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Guideline on quality aspects of phage therapy medicinal products

Draft

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Executive summary

The aim of this guideline is to clarify the regulatory expectations for quality documentation of bacteriophage active substances and finished products for human use within marketing authorisation applications. It addresses specific aspects regarding the manufacture, control of materials, characterisation, specifications, analytical control, reference standards and stability of bacteriophage active substances. In addition, guidance is given on the pharmaceutical development, manufacture, control and stability of the finished product.

1. Introduction

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

Bacteriophages (phages) are viruses that exclusively infect bacteria, replicate within them, and often cause the lysis of the bacterial cells during the release of progeny phage particles. Phage therapy refers to the use of phages for the treatment of bacterial infections, infectious diseases, or for the eradication of specific bacteria. Phages are promising agents for the treatment of infections that do not respond to conventional treatment options, either as monotherapy or in combination with antibiotics. There is an increasing interest in the use of phages for the treatment of infections or infectious diseases both from the healthcare providers and pharmaceutical industry, and the number of clinical trials is increasing.

Phage therapy medicinal products (PTMPs) fall under the definition of biological medicinal products as defined in the Directive 2001/83/EC. Various guidelines established for biological medicinal products are applicable to PTMPs. Nevertheless, phages differ from other biological medicinal products in various terms (e.g. high specificity, self-propagation, potential for evolution and risk of horizontal gene transfer), and thus, specific considerations need to be taken into account throughout their development and lifecycle. This guideline aims to establish regulatory expectations for the development, manufacture, characterisation and control of phages active substances and finished products intended for the treatment of bacterial infections and infectious diseases in humans.

The guideline is structured in accordance with the eCTD framework, ensuring concise direction regarding the required data and information.

2. Scope

This guideline establishes quality requirements for the authorisation of PTMPs mainly intended for treatment of bacterial infections or infectious diseases in humans. It applies to strictly lytic (virulent) bacteriophages, whether naturally occurring or chemically/genetically modified, which are manufactured by propagation in bacterial cells. This includes bacteriophages with synthetic genomes propagated in bacteria during production.

Cell-free production systems (such as in vitro transcription-translation systems leading to production of viable phage particles) are not specifically addressed; however, relevant principles of the guideline apply.

Where the introduced genetic manipulation(s) result in the phage being classified as a gene-therapy medicinal product, such product is then subject to the EU legislation and guidelines applicable to Advanced Therapy Medicinal Products (ATMPs). While the principles of this quality guideline apply, specific guidance for such products is not included. Applicants are recommended to seek an opinion from the Committee for Advanced Therapies (CAT) in order to confirm the classification of the product as early in development as possible.

Phage-derived products (e.g., lysins or other enzymes), magistral formulae or patient-individualised phages not intended to be authorised through MAA procedure are out of scope of the guideline.

While this guideline is not specifically intended for investigational PTMPs, the principles apply in a phase-appropriate manner to products in clinical development.

3. Legal basis

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, all relevant European guidelines, reflection papers, International Conference of Harmonisation (ICH) guidelines applicable to PTMPs and European Pharmacopoeia (Ph.Eur.) requirements. References to the relevant guidelines and reflection papers are made within the relevant sections of this document and/or are listed in section 8.

4. Active substance

A PTMP active substance is manufactured in a bacterial production strain by a controlled propagation of a phage seed lot derived from a single phage clone, resulting in a genetically and phenotypically consistent phage population.

4.1. General information

Information about the structure, including details on the capsid, tail, and any other components of the phage should be presented.

The general properties of the phage should be clearly outlined, including at a minimum the following: taxonomic classification, target bacteria, potency, particle size, genome type and size, as well as details of any notable genes present and/or genetic/chemical modifications, if applicable. Additional relevant characteristics may also be included to provide a comprehensive overview.

4.2. Manufacturers

Information on the manufacturers (including bacterial cell bank and phage seed lot manufacturing, testing and storage sites) should be provided, including the name, address, and specific responsibilities of each manufacturer and production site.

4.3. Manufacturing process and controls

The batch scale/size (including any proposed range) should be stated. Where applicable, blending of batches and/or sub-batches should be described and appropriately justified.

