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Committee for Veterinary Medicinal Products (CVMP)

Concept paper on the development and data requirements of potency tests for cell-based therapy products and the relation to clinical efficacy

Agreed by Novel Therapies and Technologies Working Party (NTWP)	24 November 2021
Adopted by CVMP for release for consultation	19 January 2022
Start of public consultation	28 January 2022
End of consultation (deadline for comments)	29 April 2022

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

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1. Introduction

Continuous progress in the fields of biology, biotechnology and medicine has led to the development of new treatments and highly innovative medicinal products, which might include viable cells. These cell-based medicinal products have a high potential in the treatment of various diseases where there is a previously unmet medical need.

Annex II of Regulation (EC) 2019/6 (section V.1.5.3, Regenerative medicine, tissue engineering and cell therapy veterinary medicinal products) states: "Cell therapy veterinary medicinal products are biological veterinary medicinal products that contain or consist of cells or tissues that have been subject to substantial manipulation in either nature or function so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor. They are presented as having properties for, or are used in or administered to animals with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues or to regenerating, repairing or replacing a tissue."

Data requirements specific to these products are listed. In section V.1.5.3.3.d information is, amongst others, requested on potency in order to obtain a marketing authorisation.

The mechanism(s) of action is/are not fully characterized for cell-based products and a link between the potency assay and relevant biological properties is thus missing in many cases. It is proposed to draft guidance on requirements for potency testing of veterinary cell-based products. The purpose of the guideline to be developed is to provide clear advice for applicants and assessors on potency testing of veterinary cell-based products by considering the mechanism(s) of action that is most relevant (most likely) for the clinical indication.

2. Problem statement

A number of cell-based products have been developed and authorised as veterinary medicines recently and it is expected that more marketing authorisation applications for such products will follow.

The mechanisms of action of cell-based medicinal products are not fully characterized or very complex and there is frequently also a lack of understanding of the biological properties of the cells, with the result that product attributes relevant to potency can be difficult to determine.

In principle, the results of a potency assay should provide assurance that the active ingredient is of sufficient quantity and quality and is consistent from batch to batch, in order to induce a meaningful biological response. In other words, the potency assay should be able to detect clinically meaningful changes in the quality and/or quantity of active ingredient in a product.

The correlation of the potency assay with clinical efficacy, the ability of the assay to differentiate between batches of sufficient and insufficient biological activity and its capability of being stability-indicating can be considered as main challenges when developing a potency assay.

3. Discussion (on the problem statement)

The guideline to be developed should include all types of cellular medicinal products that have been substantially manipulated including cell fractions, taking into consideration the origin of cells (e.g. autologous, allogenic, xenogenic, etc.) and their properties (proliferative and/or differentiation

potential), as different clinical indications are expected. Genetically modified cell products are also within the scope of the guideline.

Since the mechanism(s) of action is/are largely unknown for cell-based products, a link between the potency assay and relevant biological properties can be difficult to establish. The correlation between a biological assay and the expected clinical response could be investigated in preclinical (pharmacodynamic) studies and/or clinical trials. However, most emphasis should be given to clinical investigations.

In general, in order to provide the relation between potency and clinical efficacy, the development of a potency assay should start as soon as possible during product development. Since a clear link of the potency assay to relevant biological properties may be missing, it is necessary to define data requirements for the development of a potency assay.

Therefore, the guideline should provide the following:

- Guidance on how the relation between potency assay(s) and clinical efficacy is expected to be addressed;
- Guidance on defining the most relevant (most likely) mode of action (MoA), which is of importance for potency testing;
- Guidance on potency testing during development and characterization of the product in order to be sure that the validation state of the potency test will be in line with product development and an appropriately validated potency assay will be available at the latest for pivotal studies;
- Guidance on the type of assay or combination of assays to support the potency test; for the development phase a combination of assays might be beneficial → when relevant clinical data is available, the assay that allows most appropriate conclusions on potency might be sufficient for in-process control and release testing in routine manufacture;
- Guidance on the link between the potency assay and clinical efficacy in studies in laboratory animals, pre-clinical studies (e.g. pharmacodynamics) and clinical trials; if appropriate, the optional use of sub-potent batches in animal studies is recommended in the development of potency assays;
- Guidance regarding the evaluation of influence by the in vivo environment, e.g. ongoing inflammatory processes at the injection/graft site, which could affect biological activity and hence efficacy;
- Guidance on other components in the cell-based therapy product that might interfere with the potency assay.

4. Recommendation

The Committee for Medicinal Products for Veterinary Use (CVMP) recommends the Operational Expert Group (OEG) for cell therapies, a subgroup of the Novel Therapies and Technologies Working Party (NTWP), to draft a guideline on veterinary cell-based therapy products taking into consideration the mechanism of action, potency and clinical effects of such products.

The scope of the guideline is to give clear advice to applicants and assessors on the development and data requirements of potency tests for cell-based therapy products as well as validation of analytical methods used for the potency assay. Based on the mechanism of action that is most relevant (most likely) for the clinical indication, potency testing should aim at the product´s most relevant biological properties. Consistent functional activity of the medicinal product in the recipient has to be assured,

and the potency of the product within justified limits should be demonstrated by bioassay(s) based on defined biological effect(s) as close as possible to the anticipated mechanism(s) of action/clinical response. The relation between potency testing and clinical efficacy has to be demonstrated as good as possible based on current scientific knowledge.

5. Proposed timetable

Q1 2022	Concept paper released for public consultation
Q2 2022	End of public consultation
Q4 2022	Draft guideline to be released for public consultation.

6. Resource requirements for preparation

The development of the new guideline will involve the OEG on cell therapies, the NTWP, and the CVMP.

A total of 21 months is expected until the publication of the guideline. The OEG on cell therapies will meet virtually as required (4-6 virtual meetings). Discussion/endorsement is foreseen at 3-5 NTWP meetings and 4 CVMP plenary meetings.

7. Impact assessment (anticipated)

During relevant scientific advice and marketing authorisation procedures questions on potency testing, mechanism(s) of action and respective linkage to clinical efficacy of cell therapy products have been identified as frequent and/or major issues.

Thus, provision of clear guidance for applicants and assessors on these issues is considered to significantly improve the effective product development and the assessment of respective marketing authorisation applications. These improvements will save resources and costs for both, applicants and regulatory authorities, and will accelerate market access of innovative veterinary medicines.

8. Interested parties

Veterinary pharmaceutical industry and consultants.

EU Regulatory authorities in the EU involved in assessment of marketing authorisation applications for veterinary cell therapy products.

9. References to literature, guidelines, etc.

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC.

Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council (draft published for feedback, 10 November 2020).

Guideline on potency testing of cell-based immunotherapy medicinal products for the treatment of cancer (EMA/CHMP/BWP/271475/2006 rev.1).

Reflection paper on stem cell-based medicinal products (EMA/CAT/571134/2009).

Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006).

FDA Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products

(http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.).

VICH GL1: Validation of analytical procedures – Definition and Terminology.

VICH GL2: Validation of analytical procedures – Methodology.

Questions and answers on allogenic mesenchymal stem cell-based products for veterinary use: specific questions on tumorigenicity (EMA/CVMP/ADVENT/791465/2016).