Regulatory requirements for the authorisation of bacteriophage veterinary medicinal products

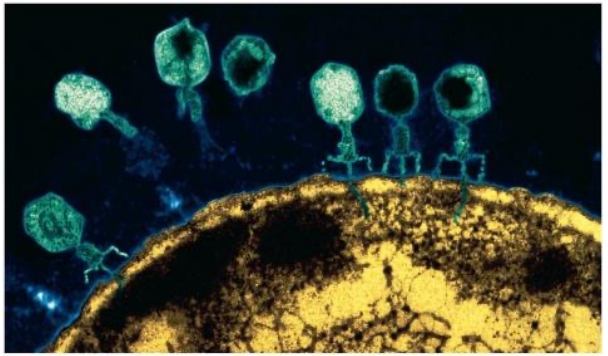

Figure 5-24
Introduction to Genetic Analysis, Tenth Edition
© 2012 W. H. Freeman and Company

2nd AVANT consortium meeting, 16-18 October 2021

Presented by Javier Pozo Gonzalez on 17 October 2021
Veterinary Biologicals and Emerging Therapies, European Medicines Agency

Content

- Regulatory framework for VMPs: where do bacteriophages fit
- General and specific data requirements for bacteriophage VMPs
- Some regulatory/scientific challenges
- EMA support to developers
- Summary - Key messages

Regulatory Framework for VMPs

Where do bacteriophages fit?

Regulatory framework for VMPs from 28 January 2022

Regulation (EU) 2019/6

Official Journal of the European Union L 4

English edition — Legislation — Volume 62, 7 January 2019

Contents

REGULATION (EU) 2019/6 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 11 December 2018
on veterinary medicinal products and repealing Directive 2001/82/EC
(Text with EEA relevance)

21.5.2021 EN Official Journal of the European Union L 180/3

COMMISSION DELEGATED REGULATION (EU) 2021/805
of 8 March 2021
amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council
(Text with EEA relevance)

- Adapt regulatory framework to innovation
- Reduce administrative burden and increase availability
- Open the scope of the centralised procedure
- Data protection for new products
- Mandate NCs to support SMEs
- Open the centralised route to all VMPs
- Tackle AMR and incentivise the development of new antimicrobials

Where do bacteriophages fit within Reg. (EU) 2019/6?

- **Veterinary medicinal product (VMP)** (Article 4)

  Any substance or combination of substances which fulfils at least one of the following conditions:

  (a) presented as having properties for treating or preventing disease in animals;

  (b) used in, or administered to, animals to restore, correct or modify physiological functions by pharmacol., immunological or metabolic action;

  (c) for medical diagnosis;

  (d) for euthanasia of animals

Bacteriophage products presented for treating/preventing disease are classified as VMPs

Where do bacteriophages fit within Reg. (EU) 2019/6?

- **'Novel therapy' veterinary medicinal product** (Article 4 (43))**:**

  a) a VMP specifically designed for gene therapy, regenerative medicine, tissue engineering, blood product therapy**, <u>phage therapy;</u>**

  b) a veterinary medicinal product issued from nanotechnologies; or

  c) any other therapy which is considered as a nascent field in veterinary medicine.

Bacteriophage VMPs are categorised as 'novel therapy' VMPs

Data requirements for novel therapy VMPs in Reg. (EU) 2019/6 apply

Where do bacteriophages fit within Reg. (EU) 2019/6?

- Article 42 – Scope of the centralised marketing authorisation procedure
  - **Mandatory scope** for novel therapy veterinary medicinal products
  - Applications for MA for bacteriophage products to be submitted to EMA
  - EMA shall issue an opinion within 210 days of receipt of a valid application
  - Marketing authorisation valid throughout the EU

Data requirements for bacteriophage VMPs

V.1 General requirements for novel therapy VMPs

- Technical data requirements for VMPs are laid down in Annex II to Regulation (EU) 2019/6
- General requirements for 'novel therapies' defined in Section V.1 of Annex II
- Depending on the active substance and the mode of action, a 'novel therapy' VMP could fall under any of the three product categories:

