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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 sterility to be addressed by ADVENT

6 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 is increasing and is raising questions for manufacturers, authorities and users.

One of the questions under discussion concerns the absence of bacteria, fungi and mycoplasma (sterlity) of the finished product. As stem cell -based products are veterinary medicinal products to be administered parenterally, they should be sterile. The final product should not contain any detectable microorganism. The active substances of stem cell -based products are living cells which themselves cannot be sterilised by physical or chemical methods, and also the final product can neither be terminally sterilised nor sterilised by filtration.

Microbiological contamination can occur at various steps from the initial sampling of the cells/tissue up to the final product when packaged into containers. A crucial step is usually the sourcing and collection of the stem cells as at this step it is not always possible to fully implement aseptic techniques. Further sources of microbiological contamination are raw materials. Also the *in vitro* processing of stem cells carries the risk of contamination.

Furthermore, the control for the absence of microorganisms is a pivotal aspect of *in process* controls and quality evaluation of cell preparations at selected stages of the production.

The manufacture of stem cell -based products does not allow terminal sterilisation of the product or removal/inactivation of microbial contaminants. Therefore it is crucial to build an overall microbiological control strategy that will not only rely on finished product testing, but ensure the microbiological purity of the product by using appropriately qualified and tested starting and raw materials and applying a validated aseptic manufacturing process including appropriate in-process controls.

Testing for sterility at the level of the final stem cell -based product for release is another aspect. Sometimes these products have short shelf-lives and therefore the classical pharmacopoeial sterility test methods cannot be applied. In these cases, other suitable (rapid) microbiological methods should be selected. Alternative validated testing methods may be acceptable, if justified. It needs to be discussed/clarified whether these methods (maybe in combination with other approaches) might be appropriate for sterility testing of stem cell -based products.

The presence of endotoxins in stem cell -based products is also a safety concern. Therefore, control of endotoxins in the manufacture of stem cell -based products is an essential element of any quality control program.

Currently no specific guidance is available for stem cell –based 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). These guidance documents request human cell -based products to be sterile. The 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 –based products for veterinary use.

For the microbiological control of medicinal products, including veterinary biologicals, a number of methods and recommendations are established and described in the European Pharmacopoeia (e.g. 2.6.1 ‚Sterility', 2.6.7 ‚Mycoplasmas', 2.6.27 'Microbiological Control of Cellular Products', 5.1.6 'Alternative methods for control of microbiological quality', 5.1.9 Guidelines for using the test for sterility). In the general text 5.14. on 'Gene transfer medicinal products for human use' the Ph Eur advices to test genetically modified cells for specific characteristics (sterility, mycoplasma, endotoxin).

The United States Pharmacopeia (USP) has established a specific chapter 1046 addressing 'Cellular and Tissue -based Products', which gives information on lots of aspects of CBMPs, also on sterility, mycoplasma and endotoxin testing.

Following a review of the scientific information relating to stem cells, ADVENT identified a number of areas 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).

Question

Microbiological control of stem cell –based products and control methods

Microbiological control: This is a pivotal aspect of process control and quality evaluation of all cell preparations and therefore tests for the absence of microbial agents, at selected stages of the production need to be established. In addition, a thorough testing for the absence of bacteria, fungi and mycoplasma should be performed at the level of the finished product at release. Classical sterility testing is addressed in various regulations worldwide, including the European Pharmacopoeia (EP). If the finished product shelf-life is extremely short the established methods for microbiological control have limitations and are normally not applicable.

Question: Are there any recommendations regarding the use of other approaches or methods or further issues applicable for the sterility control of stem cell –based products *in process* and/or at the finished product?