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

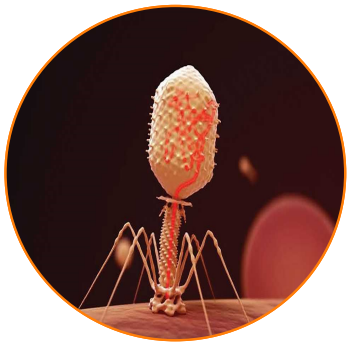
edqm

European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

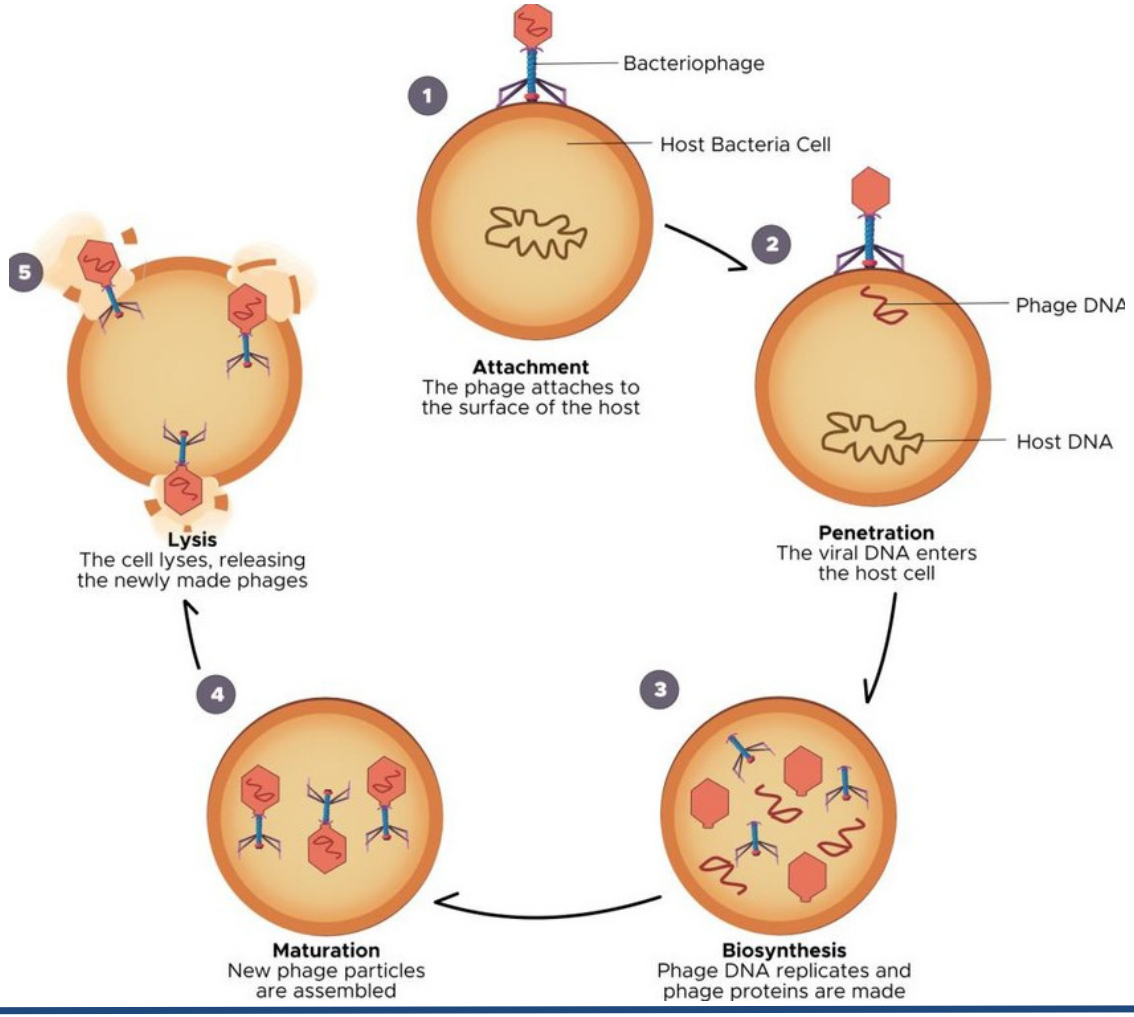
Phage therapy
An overview of the phage chapters of the Ph. Eur.



