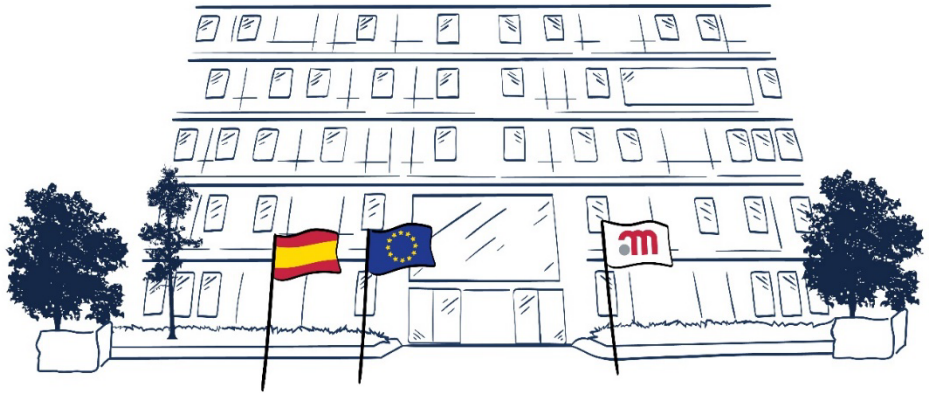
Regulatory framework applicable to phage therapy in Europe in the veterinary field

IABS meeting
November, 2024



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Regulatory framework applicable to phage therapy in Europe in the veterinary field

Bacteriophages as veterinary medicines (industrially manufactured)

Regulation 6/2019

Annex II to Regulation 6/2019

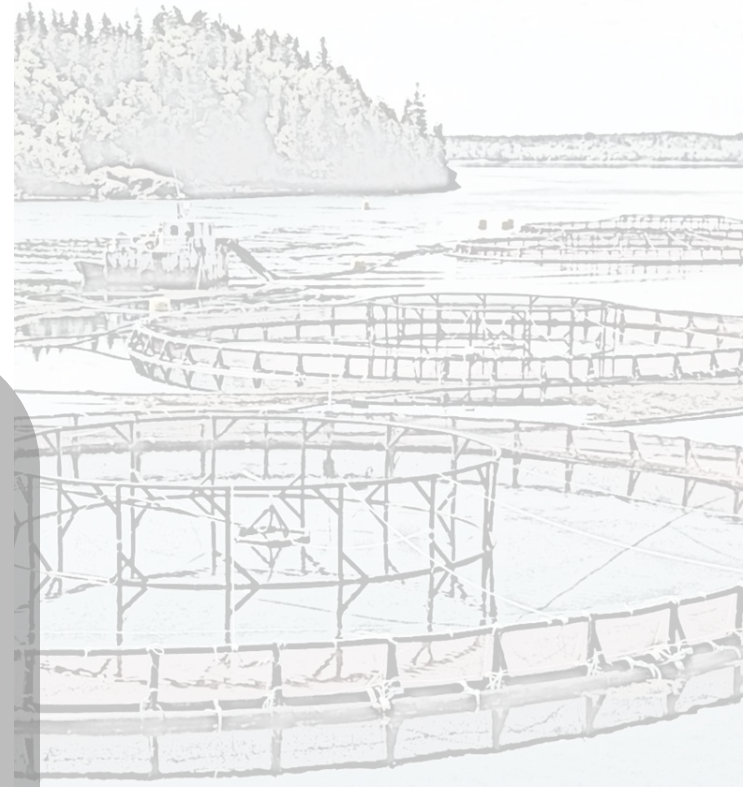
GMPs

National regulations

GL on quality, safety and efficacy of veterinary medicinal products specifically designed for phage therapy