An overview of the manufacturing process should be presented as a flow diagram, and detailed descriptions of each process step should be provided. The production process should yield a phage active substance (purified harvest) of consistent quality and stability which is ensured by monitoring of

relevant process parameters at relevant time points throughout the manufacturing process. Critical steps and intermediates should be identified and corresponding control testing with set acceptance criteria indicated.

Any hold times should be defined based on appropriate studies and justified with data demonstrating the physicochemical, biological, and microbiological quality of the in-process material under the proposed storage conditions.

4.4. Control of materials

Bacterial cell banks

The origin, history, description, and preparation of bacterial cells used for banking should be provided. Bacterial cell banks should be established in accordance with the Ph.Eur. general chapter 5.31 and principles of the ICH guideline Q5D. The use of a two-tiered seed lot system is strongly recommended.

The entire bacterial genome (chromosome) and plasmids of the master cell bank (MCB) should be sequenced by using suitable technology (e.g., next-generation sequencing, NGS), followed by annotation by bioinformatic tools.

The following quality attributes should be included in the characterisation of the MCB: identity (based on the full genome sequencing), purity (absence of detrimental phage particles, microbial purity), viability, phage sensitivity, antibiotic susceptibility, and analysis of genes encoding for potential detrimental factors (i.e. prophages, antibiotic resistance determinants, toxins, virulence factors). The use of bacterial strains whose genome contains sequences coding for detrimental factors should be avoided, unless otherwise justified. In such a case, a risk assessment should be provided and steps taken to attempt the deletion of the detrimental sequences from the host should be presented. For genetically modified bacterial production strains, the modifications must be described, verified, and their effects characterised.

WCB should be tested for identity (by any suitable method), phage sensitivity, purity (absence of detrimental phage particles, microbial purity), and viability.

Phage seed lots

The phages used to generate a seed lot should be strictly lytic, and the origin, history, and preparation of phage seed lots should be thoroughly documented. The use of a two-tiered seed lot system is strongly recommended. Phage seed lots should be established in accordance with the Ph.Eur. general chapter 5.31 and principles of the ICH guideline Q5D.

The entire genome of the master phage seed lot should be sequenced by using suitable technology (e.g., NGS). The full genome sequencing and genome annotation should be performed once for each established master seed lot. In case a working seed lot is established, the genome of the working seed lot should also be fully sequenced and compared to the master seed lot's nucleotide sequence, unless otherwise justified.

The established master and working seed lots should be characterised/tested for the following quality attributes: identity (full genome sequencing), purity (the absence of phage contaminants, sterility), potency, analysis of genes encoding for potential detrimental factors (i.e., antibiotic resistance determinants, toxins, lysogeny modules). The use of seed lots containing any detrimental factor specified above should be avoided, unless otherwise justified. In such a case, a risk assessment should be provided in the characterisation section. For genetically or chemically modified phages, the modifications should be fully described, verified, and their effects characterised.

4.5. Process validation and/or evaluation

Process validation studies should be performed in accordance with the principles of the EMA Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (EMA/CHMP/BWP/187338/2014).

In line with Ph.Eur. general chapter 5.31, process verification should address the genetic stability of the phage during the production in bacterial cell culture. For this purpose, full genome sequencing of the active substance should be performed on a suitable number of batches and compared to the master seed lot sequence to confirm that the phages are genetically stable during production in bacterial cells.

4.6. Characterisation

Characterisation is essential for gaining a comprehensive understanding of the phage active substance and to identify critical quality attributes of the active substance.

Elucidation of structure and other characteristics

A range of state-of-the-art analytical techniques should be employed to obtain a thorough understanding of the structure, biological activity, purity, and other characteristics of the phage active substance. Characterisation should be performed using appropriate and sufficiently sensitive methods, with a clear description of the methods employed.

The characterisation studies should be conducted throughout the development process at the active substance level.

Batches used for characterisation studies should be clearly identified (development, pilot, full scale) and should be representative of the batches used in pivotal clinical studies and of the batches manufactured by the proposed commercial process.

The following characterisation studies are expected to be performed as a general approach.

Phage structure

It is recommended to determine the phage morphology (e.g. by electron microscopy), especially if bioinformatic analysis of the genome is not sufficient for phage classification.