Swissmedic Expertentagung Pharmakopöe
Freitag, 18. Oktober 2024, Kursaal Bern

Dr Emmanuelle Charton, EDQM

Bacteriophages lifecycle (lytic cycle)



Introduction

- Antibiotic resistance is an increasing problem worldwide
- Phages are a promising alternative to antibiotics
- There is an increasing interest in phage therapy among healthcare providers and pharmaceutical companies
- Mostly used as compassionate use
- Little (but more and more) manufacturing and clinical experience
- Limited regulatory guidance
- Currently, one nationally authorised product in the EU (veterinary product)

PTMP – phage therapy medicinal product

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.

Bacteriophages Working Party (2020-2022)

Creation of BACT WP
Assessment of the feasibility, applicability and consequences of having a **general chapter** on Bacteriophage API in the Ph. Eur.

Addition to the WP
Phage therapy active substances and medicinal products for human and veterinary use (5.31)

167th EPC

170th EPC

06 2020 — Call for experts

03 2021

05 2021

06 2021

01 2022

06 2022

BACT WP meetings

#1

#2

#3

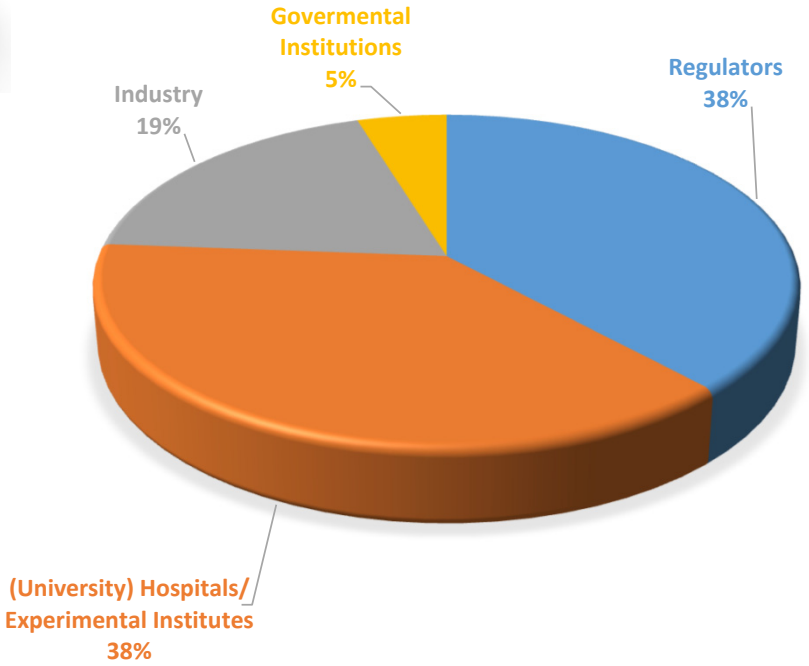
#4

- Text applicable to API and MP proposed
- Creation of the proposed general chapter judged feasible, justified and beneficial

PA/PH/Exp. BACT/T (21) 5

Bacteriophages Working Party (BACT WP)

Composition of BACT WP*



- **21 Experts from 12 countries (+7 in 2023, +2 in 2024)**
- **Human and veterinary field**

Bacteriophages Working Party (2023- now)

Addition to the WP
Bacteriophage potency determination (2.7.38)

176th EPC

03 2023

BACT WP meetings

#5

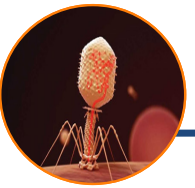
04 2023

Phpa 35.2

06 2023

Public consultation

Pharmeuropa 35.2
Public deadline: 30/06/23
NPA deadline: 31/08/23



Phage therapy medicinal products (5.31)

130 comments received

- **7 countries**
- **Academia, Consortia, NGOs, Associations, Industry, Regulators**
- **Vastly supportive**

Chapter will enable the labs and pharmacies to choose the safest, most efficient and cheapest pathway for formulation of […] phage product […]. In the same time, it is flexible enough to let further R&D happen.