Ph.Eur. General chapter

Bacteriophages as magistral formula



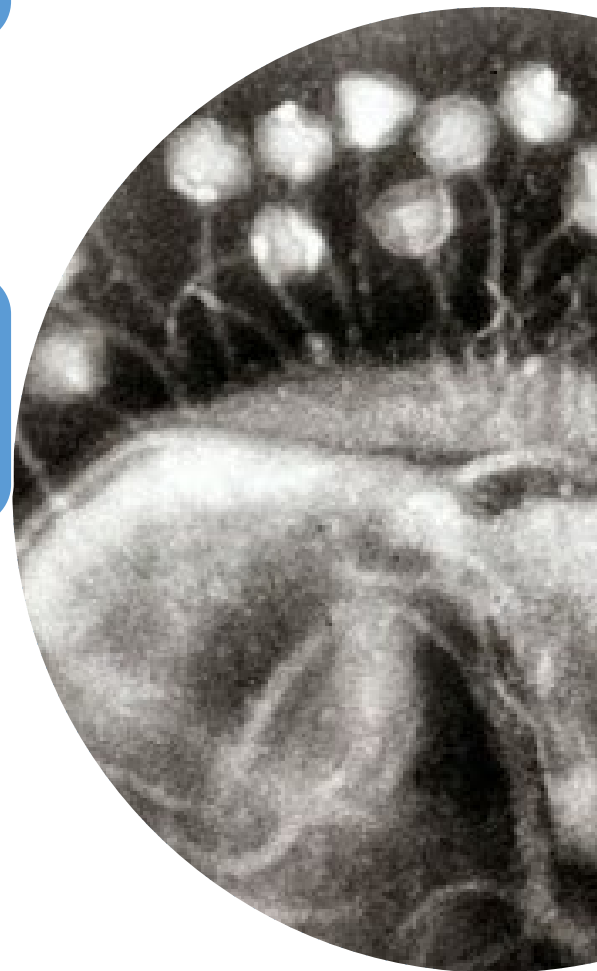
Regulation (EU) 2019/6 on veterinary medicinal products: scope and specific issues for phage therapies

Bacteriophages as veterinary medicines:

- To treat or prevent animal diseases
- Prepared industrially or by a method involving an industrial process

Classified as novel therapy veterinary medicinal product (VMPs)

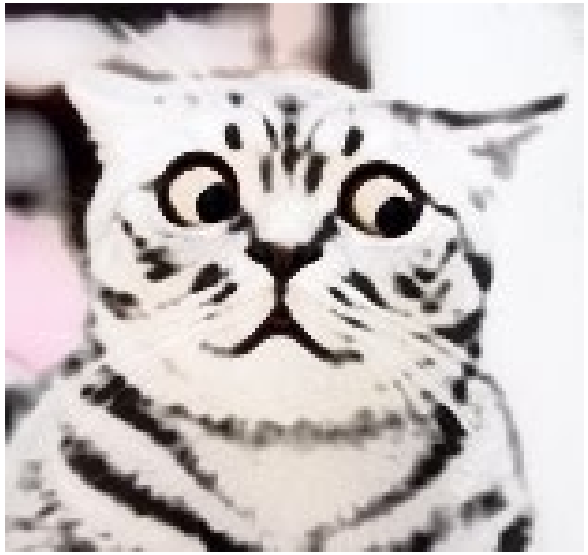
- Centralized marketing authorization procedure
- Applications to be submitted to EMA
- Marketing authorisation valid throughout the EU
- Requirements stated in Annex II to Regulation (EU) 2019/6



Regulation (EU) 2019/6 on veterinary medicinal products: marketing authorization application

Applicants must submit a full dossier containing:

- Part 1 – Administrative information
- Part 2 – Quality
- Part 3 – Safety
- Part 4 – Efficacy



Technical data requirements for VMPs are laid down in Annex II to Regulation (EU) 2019/6.

Bacteriophages are considered in general as biological other than immunologicals.

General requirements for 'novel therapies' defined in Section V.1 of Annex II to Regulation (EU) 2019/6.

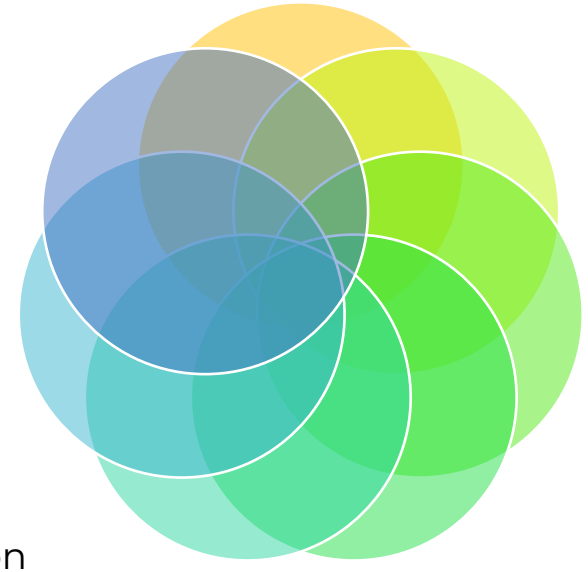
Specific requirements for bacteriophages defined in Section V.1.5.4. of Annex II to Regulation (EU) 2019/6.

