Quality documentation expected for veterinary bacteriophage medicines

- Focus on innovative aspects,
- reflecting the special provisions which are made for phage medicines and novel therapies,
- in the current EC regulation for veterinary medicines.

Regulations (EU) 2019/6 and 2021/805.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 January 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

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

Focus group meeting as part of public consultation for the draft guideline for veterinary bacteriophage medicines.

EMA, Amsterdam, 11.05.2023

https://www.ema.europa.eu/en/quality-safety-efficacy-bacteriophages-veterinary-medicines-scientific-guideline

Martin B. Oleksiewicz, DVM, Ph.D.

Head consultant, Danish Medicines Agency.

Speaking in personal capacity.

Member of the operational group responsible for drafting the guidelines.

No conflicts of interest to declare.

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

Table of contents

Annex 1: Justification of phages included in products.
Annex 2: Additional comments; genetic characterization of phage strains in products.
Annex 3: Non-binding examples of data requirements for post-authorisation updates made to phage products in order to overcome bacterial resistance or address changes in the epidemiology of bacterial pathogen(s) in the field.

Guideline sections addressed in this presentation:

- Section 4.2, and annexes 1 and 2: Quality requirements to parental products.

- Section 5, and annex 3:
- Quality requirements for post-authorisation updates made to phage products.
  - To overcome bacterial resistance.
  - To address changes in the epidemiology of bacterial pathogen(s) in the field.

What is a veterinary bacteriophage medicine ?

Lytic (bactericidal) bacteriophages

- Monophage medicine (one strain).
- Multiphage medicine (cocktail of strains).

Natural phages

Optimised phages:

- Enhanced potency

or

- Broader bacterial host range.

Optimization by classical microbiological in vitro selection.

Optimization by molecular biology methods (genetically engineered phages).

Bacteriophage particles as display platforms (e.g. for vaccines).

Use of temperate/integrating bacteriophages to modulate bacterial phenotypes.

Bacteriophage-derived products (e.g. lysins or other enzymes).

Which framework is employed to provide regulatory flexibility for veterinary phage products ?

- Quality requirements to phage products should be proportionate to the risks associated with the intended use.
  EU regulations (EU) 2019/6 and 2021/805.

- Framework: Current quality risk management principles.
  ICH Q8, Q9 and Q11 guidelines

- We have tried to clarifiy and exemplify the application of quality risk management principles in the guideline.

> ***Examples of factors influencing required level of quality documentation***:
> - Indication / medical need (e.g. severe life-threatening infections versus mild infections).
> - Route of administration (e.g. topical versus parenteral).
> - Biological complexity of product (critical quality attributes of active substances and final product).
> - The characteristics of the manufacturing process(es).
> - Acumulated commercial manufacturing knowledge.
> - The stability of the active substance and the finished product.
> - Current scientific knowledge.
> - Etc

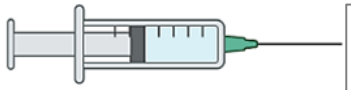
- However, nascent field: Acceptable level of adaptation of quality documentation can not be pre-specified.

- Required level of quality documentation must be evaluated on a case-by-case basis.

- If in doubt: Consider scientific advice.

Description of qualitative and quantitative composition for veterinary phage products:

Phage products with fixed composition
Akin to traditional fixed-composition products (mAb cocktails, multivalent vaccines, beta lactamase inhibitor + beta lactam, etc)

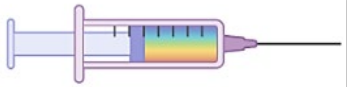


Application text (fixed-composition, multiphage product):
I would like to register a product consisting of 3 phage strains, namely the following:
Phages A, B and C.

Can be monophage preparations or multiphage preparations:

- Listing of all phage strain(s) in product.

Phage products with flexible composition
Innovation in new EU regulation for veterinary medicines



Application text (flexible composition, multiphage product):
I would like to register a product consisting of 3 phage strains, which may, according to need, be selected amongst the following strains:
A, B, C, D, E, F, G, H .....

Can be monophage preparations or multiphage preparations:

#1. Description of all different bacteriophage strains which may be included in the composition of the final product

#2. Range for the quantitative composition:
Minimum and maximum number of phage strains in the final product.

#3. For each strain as well as the phage product as a whole:
Minimum and maximum levels of bacteriophage per unit or dose.

For both product types, standard accessory information must also be given, e.g.:

- Excipients
- Accompanying reconstitution solvent(s)
- Container(s) and container closure(s) for finished product and any accompanying solvent(s)
- Devices required for delivery.
- Etc

Phage products with flexible composition; quality data:

Application text (flexible composition, multiphage product):
I would like to register a product consisting of 3 phage strains, which may, according to need, be selected amongst the following strains:
A, B, C, D, E, F, G, H .....

Phage products with flexible composition

Invariably multiphage preparations

#1. Description of all different bacteriophage strains which may be included in the composition of the final product

#2. Range for the quantitative composition:
Minimum and maximum number of phage strains in the final product.

#3. For each strain as well as the phage product as a whole:
Minimum and maximum levels of bacteriophage per unit or dose.

- Justification needed for all listed strains (as for any combination product).
  - Details in guideline annex I

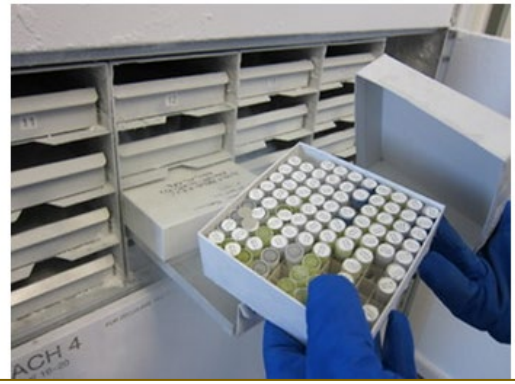
- Full quality characterization needed for all phages (biochemical, in vitro, genetic).
  - Host range, potency for bacterial pathogens, etc.
  - Details on genetic characterization in guideline annex II

- Listing may include phages not used in key safety and efficacy studies.