- Creation of **monograph** rather than a chapter suggested

- Concerns from Animal Healthcare Europe for veterinary sector

Any requirements for veterinary PTMPs must take into account the specificities of the veterinary medicine sector.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 27 January 2023
2 EMA/CVMP/NTWP/32862/2022
3 Committee for Veterinary Medicinal Products (CVMP)
4

5 Guideline on quality, safety and efficacy of veterinary
6 medicinal products specifically designed for phage
7 therapy

- **EMA liaison** in BACT WP for alignment with EMA guideline on veterinary phage therapy;
- Group involved in the review of the guideline prior to public consultation

Bacteriophages Working Party (2023- now)

Addition to the WP

Bacteriophage potency determination (2.7.38)

Adoption

Phage therapy medicinal products (5.31)

PA/PH/Exp. BACT/T (22) 1 COM

176th EPC

178th EPC

Implementation

03 2023

04 2023

06 2023

10 2023

01 2024

03 2024

01 2025

BACT WP meetings

#5

Phpa 35.2

#6

#7

Suppl. 11.6

Public consultation

Pharmeuropa 35.2

Public deadline: 30/06/23

NPA deadline: 31/08/23

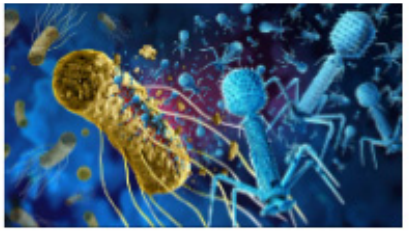
Review of comments and chapter finalisation

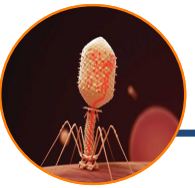
New general chapter on Phage therapy medicinal products (5.31) adopted and pre-published on the EDQM website

The EPC decided to exceptionally pre-publish the text on the website of the European Directorate for the Quality of Medicines & HealthCare (EDQM) pending its publication in Supplement 11.6 (July 2024).

See also:

- Key facts about antimicrobial resistance (WHO)
- European Pharmacopoeia
- European Pharmacopoeia Commission
- European Pharmacopoeia Commission priorities for the years 2023-2025

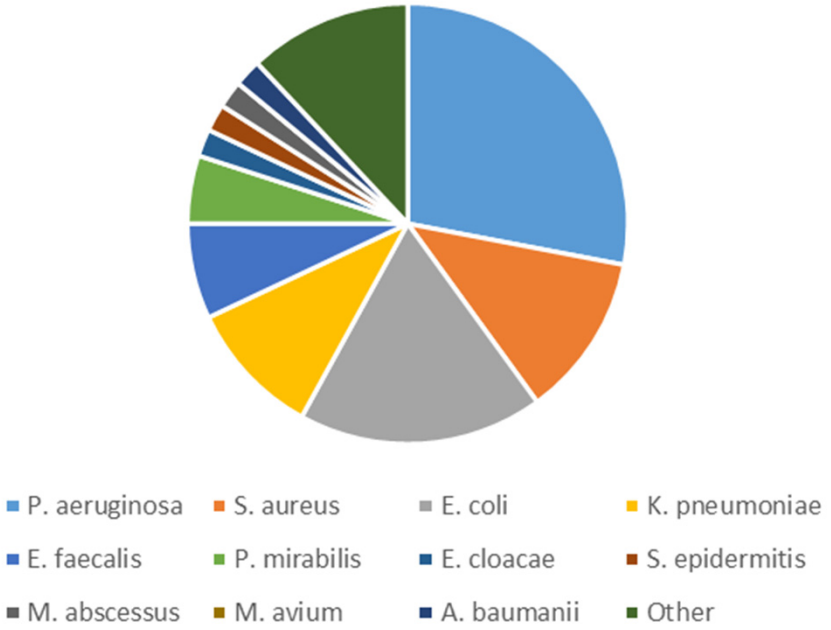




Phage therapy medicinal products (5.31)