Phage therapies: regulatory/scientific challenges

Changes in the phage composition, frequency

Correspondence between in vitro and in vivo efficacy

Risks of the presence of lysogenic phages during production



Assessment of environmental safety; genetically modified bacteriophages

Characterisation and selection of phage/bacteria strains for production

Impact on microbiota, modulation of immune responses, endotoxin release

Development of bacterial resistance to phages

The regulatory framework is expected to be flexible…

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 October 2023
EMA/CVMP/NTWP/32862/2022
Committee for Veterinary Medicinal Products (CVMP)

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

Draft agreed by Novel Therapies and Technologies Working Party (NTWP)	14 November 2022
Adopted by CVMP for release for consultation	18 January 2023
Start of public consultation	27 January 2023
End of consultation (deadline for comments)	31 May 2023
Revised draft agreed by Novel Therapies and Technologies Working Party (NTWP)	29 August 2023
Adopted by CVMP	5 October 2023
Date coming into effect	13 October 2023

Keywords	***Novel therapies, bacteriophages, phages, phage therapy***

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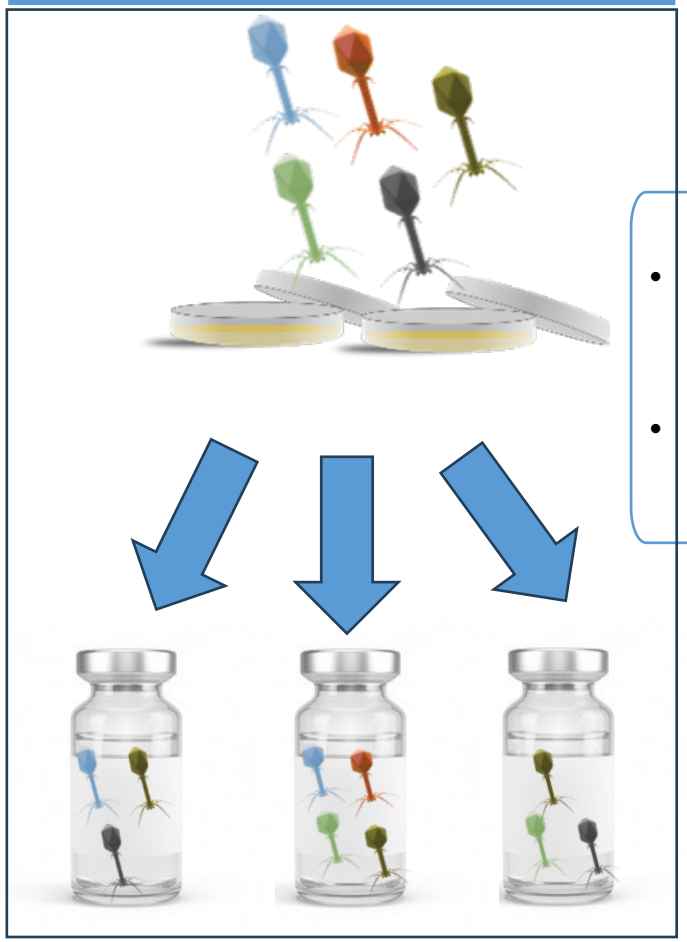
Main characteristics of the Guideline…

Quality



- Full characterisation
- Standarised manufacturing process

Safety

- Representative preparation, representing the worst case scenarios
- Extrapolation between comparable strains of bacteriophages, or between target animal species, or different route of administrations may be possible based on representative/validated in *vitro* or in *vivo* parameters

Efficacy

- Representative preparation, representing the worst case scenarios
- Extrapolation for alternative combinations based on validated in vitro or in vivo data or on a sicentific justification

MINISTERIO DE SANIDAD
agencia española de medicamentos y productos sanitarios

GMPs are of application to manufacture veterinary medicines for phage therapies

Manufacturing shall comply with the principles of GMPs adapted where necessary, to reflect the specific nature of those products.

GMPs annexes applicable to VMP are being revised by the Inspector Working Group:

"the revised Annex will clarify to what extent principles of ICH Q8, Q9 and Q10 and VICH guidelines should be followed in the design and implementation of facilities, equipment and processes for the manufacture of veterinary biological products."

https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-revision-annex-5-guidelines-good-manufacturing-practice-medicinal-products-manufacture_en.pdf

Ph.Eur. Chapter oh Phage therapies

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5.31. PHAGE THERAPY MEDICINAL PRODUCTS

This general chapter is published for information.

It offers a framework of requirements for phage therapy active substances and medicinal products for human and veterinary use and their production and control.

The provisions of the chapter do not exclude the use of alternative production and control methods that are acceptable to the competent authority.

1. DEFINITION

Bacteriophages (phages) are viruses that infect bacteria and depend on their bacterial host for replication. Phages consist of a genome comprised of single or double stranded DNA or RNA, encapsulated in a protein capsid.

Phage therapy medicinal products (PTMPs) are preparations of naturally occurring or genetically modified phages used to treat or prevent human or veterinary bacterial infections.

