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Bacteriophage-based veterinary products: aligning regulatory framework and development challenges for market integration

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ABSTRACT

The emergence of antimicrobial resistance renewed the interest in bacteriophages as complementary interventions to the use of antibiotics in veterinary medicine. The IABS workshop entitled "Avoiding Antimicrobial Resistance: Veterinary Use of Phages for Prevention, Therapy and Control of Bacterial Infections" brought together experts to discuss the scientific, regulatory and commercial challenges involved in bringing phage-based products to market. The biological characteristics of phages require innovative approaches for product development and regulatory approval. Dependent on their actual use, phages could be marketed as veterinary medicinal products, magistral preparations, food additives, or biocides, each classification implying different regulatory requirements and challenges, and none of which were originally intended for phage-based products. The meeting highlighted the need for regulatory harmonization to facilitate market access and allow manufacturers to choose the most appropriate regulatory pathway for their products. Recent EMA and EDQM guidelines offer some flexibility to take into account the biological nature of phages, but concerns remain about the feasibility of manufacturing phage-based products following existing rules for veterinary chemotherapeutants at commercially viable costs. Overcoming these regulatory and financial barriers is essential for the integration of phage therapy as a therapeutic option for control of bacterial infection and disease in veterinary medicine.

1. Introduction

The rise of antimicrobial resistance (AMR) represents a major threat to global health that significantly limits the efficacy of conventional antibiotics in both human and veterinary medicine. As part of a One-Health approach to fight against AMR, the veterinary sector is under increasing pressure to reduce the general use of antibiotics. In this context, bacteriophages (phages for short) have seen a renewed interest, used alone or as a complementary tool to improve antibiotic treatment efficacy; in both cases reducing the selection pressure for bacterial resistance.

Phages are viruses that specifically infect and lyse bacteria with a much narrower spectrum than antibiotics, providing also a more targeted method of bacterial control. Their development in veterinary medicine has been explored in both therapeutic and prophylactic applications including the treatment of resistant bacterial infections in individual animals but also in disease prevention to reduce infection pressure in animal populations. Phages have already been studied and used in various sectors such as aquaculture, beef, pig and poultry industries, demonstrating their potential as an effective strategy for reducing dependence on antibiotics.

In the European Union (EU), veterinary phage therapies are defined

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as novel therapies falling within the scope of the Regulation (EU) 2019/6 on veterinary medicinal products, which governs the marketing authorization process [1]. Given their biological nature and complexity, phage-based products are subject to a centralized approval procedure supervised by the European Medicines Agency (EMA). To provide further guidelines, the EMA has drawn up the "Guideline on the quality, safety and efficacy of veterinary medicinal products specifically designed for phage therapy" [2]. This document describes the main requirements for phage characterization, safety assessment and efficacy validation. In addition, the European Pharmacopoeia now includes a general chapter on phage therapy medicinal products for human and veterinary use that specifies quality standards for production and control [3]. In the United States (US), an alternative strategy has been developed in which the regulatory status of phage interventions depends on the intended use of each product. Phage products may thus fall under the authority of the US Food and Drug Administration (FDA) for therapeutic applications, or under the United States Department of Agriculture (USDA) for food safety [4].

Beyond phage therapy, phage-derived antimicrobials such as endolysins, depolymerases, and tailocins also offer an interesting approach to bacterial control. These alternative approaches expand the arsenal of phage-based solutions for veterinary disease control and could complement existing phage or antimicrobial control strategies. However, the specific regulatory requirements for such phage-derived antimicrobials differ from those that apply to phage therapy and they will not be discussed further in this report.

The International Alliance for Biological Standardization (IABS) online workshop "Avoiding Antimicrobial Resistance: Veterinary Use of Phages for Prevention, Therapy and Control of Bacterial Infections" held on November 19–20, 2024, brought together regulators, academics, and companies to discuss the role of phages as an alternative and/or complementary tool to conventional antibiotics in veterinary medicine. The discussions focused on both therapeutic and prophylactic applications of phages, highlighting their potential to reduce infectious pressure on animals and providing targeted treatments for bacterial infections to limit the use of critical molecules. This report summarizes key points from presentations and panel discussions regarding current practices, regulatory challenges, and industrial constraints. It also incorporates ideas and recommendations to improve the access to market for phage-based veterinary products.