  (a) VMPs other than biologicals

  (b) biological VMPs other than immunologicals

  (c) immunological VMPs

V.1 General requirements for novel therapy VMPs

- Technical data requirements for VMPs are laid down in Annex II to Regulation (EU) 2019/6
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- Depending on the active substance and the mode of action, a 'novel therapy' VMP could fall under any of the three product categories:

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  (b) biological VMPs other than immunologicals

  (c) immunological VMPs

V.1.1 General requirements for novel therapy VMPs

- Marketing authorisation application shall follow the format and the data requirements according to the category of the product.
- Applicants must submit a full dossier containing:
    - Part 1 – Administrative information
    - Part 2 – Quality
    - Part 3 – Safety
    - Part 4 - Efficacy
- Deviations from requirements of the Annex II possible when justified.

V.1 General requirements for novel therapy VMPs

- **GMP requirements**
  - Manufacturing processes for novel therapies shall comply with the principles of GMP but can adapted where necessary, to reflect the specific nature of products.
  - Guidelines specific to novel therapies shall be developed.
- **Inherent risks** to the product shall be identified – risk profile.
- Possibility to address data gaps by implementation of **post-authorisation measures/studies**, on a case-by-case basis. **Risk management plans**.
- It is recommended to **seek advice** from the Agency on classification, dossier structure, and the data set to support quality, safety and efficacy.

V.1.5.4 Specific data requirements for phage therapy

- Definition of bacteriophages (single, double-stranded DNA or RNA, capsid)
- Bacteriophages cited as **alternatives to antibiotics**
- **Selection of suitable strains on a case-by-case basis** due to diversity of the intended targets and specificity of bacteriophages
- Fixed composition may not be possible generally. A **variable composition** based on a stock of bacteriophage strains is possible (similar to multi-strain dossier concept for veterinary vaccines*)

*Allows the selection of the strains to be included in the final product from a pool of strains authorised in the dossier. Formulation is based on field need. Addition or replacement of strains is possible via variation with a reduced data package.

V.1.5.4 Specific data requirements for phage therapy

- Bacteriophages and host bacteria cell banks preferably based on a **master seed system**.
- Confirmation that the bacteriophage strain(s) used are **lytic**.
- **Absence of resistance gene(s) and of genes coding for virulence factors** shown on all master seeds.
- The indication shall be for **prophylactic, metaphylactic and/or treatment** of specific infection(s) or infectious disease(s).
- For **genetically-modified phages**, the genetic modification shall be described.

Structure of dossier and general data requirements for biological other than immunological VMPs

Section IIIa of Annex II of Reg. (EU) 2019/6

Part 1: Summary of the dossier

- 1A. Administrative information
  - Legal basis
  - Applicant
  - Identification of VMP
  - Manufacturing and pharmacovigilance information
- 1B. Veterinary medicinal product information
  - Summary of product characteristics (SPC)
  - Description of final presentation
  - Package leaflet and labelling
- 1C. Critical expert reports on quality, safety and efficacy

Part 2: Quality documentation

- IIIa.2A Product description
  - IIIa.2A.1 Qualitative and quantitative composition
  - IIIa.2A2 Product development
  - IIIa.2A.3 Characterisation
- IIIa.2B Description of the manufacturing method (description, flow chart, list of substances used, blending, list of in-process control tests, validation of critical steps)
- IIIa.2C Production and control of starting material (TSE, CEPs, Cas)
  - IIIa.2C.1 Starting materials listed in pharmacopeias
  - IIIa.2C.2 Starting materials not listed in a pharmacopeia (biological/non-biological, EAs)

Part 2: Quality documentation

- IIIa.2D Control tests during the manufacturing process
- IIIa.2E Control tests on the finished product
  - IIIa.2E.1 Final product specification
  - IIIa.2E.2 Method descriptions and validation of release tests (general characteristics, identification and potency test, sterility and purity, etc)
- IIIa.2F Batch-to-batch consistency (active substance, finished product)
- IIIa.2G Stability tests (active substance, finished product, in-use shelf life, preservative)

