance and constituents. These substances are classified as structurally diverse substances.

2. Commodity oils, juices and exudates of plants shall be separate substances. Oils and juices shall be described as fractions of the material from which they are isolated. The materials and processes (i.e. time, temperature, solvent) used to prepare extracts vary. Therefore, tinctures, infusions and decoctions shall not be defined as separate substances but will map to the parent organism and part from which they were derived.

EXAMPLE: Olive oil is Olea europaea fruit oil. Orange juice is Citrus sinensis fruit juice. Green tea and green tea extracts shall be defined as the leaves of Camellia sinensis. Juices and Oils are classified as group 1 specified substances.

There is a rule regarding the naming convention of 'oil', 'essential oil', 'essence oil'. In XEVMPD 'essential oil' is always a synonym of 'essence oil'. However in order to determine whether the 'essential oil' is a synonym of the 'oil' the type of plant concerned should be identified. When the 'oil' is referring to an aromatic plant then it should be considered as synonym of the 'essential oil'.

EXAMPLE: ORANGE OIL should be considered as a synonym of ORANGE ESSENCE and ORANGE ESSENTIAL OIL.

In order to verify whether the plant is an aromatic one it is recommended to refer to the Latin name of the plant. A useful reference source is the Ph. Eur. In cases where the term 'Aetheroleum' is found in the Latin title section it means that the plant is aromatic and therefore the oil of the plant is an essential oil.

EXAMPLE: The latin name of 'Clove oil' in the Eu. Ph. is Caryophylli floris aetheroleum.

3. An important issue regarding herbals is the relation between the Latin name and common plant name i.e. the identification of appropriate synonyms.

To handle this case an appropriate reference sources should be checked to identify how to link the plant common name with the Latin name. In particular, the below table helps understand to which level of granularity of the Latin name, the common plant name corresponds:

Preferred Term	Synonym common name
Helianthus	Sunflower
Helianthus seed	Sunflower seed
Helianthus annuus	Common sunflower or Garden sunflower

Preferred Term	Synonym common name
Atropa Belladonna	Deadly Nightshade
Atropa Belladonna	Belladonna

Note that 'Belladonna' is not an English common name of *Atropa Belladonna*, the English common name is 'Deadly Hightshade'. However Belladonna is used as a common name in homeopathic preparations. In this respect it makes sense to consider synonyms e.g. *Atropa Belladonna* D3 with Belladonna D3.

If the relation of the common name to the plant Latin name cannot be identified in appropriate reference sources then:

- The common name should be linked to the Genus + Species level of the Latin name, unless the common name clearly refers to the Genus level only as explained below.
  - If the common name clearly refers to the Genus level only, it should be linked to the Genus level such as in the Sunflower/ *Helianthus* example.
4. Allergen pollen should be treated as herbal substances. Usually herbal substances used in allergen products are identified with a number in brackets, specific to the product. In these cases they are classified as group 1 specified substances.

EXAMPLE:

PHLEUM PRATENSE (225)

ARRHENATHERUM ELATIUS (205)

Allergens can't be inserted in the XEVMPD as general terms such as 'ALLERGEN EXTRACT' or 'GRASS POLLEN ALLERGEN EXTRACT' even though these can be found in Section 2. Qualitative and Quantitative Composition of the SmPC. The correct way to handle this class is to insert each component separately. This is important when there is more than one composition in the same product.

EXAMPLE:

Grass pollen allergen extract from: Cocksfoot (*Dactylis glomerata* L.), Sweet vernal grass (*Anthoxanthum odoratum* L.), Rye grass (*Lolium perenne* L.), Meadow grass (*Poa pratensis* L.) and Timothy (*Phleum pratense* L.)

For this product 'Grass pollen allergen extract' is not a valid substance name; all the allergens present have to be inserted as:

*Dactylis glomerata* L.

*Anthoxanthum odoratum* L.

*Lolium perenne* L.

*Poa pratensis* L.

*Phleum pratense* L.

The common name can be inserted as synonym of the Latin name according to the rules for Herbals.