A PTMP can contain one phage, i.e. a single phage therapy active substance, or a mixture of phages, combined with excipients. PTMPs can be administered by various routes and are available in different dosage forms.

2. PRODUCTION

2-1. *GENERAL PROVISIONS*

Phages are obtained by propagation in bacterial host strains and are purified using suitable methods.

The production process yields a PTMP of consistent quality

Microbial purity. The absence of microbial contaminants is determined by plating or any other suitable method.

Viability. The number of viable cells is determined by a plate count or any other suitable viable cell count method.

Phage sensitivity. The susceptibility of the strain to the phage therapy active substance is demonstrated using a plaque assay or any other suitable method.

Absence of detrimental phages. The absence of phage particles that could be detrimental to the quality of PTMPs is confirmed.

If a working cell bank (WCB) is used for production, it is a clonal derivative of the MCB and complies with the requirements for MCB.

2-3. *PHAGE SEED LOTS*

Phage seed lots used in PTMP production are derived from a single phage clone and must be characterised in detail. Information on the phage source, nucleotide sequence and susceptible bacterial species and/or strains is to be provided. Other parameters such as plaque morphology or phage morphology are determined, if relevant.

Phages whose genome contains sequences coding for known or potential detrimental genetic factors, e.g. antibiotic resistance determinants, toxins or lysogeny modules, are avoided, unless otherwise justified and authorised. For genetically or chemically modified phages, the modifications must be described and their effects characterised.

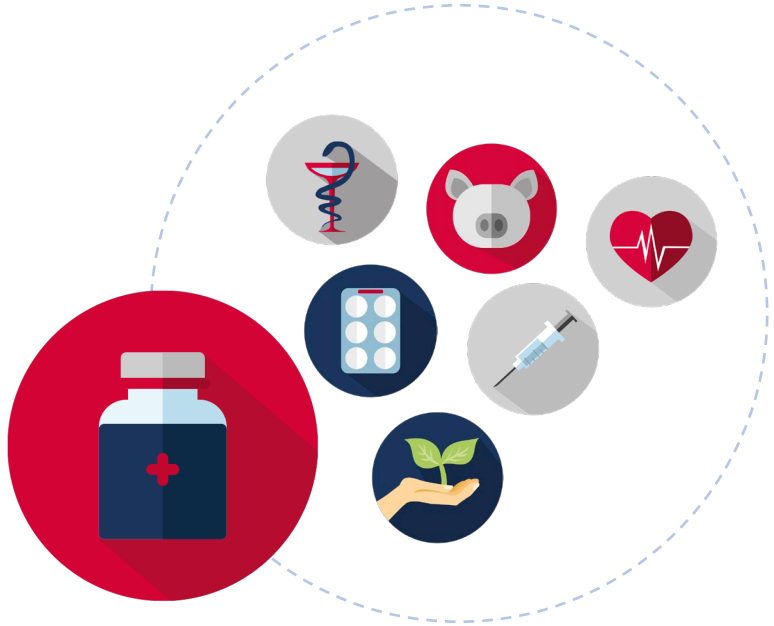
A phage master seed lot complies with the following requirements:

Identification. The phage seed lot is identified by a suitable method.

Microbial purity. The absence of microbial contaminants is demonstrated by a suitable method.

Phage purity. The absence of extrinsic phage contaminants is confirmed by a suitable method; however, as intrinsic

5. General texts



Thank you for your attention

Quality requirements

IIIa.2A1. Qualitative and quantitative composition

- ❑ Phage products with fixed composition
- ❑ Phage products with flexible composition **(parental preparation)**:
  Different bacteriophage strains which may be included in the composition of the final product, including phages not used in key safety and efficacy studies during product development

IIIa.2A2. Product development

- ❑ Justification of product composition
- ❑ Manufacturing process robustness

IIIa.2A3. Characterisation

- ❑ Genetic characterisation
- ❑ Phenotypic characterisation
- ❑ Host range
- ❑ Potency

