1 14 July 2016
2 EMA/CVMP/ADVENT/193811/2016
3 Committee for Medicinal Products for Veterinary Use (CVMP)

4 Stem cell-based products for veterinary use: specific 5 questions on target animal safety to be addressed by 6 ADVENT

7 Draft

Draft agreed by Ad Hoc Expert Group on Veterinary Novel Therapies (ADVENT)	June 2016
Adopted by CVMP for preparation of a Question and Answer document	14 July 2016
Start of public consultation	25 July 2016
End of consultation (deadline for comments)	30 September 2016

8

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

9

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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 concern in relation with the stem cell -based products is how to provide safety data in target species. There are specific safety concerns related to stem cell treatment as tumour induction, biodistribution of cells to other organs, ectopic tissue formation, immune rejection and increased susceptibility to the disease the cells are meant to treat.

Safety related to stem cell treatments could be specifically assessed in laboratory studies, and together with supporting information, bibliographic data and surveillance in efficacy studies, it could be sufficient to address the risk. In general systemic and local safety in target species may be monitored in efficacy studies.

There are specific safety concerns that need to be assessed, for instance, the immunogenicity of mesenchymal stem cells (MSC). Although *in vitro* studies support that MSCs exhibit marked immunomodulatory activity a direct translation to the *in vivo* situation cannot be established. In some *in vivo* studies MSCs proved to be strongly immunogenic and sensitising against subsequent repeated administrations. It appears that MSCs exert their biological function mainly, if not exclusively, via trophic mechanisms. Anti-inflammatory and immune-modulatory molecules produced by cells can potentially delay time to rejection providing a window of therapeutic benefit but limiting the option for subsequent re-exposure.

It appears also that pre-existing inflammatory reactions could enhance rejection. Given that MSCs will be administered into regions subject to local or systemic inflammation this may increase the risk of immune rejection (in the absence of immunosuppressive therapies).

Because stem cell -based products are novel therapies, different from both pharmaceutical and immunological products, relevant and feasible parameters in relation to different safety concerns to be monitored in efficacy studies need to be considered. Additional consideration is required whether all data on target animal tolerance could be obtained from efficacy studies or whether it is necessary to perform specific target animal safety (TAS) studies in order to obtain more specific information.

Specific aspects should be taken into account if a TAS study is required. The design of the study shall include all critical elements to provide pivotal data on tolerance of the treatment. Currently no specific guidance is available for stem cell -products for veterinary use. Guidance documents have been established for human cell -based products but they are not applicable when safety on target species

needs to be assessed. Different pharmaceutical and immunological guidelines (Guideline on target animal safety for veterinary pharmaceutical products, VICH GL43, and Guideline on target animal safety for veterinary live and inactivated vaccines, VICH GL44) provide guidance for the traditional design of a TAS study but deviations from the traditional design may be justified in order to obtain relevant safety information on the treatment.

Following a review of scientific information related to target animal safety of stem cell -products, 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).

Four specific questions for further consideration have been identified. These questions are presented below.

With regard to the questions raised here focus should be given only on the use of allogeneic MSCs.

Questions

Question 1: Which would be the major safety limitations that cannot be solved in efficacy studies and should be addressed by a different approach such as a specific TAS?

Question 2: As it has been shown that mesenchymal stem cell therapy could be strongly immunogenic and sensitising against subsequent repeated administrations and that pre-existing inflammatory tissues could enhance rejection, how should a TAS study be designed to investigate these potential issues?

Question 3: What would be considered relevant and feasible parameters to be included in monitoring safety in efficacy studies in order to have a well-documented margin of safety in stem cell -based products?

Question 4: How should a TAS study be designed to include all critical elements (physical examinations, clinical pathology tests, biopsies and post-mortem examination) to provide pivotal data on local tolerance?