- In this case, existing knowledge should be sufficiently predictive to justify their registration as part of the flexible product composition.

- Flexible composition may not carry with it unacceptable risks for quality, safety, efficacy and traceability of the final product.

Prerequisite for flexible composition:
- Biobank with the phages claimed for the flexible compostion.



Phage products with flexible composition; general dossier requirements:

- The provided dossier must be sufficient to document that the flexible composition does not carry with it unacceptable risks for quality, safety, efficacy and traceability of the final product.
- Requirements for novel therapy products should be proportionate to the risks associated with their intended uses.

Application text (flexible composition, multiphage product):
I would like to register a product consisting of 3 phage strains, which may, according to need, be selected amongst the following strains:
A, B, C, D, E, F, G, H .....

Phage products with flexible composition

Invariably multiphage preparations

#1. Description of all different bacteriophage strains which may be included in the composition of the final product

#2. Range for the quantitative composition:
Minimum and maximum number of phage strains in the final product.

#3. For each strain as well as the phage product as a whole:
Minimum and maximum levels of bacteriophage per unit or dose.

Therefore:

(A) Manufacturers may freely pick monophage components from those included in the approved dossier,
i.e. may freely customize product,
for these purposes:

- Match the geographical distribution of targeted bacterial pathogens in different countries.
- Match phage resistance patterns of targeted bacterial pathogens in different countries.
- Address individual bacterial disease outbreaks.

(B) Such customisation of flexible phage products does not require variation applications.

Different phage compositions can be marketed in different countries.

Phage products with flexible composition; manufacturing process development:

- Quality documentation to support a flexible composition expected to be minimised if the anticipated changes to the product composition do not cause substantial changes to manufacturing processes.

- If flexible composition is required, scientific understanding of product and knowledge-based design of manufacturing processes is expected.

- In other words, flexible composition option provides opportunities as well as product development challenges.

(Just some) examples of product development/quality challenges:

- Upstream part(s) of manufacturing process(es) will likely differ (e.g. bacterial host strains).
- Can required purity be maintained for different individual phages ?
- Are blending and formulation steps able to accomodate all phage combinations in final product ?
- Is product formulation likely to be able to maintain stability of different phage combinations in final product ?
- Are QC analytical techniques able to accomodate all phage combinations in final product ?
- Etc

- Data requirements will be evaluated on a case-by-case basis.
- If in doubt: Consider scientific advice.

Post-marketing changes to address epidemiology and/or resistance patterns in bacterial pathogens; general remarks:

- Will require applications to EMA for changes to the terms of the marketing authorisation.

- Variation applications aimed at correcting resistance development may be urgent.

- Thus, to provide maximal regulatory flexibility, it is recommended to formalize this with EMA in the form of post-approval change management plans (PACMP).

  Examples of themes in PACMP:
  - Pre-defined monitorable and quantifiable criteria which may trigger product updates
  - How will development of bacterial resistance be detected?
  - What level of resistance is acceptable?
  - How are new monophage components expected to be generated?
  - Which data is expected to be required to document that apart from overcoming the developed resistance, the updated product is comparable to the parental product?
  - Etc

- Post-approval change management protocols should be realistic (feasible and plausible).
- Should be based on relevant scientific knowledge and understanding of manufacturing processes and product characteristics.

- See details in guideline section 5 and annex III.

Post-marketing changes to address epidemiology and/or resistance patterns in bacterial pathogens; fictitious examples for quality data requirements:

Marketed product: Phages A, B, **C** ← Bacterial resistance has developed against C.

Proposed updated product: Phages A, B and **C+** ← C+ is phage C which was trained in vitro to overcome bacterial resistance.

Complexity of product update:	Likely quality data requirements for approval of updated phage product:
• Except for the prosed exchange of phage C with phage C+, the product composition is not altered. • C and C+ phages are otherwise comparable. • Minimal changes to manufacturing process. • Minimal changes to analytical technologies. • No change in product specifications.	• Minimal
• Phage C+ exhibits significant phenotypical differences from C. • Manufacturing process needs to be adapted for C+ (e.g. change in host strain). • The proposed change causes worsening of the product impurity profile. • Changes in product specification required.	• Re-validation of manufacturing processes • Re-validation of associated analytical technologies. • Re-assessment of stability. • Etc

Summary, quality requirements for veterinary bacteriophage products:

Nascent field.

Issues must be evaluated on a case-by-case basis.

Consider scientific advice at relevant stages through product development.

- General / default requirements to quality documentation:
  - As for biological veterinary medicinal products other than immunologicals.

- Quality requirements in guideline are overall coordinated with Ph.Eur.
  - Texts are however not identical.
  - Both should be considered during product development.

- Flexible regulatory approach expected for novel therapies.
  - Quality documentation can be adapted based on quality risk management principles.

- Flexible composition option available for phage medicines.
  - Advantage(s):
    - Ability for rapid customization of product to address changes in epidemiology and/or resistance patterns in targeted bacterial pathogens in the field.
  - Challenges:
    - Scientific understanding of complex products.
    - Robustness of manufacturing processes.

- If need for regular post-approval changes to address epidemiology and/or resistance patterns in bacterial pathogens is foreseen:
  - To maximize regulatory flexibility, recommended to formalize this with EMA in the form of post-approval change management plans.

Thank you for your attention !