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

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EMA, Amsterdam, 11.05.2023

Focus group meeting on bacteriophages

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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 4.4:** Efficacy requirements to parental products.
- **Section 4.5:** Concomitant use of bacteriophages with conventional antibiotics.
- **Section 5, and annex 3:** Efficacy 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.

4.4. Efficacy Documentation

Annex II of Regulation (EU) 2019/6, Section IIIa for biological VMPs other than immunological VMPs

CVMP and VICH guidelines concerning efficacy

Control/mitigation measures to ensure risks remain at acceptable levels when adaptations are proposed

- A full efficacy package should be provided for a representative **monophage or multiphage preparation**

- Extrapolation of efficacy for **alternative combinations** based on validated *in vitro* or *in vivo* data or scientific justification

Efficacy and safety should normally be demonstrated by studies in the target animal species under laboratory conditions (pre-clinical studies) and supported by field conditions

4.4. Efficacy Documentation

Pre-clinical studies

- **Pharmacology**
- Development of **phage resistance** and related risk in animals
- **Dose determination** and **confirmation studies**
- **Tolerance** in the target animal species

Clinical Trials

- Special considerations for **metaphylaxis** claims
- Special considerations for **prophylaxis** claims.

Concomitant use of bacteriophages with conventional antibiotics

Pre-clinical studies

Studies in **target animal species**

Omission or replacement in **non-target animal species or *in vitro* data** may be possible if sufficiently scientifically justified.

- Support the use under recommended conditions (route of administration, dose, dose interval, resistance)
- In general in **target animals** for the representative monophage or multiphage preparations (justified considering the indication)
- ***In vitro* data** for alternative combinations to the representative one based on scientifically valid extrapolation

Pharmacology

Pre-clinical studies

Mode and mechanism of action

Demonstrate that:
- They are **lytic**

- Do not contain genetic determinants that confer **lysogeny** to the phage, or **virulence** or **antibiotic resistance** to bacteria

(Quality documentation)

Range of host bacteria and in vitro susceptibility test

Should support the claims

- *In vitro* **susceptibility tests** could be used

- Activity against target pathogens and non-targeted bacteria.

- **Isolates clinically representative** of the strains found in the field (clinical trials, models)

Posology

Suggested to demonstrate, that the recommended dose and dosage, and the administration route of the representative monophage or multiphage preparation, results in a productive bacteriophage infection at the site of bacterial infection in the target animal species (e.g. by means of PK/PD models)

A representative *in vivo* model of infection might also be useful.

The immune response to the effect of bacteriophage treatment in target bacteria

Data from the literature

- In **Repeated treatments** to document that the responses do not negatively impact the therapeutic effect

Comparability data to support a flexible composition of monophage or multiphage preparations

Possible based on representative/validated *in vitro* or *in vivo* data or parameters, or based on a scientific justification.

- **Comparable biodistribution, immune clearance and MOI** support should be provided to demonstrate comparability between representative and alternative preparations.

Pre-clinical studies

Development of **phage resistance** and related risk in animals

- Coevolution of bacteriophages and host bacteria, the risk of appearance and dissemination of resistant bacteria, the resistance mechanisms and the molecular genetic basis of resistance

- Peer-reviewed journals or proprietary studies

- Measures to limit the development of resistance in bacteria

Pre-clinical studies

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Dose determination and **confirmation studies**

- The **minimum effective dose**, the **proposed dosing interval**, the **duration of treatment** and, where relevant, any proposed repeated treatment should be provided for the representative monophage or multiphage preparation
- In **each target bacterium, each target animal species** and **recommended route of administration**
- **Experimental models of infection** in the target animal
- Justification based on literature data may be considered acceptable provided that the posology is supported in a preclinical or clinical study in the target animal species
- These studies may also serve to evaluate any potential impact on immunological function

Pre-clinical studies

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Tolerance in the target animal species

- Characterize the safety profile of the product **before introducing it in the field**
- On the basis of the route of administration and dosage, including repeated administration and treatment duration intended for use of the product in its final formulation
- **1X dose** is acceptable
- Post-mortem examinations could be omitted
- **Healthy animals**
- Safety data derived from use of bacteriophages in diseased animals is generally expected to be more informative
- **When specific risks are identified** TAS in healthy animals could be required (for example, when the targeted bacteria are also commensal).