Plaque phenotype

An image of the plaques should be provided, accompanied by a description of their size and morphology, including characteristics such as clarity (e.g., clear or turbid/cloudy) and the presence or absence of halos. The host bacteria on which plaque morphology has been determined should be stated.

Genome characterisation

It is acceptable to perform the whole genome sequencing and detailed genomic analysis at the level of master seed lot. Provided that genetic stability of a phage is demonstrated during process validation the full genome characterisation does not need to be repeated at the active substance level (since the master seed lot is considered representative of the active substance in terms of the nucleic acid sequence). The detailed analysis of the results should be presented either in the characterisation or starting materials section with appropriate cross-reference.

The entire genome of the phage should be sequenced by appropriate high-throughput sequencing technology such as next-generation sequencing. Bioinformatic tools should be employed to predict Open Reading Frames (ORFs) and other genetic elements, as far as possible. A detailed genome map should be provided, which includes information about the genome size, type, and GC content, along with the function of each identified ORF.

A comparative genomic analysis should be carried out to classify the phage within its taxonomic group. The percentage of genetic identity (degree of similarity) to the closest relative(s) should be reported, and coverage indicated.

The genome should also be analysed for the presence of genetic sequences coding for detrimental factors (antibiotic resistance determinants, toxins, or lysogeny modules). In case the genomic analysis reveals the presence of genes encoding for detrimental factors, a thorough evaluation should be performed to confirm that these factors do not pose a risk to patients. The absence of lysogeny should be demonstrated. In the case of genetically modified phages the presence and integrity for recombinant sequences should be verified.

Host range

The determination of the host range of a phage implies the study of its ability to form plaques on a set of bacterial pathogens. In addition to the bacterial strain used for production, the host range study should encompass a diverse range of bacteria, including multiple strains of the target species as well as closely related species. Strains representing clinically relevant isolates and growth forms (e.g., planktonic, biofilm-forming strains) of the bacterial strains intended to be treated should be included in the study. If the PTMP is intended for use in specifical geographic locations with distinct host subpopulations, host strains should be ideally selected from those geographical regions. The number and variety of the bacterial strains/species included in the study should be justified.

Various assays may be employed for host range studies such as spot testing or plaque assay. The determination of host range may be supported by available knowledge on the receptor usage.

Potency

The biological activity of the phage consists in its ability to propagate in bacteria, to lyse the bacterial pathogen and subsequently to release the newly formed phage particles from the bacterial cell, constituting the phage lytic activity. This activity should be measured by determination of the infectious phage titre by a double layer plaque assay or any other suitable method in a defined bacterial strain (see Ph.Eur. general chapter 2.7.38[i]).

If the mechanism of action involves activity towards bacterial biofilms, this should be investigated and data presented.

Transducing capacity

Some phages can package host bacterial DNA into their capsid instead of or alongside their own DNA and transfer it into a receiving cell in a process known as transduction. This transducing capacity may enable the transfer of detrimental factors from the producer cells to the patient´s strain. Specialised transduction where only the host DNA flanking the prophage are packaged, occurs exclusively in temperate phages and is not a concern for phages demonstrated to be strictly lytic. However, generalised transduction involves the random packaging of host DNA during the phage´s DNA packaging process and can occur with exclusively lytic phages. Therefore, the capacity of the phages to mediate generalised transduction should be addressed in the regulatory filing.

Impurities

Product-related impurities

Product-related impurities refer to variants of the desired product that differ in properties such as activity, efficacy and safety, compared to the intended therapeutic product. For phages, these impurities may include for example phage aggregates or non-infective phage particles

The propensity of phage active substance to aggregate should be thoroughly evaluated using appropriate (orthogonal) methods such as high-pressure liquid chromatography, dynamic light scattering, or analytical ultracentrifugation.

Process-related impurities

Process-related impurities are those derived from manufacturing process. These impurities may originate from cell substrates (residual host cell proteins, host cell DNA, pyrogens), cell culture (e.g., media components or other reagents) or downstream purification processing (e.g., residual reagents, column leachables, DNAse). All the bacterial derived impurities should be discussed and evaluated with regards to the production strain and proposed route of administration.

