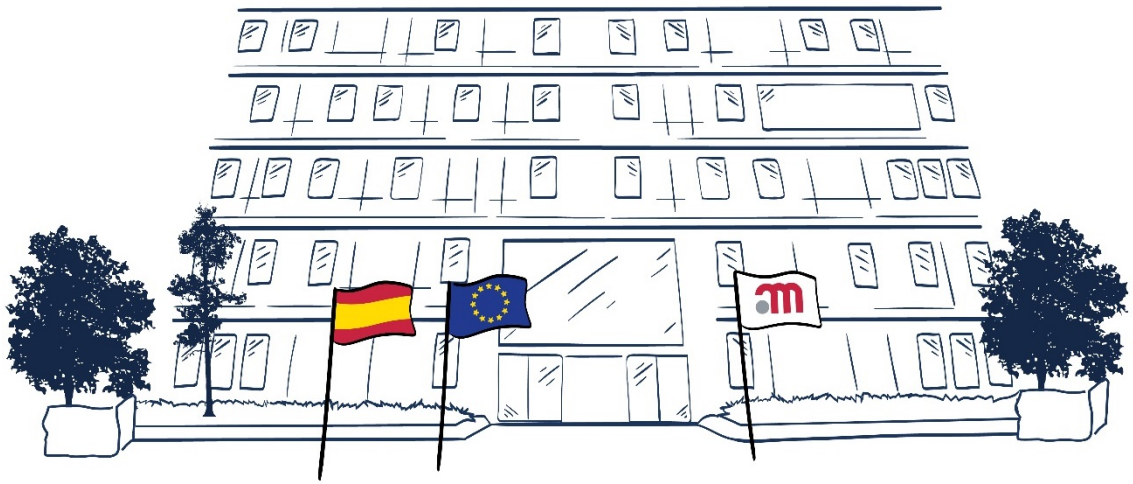
Setting the scene: introduction on the background and expected outputs for the meeting

11th of May of 2023



Susana Casado
Vice-Chair NTWP

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- Guideline on quality, safety and efficacy of veterinary medicinal products specifically designed for phage therapy
- Expected output from the meeting
- Questions and comments

Phage Therapy – history of a hundred-year-old new therapy

Table 1. Summary of the data analyzed in this manuscript (first column from the left: bacterial species analyzed in the study. Second column from the left: phage therapy utilized to reduce the bacterial species considered. Third column from the left: substrate used in the research to analyze the phages effect. Fourth column from left: reference number of the study).

Target Bacterial Species	Type of Phage Preparations Administrated	Animal Species or Cellular Substrate Used	References
Bordetella bronchiseptica	Monophage preparation (Bor-BRP-1)	Swine nasal turbinate cells	[88]
Bordetella bronchiseptica	Monophage preparation (Bor-BRP-1)	Swine nasal turbinate cells	[89]
Campylobacter jejuni	Monophage preparation(NCTC 12669 and NCTC 12671)	Chickens (one day old)	[58]
Campylobacter jejuni	Multiphage preparation(HPC5 and GHC8)	Chickens (25 days old)	[60]
Campylobacter jejuni	Multiphage preparation(F198, F287, F303, and F326)	Chickens (one day old)	[64]
Campylobacter jejuni	Multiphage preparation in different combinations (F198, F287, F303, and F326).	Chickens gut microbiota	[64]
Campylobacter jejuni	Multiphage preparation (CP1, CP14, F14, CP32, CP81, CP78, CP75, CP84, CP7; CP83, CP21)	Chickens (one day old)	[65]
Campylobacter coli and *Campylobacter jejuni*	Multiphage preparation (phiCcoIBB35, phiCcoIBB37, phiCcoIBB12)	Chickens (one day old)	[66]
Clostridium perfringens	Multiphage preparation (cocktail name INT-401)	Chickens (28 years old)	[68]
Escherichia coli	Monophage preparation (SPR02)	Chickens (3 days old)	[52]
Escherichia coli	Multiphage preparation(DAF6, SPR02)	Chickens (7 days old)	[53]
Escherichia coli	Multiphage preparation combined or not with enrofloxacin (DAF6 and SPR02)	Chickens (7 days old)	[54]
Escherichia coli	Monophage preparationSPR02	Chickens one day old	[56]
Escherichia coli ($K1^+$ strain)	Monophage preparation(R)	Chickens (3 weeks old) and calves	[57]
Escherichia coli	Monophage preparation(CJ12)	Weaned pigs (3 weeks of age)	[83]
Escherichia coli	Multiphage preparation(phi F78E, phi F258E, and phi F61E)	Chickens (5 days of age)	
Escherichia coli	Multiphage preparation(B44/1, B44/2, B44/3)	Calves, piglets and lambs (age not reported)	[80]