2. Phage therapy in veterinary medicine: applications and challenges

Phage applications are increasing, notably in livestock, companion animals, or aquaculture with approaches ranging from individualized treatments to broader strategies for controlling and preventing infections in large populations. The following examples illustrate these applications and are taken from the presentations given during the workshop.

A promising antibacterial solution in aquaculture is a phage-based product specifically designed to control *Yersinia ruckeri*, the causative agent of yersiniosis in salmonid farms. Atlantic salmon are infected by *Y. ruckeri* early in life, during their freshwater life stage. Initially, only a subpopulation of the fish gets infected, whereupon the bacterium will enter a sub-clinical carrier state. Clinical disease outbreaks occur after triggering events such as sorting, vaccination, transport and delousing. Events in which animal stress induce a combination of high shedding from carrier fish at the same time as the naïve subpopulation is susceptible to disease. Application of specific *Y. ruckeri* bacteriophages during such critical operations has been shown to effectively prevent disease outbreak by decreasing bacterial pressure in the water [5]. In aquaculture, phage-based interventions have also proven effective protecting whiteleg shrimp against *Vibrio parahaemolyticus* and Nile tilapia (*Oreochromis niloticus)* against *Streptococcus agalactiae* [6].

In poultry farms, controlling *Campylobacter* and *Salmonella* remains a major challenge for the industry. Campylobacteriosis is caused by *Campylobacter jejuni* and *Campylobacter coli,* which are responsible for gastroenteritis in humans if transmitted through the consumption of contaminated products. Phage therapy has been assessed in this context to reduce *Campylobacter* colonization in broiler chickens and poultry products. Phages can significantly reduce *C. jejuni* caecal colonization in broiler chickens with reported decreases ranging from 2 to 5 $\log_{10}$ colony forming units (CFU)/g. Risk models indicate that a 3 $\log_{10}$ reduction in caecal *C. jejuni* levels could lead to a 58 % decrease in human infections highlighting the potential of phage therapy as a targeted intervention to improve food safety [7–9]. Additionally, a reduction of approximately 2 $\log_{10}$ can be achieved on chicken skin [10]. Phages are also able to disrupt *Campylobacter* biofilms, further limiting bacterial persistence in the environment [11]. Some *C. jejuni* strains may develop phage resistance but these resistant variants often exhibit impaired motility making them less competitive for colonization. Beyond their use in reducing infection, *C. jejuni* specific phages can also be used as bacterial detection tools by using their receptor-binding proteins (RBPs) for specific recognition and identification of *Campylobacter* strains. Poultry meat also represents an important reservoir of *Salmonella enterica*. A 4-phage cocktail targeting 25 representative *S. enterica* strains from Indonesian farms was able to decrease colonization both in chicken broilers and carcasses [6].

Studies on the use of phage therapy to modify disease processes in pigs are limited and most published studies relate to their use as these animals are primarily used as models for human infections. Murine models are often preferred for studying phage applications in pigs due to ethical considerations, to reduce the costs and avoiding the need for specialized pig research infrastructure. The main bacterial pathogens studied are *Escherichia coli* and *Salmonella* which are of concern in both human and animal health. In post-weaned piglets, enterotoxigenic *E. coli* (ETEC) infection leads to severe diarrhea, dehydration, and increased mortality. Co-infections with *Salmonella* and *Campylobacter* further complicate disease management. Research demonstrated the potential of phages to reduce mortality, decrease bacterial shedding and improve faecal consistency scores [12,13]. A phage cocktail targeting *Salmonella* showed a reduction in bacterial load in post-weaned piglets, however, the results were more variable in adult pigs due to variability in bacterial colonization [14]. Several studies have also demonstrated the potential of phage interventions for decontaminating pig skin and pork products, with reductions of 1–4 $\log_{10}$ CFU [15].

