THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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COUNCIL OF EUROPE

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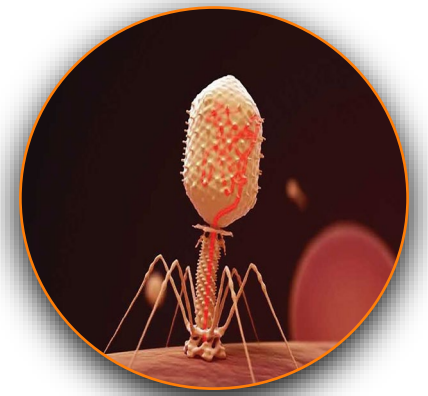
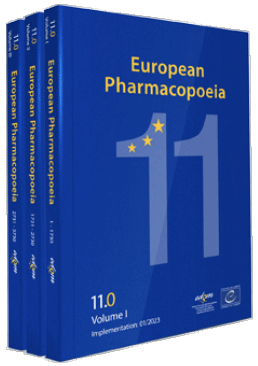
Bacteriophages - activities of the European Pharmacopoeia





Focus Group Meeting on Bacteriophages
Amsterdam, 11 May 2023

Dr Olga Kolaj-Robin, EDQM

European Pharmacopoeia

- Protecting public health – one common compulsory standard
- Official pharmacopoeia in Europe (complemented by national pharmacopoeias)
- Legally binding quality standards for ALL medicinal products i.e. raw materials, preparations, dosage forms, containers…
- Mandatory at the same date for all Members

- 40 Members (39 Member States & EU)
- 31 Observers (5 European, 24 non-European countries, TFDA, WHO)
- Supplement 11.2: 2474 monographs, 387 general texts, ~2870 reagents

Ph. Eur.: Content and structure

Ph. Eur. Reference standards / preparations & reagents

General chapters & general texts

- avoid repeating standard procedures or requirements in each monograph; aspects that cannot be treated in each monograph
- become mandatory when referred to in a monograph
- provide standard analytical procedures; guidance

Individual monographs

- Specific but not a stand alone text
- Analytical procedures and acceptance criteria represent required quality standards
- Based on approved specifications backed up by batch data
- Reliance on manufacturers' feedback (public consultation)

General notices

- Essential reading
- Apply to all texts
- Address general topics
- Provide basic information
- Include rules to understand texts, conventional expressions

General monographs

Dosage form monographs

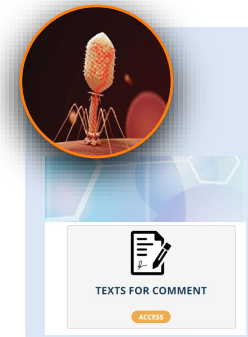
- Classes of substances/medicinal products
- Mandatory for all substances/products within scope of their definition
- Aspects that cannot be included in each individual monograph
- Not cross-referenced in individual monographs (exceptions)

Bacteriophages Working Party (BACT WP)

Creation of BACT WP

Addition to the WP

Phage therapy active substances and medicinal products for human and veterinary use (5.31)



Public consultation

Public deadline: 30 June 2023
NPA deadline: 31 Aug 2023

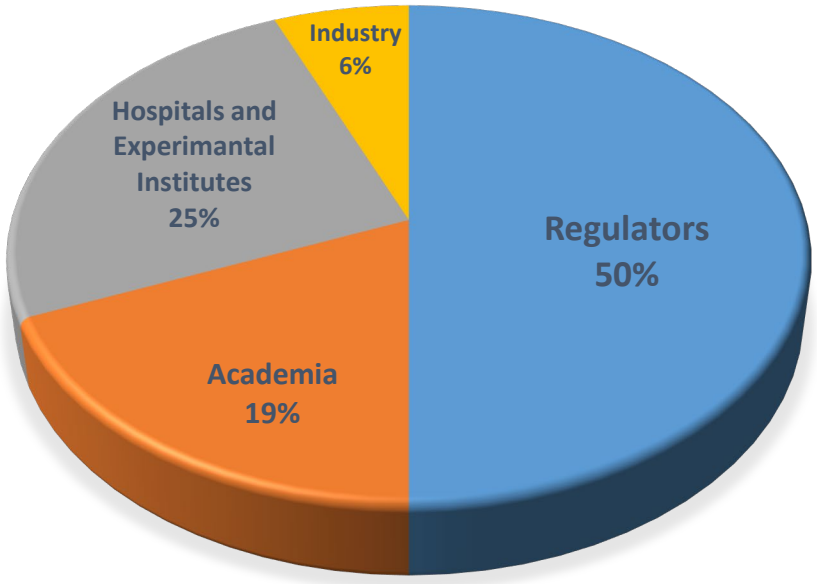
167th Ph. Eur. Commission — 06 2020

170th Ph. Eur. Commission — 06 2021

Pharmeuropa 35.2 — 04 2023

Bacteriophages Working Party (BACT WP)