The manufacturing process should be evaluated for the capacity to remove process-related impurities. Further considerations should be considered for the following process-related impurities:

Pyrogens

The manufacturing process should be evaluated for the capacity to remove pyrogenic impurities (see Ph.Eur. general chapter 5.1.13). Cross-reference to process validation data (impurity clearance) is acceptable.

Host cell proteins

The residual host-cell proteins should be quantified. Where the genome analysis of the bacterial strain, or other relevant information indicates potential for production of toxins or other virulence factors that may pose safety risk to patients, the presence and quantity of these should be investigated by suitable methods to establish an adequate control strategy.

Host cell DNA

The residual host cell DNA should be quantified using a suitable method.

Induced prophages

In exceptional cases where it is not feasible to use bacterial host cells devoid of prophage sequences, the use of such production cells may be permitted based on a thorough justification and risk assessment. In such cases, the prophage should be fully characterised, including full genome sequencing and an assessment of its potential to impact on product quality and safety.

4.7. Control of active substance

Active substance specification

A relevant release and shelf-life specification should be established and justified in accordance with the Ph.Eur. general chapter 5.31. Specifications should consider relevant quality attributes identified in characterization studies. The acceptance criteria should be established and justified based on clinical

data, safety margins derived from toxicological and clinical studies, and manufacturing process capacity.

Identity

The identity test should exhibit high specificity, ensuring the ability to differentiate between different phages (e.g. phages produced within the same manufacturing facility). qPCR, genomic fingerprinting or other state-of-the-art methods may be used for confirming the identity of the active substance.

Potency

Potency refers to the infectious titre of the phage and is commonly determined using a plaque assay, which is also used to assess phage quantity. Potency is typically expressed in plaque forming units (PFU) per mL. Further guidance on phage potency testing is provided in Ph.Eur. general chapter 2.7.38[ii].

Aggregation

Phage aggregation can lead to the decrease of the infectious titre. If relevant, phage aggregation should be determined by appropriate methods based on the results of the characterisation studies.

Residual Host cell proteins

Residual host cell proteins should normally be included in the active substance specification and controlled by a method capable of detecting a wide range of proteins and considering the recommendations given in general chapter 2.6.34. In certain cases, it may be acceptable not to test routinely the residual level of HCP. In such cases, a risk analysis should be provided to demonstrate the low risk for the patient with regards to the route of administration. In addition, clearance studies should demonstrate that the manufacturing process effectively removes residual HCP to levels deemed acceptable for the intended use.

Residual Host cell DNA

Residual host cell DNA should normally be included in the active substance specification. However, the testing requirement may be waived if process validation studies (e.g., spiking studies, clearance capacity of the purification steps), based on sufficient number of batches, provide sufficient evidence that the manufacturing process consistently and effectively ensures the removal of residual host cell DNA to levels deemed acceptable for the intended use.

Pyrogenicity

Pyrogenicity should be determined, unless otherwise justified. It should be controlled according to the requirements of the General chapter Ph.Eur. 5.1.13.

Microbiological quality

In case the active substance is claimed to be sterile, the active substance should be tested for sterility (Ph.Eur. 2.6.1). Otherwise, microbial quality should be controlled by a suitable method.

Residual reagents

Residual reagents (e.g. DNAse) derived from the manufacturing process which might pose safety concerns should be controlled based on a safety risk-assessment and impurity clearance studies.

Induced prophage

In exceptional cases where it is not feasible to use bacterial host cells devoid of prophage sequences, the use of such production cells may be permitted based on a thorough justification and risk

assessment. The absence of expression of prophages should be verified in the active substance or its content determined and proposed limit justified from a safety point of view.

4.8. Analytical considerations

Analytical procedures should be described for each active substance. In case the same procedure is applied to more than one active substance, cross-reference could be made. Analytical procedures must be developed and validated according to ICH Q14 and ICH Q2 guidelines, and validation summaries should be provided. In certain cases, based on scientific justification and risk-based evaluation, platform analytical procedures could be considered.

4.9. Reference standards or materials

Reference standards for PTMPs are mainly used for method validation and system suitability testing of potency determination by the plaque assay. Reference standards can also be used for release testing if appropriate/relevant. Regardless of the specific use, reference standards should be established in line with relevant ICH guidelines, should be well-characterised with respect to their identity, purity, biological activity, and other relevant characteristics, and their stability should be appropriately monitored.