Bovine mastitis is a significant disease affecting dairy cattle worldwide, leading to reduced milk production and quality, and imposing substantial economic burden on dairy farmers. The disease is characterized by inflammation of the mammary gland and is frequently caused by infection with *Streptococcus uberis* or *Staphylococcus aureus*. Affected cows show high somatic cell counts in milk, causing milk rejection. Additionally, mastitis causes pain and discomfort in affected animals. Chronic or severe cases can necessitate early culling. may Antibiotic resistance, particularly due to methicillin-resistant *S. aureus* (MRSA) strains, reduces the success rate of *S. aureus* treatment for mastitis to less than 50 % [16]. In this context, phage therapy has emerged as a promising alternative with, for example, the design of a phage cocktail targeting 97 % of relevant strains that is highly stable in raw milk. This investigative veterinary medicinal product showed a high success rate in field trials, providing a cost-effective solution compared to antibiotics when manufactured to a high standard but without GMP compliance [6]. Manufacturing to full GMP compliance is much more expensive and is likely to make the treatment financially unviable given the relatively low economic returns in the dairy production sector.

In human medicine, phage therapy, particularly in combination with antibiotics, is being explored as an additional tool to combat difficult-to-treat infections. In this context, Belgium has implemented a dedicated phage therapy framework in 2018, based on magistral preparation of personalized phage therapeutics and which enabled the individualized treatment of more than 200 patients with various types of difficult-to-

treat infections [17]. A recent analysis of the first 100 cases showed clinical improvement in 77.2 % of patients and bacterial eradication (mostly *S. aureus* and *P. aeruginosa*) in 61.3 % of infections, with a significantly lower success rate when phages were used without antibiotics [18]. These results highlight the potential of complementary phage-antibiotic therapies. These personalized magistral phage preparations can also be evaluated in controlled clinical trials, such as the ongoing PHAGEFORCE study [19]. A similar individualized approach is also relevant for companion animals where phage therapy remains largely unexplored. Companion animals including among other dogs, cats, rabbits, horses and birds share close contact with humans and can exchange bacteria carrying antimicrobial-resistant (AMR) genes which represent a high public health hazard. However, the literature about phage therapy in companion animals remains scarce. Reported cases of phage therapy include the treatment of external otitis and uterine infections in dogs, osteoarticular implant infections in cats and pyoderma in horses [20–23].

All these examples demonstrate that the exploration of phage therapy in the veterinary sector is relevant in livestock, aquaculture and companion animals but the successful implementation of phage based veterinary interventions still has several challenges to overcome. Researchers and industry stakeholders must balance the economic impact of regulatory requirements against the commercial value of the phage product to be commercially viable. Because bacteriophages are narrow spectrum by nature, no “blockbuster” phage products can be expected. Moreover, in the veterinary field, farmers operate on low financial margins, necessitating low-cost medical treatments. Unlike the conventional antibiotics chemotherapies that follow well established regulatory requirements, phage-based interventions present novel challenges related to specificity, adaptability, and production. A future increased use of phages in veterinary medicine will require not only additional scientific research but also a suitably adapted new regulatory framework that promotes innovation whilst ensuring adequate and appropriate levels of safety and efficacy.

3. Current pathways to market for phage-based veterinary products

The pathway to market for phage-based veterinary products is complex and requires alignment with regulatory, manufacturing, and commercial challenges.

