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Concept paper on quality, safety and efficacy of bacteriophages as veterinary medicines

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1. Introduction

Regulation (EC) No 2019/6 of the European Parliament and of the Council refers, for the first time in European legislation on veterinary medicinal products, to novel therapy veterinary medicinal products (Article 4 (43)).

Section V.1 of Annex II of the Regulation 2019/6 amended by Commission Delegated Regulation (EU) 2021/805 of March 2021 lays down general requirements for marketing authorisation applications for novel therapy veterinary medicinal products, together with specific requirements for identified veterinary medicinal products related to the nature of the active substances contained therein. The specific requirements for bacteriophages are as follows:

- *V.1.5.4.1. Bacteriophages are viruses that depend on bacterial hosts for proliferation and act very specifically on certain bacterial strains. Phage therapy may be used, for example, as an alternative to antibiotics. Generally, bacteriophages consist of a genome, comprised of single or double stranded DNA or RNA, encapsulated by a protein capsid. Due to the diversity of the intended targets for treatment and the specificity of the bacteriophages, it will be necessary to choose the suitable bacteriophage strain against the disease-causing bacterial strain on a case-by-case basis for the individual outbreak of the disease.*
- *V.1.5.4.2. The quality and quantity of the bacteriophages to be used in the finished product are normally variable. Therefore, a fixed qualitative and quantitative composition of bacteriophages will not be the usual situation as the phages need to be adapted on an ongoing basis. Based on this a seed stock of bacteriophages strains need to be established and maintained (comparable with a multi-strain approach).*
- *V.1.5.4.3. Bacteriophages as well as host bacteria/master cell banks for manufacturing shall preferably be produced based on a master seed system. Confirmation shall be provided that the bacteriophage used is lytic.*
- *V.1.5.4.4. The absence of resistance gene(s) and the absence of genes coding for virulence factors shall be shown on all master seeds.*
- *V.1.5.4.5. The indication shall be for prophylactic, metaphylactic and/or therapeutic treatment of one or several specific infection(s) or infectious disease(s). Efficacy of treatment is linked to the lytic activity of phages that confers bactericidal activity on those bacteriophages with specificity for the bacterial strain concerned.*
- *V.1.5.4.6. For genetically modified phages, the genetic modification shall be described.*

There is an increased interest on the use and promotion of bacteriophage therapy in particular because of its potential use as an alternative to antibiotics. The biological characteristics of these viruses and the reciprocal evolution between bacterial hosts and bacteriophage, are very particular. Bacteriophage therapy, originally undertaken during early 1900ies, was stopped when antibiotics therapies were developed, but has been used again in humans in the 90’s for last-resort treatments of multiresistant bacteria which have escaped multiple-line antibiotic treatments.

As bacteriophage medicinal products are classified as novel therapies, the centralised marketing authorisation procedure is mandatory.

There is currently no detailed guidance for quality, safety and efficacy requirements for this product class. Thus, the novel therapies working party (NTWP) has been tasked with the preparation of a general guidance with a focus on the establishment of a suitable regulatory framework for bacteriophage products, to encourage the development of these innovative therapies.

Technical/scientific data requirements needed to support the use of bacteriophages as veterinary medicinal products should be identified.

Other European bodies are also developing requirements to facilitate the use of bacteriophages as medicinal products for human and veterinary use, for example with a focus on quality aspects of products designed for phage therapy (EDQM).

2. Problem statement

Application of the current regulatory framework for veterinary medicines to bacteriophages is challenging because of certain characteristics of this type of product. For example:

- Bacteriophages have narrow host ranges and act very specifically on certain bacterial strains. The development of bacteriophage resistance by host bacteria may occur frequently and rapidly.
- Bacteriophages amplify during treatment, depending on the abundance of susceptible bacteria and immune responses against bacteriophages and bacteria (complex pharmacology).
- Bacteriophage treatment is a dynamic process whereby bacteriophages and host bacteria may co-evolve over successive infection cycles depending on complex reciprocal selection pressures acting in the given host-bacteriophage system (e.g., bacteriophage resistance may impact bacterial fitness), and factors such as the initial heterogeneity of the bacterial population (% of resistant bodies) and the bacteriophages in the product, the genetic stability of bacteriophage and host, and immune responses against bacteriophages and bacteria.

These characteristics may require the use of a mix of active substances (i.e. products comprising cocktails of different bacteriophages), and the ability to update product cocktails with new bacteriophages on an ongoing basis. Consequently, there will be a dynamic, evolving qualitative and quantitative composition of the finished product.

While the current regulatory framework (Directive 2001/82) is not suited to the authorisation/regulation of products with variable composition, Annex II of Regulation (EU) 2019/6 includes specific provision for the authorisation of such products. However, it is necessary to define how the concept of variable composition for an authorised product can be applied in practice.