4.10. Stability

The stability of the phage active substance can be impacted e.g. by temperature, pH or agitation. Relevant ICH stability guidelines should be followed to establish the shelf life of the active substance. Stability indicating parameters should be identified in characterisation studies but should include at least appearance, potency, microbiological quality, and pH. There are no specific requirements relating to container closure system. Relevant EMA and ICH Guidelines should be considered.

5. Finished product

The finished product can contain one active substance (i.e. single phage) or a combination of active substances (i.e. several different phages). A finished product that consists of more than one phage is referred to as a multiphage product or a phage cocktail.

5.1. Description and composition of the finished product

The qualitative and quantitative composition of the finished product should be indicated. The composition should be stated listing all components, their amount and function, and a reference to their quality standards (e.g. compendial monographs or manufacturer´s specifications). The composition should be stated on a per-unit base. The content of each phage is typically expressed in PFU/mL. The container closure system used for the dosage form should be outlined. Solvents for reconstitution, diluents for dilution before administration and medical devices used for administration (e.g. inhaler) should be indicated, if applicable.

5.2. Pharmaceutical development

The formulation development including the choice and quantity of excipients used should be detailed with respect to their impact on the phage active substance critical quality attributes (e.g. phage activity). Comparability of product formulations employed during clinical studies with the commercial formulation should be demonstrated, or differences discussed where relevant.

The quality target product profile of the product should be presented and critical quality attributes indicated. The critical process parameters should be identified. Differences in the manufacturing processes during process development should be indicated.

If the product to be administered consists of a mixture of phage active substances, justification for combining phage active substances should be provided. This includes the cases where different phages are mixed at the time of administration as recommended by the SmPC. If relevant, requirements of combination packs need to be considered. Any recommendation as regards the maximum number of phages to be combined should be justified and limited, if necessary. The potential interactions between phages mixed in the product to be administered should be discussed. In-use stability should be established, if relevant.

If the phage finished product requires additional preparation (e.g. reconstitution, dilution, mixing with other phages) before administration, the used materials (e.g. solvents, diluents, bags and sets of administration) should be identified, and the method of preparation summarised. Compatibility studies should be performed and the in-use stability data provided to confirm the maintenance of the product quality profile.

There are no additional requirements relating to container closure system. Relevant EMA and ICH Guidelines should be considered.

If a medical device is intended to be used for the administration, the recommendations of the Guideline on quality documentation for medicinal products when used with a medical device, (EMA/CHMP/QWP/BWP/259165/2019), and other relevant EMA guidance documents should be applied. The pharmaceutical development should also include usability studies to ensure appropriate use of the finished product at the time of administration.

5.3. Manufacture

The manufacturing process should be appropriately described and validated. Refer to relevant active substance section of this guideline.

Hold Times

Any hold times should be defined based on appropriate studies and justified with data demonstrating the physicochemical, biological, and microbiological quality of the in-process material under the proposed storage conditions. For example, in the manufacture of multiphage products, the mixtures of drug substances which have not yet undergone final processing should be considered finished product intermediates and controlled using in-process testing against predefined criteria.

5.4. Control of finished product

A relevant release and shelf-life specification should be established and justified in accordance with the Ph.Eur. general chapter 5.31. The specification should comprise the critical quality attributes of the finished product, analytical procedures employed for determination of these attributes and acceptance criteria and/or limits. The proposed acceptance criteria should be justified based on clinical data, safety margins derived from toxicological and clinical studies, and manufacturing process capability.

Tests for appearance, potency, identity and microbiological quality are mandatory. Depending on the route of administration, pharmaceutical form and other characteristics of the finished product, additional tests (e.g. pH, osmolality, visible and subvisible particles, extractable volume, uniformity of dosage units, moisture content) may also be relevant for inclusion in the specification. If aggregation has been detected, it should be addressed in the specification, unless justification is provided for its exclusion. Reference is made to active substance specification where appropriate.

