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SCIENCE MEDICINES HEALTH

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Committee for Veterinary Medicinal Products (CVMP)

Guidance and template on the risk management plan (RMP) for novel therapy veterinary medicinal products

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General considerations

For the authorisation of veterinary medicinal products (VMPs) qualified as novel therapies (NTs), a risk management plan (RMP) is required in accordance with Regulation (EU) 2019/6, Annex II, section V.1.1.6 and the Guidance to Applicants - Veterinary Medicinal Products (C/2024/1443).

A risk management plan should be provided by the applicant in the initial marketing authorisation dossier submission (Part 1a).

The proposed risk management plan will be assessed by the CVMP as part of the evaluation of the marketing authorisation application and a summary will be published as part of the European public assessment report (EPAR).

The goals of the RMP as worded in Annex II to Regulation (EU) 2019/6 are to implement the necessary measures to:

- Detect early or delayed signals of adverse reactions*
- Prevent clinical consequences of adverse reactions and ensure timely treatment*
- Gain information on long-term safety and efficacy of novel therapy veterinary medicinal products.*

Moreover, the imposition of post-marketing authorisation studies can be considered on a case-by-case basis.

General guidance

When filling the table on the identified or potential risks, please be as concise as possible and ensure that the content is scientifically based and does not include any element of a promotional nature.

The green text is for guidance only and should be removed when completing the risk management plan.

The information contained in this template is non-exhaustive.

This document should be interpreted as a guidance wherein not all aspects are necessarily mandatory. Rather, an adaptation of the requirements to the product in question is expected.

The RMP is not intended as a re-evaluation of the available data, but rather as a reflection on the risks that may arise as a consequence of the intrinsic characteristics of the novel therapy VMP. To this end, risks should not only be identified based on the available preclinical and clinical data; specific characteristics of the novel therapy VMPs must also be taken into account (notably its composition—e.g. biological materials with particular risks—its manufacturing process, mode of action, administration, etc.).

The RMP is expected to cover particular risks that are rare and/or long-term and/or highly specific to the category of novel therapy VMP, since standard pharmacovigilance activities already cover continuous monitoring of the VMP by the marketing authorisation holder.

EU Risk Management Plan (RMP) for <Invented name> (INN or common name)

Identification of risks to be included in the risk management plan of the novel therapy VMP

This section summarises the risks that could potentially be included in the RMP according to Regulation (EU) 2019/6 Annex II, section V.1.1.6.

An identified risk is defined as an undesirable clinical outcome for which there is sufficient scientific evidence that it is caused by the VMP.

A potential risk is an undesirable clinical outcome for which there is scientific evidence to suspect the possibility of a causal relationship with the VMP, but where there is currently insufficient evidence to conclude that this association is causal.

Based on the available data for the novel therapy VMP and its intrinsic characteristics, identify the risks—whether confirmed or potential—associated to adverse events, discuss their clinical consequences, which early signals of adverse events may occur (i.e. first signs of a cytokine storm), which delayed adverse events may occur (such as tumorigenesis), timely treatment/management options, and the monitoring of long-term safety and efficacy. Discuss the methodology used to capture these events and assess whether they are adequately monitored through standard pharmacovigilance activities. Explain the routine risk minimisation measures implemented to reduce these risks.

If additional pharmacovigilance activities or risk minimisation measures are needed, provide a justification for their inclusion in the risk management plan, and summarise them in the table below.

If no additional measures are to be applied, a statement and a justification that the standard pharmacovigilance and risk minimisation activities described are sufficient to manage the safety and efficacy concerns of the VMP should be included.

The following subsections are intended solely as guidance; they are not expected to be addressed separately, as there may be overlap between them. The questions could guide the identification of the risks.

Additionally, examples of risks to the type of novel therapy VMP that may be considered are listed in the Annex.

Early or delayed adverse events

This section includes a summary of the expected adverse events for the NT VMP. To help with the content of this section the following questions could be considered by the MAH/applicant:

- Which adverse events may be expected, and how should they be managed when they occur?*
- Which early signs of adverse events may occur and how can they be detected?*
- How can it be ensured that delayed adverse events are detected?*
- Are the standard pharmacovigilance measures and risk minimisation measures sufficient to monitor these adverse events?*

Clinical consequences of adverse events and timely treatment

A summary of the clinical consequences associated to adverse events should be described here.

Guidance questions are:

- *Are there clinical consequences associated with the identified adverse events?*
- *Which treatment options are available to date for these clinical consequences?*
- *How can timely access to treatment be ensured?*

Long-term safety and efficacy

Reflection on the available information on the long-term safety and efficacy should be stated here.

Guidance questions are:

- *Do the long-term safety and efficacy of the VMP require specific follow-up?*
- *How and by which methods will the long-term safety and efficacy of the VMP be monitored?
For example, protocols for follow-up of treated animals.*
- *Do post-authorisation long-term safety and efficacy studies need to be included in the RMP,
and is the wording aligned with Annex II of the product information?*

Risk Management Plan

Include the potential and identified risks, and the additional pharmacovigilance activities and risk minimisation measures in the table below.

