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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: Definitions

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7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8668
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

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.

- 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.

- 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 can be defined as multi-substance materials (Group 1 specified substances) and not as mixture substances.

  EXAMPLE: Gentamicin can be defined as a mixture substance of Gentamicin C1A, Gentamicin C1, and Gentamicin C2. Glyceryl monoesters can 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 should not be defined as a mixture substance since these are diverse materials brought together to form a product.

- 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) can also be identified. Oligonucleotides and gene elements (i.e. promoters, enhancers, coding sequences, and silencers) can be defined as nucleic acid substances.

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

- Pharmaceutical Product refers to a technical concept, more specifically 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 cannot 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 cannot 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 can be described as protein substances. Sites of glycosylation, disulfide linkages and glycosylation type (e.g. fungal, plant, arthropod, avian, mammalian, human) can be defining elements of protein substances when known. A graphical molecular structure can 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.

  It 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 can 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 can 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 allow for 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 are used to distinguish specific pharmacopoeial and technical grades of material.

  NOTE: For most active pharmaceutical substances, typical grades are European Pharmacopoeia (EP). For herbal substances the grades would be standardized, quantified and unstandardized.

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

- 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 should 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 should 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.