Loponte *et al* 2021
Gigante *et al* 2020

Phage Therapy – history of a hundred-year-old new therapy

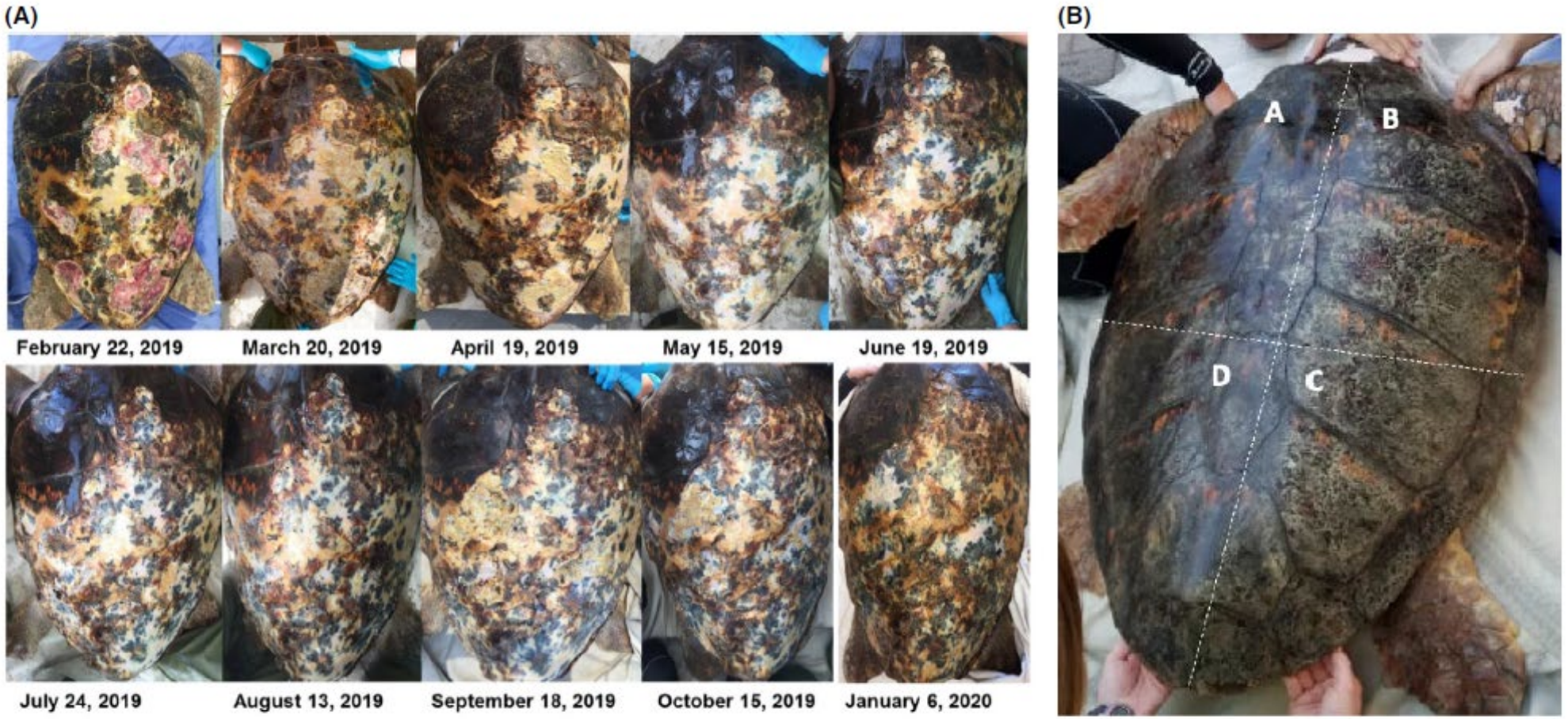


FIGURE 1. (A) Carapace healing of the affected loggerhead sea turtle with bacteriophage therapy over time and (B) unaffected (control) turtle carapace with markers indicating individual quadrants (A = cranial left; B = cranial right; C = caudal right; D = caudal left). [Color figure can viewed at afsjournals.org.]