For multiphage products, potency should be determined for each individual phage component (i.e. active substance), unless otherwise justified. For this, separate plaque-based assays should be performed using bacterial strains not susceptible to any other phages in the combination. Further guidance on phage potency testing is provided in Ph.Eur. general chapter 2.7.38[iii].

Microbiological quality should be determined depending on the route of the administration of the finished product. Analytical methods should be described, and corresponding summary of validation studies should be provided. If appropriate, reference could be made to relevant active substance sections.

5.5. Reference standards or materials

For reference standards or materials, refer to relevant section in the active substance part of this guideline.

5.6. Stability

Finished product stability can be impacted e.g. by temperature, pH and agitation. Relevant ICH stability guidelines should be followed. The guidance for potency testing of multiphage products applies also to stability studies (i.e. infectious titer of each phage should be determined).

If a medical device is intended to be used for the administration, the recommendations of the Guideline on quality documentation for medicinal products when used with a medical device, (EMA/CHMP/QWP/BWP/259165/2019) should be applied.

6. Regulatory considerations

6.1. Composition of the finished product and post-marketing authorisation change of active substance

Phages for human use are subject to requirements applicable to human biological medicinal products and governed by Directive 2001/83/EC and Regulation 1234/2008. As such, changes in the active substance and a flexible composition of the medicinal product are not contemplated in Directive 2001/83/EC. A change in the composition of an authorised medicinal product, as regards the active substance, requires a submission of an extension of the marketing authorisations stated in the Annex I to the Variations Regulation. Such change should be supported by quality data, but also if necessary non-clinical and clinical data demonstrating that the safety and efficacy of a replacement phage active substance are not significantly different from the previous one. Such change and those issues are beyond the scope of this quality guideline. Any requests for a marketing authorisation extension will therefore be assessed on a case-by-case basis and in light of the specific requirements for Phage Therapy Medicinal Products, applicants are recommended to seek scientific advice to address the specific concerns and regulatory pathways for the respective product.

6.2. Use of prior knowledge

Prior knowledge (as per ICH Q11 guideline) can be used to support a new marketing authorisation or a line extension. Nevertheless, a product-specific dossier is still required, meaning the lead documents need to be product-specific. Prior knowledge can be used throughout the dossier to support for example reduced or focused process development and/or validation activities, method validation or container closure usage.

The supportive data should always be provided along with sound justifications for its relevance to allow for proper assessment of the proposed strategy. It should be noted that there are several factors that are considered important concerning the value of the supportive data. These include, but are not limited to, the number of licensed or developed products that can be considered representative, the in-depth understanding of parameters that are product-dependent vs. product-independent, and conclusive risk assessments in case product-specific data is reduced or omitted due to prior knowledge. Therefore, it will be a case-by-case decision whether the proposed approach is considered acceptable.

Generally, it is highly recommended to obtain scientific advice to address the specific concerns and regulatory pathways for the respective products.

7. Definitions

Bacterial biofilm – A complex structured community of bacteria living within a complex extracellular matrix that can protect them from environmental damage and external agents.

Bacteriophage (phage) – Virus that infects bacteria and depends on the bacterial host for replication. Phage consists of a genome comprised of single or double stranded DNA or RNA, encapsulated in a protein capsid.

Bacteriophage active substance – Phages manufactured in a bacterial production strain by a controlled propagation of a phage seed lot derived from a single phage clone, resulting in a genetically and phenotypically homogeneous population. Corresponds to purified harvest in Ph. Eur. 5.31 terminology.

Cell-free transcription-translation system – An in vitro process that mimics the natural gene expression in a cell, but without a need for living cells.

Generalised transduction – A process where a random portion of bacterial DNA is encapsulated by a bacteriophage and transferred to another bacterium.

Host range – A taxonomic diversity of bacterial hosts a bacteriophage can successfully infect.

Induced prophage – A temperate bacteriophage that has been reactivated from its latent (prophage) state to enter the lytic cycle.

Lytic bacteriophage – Bacteriophage which is only able to sustain replicative cycles ending in bacterial lysis. Only such strictly lytic bacteriophages are considered suitable for use in phage therapy.

Multiphage product (also called phage cocktail) - Qualitatively and quantitatively characterised combination of monophage components.