5. Probiotics also have to be treated as herbals and are usually classified as structurally diverse substances.

EXAMPLE:

LACTOBACILLUS

BIFIDOBACTERIUM

#### **4.5.4. SDS- Cell therapy**

Substances approved for cell therapy are classified as structurally diverse substances. They are usually implants and they have a very specific description.

##### **4.5.4.1. Bibliographic reference**

- Ph. Eur. (European Pharmacopoeia);
- Martindale;
- Summary of product characteristics at the Community level or national level.

##### **4.5.4.2. Cell therapy rules and practical examples**

An example of substance approved for the cell therapy is a 'Matrix applied characterised autologous cultured chondrocytes'. It is important to specify that the substance name for the active ingredient will be 'autologous cultured chondrocytes', because the implantation matrix is the pharmaceutical form.

#### **4.6. Mixture substance**

According to ISO mixture substances shall be described as simple combinations of single substances that are either isolated together or are the result of the same synthetic process.

##### **4.6.1. Bibliographic reference**

- Ph. Eur. (European Pharmacopoeia);
- Martindale;
- SRS (Substance Registration System);
- NCBI – PubChem;
- National Library of Medicine (US);
- Handbook of Pharmaceutical Excipients;
- Chem industry;
- Summary of product characteristics (SmPC);
- Any other national sources or monographs.

##### **4.6.2. Mixture substance rules and practical examples**

It is important to distinguish when a substance is defined as a mixture compared to a Specified Substance Group 1 or a Structurally Diverse substance. Mixture substances shall not be combinations of diverse material brought together to form a product, because in this case the substance is not valid.

EXAMPLE 1: Simethicone, which consists of dimethicone and silicon dioxide, is not defined as a mixture because the substances are not typically isolated or synthesized together: it would be defined as a Group 1 specified substance.

EXAMPLE 2: Gentamicin would be defined as a mixture substance of Gentamicin C1A, Gentamicin C1 and Gentamicin C2.

EXAMPLE 3: Glyceryl monoesters could be defined as a mixture substance of two single substances which differ in the position of esterification.

For mixtures derived from natural sources, the source material from which the mixture was derived shall be identified.

Impurities and degradants shall generally not be considered constituents of a mixture substance.

Mixtures that cannot be described by a limited number of related substances shall be described as structurally diverse substances.

## **4.7. Specified Substance**

### **4.7.1. Specified Substance Group 1**

#### **4.7.1.1. Bibliographic reference**

- Ph. Eur. (European Pharmacopoeia);
- Martindale SRS (Substance Registration System);
- Handbook of Pharmaceutical Excipients;
- National Library of Medicine (US);
- NCBI – PubChem;
- Chem industry;
- Summary of product characteristics (SmPC);
- Any other national sources or monographs.

#### **4.7.1.2. Naming convention**

The Specified Substance Group 1 name should be described as the concatenation of the substance name of the parent substance and the additional characteristics specified in the following order:

**Substance Name - Constituent description - Preparation Form - Additional information (if applicable)**

#### **4.7.1.3. Specified Substance Group 1 rules**

1. Elements used to define Group 1 specified substance include constituents (including components for material containing multiple substances, marker substance and extraction solvents for herbals and allergenic extracts), physical form and any physical property that is essential for defining the specified substance (e.g. size of liposomal preparation).

This grouping of constituents allows for the definitions of many materials in commerce that are used in the formulation of medicinal products.

EXAMPLE: Materials such as Aluminum Lakes, Nicotine Polacrilex, and Phosphate Buffered Saline, Opadry®

- Herbal preparations are classified as specified substance Group 1 (herbal substance including information on preparation method as well as homeopathic preparation name including dilution information).

EXAMPLE: VALERIANA OFFICINALIS EXTRACTUM SICCUM and ATROPA BELLADONNA D4.

- Multiple substance materials are also classified as specified substance group 1.