Section IIIa.3 - Part 3: Safety documentation

- IIIa.3A Safety tests (potential risks to target species, humans and environment)
  - IIIa.3A.1 Identification
  - IIIa.3A.2 Pharmacology (pharmacodynamics, pharmacokinetics)
  - IIIa.3A.3 Toxicology
  - IIIa.3A.4 Other requirements (immunogenicity, development of resistance & risk in humans)
  - IIIa.3A.5 User safety (according to CVMP guidelines)
  - IIIa.3A.6 Environmental risk assessment (additional requirements for GMOs)
- IIIa.3B. Residue tests

Section IIIa.4 - Part 4: Efficacy documentation

- IIIa.4A Pre-clinical studies (target animal safety and efficacy; GLP for safety)
  - IIIa.4A.1 Pharmacology (pharmacodynamics, pharmacokinetics)
  - IIIa.4A.2 Development of resistance and related risk in animals
  - IIIa.4A.3 Dose determination and confirmation
  - IIIa.4A.4 Tolerance in the target animal species (local and systemic)
- IIIa.4B Clinical trials
  - IIIa.4B.1 General principles (examine safety and efficacy under normal conditions of use, design to support indications, conducted to GCP, controlled, favourable or not, statistics, B:R)
  - IIIa.4B.2 Documentation (results of pre-clinical studies and clinical trials)

Some regulatory/scientific challenges

- Characterisation and selection of phage/bacteria strains for production
- Risks of contamination with lysogenic phages during production
- Changes in the phage composition, frequency
- Impact on microbiota, modulation of immune responses, endotoxin release
- Assessment of environmental safety; genetically-modified bacteriophages
- Correspondence between in vitro and in vivo efficacy
- Design of studies, selection of efficacy endpoints, controls, time of administration
- Monitoring of efficacy post-marketing to ensure sustained efficacy
- Development of bacterial resistance to phages

EMA support to applicants and developers

EMA support to developers and applicants

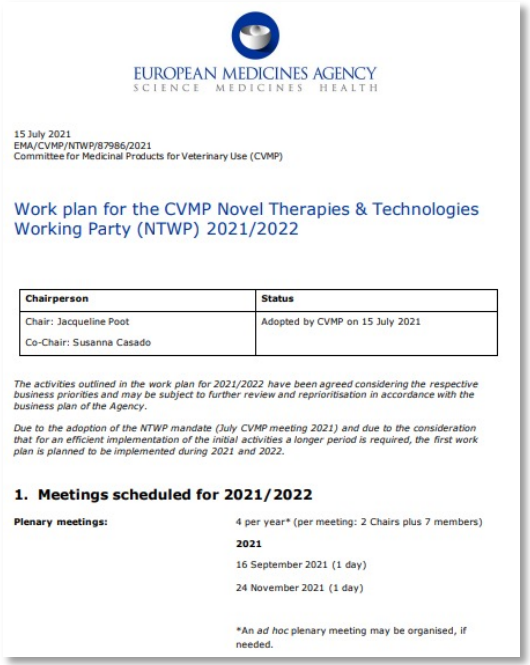
- **Innovation task force (ITF):** Early stages of development, general or product-specific, advice on legal, regulatory and /or scientific aspects – European Network of experts
- **Scientific advice:** Later stages of development, pre-submission or during evaluation – CVMP WP
- **Pre-submission meetings:** Final stages of development, product-specific
- **NTWP:** guidance on novel therapies e.g. Q&A documents on specific topics
- **Small and medium-sized enterprise (SME) scheme:** Administrative, regulatory and financial support to SMEs
- **Limited markets:** Reduction in requirements; financial incentives (food-producing species)

Novel Therapies and Technologies Working Party (NTWP)

- Working party of the CVMP established in April 2021
- Composed of European experts nominated and appointed by CVMP.
- Provides recommendations to the Committee for Medicinal Products for Veterinary Use (CVMP) on all matters relating to veterinary novel therapies and technologies.
- Main duties: development of guidelines, address queries from EMA committees and WPs, contribute to training on evaluation of NTTs
- Work plan 2021/2022 published in July 2021