Diverse approaches/products to be covered

- Off-the-shelf *vs* magistral preparations
- **Diversity of targeted bacteria vs. extreme narrow spectrum of phages**
- Include possibility of adaption to patient isolate



Open Forum Infect Dis. 2020 Aug 27;7(9):ofaa389. doi: 10.1093/ofid/ofaa389.
Viruses. 2019 Mar 17;11(3):265. doi: 10.3390/v11030265.

Phage therapy medicinal products (Ph. Eur. 11.6)

Phage therapy medicinal products (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 (human and veterinary use)**

Phage therapy medicinal products (Ph. Eur. 11.6)

Phage therapy medicinal products (5.31)

1. Definition
2. Production
   - 2.1 General Provisions
   - 2.2 Bacterial cell banks
   - 2.3 Phage seed lots
   - 2.4 Production and purification
   - 2.5 Final lot
   - 2.6 Adapted product
3. Labelling

Phage therapy medicinal products (Ph. Eur. 11.6)

Phage therapy medicinal products (5.31)

General provisions

- Production process to yield a PTMP of consistent quality and stability
- Appropriate in-process testing to be implemented at relevant time points and/or key intermediated stages of the process
- Production based on well-characterised bacterial cell bank and phage seed lot with a host-phage combination that has been shown suitable
- Possibility to used single-tiered system included
- Possibility for PTMPs to be prepared on-site based on specific clinical needs
- PTMPs to be prepared under an appropriate quality system, extent of which is driven by the risks for the patient concerned

Phage therapy medicinal products (Ph. Eur. 11.6)

Phage therapy medicinal products (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 confirmation using a suitable method
- Absence of microbial contaminants determined 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 phage particles detrimental to the quality of PTMPs confirmed

Phage therapy medicinal products (Ph. Eur. 11.6)

Phage therapy medicinal products (5.31)

Requirements for phage seed lots: phage master seed lot

- ❑ Information on source, nucleotide sequence and susceptible bacterial species and/or strains
- ❑ Phages encoding detrimental factors (known or potential) to be avoided unless otherwise justified and authorised
- ❑ Modifications (genetic or chemical) described and their effect characterised
- ❑ Identification by a suitable method
- ❑ Absence of microbial contaminants determined by plating or other suitable method
- ❑ Phage purity – absence of extrinsic phage contaminants confirmed by a suitable method; presence of unavoidable intrinsic phages may be justified and authorised when controlled by a suitable method
- ❑ Potency (infectious phage titre) by plaque assay or other suitable method
- ❑ Sterility (2.6.1)

Phage therapy medicinal products (Ph. Eur. 11.6)

Phage therapy medicinal products (5.31)

Requirements for production

- Based on bacterial cell bank and phage seed-lot system
- Cross-contamination between different phages and bacterial host strains to be strictly avoided
- 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*
- Pooling of several single harvest of the same phage clone before the purification process included

Phage therapy medicinal products (Ph. Eur. 11.6)

Phage therapy medicinal products (5.31)

Purified harvest

- ❑ Identification – confirmation using a suitable method
- ❑ 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, temperate phages) absent or within the approved limits

Final lot

- ❑ Identification – identity confirmation of **each phage** using a suitable method
- ❑ Potency (infectious phage titre) of **each phage** by plaque assay or other suitable method; compliance with the established specification
- ❑ Sterility (2.6.1) for sterile PTMPs; microbiological quality determination using a suitable method for non-sterile PTMPs
- ❑ Appearance – compliant with the established specification
- ❑ Pyrogenicity (5.1.13)* - compliance with a suitable test for pyrogenicity is applicable
- ❑ Water content (2.5.12 or 2.5.32) (for solid PTMPs)
- ❑ pH (2.2.3) (for liquid PTMPs)

** New general chapter providing guidance on the choice of pyrogen testing approach; adopted in June 2024 – minor revision of 5.31 to include the reference*

