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3 Committee for Medicinal Products for Veterinary Use (CVMP)

4 Stem cell -based products for veterinary use: Specific 5 questions on extraneous agents to be addressed by 6 ADVENT

7 Draft

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Background

Cell-based medicinal products (CBMP) are heterogeneous with regard to the origin and type of cells and to the complexity of the product.

Cells may be self-renewing stem cells, more committed progenitor cells or terminally differentiated cells exerting a specific defined physiological function.

Stem cell -based products (SCP) and animal stem cell -based products (ASCP) are a subset of cell-based medicinal products containing, consisting of or derived from cells such as stem cells, progenitor cells, precursor cells, stem cell -like cells, reprogrammed cells, and other cell types with similar properties.

The term “stem cell” means a non-terminally differentiated, self-renewing cell that harbours the ability to produce mature, differentiated daughter cells. Stem cells serve to regulate or participate in normal tissue homeostasis and embryonic and foetal development.

The use of stem cell -based products in the veterinary sector, mainly for horses and dogs, is increasing and is raising questions for manufacturers, authorities and users.

A critical aspect under discussion concerns the freedom of extraneous agents of the stem cell -based product. Freedom from extraneous agents is a high priority for any veterinary medicinal product, including therefore stem cell -based products veterinary medicinal products to be administered parenterally, and the requirement to test veterinary medicinal products for potential infectious contaminants is specified in Directive 2001/82/EC and in the European Pharmacopoeia (Ph. Eur.).

Contamination could originate from the starting or raw materials, or adventitiously introduced during the manufacturing process. Differentiation between the cell sourcing steps, which include donor/tissue screening for extraneous agents (viruses, bacteria, protozoa), and the process thereafter during manufacture where typical microbiological contamination (not related to donor/tissue) might occur (viruses, bacteria, mycoplasma) is reasonable.

Freedom of extraneous agents is crucial when donor animals need to be qualified as source of tissues/fluids/cells which contain the stem cells wanted.

Defining freedom from extraneous agents poses a real challenge taken into account that the ideal absolute freedom from extraneous agents or residual pathogenicity is neither possible nor realistic. The detection of extraneous agents depends on the amount of agent present in the raw material as well as the methods used for sampling and detection.

The manufacture of stem cell -based products usually does not include terminal sterilisation of the product or removal or inactivation steps for viruses and parasites. Therefore it is crucial to define acceptance criteria for starting and raw materials derived from human or animal origin taking into consideration the intended use.

Animal stem cells must be sourced from donor animals which are appropriately screened and tested for the absence of extraneous agents. Risk control for extraneous agents includes control of sourcing, testing of starting materials of animal origin and/or subjecting them to validated inactivation procedures, validation of the capacity of the manufacturing process of the product to remove and/or inactivate viruses, and, if deemed necessary, testing of the final product.

Currently no specific guidance is available for stem cell -products for veterinary use. Guidance documents have been established for human cell-based products (CHMP Guideline on human cell-based products, EMA/CHMP/410869/2006 and CAT Reflection paper on stem cell -based medicinal

products, EMA/CAT/571134/2009). The CHMP Guideline on human cell-based products describes the general procedure to ensure quality during collection of source material and manufacturing process.

The EU Guide to good manufacturing practice - GMP (provided in Eudralex Volume 4) covers in Part I basic GMP principles for the manufacture of human and veterinary medicinal products. Annex 2 to this guide covers the manufacture of human biological products including advanced therapy medicinal products (ATMP). The principle provisions laid down in that Annex are considered to be applicable also to stem cell -products for veterinary use.

Safety aspects of extraneous agents with regard to veterinary medicinal products are included e.g. in the following documents:

- The table of extraneous agents to be tested for in relation to the general and species-specific guidelines on production and control of mammalian veterinary vaccines should be taken into consideration for viral safety testing of materials of animal species (Eudralex Vol. 7, Blm10a). This table is intended to be replaced by the CVMP guideline on the requirements for the production and control of immunological veterinary medicinal products (Annex 2- The approach to demonstrate freedom from extraneous agents as part of the production and control of immunological veterinary medicinal products for mammalian species and fish). (EMA/CVMP/IWP/206555/2010-Rev.1, under development)
- Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3).
- The position paper of the Coordination Group for Mutual Recognition and Decentralised Procedures - Veterinary (CMDv/POS/001) on requirements for starting material of animal origin.

Principles on viral safety are also laid down in the European Pharmacopoeia (Ph. Eur.) (e.g. Chapter 5.2.5:Substances of animal origin for the production of veterinary vaccines'; Chapter 5.1.7: Viral safety; Chapter 5.2.8: Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products).

The European Pharmacopoeia has recently adopted the general chapter on microbiological products: Chapter 5.2.12: Raw materials of biological origin for the production of cell-based and gene therapy medicinal products which will be published in the 9th edition (July 2016) and will come into force 01 January 2017.

The United States Pharmacopeia (USP) has established a specific chapter 1046 addressing cellular and tissue-based products, which gives information on several aspects of CBMPs, including freedom from extraneous agents.

Following a review of the scientific information relating to extraneous agents of stem cell –products for veterinary use, a number of areas have been identified that would benefit from further consideration by relevant experts and, where appropriate, the elaboration of specific guidance in the form of question and answer (Q&A).

Three specific questions for further consideration have been identified. These questions, together with a brief comment outlining the background, are presented below.

Questions

Freedom from extraneous agents of stem cell -products

Freedom from extraneous agents is a crucial aspect of quality evaluation of stem cell -based preparations and therefore appropriate acceptance criteria for starting and raw materials derived from human or animal origin need to be established.

Question 1: Is the currently available guidance on demonstration of freedom from viruses and bacteria (list of viruses and bacteria which must be taken into account) appropriate and sufficient for stem cell -based products intended for use in horses and dogs?

If not, would it be beneficial to elaborate further specific guidance and appropriate requirements for stem cell -products intended for use in horses and dogs?

Question 2: As no EU guidance is currently available on demonstration of freedom from parasites, especially protozoa, which protozoa should be specifically taken into account for stem cell -based products intended for horses and dogs?

Question 3: Are there (would you have) any recommendations regarding other aspects or approaches to be taken into account (risk control, risk analysis, risk mitigation, risk management) concerning the freedom of extraneous agents of stem cell- based products for horses and dogs?