Quality requirements

IIIa.2B. Production and control of starting materials

Quality controlled seed lots of
- ❑ Monophages
- ❑ Bacterial hosts

IIIa.2C. Control tests on the finished product

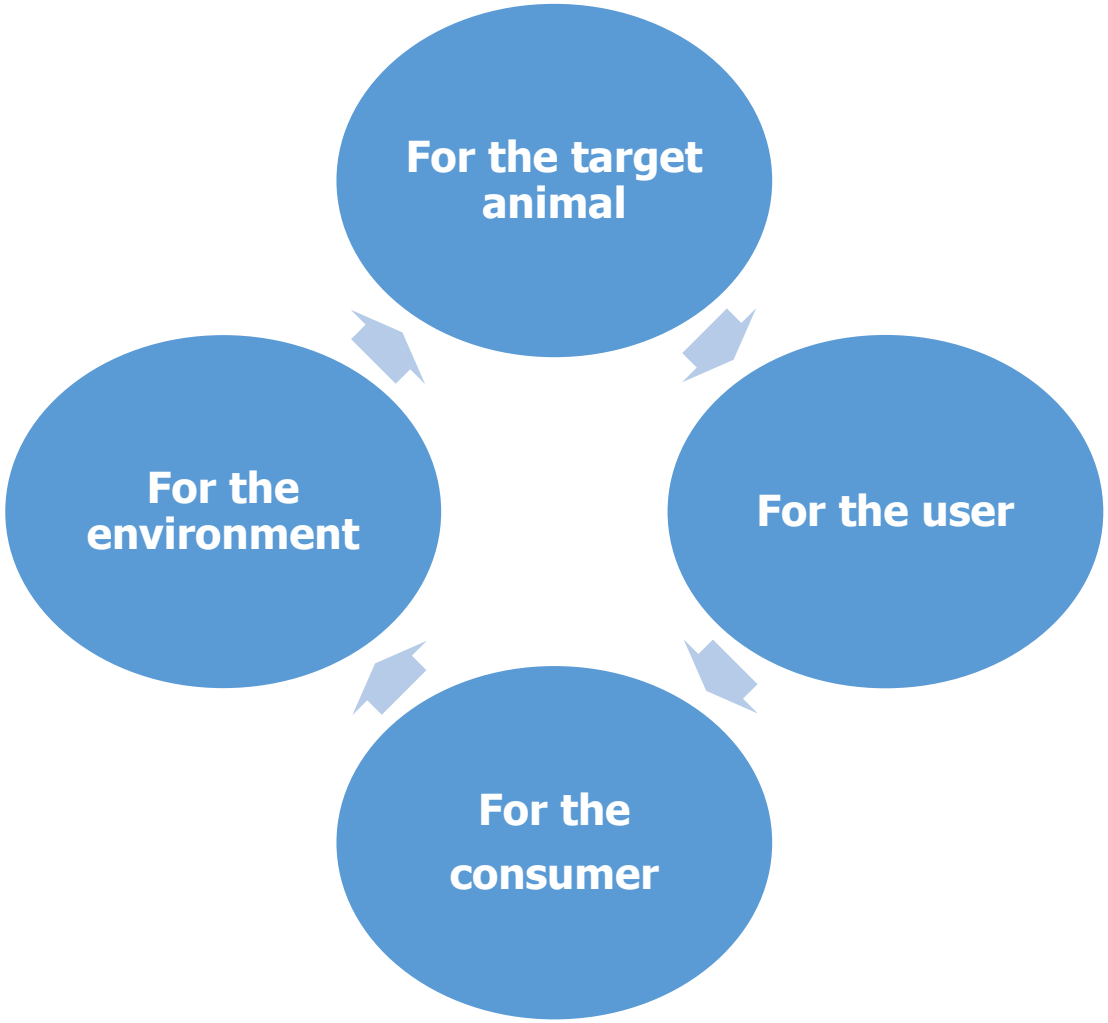
- ❑ Identity
- ❑ Potency
- ❑ Pyrogen content
- ❑ Total protein concentration
- ❑ Residual/free nucleic acid content
- ❑ Host DNA cells
- ❑ Other impurities
- ❑ General tests
- ❑ Water content
- ❑ Sterility

IIIa.2A3. Batch-to-batch consistency

IIIa.2E. Stability

Three batches

Safety



Requirements stated in Annex II of Regulation (EU) 2019/6, CVMP and VICH guidelines