Phage therapy medicinal products (Ph. Eur. 11.6)

Phage therapy medicinal products (5.31)

Final lot

- ❑ Various routes of administration and different dosage forms covered
- ❑ Additional tests required depending on the route of administration and the dosage form
- ❑ Other suitable methods to ensure the appropriate quality in accordance with the risk assessment and any local guidance or legal requirements for unlicensed pharmaceutical preparations possible

** New general chapter providing guidance on the choice of pyrogen testing approach; adopted in June 2024 – minor revision of 5.31 to include the reference*

Phage therapy medicinal products (Ph. Eur. 11.6)

Phage therapy medicinal products (5.31)

Adapted products

- Phage adaptation (training) – process to direct phages to evolve in order to increase their potency against (a) clinical isolate(s)
- Phage adaptation of a clinical isolate for an individual patient addressed
- Starting point – phage or mixture of phages compliant with requirements for *Phage seed lots* (section 2-3)
- Adapted PTMP compliant with requirements for *Final lot* (section 2-5) unless otherwise justified and authorised
- Increased potency of the adapted PTMP confirmed, serving also as an appropriate substitute for the identification test

Bacteriophage potency determination

Phage therapy medicinal products (5.31)

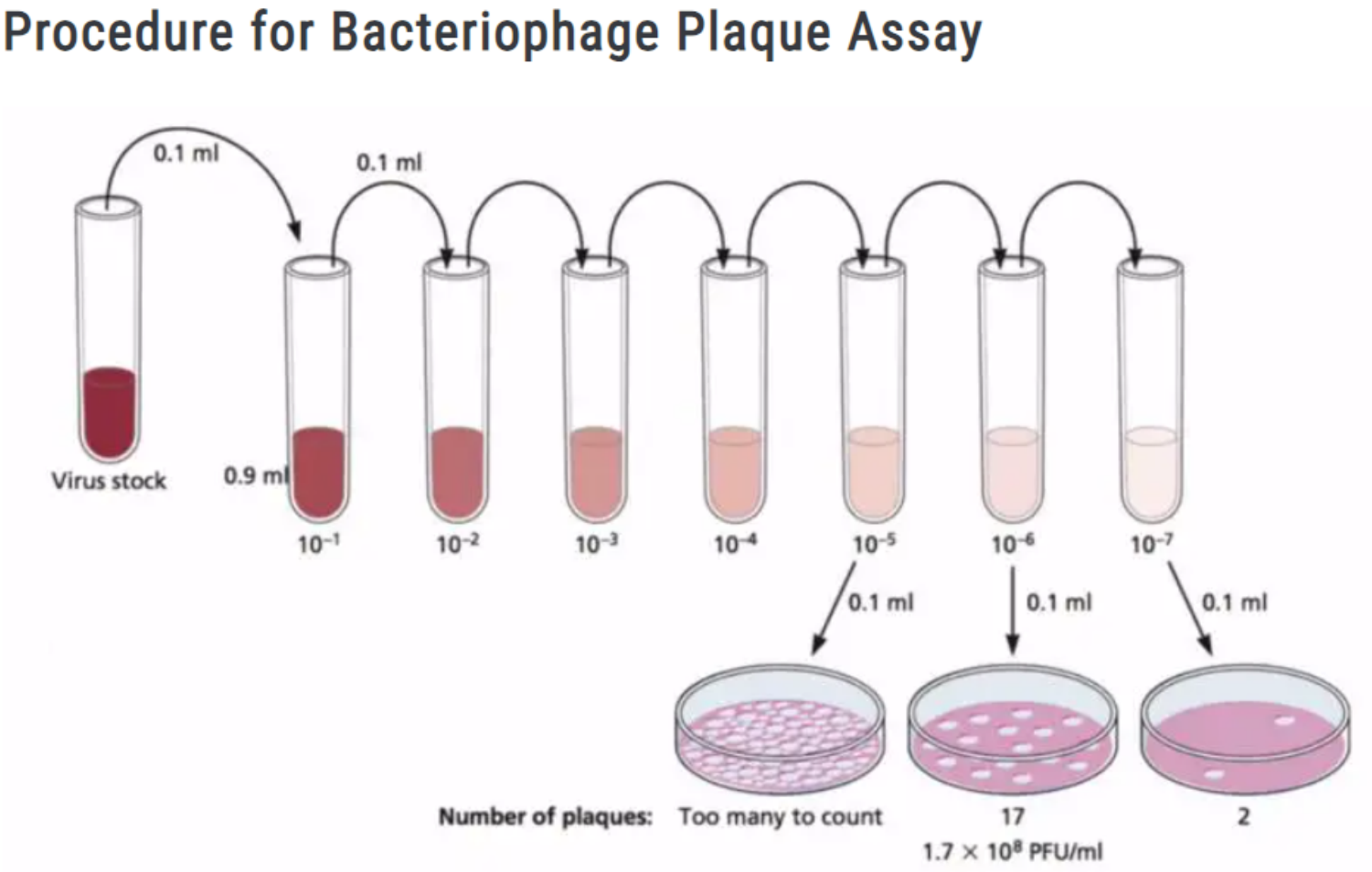
Potency (infectious phage titre) of **each phage**