Composition of BACT WP*



- 16 representatives from 10 countries
- Human and veterinary fields

** as of April 2023*

Bacteriophages and Ph. Eur. Commission

Ph. Eur. Commission: Priorities 2023-2025

https://www.edqm.eu/en/the-european-pharmacopoeia-commission

2.2. Biologicals

Biologicals is a fast moving field and the expectations from the Ph. Eur. are increasing. Fulfilling these expectations and being prepared for the future is a priority for the Presidium. A number of significant projects are in the pipeline, including several new general texts, such as those related to the **new approach to gene therapy medicinal products for human use**, and the information chapters on **cell-based preparations**, on the quality of **phage therapy** active substances and medicinal products for human and veterinary use, and on the quality of **mRNA vaccines** and their components. Regarding the latter, the newly created **mRNAVAC WP** will be in charge of developing quality standards supporting this emerging field.

Phage therapy general chapter (5.31)

Phage therapy active substances and medicinal products for human and veterinary use (5.31)

- **Published for information**
- **Framework of requirements for phage therapy API and phage therapy medicinal products (PTMPs) production and control**
- **Alternative production and control approaches allowed (subject to approval by the competent authority)**
- **Applicable to preparations of naturally occurring or genetically modified, single phages or their mixtures administrated by various routes**

Phage therapy general chapter (5.31)

Phage therapy active substances and medicinal products for human and veterinary use (5.31)

1. Definition
2. Production
   - 2.1 General Provisions
   - 2.2 Bacterial MCB and WCB
   - 2.3 Phages used for production of PTMPs
   - 2.4 Production and purification
   - 2.5 Final lot
   - 2.6 Adapted product
3. Labelling

Phage therapy general chapter (5.31)

Phage therapy active substances and medicinal products for human and veterinary use (5.31)

Requirements for bacterial host cells: MCB

- ❑ Information on source, subsequent manipulations and strain characterisation tests;
- ❑ Strains encoding prophages, antibiotic resistance determinants, toxins and other detrimental factors to be avoided unless otherwise justified and authorised
- ❑ Identification by phenotypic and genotypic methods including:
  - Determination of antibiotic susceptibility profile
  - Sequencing (preferably whole genome)
- ❑ Microbial purity by plating or other suitable method
- ❑ Cell viability by plate counting or other suitable method
- ❑ Strain susceptibility to the phage by a plaque assay or other suitable method
- ❑ Absence of detrimental (e.g. lysogenic) phages

Requirements for bacterial host cells: WCB

Phage therapy general chapter (5.31)

Phage therapy active substances and medicinal products for human and veterinary use (5.31)

Requirements for phages used in production: MPB

- ❑ Information on source, nucleotide sequence and susceptible bacterial species
- ❑ Phages encoding detrimental factors (known or potential) to be avoided
  unless otherwise justified and authorised
- ❑ Identification by phenotypic and genotypic methods including:
  - phage morphology
  - whole genome sequencing
  - modifications (chemical or genetic) description and effect characterisation
- ❑ Phage purity - single phage clone with one plaque morphotype
- ❑ Potency (infectious phage titre) by plaque assay or other suitable method
- ❑ Sterility (2.6.1)

Requirements for phages used in production: WPB

Phage therapy general chapter (5.31)

Phage therapy active substances and medicinal products for human and veterinary use (5.31)

Requirements for production

- ❑ Based on seed-lot system using a suitable host-phage combination
- ❑ Cross-contamination between different phages and bacterial host strains to be strictly avoided
- ❑ Yielding PTMP of consistent quality and stability
- ❑ Appropriate in-process testing implemented at relevant time point and/or key intermediate stages
- ❑ Use of raw materials of pharmaceutical grade and compliance with general chapter *5.2.12 Raw materials of biological origin for the production of cell-based and gene therapy*

Phage therapy general chapter (5.31)

Phage therapy active substances and medicinal products for human and veterinary use (5.31)

Purified harvest

- ❑ Identification – confirmation using relevant genotypic and phenotypic markers
- ❑ Potency (infectious phage titre) by plaque assay or other suitable method
- ❑ Microbiological examination (2.6.12) - compliant with the established specification
- ❑ Residual reagents – based on risk analysis
- ❑ Host-cell impurities and contaminants (e.g. toxins, host-cell proteins & DNA) absent or within the approved limits