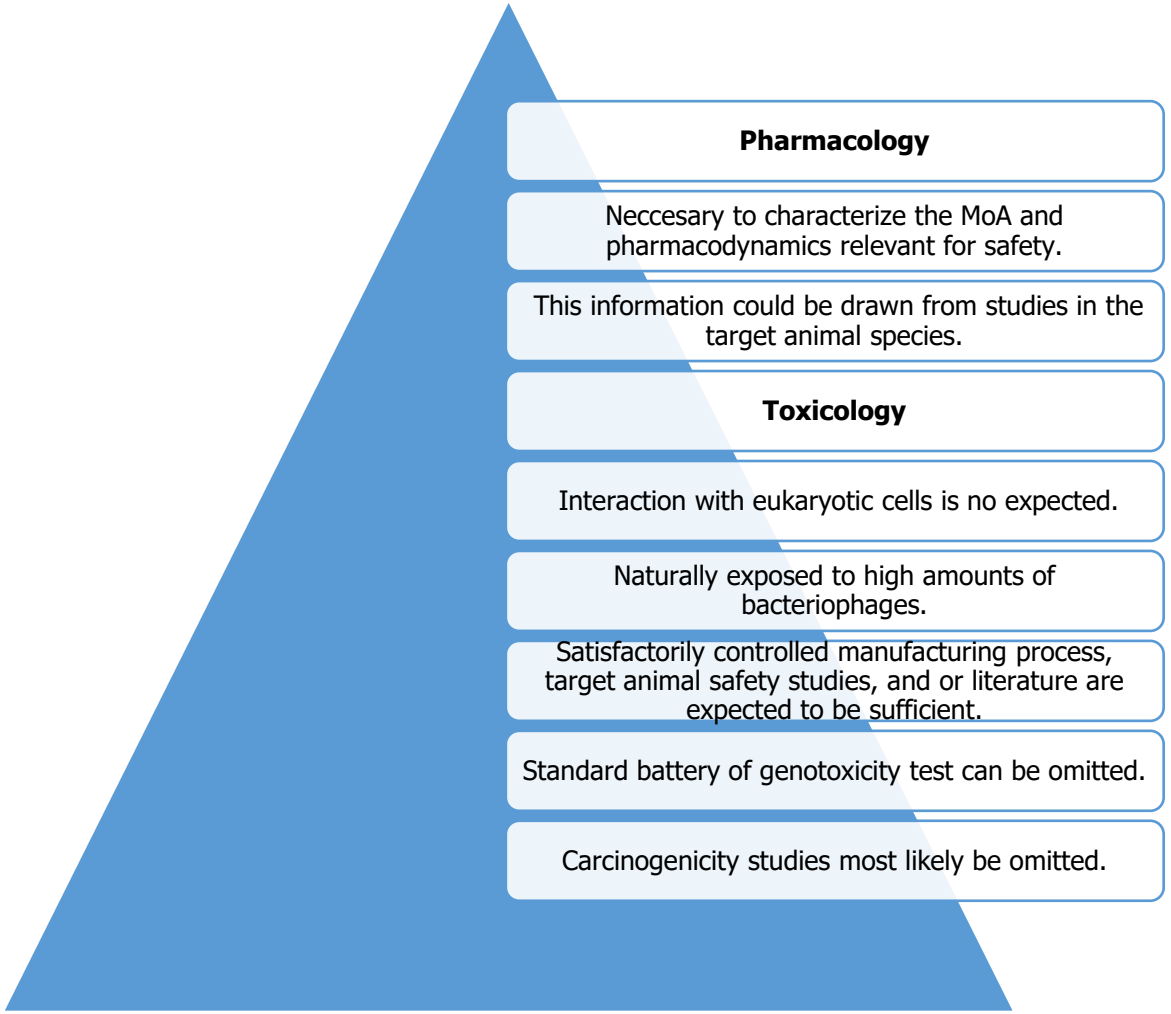
Safety Adaptation

- Adaptation of safety requirements based on product properties
- Identification of specific safety concerns (e.g., bacteriophage types)
- Proactive risk profiling and quality risk management approaches

Safety tests

Representative preparation,
representing the worst case scenarios

Extrapolation between comparable strains of bacteriophages, or between target animal species, or different route of administrations may be possible based on representative/validated in *vitro* or in *vivo* parameters



Safety tests, user safety and ERA

Development of resistance and related risk in humans

- Unlikely
- Specific studies might be omitted if appropriately justified
- Over time bacteria most likely develop resistance to bacteriophages. The applicant should reflect upon the risk of developing/spreading resistance in the environment and the related risks to humans associated with the use of the product

User safety

- Application of general user safety principles (Guideline on user safety for pharmaceutical VMPs)
- Hazard identification, exposure assessment, risk assessment-appropiate warnings or other risk management measures

Environmental Risk Assessment

- Impact of bacteriophages on environment
- Uncertainties and potential ecosystem effects
- The applicant should reflect upon the environmental impact to soil bacteria and soil function
- GMO additionally assessed following IIIa.3A6.2 of Annex II to Regulation (EU) 2019/6