Within the EU, industrialized veterinary phage products and magistral phage preparations are regulated under different frameworks. Industrialized products are governed by Regulation (EU) 2019/6, the Annex II of the Regulation (EU) 2019/6, to which GMP requirements apply [1]. Magistral preparations used for therapy, on the other hand, are subject to national regulations which usually require adherence to the General Chapter of the European Pharmacopoeia or a relevant national pharmacopoeia. Moreover, GMP requirements or other manufacturing standards (e.g. described in a monograph) can be applied based on national regulations. According to Regulation (EU) 2019/6 on veterinary medicinal products, when authorized as veterinary medicines, bacteriophages are now classified as novel therapy veterinary medicinal products and must be authorized through the centralized marketing authorization procedure with applications submitted to the EMA. The application procedure thus involves four parts related to administrative information, quality, safety and efficacy. The technical requirements for veterinary medicinal products (VMP) can be found in the Annex II of the Regulation (EU) 2019/6 with general requirements in section V.1 as well as specific requirements in section V.1.5.4. The EMA has recently published the “Guideline on quality, safety and efficacy of veterinary medicinal products specifically designed for phage therapy” (EMA/CVMP/NTWP/32862/2022) [2]). The main characteristics include – like for chemotherapeutants - full characterization and standardized manufacturing processes. It recommends the use of representative preparations of phages that reflect the worst-case scenarios to ensure safety and efficacy. Moreover, extrapolation between comparable strains of phages, target animal species, or different routes of administration may be possible if supported by validated *in vitro* or *in vivo* data. Compliance with GMP is required for manufacture of phages as VMPs. Veterinary-specific annexes to the EU GMP Guide are in preparation and will clarify the GMP requirements for novel veterinary medicinal products, including phage therapies. This new annex should describe the requirements for design and operation of facilities, equipment and processes for the production of phage-based VMPs.

In parallel to the EMA guidelines, the European Pharmacopoeia Commission has prioritized the development of guidance on phage therapies for both human and veterinary medicine. In recent years, the European Pharmacopoeia Commission has made the development of standardized requirements for phage therapy a strategic priority for the 2023–2025 period. The first released text was the general chapter 5.31 on phage therapy medicinal products which provides a flexible framework for the production and quality control of phage therapy products [3]. Efforts are now focused on a new chapter on bacteriophage potency determination that aims at standardizing activity testing of single phage preparations and providing guidance for activity testing of multi-component phage mixtures.

At the national level, Belgium has established a regulatory framework for phage therapy when used as magistral preparations for individual patients. A two-step quality control process performed by the Belgian Scientific Institute of Public Health “Sciensano” ensures the safety of phage active pharmaceutical ingredients (APIs). The first step involves creating a genetic passport for each phage detailing its lifestyle genomic characteristics and potential for horizontal gene transfer. Tested phage APIs were shown to be genetically very pure (>99 %). The second step assesses the identity, potency, microbial contamination, endotoxin levels, and pH of produced phage API batches using either European Pharmacopoeia standards or validated in-house protocols [6]. Despite this structured approach, several challenges remain. The pyrogenicity of phage APIs for human use is generally low but only IL-6 is tested and the intrinsic anti-inflammatory response of phages could interfere. Additionally, the absence of reference materials and standardized tests limits broader implementation of potency and genetic testing. Efforts are ongoing to improve the genomic analysis of phages, particularly through automated annotation tools. One example is RimeTOOLS2, which enhances the accuracy of genome annotation, reaching performances close to manual approaches. However, for therapeutic applications, manual verification still remains essential to ensure safety [6].

Feed additives are used in animal nutrition to enhance feed quality, improve food products of animal origin or support animal health and performance (Regulation (EC) No 1831/2003) [24]. These products require prior authorization based on a scientific evaluation confirming their safety for human and animal health, as well as for the environment. The European Food Safety Authority (EFSA) conducts these evaluations providing scientific advice through its Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). This panel assess the safety and efficacy of additives including biological products like bacteriophages used in animal feed. Unlike VMPs, phage-based feed additives do not have to be manufactured to GMP standards but must be administered to healthy animals in feed or water with a fixed formulation during the whole lifetime or a defined stage of production. To date, EFSA has evaluated one phage-containing feed additive, Bafasal®, aimed at reducing *Salmonella* contamination in poultry and the environment. While the safety of the product was established, EFSA issued two inconclusive opinions regarding its efficacy with the latest in 2023 [25]. The FEEDAP Panel also recommended a post-market monitoring plan to address the potential selection and spread of resistant variants of *Salmonella* to Bafasal® [25]. To support future evaluations, EFSA plans to publish guidance on the characterization and risk assessment of microorganisms used in the food chain in 2025.