Naturally occurring phage: Bacteriophage isolated from the environment, whose specificity or biological activity may be enhanced through directed evolution or phage adaptation, without chemical modification or genetic engineering.

Phage – see bacteriophage

Phage cocktail - see multiphage finished product.

Phage seed lot – A collection of bacteriophages derived from a single clonal lineage, whose characteristics and composition are defined and consistent, stored in appropriate containers under controlled conditions. Each container contains an aliquot from a single, well-defined pool of bacteriophages.

Phage therapy – Use of bacteriophage products mainly for treatment of bacterial infection(s) or infectious disease(s). Efficacy of treatment is linked to the lytic activity of bacteriophages that confers bactericidal activity on those bacteriophages with specificity for the bacterial strain concerned.

Phage therapy medicinal product (PTMP) – Preparation of phages used to treat or prevent human or veterinary bacterial infections. A PTMP can contain one phage, or a combination of phages, combined with excipients.

Specialised transduction – A process where a region of the host DNA that flanks the prophage is encapsulated by a bacteriophage and is transferred to another bacterium. This type of transduction occurs only in temperate phages.

Temperate bacteriophages - Bacteriophages which are dually able to sustain dormancy (typically by integration into the bacterial chromosome; lysogeny) as well as lytic replication in host bacteria, depending on e.g. environmental conditions.

Transduction – A phenomenon in which bacterial DNA is transferred from one bacterial cell to another by phage particle.

8. References

Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (Text with EEA relevance). Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32008R1234&qid=1749632821034

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the "Community code relating to medicinal products for human use", as amended. Available at: https://eur-lex.europa.eu/eli/dir/2001/83/oj/eng

EMA Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (EMA/CHMP/QWP/BWP/259165/2019). Available at: https://www.ema.europa.eu/en/process-validation-manufacture-biotechnology-derived-active-substances-data-be-provided-regulatory-submission-scientific-guideline

EMA BWP Questions and answers for biological medicinal products. Available at: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/biological-guidelines/questions-answers-biological-medicinal-products

EMA Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications targeting an unmet medical need - Scientific guideline. Available at: https://www.ema.europa.eu/en/toolbox-guidance-scientific-elements-and-regulatory-tools-support-quality-data-packages-prime-and-certain-marketing-authorisation-applications-targeting-unmet-medical-need-scientific-guideline

European Parliament legislative resolution of 10 April 2024 on the proposal for a directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC (COM(2023)0192 – C9-0143/2023 – 2023/0132(COD)). Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52024AP0220&qid=1749633055575

ICH Q2 Validation of analytical procedures. ICH Q3A-Q3E Guidelines on Impurities.

ICH Q5D Derivation and characterisation of cell substrates used for production of biotechnological/biological products.

519 ICH Q5E Comparability of biotechnological/biological products subject to changes in their
520 manufacturing process.

521 ICH Q6B Specifications: Test procedures and acceptance criteria for biotechnological/biological
522 products.

523 ICH Q8 Guideline on Pharmaceutical development.

524 ICH Q9 Guideline on Quality risk management.

525 ICH Q10 Guideline on Pharmaceutical quality system.

526 ICH Q11 Guideline on Development and manufacture of drug substances (chemical entities and
527 biotechnological/biological entities).

528 ICH Q12 Lifecycle management.

529 ICH Q14 Analytical procedure development.

530 Ph.Eur. General chapter on "Sterility" (2.6.1).

531 Ph.Eur. General chapter on "Pyrogenicity" (5.1.13).

532 Ph.Eur. General chapter on "Bacteriophage potency determination" (2.7.38[iv]).

533 Ph. Eur. General chapter on "Phage therapy medicinal products (5.31)

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[i] Ph. Eur. general chapter 2.7.38 is in preparation. The draft has been made available for public comments in Pharmeuropa Online, issue 37.2
[ii] Ph. Eur. general chapter 2.7.38 is in preparation. The draft has been made available for public comments in Pharmeuropa Online, issue 37.2
[iii] Ph. Eur. general chapter 2.7.38 is in preparation. The draft has been made available for public comments in Pharmeuropa Online, issue 37.2
[iv] Ph. Eur. general chapter 2.7.38 is in preparation. The draft has been made available for public comments in Pharmeuropa Online, issue 37.2