Clinical Trials

Under field conditions should examine the efficacy and safety in the target animal.

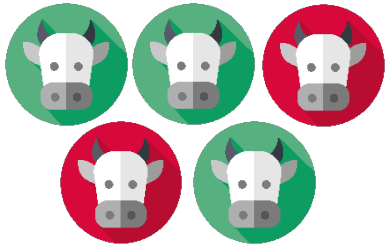
In accordance with good clinical practice principles (GCP) (VICH GL9).

- Final formulation including a representative preparation.
- Diagnostic methods and clinical conditions of the animals.
- Study endpoints should support each indication, targeted bacteria, animal species.
- Clinical and microbiological inclusion and exclusion criteria.
- Isolation of the target pathogen and susceptibility *in vitro* test.
- Endpoints (clinical cure rate and/or microbiological cure rate) and timing of the efficacy assessment.
- Statistical methods (CVMP guideline on statistical principles for clinical trials for VMP).
- Other designs could be accepted.

Clinical Trials

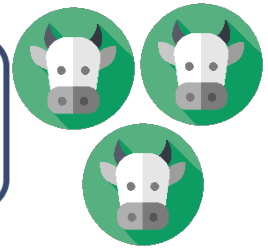
Claims: treatment, metaphylaxis and prophylaxis of specific infectious diseases or infections caused by one or several specific bacterial species.

Special considerations for **metaphylaxis** claims



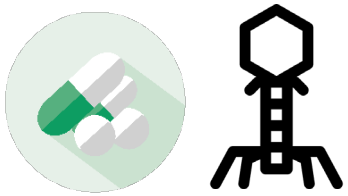
- Justified from an epidemiological point of view.
- Presence of the disease in the group should always be confirmed before.
- In conjunction with a treatment claim.
- The threshold for the initiation of the treatment should be justified on epidemiological and clinical grounds.
- Justification may be based on literature.

Special considerations for **prophylaxis** claims.



- Fully justified for each target species and indication

4.5. Concomitant use of bacteriophages with conventional antibiotics



Any specific claim is required to be supported by data (literature and supported by studies).

Could be considered if:

- Significant **therapeutic benefit** is demonstrated.

And

- **Risks of** development of antibiotic/phage **resistance** are addressed.

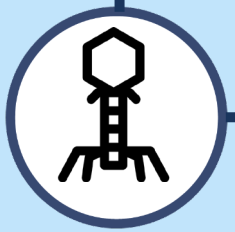
5. Post marketing authorisation changes (Efficacy)

- It is recognised in **Annex II of Regulation (EU) 2019/6** that phage products will likely need to be **updated** on a regular basis **due to development of resistance or changes in the epidemiology** of bacterial pathogen(s) in the field.

- It may be necessary to use trained versions of monophage components for the parental product or new monophage components.

- Updates on the authorised product.

Description of postauthorisation phage product update



Addition of a monophage component which is **comparable** to a component which is authorised with the Marketing authorisation application

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

Category of phage product update

Level of changes to manufacturing process(es)

Likely efficacy data requirements for approval of updated phage product

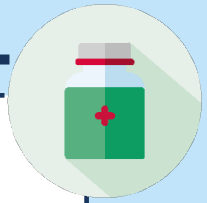
Simplest

Complex

Not substantial

May be substantial

Expected to be approvable based on **quality data**



- Data from **laboratory** efficacy studies in target animal species or representative species may be required.

- In worst case scenarios data from **clinical trials**

- **Alternative tools:** surrogate efficacy endpoints established and validated for the parental product might be used

¡Thank you!