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Question 1

What is the definition of a biological medicinal product?

Answer:
A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source, such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells) and for which a combination of physico-chemical-biological testing and the production process and its control is needed for its characterisation and the determination of its quality. This definition is given in Part I of Annex I of Directive 2001/83/EC (as amended by Directive 2003/63/EC).

According to this definition the substance should be of biological origin and, due to its complexity, a combination of physico-chemical-biological testing together with testing and control of the production process is needed for its characterisation and determination of quality.

Question 2

How is this definition applied?

Answer: The legislation makes it explicit that as a result, the following shall be considered as biological medicinal products: recombinant proteins, monoclonal antibodies, blood products, immunological medicinal products such as sera and vaccines, allergens, and advanced technology products such as gene and cell therapy products. In addition, a number of other products should be considered biological medicinal products, because they meet the aforementioned legal criteria of biological origin and complexity.

For a (non-exhaustive) list of these other biological medicinal products, click here. Based on scientific reasoning, analogous products not mentioned in this list should also be considered as biological medicinal products.

Question 3

Are there special requirements for biological medicinal products?

Answer: Yes, the regulatory approach to biological medicinal products differs in several ways.

- In general, for abridged applications of biological medicinal products the legal basis should be Article 10(4) of Directive 2001/83/EC. Exemptions might only be possible in rare exceptional cases and should be discussed with the RMS well in advance of submission to give the RMS the opportunity to discuss this in CMDh (see Q/A 4)

- Given the complexity of the characterisation of the product, bibliographic applications according to Article 10a of Directive 2001/83/EC are normally not applicable. In that case, an application according to Article 8(3) of Directive 2001/83/EC would be the appropriate legal basis. In exceptional cases however,
Article 10a might be considered based on the available bibliographic data and should in that case be discussed with the RMS well in advance of submission to give the RMS the opportunity to discuss this in CMDh.

- Due to this complexity, it is also not possible to use the ASMF-procedure (see: Guideline on Active Substance-Master-File Procedure - CPMP/QWP/227/02 current revision).

- With regard to variations, specific conditions apply for biological medicinal products because of their complexity. (see Notice to Applicants (NTA), Vol. 2A, Chapter 5: Guidelines of 16 May 2013 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures - C (2013) 2804 (OJ C 223, 2.8.2013, p. 1–79).

- Separate guidelines are available for biological medicinal products. These can be accessed at the EMA website (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_con
tent_000082.jsp&mid=WC0b01ac0580027547).

- Biological medicinal products can be registered through the mutual recognition or decentralised procedures, provided that they do not fall within the Annex to Regulation (EC) No 726/2004 - Medicinal products to be authorised by the Community, in which case the centralised procedure has to be followed.

**Question 4**

**What is the acceptable legal basis for an abridged application for denatured human albumin nanocolloid containing medicinal products used for radiolabelling?**

**Answer:** Although denatured human albumin nanocolloid is produced from biological source (human serum albumin) which normally requires Article 10(4) as legal basis (see Q/A 2) abridged applications according to Art. 10 (1) or 10(3) might be acceptable considering that the nanocolloid is produced by denaturation of human serum albumin and the physico-chemical aspects, mainly the particle size and particle size distribution are the most critical attributes in relation to the characterisation and demonstration of similarity. Denatured albumin is intended to carry or bind the radio-nuclide, biological activity is not expected.

The following rules apply:

- An application according to Art. 10(1) is acceptable in case similarity can be fully demonstrated based on physico-chemical criteria, mainly particle size and particle size distribution

- An application according to Art. 10(3) is acceptable in case there are minor differences in these quality criteria (e.g. minor deviation in the particle size distribution), but these differences are clinically not relevant, which is demonstrated with appropriate pre-clinical tests or clinical trials or justification based on literature (“diagnostic” equivalence can be shown)

- An application of Art. 10(4) should be submitted in case major differences in the quality attributes occur (e.g. from different manufacturing process) so that an impact
on efficacy and safety cannot be excluded. In these cases similarity can only be
demonstrated through pre-clinical tests or clinical trials.

In case such an abridged application is envisaged, it is strongly recommended to discuss the
regulatory approach with the RMS early in advance of the submission so that the RMS might
discuss subsequently the proposed legal basis in CMDh before the application will be
submitted.