EXAMPLE: SIMETHICONE

#### **4.7.1.4. Specified Substance Group 1- practical examples**

**SCENARIO 1:** The concentration is one of the elements that can be used to describe substances or materials and for this reason when a concentration or a level of measurement is indicated, the substance is considered Specified substance group 1.

How do we handle cases where the concentration of the substance is specified as part of the name? For example, substance names specifying different levels of measurement as: %, % (w/w), % (v/v) or with the expression of molarity and normality.

EXAMPLE 1

HYDROCHLORIC ACID 1M: EV Code 1

HYDROCHLORIC ACID 5N: EV Code 2

If the concentration is indicated in the substance name, distinct EV Code should be specified for each name.

EXAMPLE 2

The same principle should apply also for homeopathic, herbal substances and herbal preparations where the dilution is specified as part of the substance name:

HYPERICUM PERFORATUM D6: EV Code 3

HYPERICUM PERFORATUM D5: EV Code 4

**SCENARIO 2:** How to handle cases where the specification 'FOR pH ADJUSTMENT' is included in the substance name?

EXAMPLE:

HYDROCHLORIC ACID 36%: EV Code 5

HYDROCHLORIC ACID 10%: EV Code 6

HYDROCHLORIC ACID 10% (FOR PH ADJUSTMENT): EV Code 6

The term HYDROCHLORIC ACID 10% (FOR PH ADJUSTMENT) can be linked as a synonym to HYDROCHLORIC ACID 10%. HYDROCHLORIC ACID 36% should have a distinct EV Code.

**SCENARIO 3:** Flavours and excipient/ colours are also classified as group 1 specified substances. Where additional specifications are not part of the substance name (code, name of the manufacturer etc.) they may also be classified as mixture substances, if applicable, taking into account the definition of mixture substances.

EXAMPLE:

'MINT FLAVOUR 005' is classified as a specified substance group 1

'MINT FLAVOUR' is classified as a mixture

NOTE: The following terms are handled as synonyms in XEVMPD:

- AROMA;

- FLAVOUR;
- ESSENCE;
- SCENT;
- FLAVOURING;
- PERFUME;
- FRAGRANCE.

There is no preference for the preferred term, but usually it is 'FLAVOUR'.

In cases where the excipient is specified in the SmPC as 'Cherry flavour (acetic acid, p-toluic aldehyde, benzaldehyde, cherry extract, glyceroltriacetate, ethanol)', how should this substance name be inserted in XEVMPD?

The name 'Cherry flavour (acetic acid, p-toluic aldehyde, benzaldehyde, cherry extract, glyceroltriacetate, ethanol)' is not a valid substance name.

The name 'Cherry flavour' should be inserted as a substance preferred name. This substance should be referenced in the pharmaceutical product.

An alternative option could be to insert every single ingredient in the brackets as a separate substance name. In this case, in order to reference this information in the pharmaceutical product, each substance should be entered as a separate excipient and it would not be possible to indicate that these are part of the flavour.

## 4.7.2. Specified Substance Group 2

### 4.7.2.1. Bibliographic reference

- Ph. Eur. (European Pharmacopoeia);
- Martindale SRS (Substance Registration System);
- Handbook of Pharmaceutical Excipients;
- NCBI – PubChem;
- National Library of Medicine (US);
- Chem industry;
- Summary of product characteristics (SmPC);
- Any other national sources or monographs.

### 4.7.2.2. Naming convention

The Specified Substance Group 2 name should be based on a concatenation of the Substance or the Specified Substance Group 1 name (the most granular and the manufacturer information applicable specified in the following order:

**Substance Name/Specified Substance Group 1 name - (Herbal) Production Method - Production System – Manufacturer - Any other information**

#### **4.7.2.3. Specified Substance Group 2 rules**

Elements used to define Specified Substance Group 2 include limited manufacturing information, parent substance or Group 1 specified substance, manufacturer, high-level production method, overall production method type (e.g. synthetic, extractive, recombinant) production system type (i.e. cell line, plant or animal tissue), production system (specific cell line).