Bacteriophage potency determination (2.7.38)

- ❑ Aiming at standardising the potency testing of single phage preparations
- ❑ Providing guidance for potency determination of multicomponent phage preparations
- ❑ Scope: phages causing productive lysis; potency expressed as infectious titre
- ❑ Focus: plaque assay; alternative approaches also to be covered

- ❑ Numerous phage-host combinations influencing assay
- ❑ Potential spectrum overlap in multiphage preparations
- ❑ Lack of direct correlation of surrogate assays with phage infectivity
- ❑ Phage stability (especially for multiphage preparations)

Bacteriophage plaque assay



Bacteriophage plaque assay

Next steps

Added to the WP June 2023

Bacteriophage potency determination (2.7.38)

01 2024 — **BACT WP meetings** — **#7**

04 2024 — **#8**

10 2024 — **#9**

04 2025 — **Phpa 37.2**

! Tentative !
Public consultation

Pharmeuropa 37.2
Public deadline: 30/06/25
NPA deadline: 31/08/25

Acknowledgements

- All members of the the Bacteriophages Working Party of the Ph. Eur. « BACT WP »
- Pieter-Jan Ceyssens, Sciensano, Belgium, Chair of the BACT WP
- Olga Kolaj-Robin, Scientific Programme Manager for the BACT WP, EDQM

Thank you for your attention

Stay connected with the EDQM

EDQM Newsletter: **https://go.edqm.eu/Newsletter**
LinkedIn: **https://www.linkedin.com/company/edqm/**
Twitter: **@edqm_news**
Facebook: **@EDQMCouncilofEurope**

Phage therapy medicinal products (5.31)

130 comments received

Comment	%
Editorial/terminology/FR version/for info only	34%
Irrelevant/incorrect/lack of knowledge of Ph. Eur.	
Request for more details/specifications	
Suggestion to cite other Ph. Eur. texts	
Identification (including phenotypic methods and sequencing)	31%
Confusion around single/multiphages API	
Prophages	
patient's isolates/magistral preparations	
phage adaptation	

Phage therapy medicinal products (5.31)

Main adjustments after Pharmeuropa

- Simplification of the **title**, clarification of terminology;
- Change in the description of Identification (adaptation to the QC settings);
- Replacing the requirement for sterility of phage seed lots with **microbial purity (absence of microbial contaminants); sterility test maintained in the final lot** for sterile PTMP;
- Clarification on active substance containing one phage;
- Introduction of possibility to start production directly from bacterial master cell bank and phage master seed lot;
- **Clarification on prophages** (intrinsic phages may be unavoidable when using clinical isolates for production);
- Reproduction of the paragraph from general monograph (2619) on unlicenced pharmaceutical preparations;
- Restriction of *Adapted products* section to **phages to be used in the individual patient that was also the source** of the clinical isolate.