In the United States, the regulation of phage-based therapies is

managed by the FDA and the Center for Veterinary Biologics (CVB) [4]. Products that exert their effects through immunological activity fall under the jurisdiction of the CVB while others, like antimicrobials, are regulated by the FDA. This distinction is important for applicants seeking approval for phage products, as they may need to consult both agencies to determine the appropriate regulatory pathway for their product. Generally, phages that act directly on bacteria as antimicrobials fall under FDA regulation. In case of doubt, a joint FDA-CVB committee will advise applicants on the appropriate agency to which an application for a phage product should be submitted.

The production of phage-based veterinary medicines in the US faces significant challenges, particularly in meeting regulatory requirements that have evolved for chemotherapeutants. The Chemistry, Manufacturing, and Control (CMC) section of the regulatory dossier is crucial for approval and marketing of phage-based products. It must define production specifications for each phage in a cocktail and the process for combining them. Due to the potential of phages to cause contamination, dedicated GMP manufacturing facilities are likely to be essential and will require substantial capital investment. This is a challenge notably for products targeting production animals like poultry where large-scale production is necessary to meet demand.

Some companies are exploring an “individualized” concept for veterinary applications including therapy for bovine mastitis. Vesale Bioscience has developed a system to select personalized phage therapy products in less than 4 h using an automated susceptibility test against a panel of up to 38 phages. This phagogram was initially designed for human applications and was tested in a pilot project targeting bovine mastitis. Several challenges specific to this application were highlighted, including the lack of standardized protocols and reference reagents, the necessity of a herd-based approach, and the potential need for combination with antibiotics. This example shows that the transposition of human medicine models cannot be directly done for veterinary applications without adaptation to the specific needs and market conditions of the veterinary sector.

4. Choosing the path: key considerations for bringing phage products to market

This section summarizes the key points and discussions from the workshop panel session, highlighting the main challenges, regulatory considerations, and advancements in the field of phage therapy. It provides an overview of the most relevant insights shared by the experts. The discussion focused on the different routes by which a phage product can be brought to the market. The factors to be considered in deciding which route to follow include the nature of the product itself, its mode of action, the route and form in which the product is administered, the claims made for the product and the legislative framework in place in the country or region in which the product will be marketed. No single optimal route to follow exists, and manufacturers must consider each of these factors in deciding the route to market. It was highlighted that the major drawbacks to bringing phage products to market are rooted in the combination of biological, regulatory and financial challenges.

In terms of biological factors, the specificity of phages leads to the frequent need to use multiple active ingredients, in the form of a phage cocktail. Furthermore, it is frequently necessary to update the phages present in these cocktails due to the emergence of phage resistance in the target pathogen or to adapt the product to variations in the pathogen that occur over time or across different populations. This presents a considerable challenge as the conventional regulatory model consists of approving one or more phage ingredients for each therapy and only allowing changes to through a rigidly controlled process of variation or filing for a new approval for each new phage.

The meeting highlighted that phages could be released onto the market as VMPs, as feed additives, as biocides, or as conditioning agents for use on foodstuffs of animal origin. Each of these approaches have their own requirements and differ in their approach as to how, or if, changes in phage composition can be accommodated within the approval procedure. These differences in approach and requirements mean that the economic cost benefit analysis can be very different depending on the route to market. Participants emphasized the challenges in determining the regulatory classification of their products. Regulators advised that in case of uncertainty, applicants should seek classification from the Coordination group for mutual recognition and decentralised procedures for veterinary medicinal products (CMDv) Borderline Products Group in the EU or follow the guidance provided by the CVB and CVM in the USA. The main elements considered for different types of approval are considered below.

4.1. Phage therapies as veterinary medicinal products

The recently published EMA guideline introduces the possibility to apply modern quality risk management approaches allowing changes to the phage based VMP within a defined "design space." Applicants must establish the genomic, biological and quality parameters of the phages used ensuring that any changes to the phage in the product remain within these predefined limits and preserving the product’s essential characteristics. While this innovative approach offers flexibility, it requires significant effort and investment to implement quality by design principles in the emerging field of phage therapy. Although quality by design has been well-established in human medicine through ICH guidelines, there is no equivalent guideline for veterinary medicinal products and both industry and regulators have limited experience applying these principles in this field.