Regarding the additional pharmacovigilance measures, this section should include a brief description of the pharmacovigilance activities beyond adverse event reporting and signal detection. In general terms, activities which are mandatory for all VMPs and included in the pharmacovigilance system master file do not need to be included here. For well-characterised potential risks identified for the RMP in the section above, standard pharmacovigilance may be sufficient. If additional pharmacovigilance activities are needed, these should be included in the table. The following questions guide the reflection on the pharmacovigilance measures that may be needed for potential risks to be included in the RMP:

- ✓ *Are all the potential and identified risks for the RMP covered in the pharmacovigilance system?*
- ✓ *Are standard pharmacovigilance activities adequate or are additional pharmacovigilance activities necessary?*
- ✓ *Are the activities in the pharmacovigilance system clearly defined, described and suitable for identifying or characterising risks or providing missing information?*
- ✓ *Are the safety and/or efficacy studies that have been imposed as conditions clearly identified?*
- ✓ *Are the proposed additional studies necessary, feasible, non-promotional and able to provide the required further characterisation of the risk(s) and address the scientific questions?*

- ✓ Are timelines and milestones appropriate and feasible for the proposed actions, including those for the submission of results?

To decide on the risk minimisation measures to be taken, the following questions could be considered:

- ✓ Are standard risk minimisation measures sufficient or is there a need for additional risk minimisation measures?
- ✓ Have additional risk minimisation measures been suggested and, if so, are these sufficiently justified and risk-proportionate? Is implementation feasible in all Member States?

Identified or potential risk 1:	
Evidence for linking the risk to the VMP	<i>Describe why the risk may be linked to the VMP</i>
Additional pharmacovigilance activities	<p><i>The Applicant should describe additional pharmacovigilance activities related to the:</i></p> <ul style="list-style-type: none"> • <i>Collection of information on long-term safety and efficacy</i> <p><i>And where applicable:</i></p> <ul style="list-style-type: none"> • <i>Detection of early signs of adverse events (i.e. the first signs to appear: for instance, fever at the start of a cytokine storm)</i> • <i>Detection of delayed adverse events (e.g. regular health checks)</i> • <i>Prevention of clinical consequences of adverse events and assurance of timely treatment</i> • <i>Use of traceability data for surveillance purposes (e.g. an established registry of batches of VMP distributed to a particular centre and its record linkage to the pharmacovigilance database of reports received from that centre).</i> <p><Post-authorisation study name></p> <p><u>Study title:</u></p> <p><i>e.g. - Surveillance study to collect long-term safety data on the VMP</i></p>
Additional risk minimisation measures	<p>Additional risk minimisation measures:</p> <p><i>e.g. guides for veterinarians/owners, owner's diary, checklist for veterinarians for risk minimisation measures.</i></p>

Annex: Examples of risks for specific types of novel therapy veterinary medicinal products

This subsection provides an overview of risks commonly linked to the different categories of novel therapies. This is not an exhaustive list. When preparing a risk management plan for a particular novel therapy VMP, comprehensive scientific consideration should be given to the important identified or potential risks, and to the important missing information.

Examples of risks associated with cell-based VMPs:

- Risk of transmission of diseases due to use of biological materials.
- Risk of tumorigenicity: Depending on the characteristics of the VMPs (e.g. if the manufacturing process includes extensive culture of proliferating cells, like mesenchymal stem cells); the differentiation capacity of the cells may be affected, potentially leading to a risk of tumorigenicity.
- Risk of unwanted immunogenicity: including, but not limited to, anaphylaxis, graft versus host disease, hypersensitivity reactions.
- Risk of lack of expected efficacy: related to quality assurance and characteristics of the finished product as well as storage and distribution and administration procedures.
- Long-term efficacy: risks related to reduced efficacy upon repeated exposure, reduction of the original effect over time and (enhanced) flare-ups of the condition after treatment. Collected data may also be relevant to establish a re-treatment interval.

Examples of risks associated with gene therapy VMPs:

- Risks related to infection with a vector, for example due to persistence, latency and reactivation, integration into the host genome, prolonged expression of the transgene and altered expression of host's genes.
- Risks related to intended and unintended genetic modification of the host cells after treatment or exposure, including, but not limited to, apoptosis, change of function, alteration of growth and/or differentiation, malignancy and autoimmunity.
- For RNAi and RNA antisense VMPs: risks related to on- or off-target binding or interference, accumulation, pro-inflammatory responses, aptamer binding and crossing of the blood-brain barrier leading to central nervous system disorders. Risks related to immunotoxicity, exaggerated immune response, toxicity on non-target organs (hepatotoxicity, renal toxicity, thrombocytopenia etc.) and risks related to long-term silence/oversilence/delay on physiological effects.
- Environmental risks related to effects on non-target species.
- Risk to offspring due to germ-line integration, foetal transmission.
- Long-term efficacy: risks related to reduction of the original effect over time.

Examples of risks associated with bacteriophage VMPs:

- Short-term safety risks: inflammatory reactions, immune responses, effects due to disturbance of the microbiome.
- Environmental risks associated with -large scale- application and shedding of bacteriophages; effects on environmental bacterial communities.

Examples of risks associated with VMPs issued from nanotechnologies:

- Risks related to immunotoxicity, immunomodulation.
- Risks associated with inflammatory or allergic reactions such as intravascular coagulation or fibrinolysis.
- Risks for accumulation and/or persistence in tissues, chronic inflammation.