NTWP secretariat contact: NTWP@ema.europa.eu

Novel Therapies and Technologies Working Party (NTWP)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 July 2021
EMA/CVMP/NTWP/87986/2021
Committee for Medicinal Products for Veterinary Use (CVMP)

Work plan for the CVMP Novel Therapies & Technologies Working Party (NTWP) 2021/2022

Chairperson	Status
Chair: Jacqueline Poot Co-Chair: Susanna Casado	Adopted by CVMP on 15 July 2021

The activities outlined in the work plan for 2021/2022 have been agreed considering the respective business priorities and may be subject to further review and reprioritisation in accordance with the business plan of the Agency.

Due to the adoption of the NTWP mandate (July CVMP meeting 2021) and due to the consideration that for an efficient implementation of the initial activities a longer period is required, the first work plan is planned to be implemented during 2021 and 2022.

1. Meetings scheduled for 2021/2022

Plenary meetings: 4 per year* (per meeting: 2 Chairs plus 7 members)

2021

16 September 2021 (1 day)

24 November 2021 (1 day)

*An *ad hoc* plenary meeting may be organised, if needed.

2.5. Bacteriophages

2.5.1. Guideline on quality, safety and efficacy of bacteriophages as veterinary medicines

Action: Concept paper to be developed and released for public consultation (Q1 2022).

Guideline to be developed and released for public consultation (Q4 2022).

Priority 1. Start date: September 2021, Completion date: December 2022.

Comments: The NTWP aims to develop general guidance with a focus on the establishment of a suitable regulatory framework for phage products, to encourage the development of innovative veterinary phage therapies.

An operational expert group will be established [see section 3.2.].

All stakeholders/interested parties are invited to send comments during the public consultations

*Work plan for the CVMP NTWP 2021/2022 (europa.eu)

Novel Therapies and Technologies Working Party (NTWP)

5.3. Collaboration with EDQM

5.3.1. Collaboration with the EDQM expert group on phage therapies

Action: Establishment and coordination between the NTWP OEG on bacteriophages and EDQM expert group working on this topic (Q3 2021).

Comments: A regular, bilateral exchange should be initiated after establishment of the NTWP OEG on bacteriophages.

Update to work programme of the European Pharmacopoeia

(June 2021)

The following items have been added to or deleted from the work programme during the 170th session of the European Pharmacopoeia Commission. Consult the Knowledge Database to follow the work on individual texts.

Interested parties are invited to contact the EDQM via the HelpDesk with a view to participating in the work on items of interest.

ADDITIONS TO THE WORK PROGRAMME
(new texts to be elaborated)

2.6.41.	High throughput sequencing for the detection of extraneous agents	N/A
5.1.13.	Pyrogenicity	Pyrogénicité
5.31.	Phage therapy active substances and medicinal products for human and veterinary use	Substances actives et médicaments à usage humain et vétérinaire utilisés en phagothérapie

Summary – Key messages

Summary – Key messages

- Bacteriophage products administered to animals for prevention or treatment of infection or disease are classified as VMPs
- Regulatory framework for VMPs and requirements in Reg. 2019/6 apply
- Centralised route of authorisation for bacteriophage VMPs (novel therapy)
- General data requirements for novel therapies and specific for phage therapy are described in Annex II of the Regulation 2019/6
- Special provisions have been introduced to allow the required flexibility for bacteriophage products (variable composition, multi-strain dossier)

Summary - Key messages

- Dossier structure and data requirements for biological non-immunological VMPs will follow in general, adapted where relevant to the nature of product
- Further guidance on quality, safety and efficacy for bacteriophage VMPs under development (EMA/NTWP, EDQM/Ph. Eur.)
- Bacteriophage therapies pose significant regulatory and scientific challenges
- Developers and applicants are encouraged to seek advice from EMA as early as possible during development and maximise the use of existing support tools (ITF, scientific advice, NTWP GLs)

Thank you for your attention

Further information

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