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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the establishment of a Guideline on the development and manufacture of human medicinal products specifically designed for phage therapy

Agreed by Biologics Working Party	31 October 2023
Adopted by CHMP for release for consultation	4 December 2023
Start of public consultation	22 December 2023
End of consultation (deadline for comments)	31 March 2024

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Keywords	Guideline, Bacteriophage, Phage Therapy, Development and Manufacture, Active Substance, Finished Product, Antimicrobial Resistance

1. Introduction

This concept paper proposes to establish a scientific guideline for the pharmaceutical development and manufacture of bacteriophage medicinal products intended for the therapeutic treatment or prophylaxis of one or more specific bacterial infection(s) or infectious disease(s) in humans. Although an EMA guideline for such products exists for veterinary medicinal products, there is currently no appropriate regulatory guidance for medicinal products for human use in the EU.

2. Problem statement

The number of bacteria resistant to antibiotic treatment is dramatically increasing, and these cause life threatening infections such as pneumonia, urinary tract infections, bloodstream infections, wound infections, infections in cystic fibrosis and medical-device related infections. Antimicrobial resistance has become a serious problem worldwide contributing to morbidity and mortality, and increasing the burden for society and hospitalisation costs.

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Bacteriophages are a promising alternative to antibiotics for the treatment of infections that do not respond to conventional treatment options. There is an increasing interest in the use of bacteriophages for the treatment of infections both from the healthcare providers and pharmaceutical industry.

There are in principle two distinct approaches for phage therapy. In the first approach, the phage therapy medicinal product (PTMP) is a pre-defined (standardised) finished product consisting of one or more bacteriophage strains. In the second, more personalised approach, the active bacteriophages for treatment are selected from a pre-existing phage collection and produced for an individual patient. However, different quality expectations may be regarded necessary for both kinds of PTMPs. In case the available bacteriophages are not active against the disease-causing bacteria or in case of resistance emergence during treatment, phage exchange or adaptation may be necessary in very short time in order to ensure the potency of the PTMP. This will be challenging to implement in the case of pre-defined finished products. In both cases of pre-defined finished products or more personalised approach, complexity arises from the high specificity of bacteriophages against the host bacteria. Particularly, for efficient treatment it may be necessary to use a mixture of different bacteriophage strains (i.e., phage cocktails) rather than monophage preparations. This could lead to a bacteriophage medicinal product consisting of a number of different strains, adding complexity to their development and manufacture.

To our knowledge, and according to consulted data, there is currently one nationally authorised bacteriophage medicinal product in the EU, and the number of clinical trials investigating phage therapy products is fairly limited. This stems mainly from two interconnected issues: Firstly, the lack of distinct regulatory and scientific guidance throughout the life-cycle of such products is not supportive to potential sponsors and developers. Secondly, because of the relative paucity of clinical and manufacturing experience with the phage therapy products, a scientific guideline has for a long time not been considered feasible. The intention behind the proposed guideline is to solve this issue by clarifying the quality requirements and therefore minimizing the regulatory and scientific gap to innovators addressing the problem of antimicrobial resistance.

3. Discussion (on the problem statement)

From a quality point of view, bacteriophages differ from other medicinal products in various terms and therefore, specific considerations need to be taken into account for these types of products.

The proposed guideline will address the following aspects:

- Establishment of phage-specific terminology
- The selection, characterisation and quality control of starting materials (i.e., phage banks and bacterial cell banks)
- Development of manufacturing process and control strategy to ensure consistent quality of bacteriophage active substances and finished products.
- Characterisation of bacteriophage active substances
- Control of process- and product-related impurities and other contaminants
- Potency assay development and qualification
- Recommendation on the justification of use of platform manufacturing and prior knowledge
- Additional requirements for the genetically modified bacteriophages and cross-reference to the regulatory implications of using genetically modified organisms (GMOs)
- Quality requirements for investigational bacteriophage products
- Specific considerations for Good Manufacturing Practice (GMP) aspects

- Additional information that should be included in the Summary of Product Characteristics (SmPC) of bacteriophage medicinal products

The proposed guideline will largely follow the structure of Common Technical Document (CTD) Module 3. The guidance will be given on bacteriophage products intended for the prophylactic or therapeutic treatment of bacterial infection(s) or infectious disease(s), eradication of specific bacteria.

The guideline will include specific requirements for bacteriophages produced by genetic engineering to improve certain properties (e.g., deletion of lysogenic, toxic, virulence, antibiotic resistance genes, increasing the infectivity) of those bacteriophages. For bacteriophages falling under the definition of gene therapy medicinal products the principles delineated in the present guidance should be followed, when relevant. However, for these products, other dedicated guidelines should also be followed. In addition, magistral formulae, bacteriophage-derived products (e.g., lysins or other enzymes) and chemically synthesised bacteriophages will be out of scope of the guideline, although the principles of the guideline might be applicable. Likewise, other uses of bacteriophages, e.g., the use of bacteriophage particles as display platforms for vaccines or use of temperate/integrating bacteriophages to modulate bacterial phenotypes, are outside the scope of the future guideline.

4. Recommendation

The Biologics Working Party recommends drafting a guideline for bacteriophage products for the treatment of infections and infectious diseases taking into account the issues identified above.

5. Proposed timetable

The concept paper will be published for a three-month public consultation period.

BWP will take account of all comments received during the public consultation on the concept paper when preparing the draft guideline.

The draft guideline will be published for a six-month public consultation period.

BWP will take account of all comments received during the public consultation of the draft guideline when preparing the final guideline text. It is expected that the final guideline will come into operation six months after publication following adoption by CHMP.

6. Resource requirements for preparation

The development of the guideline will involve the EMA-BWP Secretariat, the CHMP Biologics Working Party, CHMP, GMP/GDP Inspectors Working Group and EMA QRD Working Group, who would be consulted, as necessary. The BWP should appoint a rapporteur and a drafting group.

7. Impact assessment (anticipated)

No adverse impact on industry with respect to either resources or cost is foreseen.

The guideline will clarify requirements for regulators and industry with respect to the development and manufacture of bacteriophages for antimicrobial use taking into account the peculiarities of these types of medicinal products. This guideline will be developed in accordance with the EMA guideline on veterinary phage therapy products and the European Directorate for the Quality of Medicines & HealthCare (EDQM) general chapter on phage therapy active substances and finished products. A positive impact is foreseen as a result of harmonious integration of these pivotal EU guidelines, thus supporting the development and manufacture of PTMPs for clinical trials and for marketing.

8. Interested parties

Pharmaceutical Industry, healthcare professionals, academic networks, patients' organisations, EU Competent Authorities, GMP/GDP Inspectors Working Group and EMA QRD Working Group.

9. References to literature, guidelines, etc.

- Draft Ph. Eur. general chapter 5.31 "Phage therapy active substances and medicinal products for human and veterinary use"
- Draft "Guideline on quality, safety and efficacy of veterinary medicinal products specifically designed for phage therapy"
- ICH Q8 (R2) Pharmaceutical development, ICH Q9 (R1) Quality risk management, ICH Q10 Pharmaceutical quality system, ICH Q11 Development and manufacture of drug substances
- ICH Q5D Quality of biotechnological products: derivation and characterisation of cell substrates used for production of biotechnological/biological products
- Requirements for quality documentation concerning biological investigational medicinal products in clinical trials - Scientific guideline