Final lot

- ❑ Identification – verification of identity of **each phage** using relevant genotypic and phenotypic markers
- ❑ Potency (infectious phage titre) of **each phage** (in PFU/mL of PFU/mg) by plaque assay or other suitable method; within the approved limits
- ❑ Sterility (2.6.1) or microbiological quality (recommendations of 5.1.4)
- ❑ Appearance – compliant with the established specification
- ❑ Pyrogenicity (5.1.13)* - compliance with a suitable test for pyrogenicity, if applicable
- ❑ Water content (2.5.12 or 2.5.32) (for freeze dried PTMPs)
- ❑ pH (for liquid PTMPs)

** New general chapter providing guidance on the choice of pyrogen testing approach; Pharmeuropa 35.1*

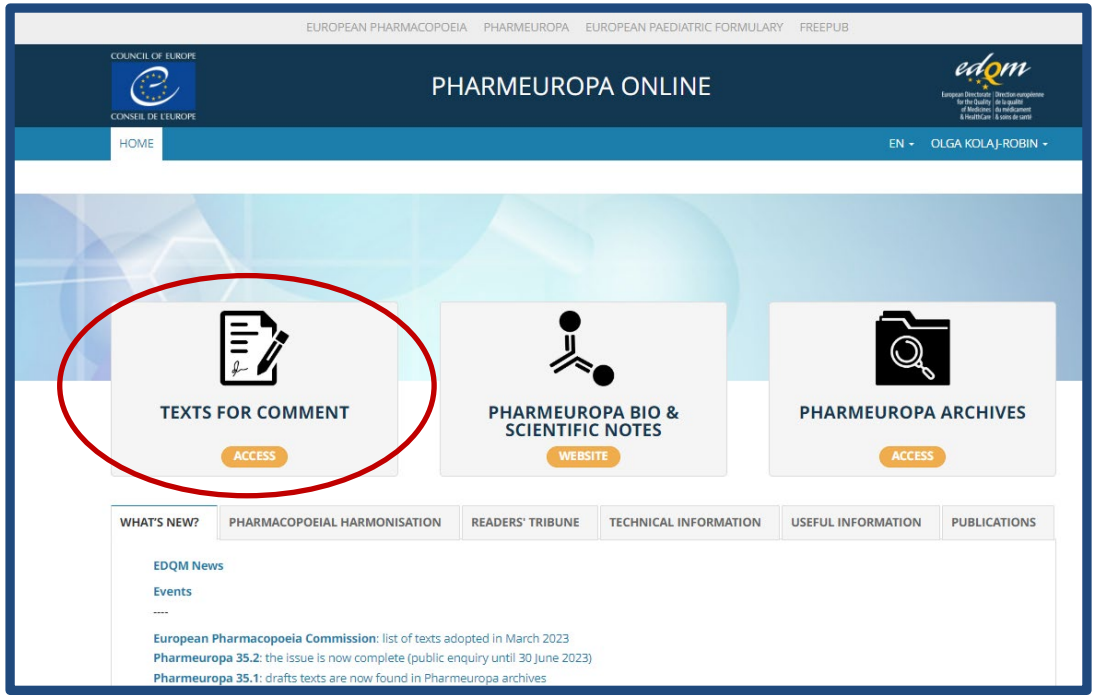
Phage therapy general chapter (5.31)

Phage therapy active substances and medicinal products for human and veterinary use (5.31)

Adapted products

- ❑ Direction of a PTMP to evolve in order to increase potency against a clinical isolate from an individual patient
- ❑ Starting point – phage or mixture of phages compliant with requirements for *Phages used for production of PTMP* (section 2-3)
- ❑ Potency of the adapted PTMP determined against the target clinical isolate
- ❑ Compliance (unless otherwise justified and authorised) with the following tests in *Final lot* (section 2-5):
    - Appearance
    - Sterility/Microbial quality
    - Pyrogenicity

Phage therapy general chapter (5.31)



Pharmeuropa 35.2

Public deadline: 30 June 2023
NPA deadline: 31 Aug 2023

https://pharmeuropa.edqm.eu/home

Approx. 6 months

Approx. 6 months

2 Pharmeuropa (5 months)

Adaptation if needed

Text finalised => approval by the group => Submission to EPC for adoption

3 Adoption by **Consensus**

4 Publication

Implementation

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