EXAMPLE:

insulin human rDNA, salmon calcitonin synthetic

The minimal manufacturing information shall include the overall production method type (e.g. synthetic, extractive, recombinant), production system type (e.g. cell line, plant or animal tissue) and production system (specific cell line).

NOTE: Group 2 elements would allow the tracking of the substance to the manufacturer. This is important for substances in biosimilar or other generic products. It also allows the distinguishing of synthetic peptides from recombinant peptides and the capture of the product cell line.

### **4.7.3. Specified Substance Group 3**

#### **4.7.3.1. Bibliographic reference**

- Ph. Eur. (European Pharmacopoeia);
- Martindale SRS (Substance Registration System);
- Handbook of Pharmaceutical Excipients;
- NCBI – PubChem;
- National Library of Medicine (US);
- Chem industry;
- Summary of product characteristics (SmPC);
- Any other national sources or monographs.

#### **4.7.3.2. Naming convention**

In the absence of a European Pharmacopoeia monograph, the Specified Substance Group 3 name should be specified as a concatenation of the name of the Parent Substance which can refer to a Specified Substance Group 1 or Specified Substance Group 2 (the most detailed should be used) and the additional information as follows:

**Substance Name/Specified substance Group 1 name/ Specified substance Group 2 name - [grade type] - Additional information (if applicable)**

#### **4.7.3.3. Specified Substance Group 3 rules**

Elements used to define Group 3 specified substance include parent substance or Group 1 specified substance, grade and source of grade (pharmacopoeia, technical).

Group 3 elements shall capture the grade of the material along with the source that defines the given grade. In addition, Group 3 elements shall be used to distinguish specific pharmacopoeial and technical grades of material.

EXAMPLE:

For the substance Water, the Group 3 specified substance can be 'Sterile Water for Injection EP'.

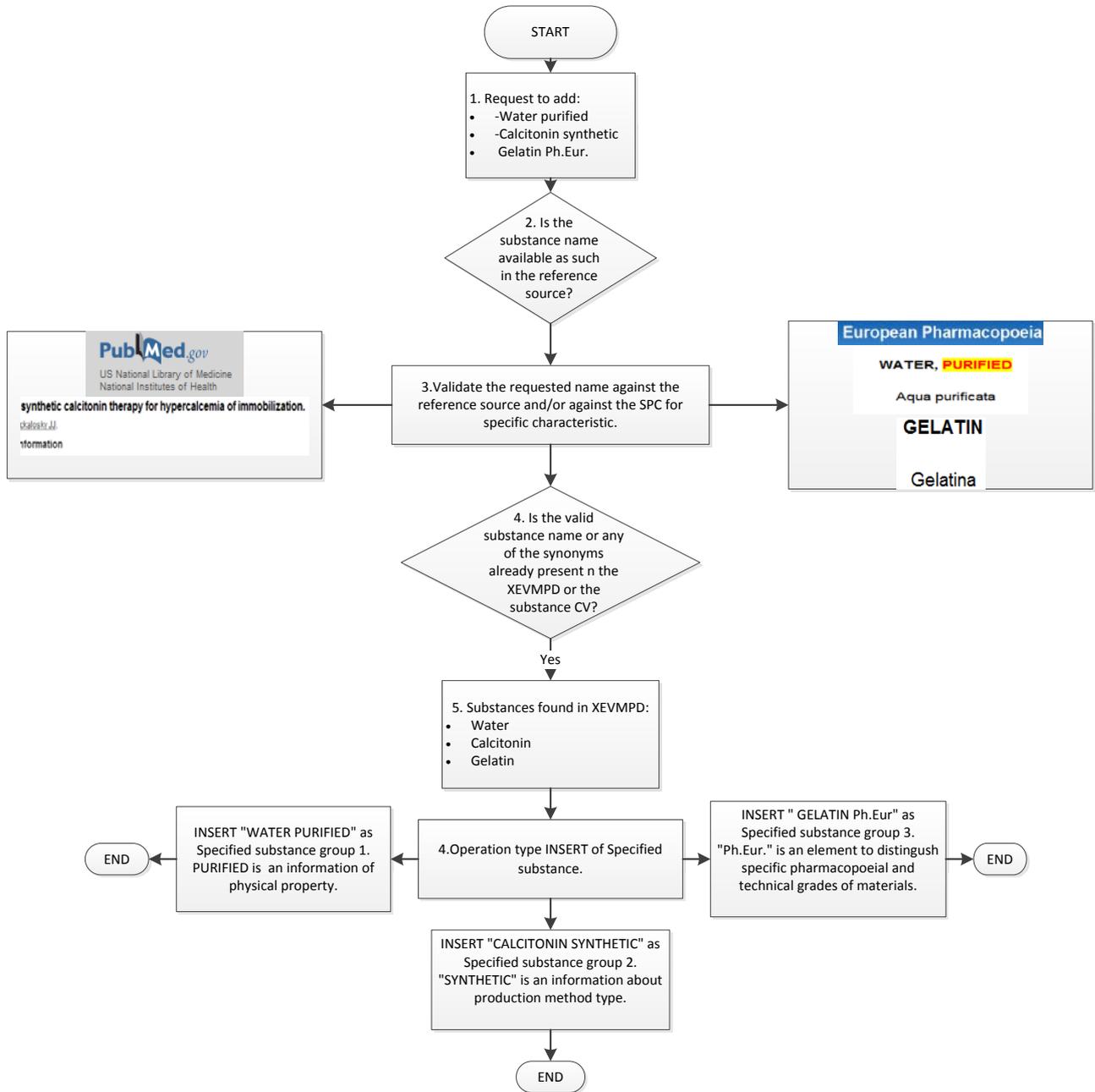
If the pharmacopoeial monographs related to a substance are not harmonized, the grade for each pharmacopeia shall be a separate Group 3 specified substance. The parent substance shall refer to the substance or Group 1 specified substance to which the grade refers.