In addition to the costs of applying the quality by design approaches outlined in the EMA guidelines, concern was expressed about the requirement to apply GMP to the manufacture of phage therapies as authorized VMPs. Based on their experience of developing veterinary phage therapies, several participants expressed concerns that producing VMPs under GMP would likely never be commercially viable, particularly in aquaculture and other industrial animal productions where treatment involves the administration of large quantities of phages over prolonged periods to large numbers of animals often held in large populations. In such situations the market is extremely price-sensitive and the cost per dose is measured in cents rather than euros or dollars. The high cost of manufacturing products with GMP and the extensive laboratory and field testing required for approval make the development of phage-based products as veterinary medicines a high-risk investment with a low probability to recover development costs within a reasonable timeframe. It was pointed out that the market for VMPs in companion animals was less price-sensitive and could potentially be viable.

Other concerns were expressed regarding the inclusion of phages within the definition of novel therapy medicinal products which require authorization through the EU Centralized Procedure and could therefore add cost and reduce flexibility as compared to national authorization procedures. In response to that, EU regulators recommended participants to take advantage of the various dispositions available to assist applicants developing novel therapies such as phages. These include seeking formal scientific advice from the EMA or national authorities, consulting the EMA Innovations Task Force, taking advantage of support offered too small to medium enterprises (SMEs) and requesting product classification for limited markets where appropriate. Regulators pointed out that the new phage guideline had only recently been published and recommended participants to use it to accumulate experience and assess its usefulness in incentivizing the development of phages as VMPs.

Similar difficulties in meeting GMP requirements are also present for other novel veterinary therapies and for other types of veterinary products such as autogenous vaccines for which there is a need to adapt GMP requirements to reflect the particular nature of the product being manufactured. The EMA GMPD Inspector’s Working Group is currently developing veterinary-specific annexes to the GMP guideline. It will be important for regulators to introduce flexibility for manufacturing such

VMPs by following a risk-based approach focusing on the quality of the final product and effective documentary systems to assure consistency of production.

Currently no specific guidelines exist for the authorization of phage-related VMPs such as lysins and depolymerases. Given their antibacterial effects, it is likely that the requirements for authorization will be based on those that apply for conventional antibiotics, adapted as required to reflect the biological nature of the active substance. It was recommended that regulators develop specific guidance for this type of biological product in view of the urgent need to develop VMPs that have the potential to reduce or replace the use of conventional antibiotics.

The discussion on phage resistance was extensive with general agreement that resistance will inevitably develop even if specific mitigation strategies are implemented [6,26]. It was suggested that surveillance for resistance should be a mandatory condition for authorization to prevent repeating past mistakes made with antibiotics.

It was noted that in some cases, phages can be used as an adjunct therapy in combination with antibiotics to improve treatment of infections and reduce the risk of resistance. The EMA guideline on requirements for phage therapies provides guidance on the approval requirements for this approach. It was recommended to implement the concrete measures identified above as part of any strategy to reduce the use of antimicrobials to encourage the authorization of phage products. The current high political profile on AMR should help to direct resources to support therapies like phages which contribute to the AMR control strategy.

4.2. Phages as feed additives

For use as feed additives, phages do not need to be produced to GMP and there is no fee for evaluation of applications for approval. However, developers must be aware that once phages are approved as feed additives it is not possible to modify the phages included in the product. This means that strategies for managing resistance such as phage training, a process in which phages are repeatedly exposed to resistant bacterial host to select for variants with improved infectivity, may not be used once a product is authorized.

There is currently insufficient experience with the approval of phages as feed additives to assess the attractiveness of this route for approval. It is expected that approval as a feed additive will attract only a small segment of the phage market due to the strict eligibility requirements. These includes the condition that products must be administered to healthy animals in food or water and must follow a fixed formulation throughout the animal's life or during a specific production stage. The inability to modify phages in an approved feed additive restricts further the viability of this option for widespread use.

