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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

Chapter 6: Annex

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Annex: Definitions

- Chemical refers to a type of substance defined by a single molecular structure that is not a protein or nucleic acid substance.

  NOTE: Chemical substances are generally considered “small” molecules which have associated salts, solvates or ions and may be described using a single definitive or representative structure.

- Component refers to an intended constituent of a specified substance.

  EXAMPLE: Dimethicone and silicon dioxide are components of simethicone. Human Insulin protamine and zinc are the components in Human Insulin Isophane.

  NOTE: Components are used to describe the substances and specified substances that form a multi-substance material.

- Constituent refers to a substance or specified substance present within a specified substance.

  NOTE: Constituents can be impurities, degradants, active marker or signature substances, or single substances mixed together to form a product. Constituents shall have an associated role and amount. Constituent specifications shall be used to describe components as well as limits on impurities or related substances for a given material.

- Controlled vocabulary refers to a finite set of values that represent the only allowed values for a data item.

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

- Fraction refers to a distinct portion of material derived from a complex matrix, the composition of which differs from antecedent material.

  EXAMPLE: Sera to Immunoglobulins to polyclonal IgG is an example of recursive fractionation.

  NOTE: Concept used to describe source material. Concept is recursive in that a subsequent fraction can be derived from an antecedent fraction, which is implied in the order of listing.

- Grade refers to a set of specifications indicating the quality of a specified substance.

- Manufacturing refers to the process of production for a substance or medicinal product from the acquisition of all materials through all processing stages.

- Material refers to any entity that has mass, occupies space and consists of one or more substances.

- Mixture Substance is a type of polydisperse substance that is a combination of single substances isolated together or produced in the same synthetic process. Single substances of diverse origin that are brought together and do not undergo a chemical transformation shall be defined as multi-substance materials (Group 1 specified substances) and not as mixture substances.

EXAMPLE: Gentamicin would be defined as a mixture substance of Gentamicin C1A, Gentamicin C1, and Gentamicin C2. Glyceryl monoesters could be defined as a mixture substance of two single substances which differ in the position of esterification. Simethicone which consists of dimethicone and silicon dioxide would not be defined as a mixture substance since these are diverse materials brought together to form a product.

- Moiety refers to an entity within a substance that has a complete and continuous molecular structure. Moiety in this document may also be used to represent modification to a given substance.

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

  NOTE: Within this document, moiety shall be used in the context of non-stoichiometric chemical substances and in modification of nucleic acid, proteins, polymers and structurally diverse substances. Moieties shall be single substances, ions, or solvate molecules.

- Molecular Fragment refers to the portion of a molecule that has one or more sites of attachment to other fragments or moieties.

  NOTE: Molecular fragments will be used in the description of polymers to represent substituents and structural modifications to a given substance.

- Molecular Structure refers to the unambiguous representation of the arrangement of atoms. For the purposes of defining substances, the three dimensional conformations shall not be captured. Individual conformations or conformers of substances would only be captured in either a general sense for proteins (i.e. denatured) or when a given rotation about a single bond is restricted in such a way that the two different conformers are isolatable from each other and do not interconvert at room temperature (i.e. substituted biphenyls).

  NOTE: This representation should be generally translatable into a graphical representation.

- Molecular Weight refers to the mass of one molecule of a homogenous substance or the average mass of molecules that comprise a heterogeneous substance. The unified atomic mass unit is the unit of molecular weight. The type of molecular weight should always be captured.

  NOTE: For polymers there are several different types of molecular weight (weight average, number average).

- Multi-Substance Material refers to multiple substances and/or specified substances of diverse origin used as a component in the formulation of a medicinal product.

  EXAMPLE: Materials such as Human Insulin Isophane, Simethicone (Simeticone), Aluminum Lakes, Nicotine Polacrilex, and Phosphate Buffered Saline are all multi-substance ingredients.

NOTE: Multi-substance materials are Group 1 specified substances. Any medicinal product used to formulate another medicinal product could also be considered a multi-substance material.

- Nucleic Acid Substance refers to the type of substance that can be defined by a linear sequence of nucleosides typically linked through phosphate esters.

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

- Official name refers to the name given by an official registration authority.

- Pharmaceutical Product refers to the qualitative and quantitative composition of a medicinal product in the dose form approved for administration in line with the regulated product information.

  NOTE 1: A medicinal product may contain one or more pharmaceutical products.