Safety

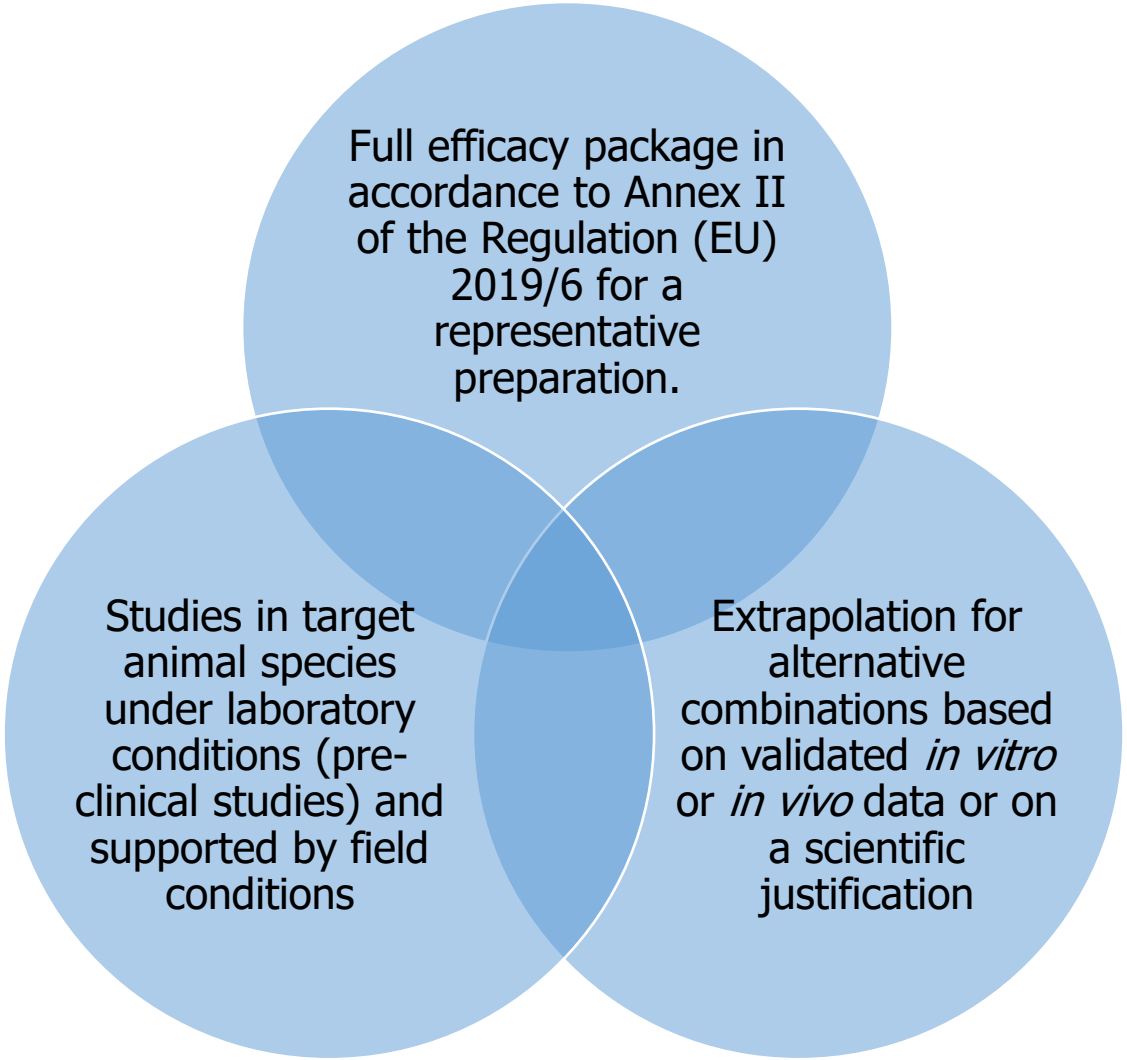
Marketing Authorization for Food-Producing Species

•Withdrawal period(s) should be established

•Consideration of Maximum Residue Limits (MRLs) in accordance with Regulation (EC) 470/2009 in advance (for active substances and excipients)

•Consultation with European Medicines Agency (EMA) for the need of a MRL evaluation