3. Discussion (on the problem statement)

While the Annex II of Regulation (EU) 2019/6 lays down some requirements for veterinary medicinal product specifically designed for bacteriophage therapy, there is a need for a more specific guidance applicable to these products, i.e. containing bacteriophages, bearing in mind their particularities and taking account of the new legal basis and the provisions in Regulation (EU) 2019/6.

The guideline will focus on replicative bacteriophages (natural as well as engineered and synthetic bacteriophages) as veterinary medicinal products. Bacteriophage derived products (e.g. lysins or other enzymes) are not within the scope of the proposed guideline.

The regulatory framework is expected to be flexible in terms of requirements because:

- bacteriophage products may require the use of cocktails and need to update their composition on an ongoing basis.
- the technical/scientific requirements for the various products should be proportionate to the risks associated with their intended uses, whether they are intended for pets or for livestock animals,

whether they are for prophylaxis, treatment and metaphylaxis, individual and/or personalized treatments, first line treatments or last resort treatments.

In drafting the bacteriophage guideline, the NTWP will take account of existing EMA approaches for product types requiring a similar flexible/adaptive regulatory framework (e.g. allergens for human use, the concept of the multi-strain dossier for veterinary vaccines, the vaccine antigen master file, the authorization of a manufacturing process for human prototypical/generic products of autologous stem cell therapies, or of pandemic flu vaccines). In addition, existing national guidelines for magistral bacteriophage medicines will be considered and taken into account, where appropriate. As part of this work, the guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances will also be taken into account (EMA/CVMP/627/2001-Rev.1).

The guidance is expected to address at least the following specific issues:

- Administrative information to be provided in the marketing application.
- Quality requirements for bacteriophage seed stocks, bacteriophage drug substances, bacterial host strains, and pools of bacteriophages (final product). Specific GMP requirements will also be addressed.
- Safety requirements including toxicology, user safety and environmental risk assessment.
- Requirements for target animal safety.
- Efficacy requirements bearing in mind the unusual pharmacology of bacteriophages, and including description of e.g. intended uses, studies in the target animal, determination of the minimum effective dose, posology, treatment duration.
- Potential development of resistance.
- Quality, safety and efficacy requirements for updating already authorised bacteriophage products (i.e. introduction of new bacteriophages in already approved bacteriophage cocktails).
- Particularities of the SPC for this type of product.
- As veterinary phage therapy is a new and complex area, the guideline will also include a comprehensive glossary section with precise definition of employed terms (e.g. bacteriophages, genetically modified bacteriophages, engineered bacteriophages, synthetic bacteriophages, etc).

4. Recommendation

The NTWP Working Party recommends drafting a guideline on data requirements for bacteriophages medicinal products.

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 operational expert group (OEG) on bacteriophages, the NTWP, and the CVMP.

A total of 21 months is expected to be required for the work. The OEG on bacteriophages drafting group will meet virtually as required (e.g. 3-4 virtual meetings). Discussion is foreseen at 3-4 NTWP plenary meetings.

7. Impact assessment (anticipated)

It is anticipated that the guideline would benefit academia, industry and regulators, due to provision of a relevant guidance on data requirements for veterinary bacteriophages medicinal products. It will facilitate and speed up the development and authorisation of veterinary medicinal products specifically designed for bacteriophage therapy, hence contributing to increase the availability of the veterinary medicinal products that may be used as alternatives to antibiotics.

8. Interested parties

Academic organisations involved in research and development in the field of veterinary bacteriophage therapy.

Veterinary pharmaceutical industry and consultants.

EU Regulatory authorities involved in assessment of marketing authorisation applications.

Other European bodies.

9. References to literature, guidelines, etc.

Guideline on data requirements for multi-strain dossiers for inactivated veterinary vaccines (EMA/CVMP/105506/2007 Rev 2).

Guideline on Influenza vaccines – Quality module (EMA/CHMP/BWP/310834/2012 Rev.1.

Guideline on Influenza Vaccines-Non-clinical and Clinical Module (EMA/CHMP/VWP/457259/2014).

Monograph-version 1.0-PHAGE ACTIVE PHARMACEUTICAL INGREDIENTS (supplementary material Pirnay JP, Verbeken G, Ceyssens PJ, Huys I, De Vos D, Ameloot C, Fauconnier A. The Magistral Phage. Viruses. 2018 Feb 6;10(2):64. doi: 10.3390/v10020064. PMID: 29415431; PMCID: PMC5850371.).

Guideline on data requirements for vaccine antigen master files (VAMF) (EMA/CVMP/IWP/258755/2021).

Guideline on allergen products: production and quality (EMEA/CHMP/BWP/304831/2007).

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

Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1.