Greene *et al* 2021

Regulatory framework worldwide

GRAS (generally recognized as safe)
EXEMPTION CLAIM, 21 CFR 170
All lytic phages are by nature GRAS

Table 1 Phage preparations and respective regulatory clearances

Company	Phage product	Target organism(s)	Regulatory	Certifications
FIN TEC GmbH (Hamm, Germany)	Secure Shield E1	*E. coli*	FDA, GRN 724	
Intralytix, Inc. (Baltimore, MD, USA)	Ecolicide® (EcolicidePX™)	*E. coli* O157:H7	USDA, FSIS Directive 7120.1	
	EcoShield™	*E. coli* O157:H7	FDA, FCN 1018; Israel Ministry of Health; Health Canada	Kosher; Halal
	ListShield™	*L. monocytogenes*	FDA, 21 CFR 172.785; FDA, GRN 528; EPA Reg. No. 74234-1; Israel Ministry of Health; Health Canada	Kosher; Halal; OMRI
	SalmoFresh™	*Salmonella* spp.	FDA, GRN 435; USDA, FSIS Directive 7120.1; Israel Ministry of Health; Health Canada	Kosher; Halal; OMRI

Attebury *et al* 2021

Individual use regulated by national laws

VMP prepared industrially or by a method involving an industrial process, regulated by Regulation (EC) 2019/6 and Regulation (EC) 2021/805

Feed aditives: Regulation (EC) 1831/2003 and no-specific guidance available. Conducted according to FEEDAP guidance documents: https://www.efsa.europa.eu/en/applications/feedadditives/regulationsandguidance

Decontaminating agents: Regulation (EC) 853/2004 and Guidance on the submission of data for the evaluation of the safety and efficacy of substances for the removal of microbial Surface contamination of foods of animal origin intended for human consumption https://www.efsa.europa.eu/en/efsajournal/pub/1544

Phages under other EU regulations	EU bodies	Products
Food decontaminant / biocide	EFSA	Listex P100 (EFSA-BIOHAZ 2012)
Feed additive	EFSA	Bafasal (S. gallinarum) (EFSA-FEEDAP 2021)

Regulatory framework of bacteriophages as VMP (Regulation (EU) 2019/6)

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

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

  (a) presented as <u>having properties for treating or preventing disease in animals</u>;

  (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

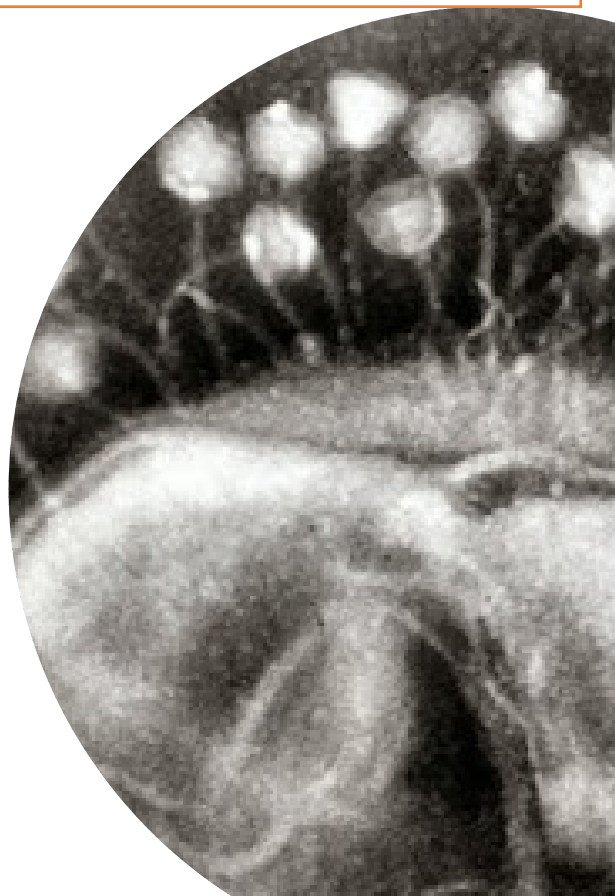
- **'Novel therapy' veterinary medicinal product** (Article 4 (43))**:**

  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

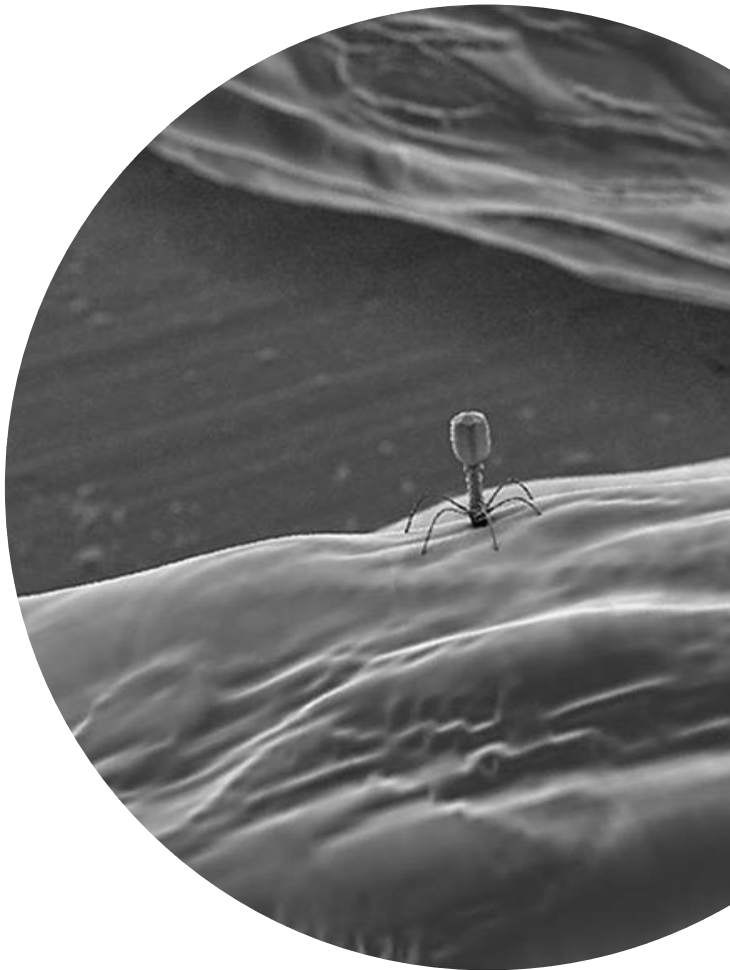
  c) any other therapy which is considered as a nascent field in veterinary medicine.