NOTE: For most active pharmaceutical substances, typical grades are USP, EP, or JP.

EXAMPLE:

'Water' is the parent substance for the Group 3 specified substance 'Sterile Water for Injection USP'.

#### 4.7.4. Specified Substance Group 1, 2, 3 practical examples



#### 4.7.5. Examples of herbal preparations classified as Specified Substance Group 1, 2 or 3

Herbal preparations are classified as Specified substances. Below there are two examples.

##### EXAMPLE 1

Substance name that correspond to collections of herbs in a composite where the components are extracted together and the final preparations is an 'extractum compositum' are valid substance name and classified as Specified substance group 2.

EXAMPLE: EXTRACTUM COMPOSITUM 91:1,3-1,6) EX: AGROPYRI RHIZOMATE 12,5 P., ALLII CEPAE SQUAMA 5,0 P., BETULAE FOLIO 10,0 P., FOENUGRAECI SEMINE 15,0 P., PETROSELNI RADICE 17,5 P., SOLIDAGINIS HERBA 5,0 P., EQUISETI HERBA 10,0 P., LEVISTICI RADICE 10,0 P., POLYGONI AVICULARIS HERBA 15,0 P.

##### EXAMPLE 2:

- CARDUI MARIAE FRUCTUS EXTRATUM SICCUM (36- 44: 1), ETHYLACETATE- ETHANOL 96% (V/V)-HEXANE;
- MILK THRISTLE DRY EXTRACT, REFINED AND STANDARDISED 177,4- 240,4 MG CORRESPONDING TO 108,2 MG OF SYLMARIN, CALCULATED AS SYLBIN;

These substance names are valid. The first substance is a Specified substance group 2, the second is classified as Specified substance group 3, because for herbal substances the grades would be standardized, quantified and unstandardized. For standardised herbal extract it is correct to include also the name and the content of the constituent(s). It is also correct to insert the drug extract ratio (DER genuine) or equivalence in the quality of the herbal substance (as a range) (quantified and other herbal preparations).

#### 4.7.6. Classification of substances used in homeopathic medicinal products

In XEVMPD homeopathic preparations can be classified as Specified substance group 1, 2 or 3.