  NOTE 2: In many instances the pharmaceutical product is equal to the manufactured item. However, there are instances where the manufactured item must undergo a transformation before being administered to the patient (as the pharmaceutical product) and the two are not equal.

- Polydisperse Substance refers to a substance containing multiple related molecular components.

  NOTE: Chemical substance salts and solvates shall not be defined as polydisperse substances.

- Polymer refers to the type of polydisperse substance that contains structural repeating units linked by covalent bonds.

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

- Protein refers to the 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 shall be described as protein substances. Sites of glycosylation, disulfide linkages and glycosylation type (e.g. fungal, plant, arthropod, avian, mammalian, human) shall be defining elements of protein substances when known. A graphical molecular structure shall also be included in the definition of all peptides of 15 amino acid residues or less.

  NOTE 2: Protein substance may refer to one of the following type: Vaccine or Other

- Salt refers to an ionic substances formed from the neutralization reaction of an acid and base. Salts are ionic compounds composed of cations (positive ions) and anions (negative ions).

- Single Substance refers to a substance that can be described by a single representation or set of descriptive elements. A single substance can be described

using one or more of five types of elements; chemical, protein, nucleic acid, polymer and structurally diverse substances.

NOTE: 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.

- Specified Substance refers to groups of elements which describe multi-substance materials and specify further information on substances and multi-substance materials relevant to the description of medicinal products.

  NOTE 1: For example, this could include grade, units of measure, physical form, constituents, manufacturer, critical manufacturing processes (i.e. extraction, synthetic, recombinant processes), specification and the analytical methods used to determine that a substance is in compliance with a specification.

  NOTE 2: There are four different groups of elements that can be used to define a given specified substance and specific relationships between each group of elements.

- Specified Substance – Group 1 refers to material that contains multiple substances, solvents used in the preparation of herbal or allergenic extracts, specific marker or signature substances present in materials derived from biological matrices, the physical form of a substance when relevant and any properties essential to the description of the material.

  Specified Substance Level 1 includes constituents, physical form and property. Constituents consist of intended substances added to create a multi-substance material, solvents used in the preparation of extracts, marker or signature substances present in animal derived material.

  Impurities or degradents shall not be constituents for Group 1 specified substances.

  NOTE 1: This grouping of constituents allows for the definitions of many materials in commerce that are used in the formulation of medicinal products.

- Specified Substance – Group 2 refers to the manufacturer of either a substance or a specified substance Group 1, along with minimal manufacturing information.

  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), 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.

- Specified Substance – Group 3 refers to the grade of the material along with the source that defines the given grade.

  Group 3 elements shall be used to distinguish specific pharmacopoeial and technical grades of material.

If the pharmacopoeial monographs related to a substance are not harmonized, the grade for each pharmacopeia shall be a separate Group 3 specified substance.

NOTE: For most active pharmaceutical substances, typical grades are USP, EP, or JP. For herbal substances the grades would be standardized, quantified and unstandardized.

EXAMPLE: For the substance *Water*, the Group 3 specified substance shall be *Sterile Water for Injection USP*.

- Stoichiometric refers to substances that contain moieties in simple integral ratios.

  NOTE 1: Defined composition stoichiometry shall be represented in the structural representation of a given substance. Moieties shall be represented using the lowest common factors such that a fractional representation is avoided. Substances will either be defined as stoichiometric or non-stoichiometric.

  NOTE 2: Chemicals have defined composition stoichiometry when the ratio of all moieties, (ion, counter ion and solvate) can be represented as simple integral ratios.

- Stereochemistry refers to relative spatial arrangement of atoms within molecules.

- Structurally Diverse Substance refers to a 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 substance. 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 shall be defined as structurally diverse substances.

  NOTE 2: Structurally Diverse Substance may refer to one of the following type

  - Vaccine
  - Immunoglobulin
  - Blood derived
  - Herbal
  - Allergen
  - Cell therapy
  - Other

- 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 shall be 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. Pharmacopeial terminology and defining characteristics will be used when available and appropriate. Defining elements are dependent on the type of substance.

NOTE 2: 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 estrogens) 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. Substances may be salts, solvates, free acids, free bases, mixtures of related compounds that are either isolated or synthesized together.

- Substituent refers to the molecular fragment attached to a structural repeat unit of a polymer that typically replaces a hydrogen atom.

  NOTE: This information shall be captured as part of the structural repeat unit when the position of substitution is fully occupied. When occupancy of a site is incomplete, the amount of a substitiuent or substituents shall be specified as either a fragment or moiety structural modification.