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



Regulatory framework of bacteriophages as VMP (Regulation (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



Regulatory framework of bacteriophages as VMP (Regulation (EU) 2019/6)

- Technical data requirements for VMPs are laid down in Regulation (EU) 2021/805 (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.
- 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 to Regulation (EU) 2019/6 possible when justified.**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 January 2021
EMA/CVMP/179874/2020
Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP strategy on antimicrobials 2021-2025

Adopted by CVMP for release for consultation	18 June 2020
Start of public consultation	1 July 2020
End of consultation (deadline for comments)	30 September 2020
Adoption by CVMP	20 January 2021

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Key actions: The CVMP will provide regulatory and scientific advice on the development of new and existing antimicrobial medicinal products and will progress options for the regulatory framework for alternatives to antimicrobials.

Further guidance will be developed on **data requirements and** potential **claims for ATAm,** and how demonstrated treatment benefits should be factored into the benefit-risk assessment for veterinary medicines. CVMP will promote **international cooperation** and exchange of information with other regulatory regions to assist the global development and alignment of the approach to authorisation of ATAm.

Novel Therapies and Technologies Working Party (NTWP)

Working plan 2020/2021

Cell therapy	OEG: Guidance on efficacy of cell therapies: mechanism of action, potency and clinical effects
Bacteriophages	OEG: Guidance on quality, safety and efficacy of bacteriophages as veterinary medicines

Working plan 2022/2023

Nanomedicines	OEG: guideline on safety of nanomedicines of veterinary medicine containing/composed by non-biodegradable nanomaterials

Novel Therapies and Technologies Working Party (NTWP)

Working party of the CVMP established in May 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

NTWP secretariat contact: NTWP@ema.europa.eu

Some regulatory/scientific challenges

- Characterisation and selection of phage/bacteria strains for production
- Risks of the presence of lysogenic phages during production
- Changes in the phage composition, frequency
- Development of bacterial resistance to phages
- 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 post-marketing efficacy to ensure sustained efficacy

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

- The aim of this guideline is to establish the regulatory/technical and scientific requirements applicable to veterinary medicinal products (VMP) specifically designed for phage therapy and composed of bacteriophages.

- Due to the biological complexity and nascent nature of veterinary medicinal products specifically designed for phage therapy (none have yet been centrally authorised in the EU), the advice given in this document is general and does not enter into details. Developers are encouraged to seek early advice at the national or European level to guide product development.

Expected outputs from the meeting

Relevant stakeholders are invited to review the draft Guideline on bacteriophages to promote the reception of comments to the Guideline

Special attention should be taken on the applicability of the Guideline to the current (and future) products developments

Any questions?

Further information

Regulation (EU) 2019/6
https://eur-lex.europa.eu/eli/reg/2019/6/oj

Regulation (EU) 2021/805 (Annex II to Regulation 2023/6)
https://eur-lex.europa.eu/eli/reg_del/2021/805/oj

Reflection paper on promoting the authorisation of alternatives to antimicrobial veterinary
https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-promoting-authorisation-alternatives-antimicrobial-veterinary-medicinal-products-eu_en.pdf

Concept Paper on: Quality, safety and efficacy of bacteriophages as veterinary medicines
https://www.ema.europa.eu/en/quality-safety-efficacy-bacteriophages-veterinary-medicines

Guideline on quality, safety and efficacy of veterinary medicinal products specifically designed for phage therapy
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-safety-efficacy-veterinary-5-medicinal-products-specifically-designed-phage-6_en

Please contact the NTWP secretariat in case you have any further question
NTWP@ema.europa.eu