4.3. Phages as magistral preparations

In Western Europe, the clinical use of bacteriophages in veterinary medicine remains limited and largely experimental. In the absence of authorized veterinary phage products, the cascade procedure may be applied, allowing veterinarians to prescribe alternative treatments that are not officially authorized, and only if there are no other approved treatment options available. In the case of phage-based treatments, magistral preparations would need to be used. When used as magistral preparations, phages are not considered as authorized VMPs and in this case, national requirements apply which differ between countries and are less stringent than for authorized products. For veterinary products, manufacturers generally have to follow the principles of GMP although full GMP compliance is not required. The market for such products is limited as each treatment must be individually prepared with no claims or advertising allowed. The situation for veterinary products contrasts with that of human products where high fees can be charged to cover the high cost of production which is only possible in veterinary medicine in some specific situations such as treatment in companion animals.

4.4. The use of phages to reduce infectious pressure in the animal environment

Beyond therapeutic applications, bacteriophages can be considered as biocide-like products, tools for reducing infectious pressure in the animal environment with the aim of reducing pathogen loads and decreasing transmission between animals. These uses do not fall within the existing categories of magistral preparations, veterinary medicines or feed additives.

5. Conclusions and recommendations

- There is a high level of scientific interest in using phages in veterinary medicine to prevent and control bacterial infections to reduce antibiotic use and fight against multidrug-resistant bacteria.
- Phages must follow different regulatory pathways depending on their intended use (VMPs, feed additives, magistral preparation or biocide-like products) in line with relevant legislation.
- National frameworks are currently not harmonized leading to different options for making development and licensing of phage products available such as feed additives, magistral preparations, biocide-like products or fully authorized novel therapy VMPs each with different requirements. Economic cost-benefit outcomes vary significantly depending on the regulatory pathway.
- Some debate exists over whether the therapeutic use of phages in individual or small group animal treatments could and should be considered as magistral preparations similar to human medicine.
- The economic drivers between human and veterinary medicine differ significantly. Whilst high fees can be charged for individualized phage treatments in human medicine, an equivalent scale of charging in most cases is rarely viable for veterinary products.
- The current regulatory environment is not conducive to the development of phage products and is considered to act as a barrier in many cases. The classification of phages as novel therapies in the recent revision of the veterinary medicine legislation has reduced the flexibility of member states by requiring their licensing through the centralized authorization procedure run the EMA.

Several recommendations are issued from this workshop to address these challenges and facilitate the development of phage-based products in veterinary medicine.

- New measures should be considered to facilitate the market access of phage products as part of an overall strategy to reduce antibiotic use by integrating them into global and national AMR control strategies.
- Flexibility in manufacturing requirements for phage based VMPs is needed and can be achieved by adopting a risk-based approach that prioritizes the quality of the final product.
- Adaptation of the quality (GMP) and regulatory requirements for phage-based products is essential considering phage biology, host specificity, and the small return on investment for most veterinary applications. Feedback should be provided to regulators on the guidance produced to date on whether it is fit-for purpose and experts are encouraged to respond to calls for comment on guidance that is currently being prepared.
- Specific guidance for phage-based biological products and especially strategies for managing phage resistance should be developed in view of the urgent need for VMPs that can replace or reduce conventional antibiotics. Adaptation of guidelines should account for various veterinary contexts, from mass treatments in production animals to individual treatments in companion animals similar to the existing human phage therapy, and include surveillance systems to detect emerging phage resistance, similar to systems used for antibiotics.

CRediT authorship contribution statement

Céline Antoine: Writing – original draft. **David Mackay:** Writing – review & editing. **Paul Midtlyng:** Writing – review & editing. **Hans P. Kleppen:** Writing – review & editing. **Dušan Palić:** Writing – review & editing. **Jean-Paul Pirnay:** Writing – review & editing. **Damien Thiry:** Writing – review & editing. **Etienne Thiry:** Writing – review & editing.

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