Efficacy



Efficacy

Pre-clinical studies

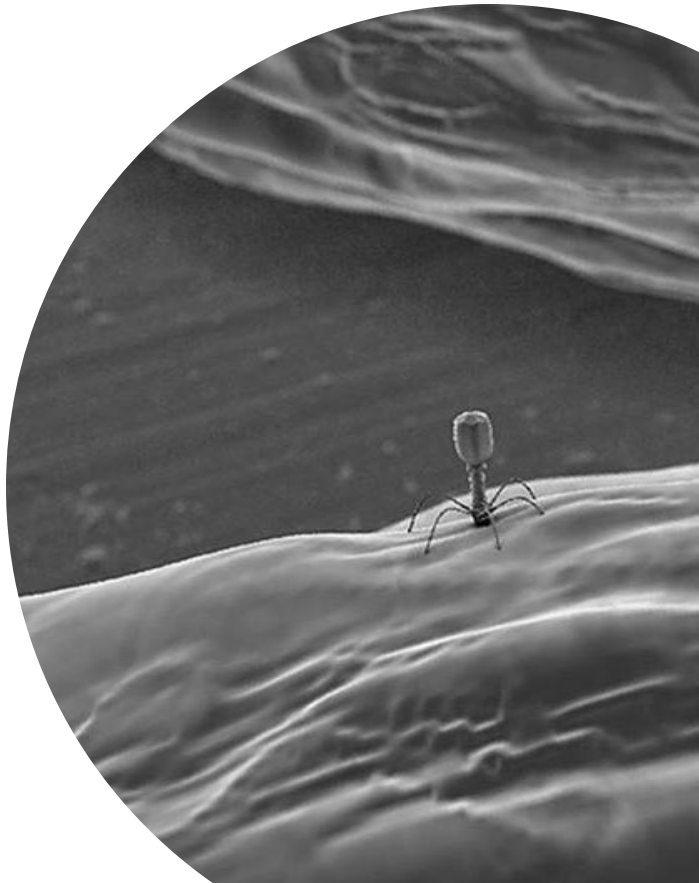
- Pharmacology: mechanism of action, range of host bacteria and in vitro susceptibility test, posology, immune response, comparability data
- Development of phage resistance
- Dose determination and confirmation studies
- Tolerance in the target animal species

Clinical trials

- Good clinical practice (VICH GL9)
- Final formulation
- Endopoints aligned with claims (prophylaxis, metaphylaxis, treatment)

Concomitant use with antibiotics

- Supported by data



Post-authorisation updates Quality

Comparability: Similarity between a bacteriophage product having undergone post-authorisation updates to overcome bacterial resistance or changes in the epidemiology of bacterial pathogens in the field (updated product) and the pre-update product.

Products are comparable if they have highly similar quality attributes, and no adverse impact on the safety or efficacy of the product is expected (ICH Q5E).

Description of post-authorisation phage product update	Category of phage product update	Level of changes to manufacturing process(es)	Likely quality data requirements for approval of updated phage product
Addition of a monophage component which is comparable to a component which is authorised with the marketing authorisation application	# Simplest	# Not substantial	§ Minimal
Addition of one or more new monophage components to product which are not comparable to a component which is authorised with the marketing authorisation application	$ Complex	$ May be substantial	Unless it can be scientifically justified that the proposed product update does not carry with it unacceptable risks to quality, safety, efficacy and traceability of product, re-validation of manufacturing processes and associated analytical technologies, as well as documentation of comparability between parental and updated product, may be required.

- ❑ Variation requiring assessment (VRA) (60 days).
- ❑ Post-approval change management protocols may or may not have been filed (see EMA/CHMP/CVMP/QWP/586330/2010).

Post-authorisation updates- Safety

Description of post-authorisation phage product update	Category of phage product update	Level of changes to manufacturing process(es)	Likely safety data requirements for approval of updated phage product
Addition of a monophage component which is comparable to a component which is authorised with the marketing authorisation application	# Simplest	# Not substantial	If monophage components are comparable, safety studies are not expected to be required (post-authorisation changes expected to be approvable based on quality data alone). Similarly, user and environmental risk assessment is not expected to be required. It is advised to consult the Agency for the need of a MRL status.
Addition of one or more new monophage components to product which are not comparable to a component which is authorised with the marketing authorisation application	$ Complex	$ May be substantial	If the impurity profile of the product is not substantially worsened, safety studies might not be required. In case of high level of complexity or lack of alternative evidence, safety data may be required. New user risk assessment and environmental risk assessment might be needed. It is advised to consult the Agency for the need of an MRL.

Post-authorisation updates- Efficacy

Description of post-authorisation phage product update	Category of phage product update	Level of changes to manufacturing process(es)	Likely efficacy data requirements for approval of updated phage product
Addition of a monophage component which is comparable to a component which is authorised with the marketing authorisation application	# Simplest	# Not substantial	If monophage components are comparable, target animal safety studies are not expected to be required (post-authorisation changes expected to be approvable based on quality data alone).
Addition of one or more new monophage components to product which are not comparable to a component which is authorised with the marketing authorisation application	$ Complex	$ May be substantial	If the new monophage components are not comparable to monophage components already present in the product, data from laboratory efficacy studies in target animal species or representative species may be required. In worst case scenarios (high level of complexity or lack of alternative evidence), data from new clinical trials in target animal species may be required. To avoid the requirement for a full efficacy package, alternative tools should be established. For example, it is expected that for in vivo studies, surrogate efficacy endpoints established and validated for the parental product might be used.

Overview of the various tools EMA has set up to provide scientific and regulatory support to those developing innovative veterinary medicines.