In the Directive 2001/83/EC '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 absence thereof, by the pharmacopoeias currently used officially in the Member States. A homeopathic medicinal product may also contain a number of principles.

In homeopathy, the active substance can be either the stock or its dilutions, whereas the stock could be processed as well as unprocessed raw material. Homeopathic medicinal products may contain large numbers of active homeopathic substances or a combination of active substances of biological, chemical and herbal origin. In addition, the finished medicinal product could be the (packed) homeopathic active substance itself or a further processed stock/dilution.

##### 4.7.6.1. Bibliographic reference

- European Pharmacopoeia Monograph;
- HAB Deutsches Homöopathisches Arzneibuch (German Homeopathic Pharmacopoeia);
- ANTHROPOSOPHIC PHARMACEUTICAL CODEX (APC);

- Community herbal monographs;
- German Commission E Monographs;
- Hagers Handbuch der Drogen und Arzneistoffe;
- Other relevant national Pharmacopoeias.

Some of the principles of the homeopathy and a useful guide among the nomenclature and the reference sources can be found in the [ANTHROPOSOPHIC PHARMACEUTICAL CODEX APC, from the International Association of Anthroposophic Pharmacists \(IAAP\)](#), since the legal status of anthroposophic medicinal products in the EU is closely related to that of homoeopathic medicinal products. Preamble of Directive 2001/83/EC (22) refers to anthroposophic medicinal products as follows: 'Anthroposophic medicinal products, which are described in an official pharmacopoeia and prepared by a homoeopathic method, are to be considered, as regards to registration and marketing authorization, as homeopathic medicinal products.'

The codex provides detailed insight into the different types of medicinal products used in Anthroposophic Medicine, including source materials, pharmaceutical processes and standards.

In the '[GUIDANCE ON MODULE 3 OF THE HOMEOPATHIC MEDICINAL PRODUCTS DOSSIER](#)' of the Homeopathic Medicinal Product Working Group (HMPWG) there are also indications on how to handle these substances.

Useful information can also be found in the [guideline issued by CHMP and the HMPC for herbal drugs, herbal drug preparations and herbal medicinal products](#).

#### **4.7.6.2. Homeopathic medicinal products rules and practical examples**

1. Where information about the dilution or trituration is part of the substance name, the substance is classified as specified substance group 1. The substance names should have distinct EV Codes and be handled as follows:

CALCIUM PHOSPHORICUM D1 → EV Code 1;

CALCIUM PHOSPHORICUM DIL. D1 → EV Code 2;

CALCIUM PHOSPHORICUM TRIT. D1 → EV Code 3.

The abbreviation 'D' means decimal dilution/ decimal potencies (symbol D, DH, X). 'DIL' means diluted and 'TRIT' triturated. The trituration is a homeopathic manufacturing method, a potentiation process affected by grinding together with lactose and solid raw material, mother tincture, solutions and their dilution as well as mixtures with lactose monohydrate as vehicle. For this section refer to [List of Terms used in Homeopathy released for public consultation by the Homeopathic Medicinal Product Working Group \(HMPWG\)](#).

2. From the same list of terms of the HMPWG we report all the synonyms, symbols and translations of 'Mother Tincture' that when refer to the same herbal substance must share the same EV Code.

Mother tincture (Symbol: MT, TM, Ø):

- DE: Urtinktur;
- FR: Teinture mere;
- ES: Tintura madre;
- IT: Tintura madre;

- NL: oertinctuur, moedertinctuur;
  - FI: Kantaliuos;
  - PT: Tintura mãe;
  - PL: Roztwór macierzysty;
  - LV: Mātes tinktūra (pamattinktūra);
  - HU: Őstinktúra.
3. Following the general rule applicable to all substances, where additional elements to describe the substances are part of the substance name, distinct EV Codes should be assigned

EXAMPLE:

AGNUS CASTUS D6 → EV Code 4

AGNUS CASTUS DIL D6 → EV Code 5

AGNUS CASTUS TRIT D6 → EV Code 6

AGNUS CASTUS (Ø 10%) D6 → EV Code 7

AGNUS CASTUS TRIT D6 (HAB 34) → EV Code 8

These terms are not synonyms and should have distinct EV Codes as each name provides a different level of detail. The classification of the substance names in this example is as follows: AGNUS CASTUS D6: Specified substance group 1, as 'D6' is a preparation form;

- AGNUS CASTUS DIL D6 and AGNUS CASTUS TRIT D6: Specified substance group 2, as 'DIL' and 'TRIT' describe the herbal production method;
  - AGNUS CASTUS TRIT D6 (HAB 34): Specified substance group 3, as HAB 34 is the indication of a specific monograph.
4. It is important to note that in homeopathy often the common plant name is used rather than the plant latin name and this should be taken into account in order to validate the names and identify synonyms.

EXAMPLE:

'Belladonna' is a substance name used in homeopathy. The corresponding plant latin names is Atropa belladonna.

## 5. Annex I: Bibliographic reference sources

- [INN \(Recommended International Non-Proprietary Name\)](#);
- Ph. Eur. (European Pharmacopoeia);
- [Substance Registration System - Unique Ingredient Identifier \(UNII\)](#);
- [NCBI – PubChem](#) for IUPAC name (website for Chemical substances);
- [DailyMed](#);
- USP (United States Pharmacopoeia);
- USAN (United States Approved Name);
- JP (Japanese Pharmacopoeia);
- JAN (Japanese Approved Name);
- Martindale;
- [SRS \(Substance Registration System\)](#);
- Index Nominum;
- Merck Index;
- Handbook of Pharmaceutical Excipients;
- [Chem industry](#);
- [Genomnet \(JP\)](#);
- [National Library of Medicine \(US\)](#);
- [Chinese medicines](#);
- [Other countries](#);
- Summary of product characteristics (SmPC);
- Any other national sources or monographs.

### **Vaccines specific:**

- European Pharmacopoeia (common names and vaccine antigens);
- Summary of Products Characteristics (Section 1 for common names where the Ph. Eur. monograph does not exist and Section 2 for vaccines antigens);
- EMA recommendations for seasonal and pandemic influenza vaccinations plans (in line with WHO proposals);
- Martindale textbook, current edition;
- WHO recommendations;
- Others (national monographs, national pharmacopoeias, national product labelling/information);
- ATC codes for vaccines.

### Herbals specific:

- European Pharmacopoeia Monograph;
- [Community herbal monographs](#);
- [Encyclopedia of life](#);
- [The plant list](#);
- [WHO Monograph on selected medicinal plants](#);
- [Global Biodiversity Information Facility](#);
- [World Checklist of Selected Plant Names, Kew royal botanic gardens](#);
- [Iplants Database](#);
- [International Plant Names Index](#);
- Index Plantarum Medicinalium Totius Mundi Eorumque Synonymorum (Penzo);
- USP (United States Pharmacopoeia);
- JP (Japanese Pharmacopoeia);
- German Commission E Monographs;
- ANTHROPOSOPHIC PHARMACEUTICAL CODEX (APC);
- [Taxonomy browser](#);
- Hagers Handbuch der Drogen und Arzneistoffe;
- Chinese Pharmacopoeia;
- Other relevant national Pharmacopoeias.

## 6. Annex II: Reference documents for definition and principles

[Detailed guidance on the electronic submission of information on medicinal products for human use by marketing authorisation holders to the European Medicines Agency in accordance with Article 57\(2\), second subparagraph of Regulation \(EC\) No. 726/2004;](#)

Food and Drug Administration Substance Registration System Standard Operating Procedure:  
[http://www.fda.gov/downloads/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/ucm127743.pdf;](http://www.fda.gov/downloads/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/ucm127743.pdf)

Defining Excipients in the Substance Registration System:  
[http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM291001.pdf;](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM291001.pdf)

ISO 11238:2012 Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on substances:  
[http://www.iso.org/iso/home/store/catalogue\\_tc/catalogue\\_detail.htm?csnumber=55031.](http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=55031)