PHAGE EU

PhageEU Coalition
Boulevard Saint Michel 47,
1040 Etterbeek, Brussels, Belgium
contact@phageurope.eu

PhageEU proposals for amendments to Pharmaceutical Package: 2023/0131 (COD) and 2023/0132 (COD)

The following amendments aim to integrate bacteriophage therapies into the draft EU Regulation and Directive of the Pharmaceutical Package (2023/0131 (COD) and 2023/0132 (COD)), preserving the overall structure of the legislation. Proposed changes include textual amendments (*italics*) and justifications, with references to sections of the Regulation/Directive and external sources.

1. Definitions

Amendment to Directive – Article 4: Add reference to phages to the definition of "antimicrobial" and define what is a bacteriophage.

Article 4(22) – Definition of Antimicrobial (amended): "Any medicinal product with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, ~~and~~ antifungals, *and bacteriophages*."

Article 4(22) (a new)- Definition of Bacteriophage (new): *"Bacteriophages are viruses that specifically infect and lyse bacterial cells. When formulated as medicinal products, they may be used as targeted antimicrobial agents to treat bacterial infections, including those resistant to conventional antibiotics."*

2. Inclusion of Phages in Antimicrobial Incentives & Transferable Rights

Amendment to Regulation – Article 40 (Priority Antimicrobials & Voucher): Add a subparagraph explicitly including phage-based products (natural or engineered) in the definition of "*priority antimicrobials*" eligible for incentives

Article 40(3) – Definition of Priority Antimicrobial (amended): An antimicrobial shall be considered a "priority antimicrobial" if it meets the criteria in points (a)-(c) (new class, distinct mechanism, novel active against multi-drug-resistant organisms). *For the purposes of this provision, bacteriophage-based therapies (including naturally occurring phages and genetically engineered phages) that satisfy these criteria shall be eligible as priority antimicrobials. In particular, phage therapies targeting WHO-listed critical or high-priority resistant pathogens shall be deemed to "represent a real advancement against antimicrobial resistance"*.

Justification:

- This ensures phage therapeutics qualify for antimicrobial innovation incentives, such as the transferable exclusivity voucher, on equal footing with antibiotics. Phages use a distinct mechanism of action – lysis of bacteria – representing a new class of antimicrobial intervention. Including both natural and engineered phages aligns with

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the EU's goal of promoting "priority antimicrobials that can help address antimicrobial resistance". Given the worsening antibiotic resistance crisis, phage therapy is recognized as a promising alternative.

- By explicitly naming phages, regulators signal that developers of phage treatments addressing multi-drug resistant infections can access incentives (e.g. the 1-year data exclusivity voucher). This mirrors the intent to focus innovation on unmet needs and AMR and acknowledges that phage therapies "bring forward significant benefit with respect to antimicrobial resistance". Including engineered phages is also important – while they may be genetically modified, they are designed to enhance bacterial killing or host range, directly contributing to the fight against AMR.
- In short, phage therapies merit inclusion because they "represent a real advancement against antimicrobial resistance", potentially qualifying as new classes or possessing novel mechanisms as required by Article 40(3).

Amendment to Directive – Incentives Recital: In the Directive's recitals on incentives for priority antimicrobials, add a sentence to emphasize phage therapies:

Recital (XX) (new) – Phage Therapies as Priority Antimicrobials: *Phage therapy medicinal products, including naturally occurring lytic bacteriophages and genetically engineered phages, should be recognized within the scope of priority antimicrobials given their potential to combat infections by multi-drug-resistant bacteria. Unlike conventional antibiotics, phages exhibit a self-replicating and adaptive mechanism that allows them to evolve alongside bacterial pathogens, reducing the likelihood of resistance development. Their ability to selectively target specific bacterial strains, while sparing beneficial microbiota, represents a novel and precision-based approach to antimicrobial therapy. These therapies align with THE objectives of addressing antimicrobial resistance and warrant inclusion in incentive mechanisms to encourage further development and accessibility across the EU.*

Justification:

- This recital supports the Regulation's operative text by explaining why phages fit the priority antimicrobial concept. Phages specifically target bacteria and can be effective against antibiotic-resistant strains. By destroying bacteria through a unique biologic process (infection and lysis), phages reduce reliance on traditional antibiotics and mitigate resistance development. Their inclusion in the voucher scheme is justified as they fulfill the same public health need as novel antibiotics – indeed, the Commission's proposal seeks to incentivize "products that bring a significant clinical benefit with respect to AMR", a criterion phage therapies can meet.
- Explicitly mentioning phages ensures incentive eligibility is clear to developers, encouraging investment in phage R&D. This is crucial because, under current frameworks, each phage might otherwise require separate approval, posing a business disincentive. The amendment thus aligns with the broader EU strategy to fix "*market failures, especially in the development of priority antimicrobials*" by broadening the *eligible modalities to include phage-based medicines*.

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3. Regulatory Sandboxes for Phage Therapies

Amendment to Regulation – Chapter IX (Regulatory Sandbox): Modify Article 113 to facilitate adaptive regulatory frameworks for innovative phage products and explicitly accommodate personalized phage therapy trials:

Article 113(1) (amended): The Commission may set up a regulatory sandbox… where all the following conditions are met: (a) it is not possible to develop the medicinal product or category of products in compliance with the usual requirements due to scientific or regulatory challenges arising from characteristics or methods related to the product; (b) those characteristics or methods positively and distinctively contribute to quality, safety, or efficacy, or provide a major advantage for patient access. *In particular, medicinal products based on bacteriophages may be considered for a sandbox when their personalization or novel manufacturing methods make standard development pathways challenging.*

Article 113(2) (amended): The sandbox framework may allow adaptive clinical trial designs and regulatory flexibility for the development of the product. *This may include tailored requirements for phage therapy trials, such as streamlined protocols for personalized phage cocktails or the use of real-world evidence to support efficacy, while ensuring patient safety.*

(Add new) Article 113(2a): *By way of example, a sandbox may enable the controlled clinical use of patient-specific phage cocktails under regulatory supervision, accelerating access for patients with resistant infections. The sandbox plan shall detail how requirements are adapted (e.g., bespoke manufacturing validations, alternative trial endpoints) and how safety is ensured for such phage therapies. Furthermore, the sandbox may facilitate the establishment of certified phage banks, where pre-characterized phages undergo regulatory validation for rapid deployment in clinical settings, including compassionate use frameworks. This model would ensure timely access to phages while maintaining rigorous quality and safety standards*.

(**Add new) Article 113(3)** – Phage Therapy Pilot Initiative - "*In order to assess the feasibility and effectiveness of phage therapy regulatory sandboxes, the Commission shall conduct a pilot initiative over a period of 2-3 years, during which selected phage-based medicinal products may undergo adaptive regulatory pathways under controlled conditions.*

The pilot shall focus on:

- *The integration of personalized phage therapies into supervised clinical frameworks.*
- *The real-time adaptation of phage cocktails based on evolving bacterial resistance profiles.*
- *The feasibility of phage banks as an emergency response mechanism for antimicrobial-resistant infections.*

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- *The development of risk-based regulatory models that can transition into long-term legislative frameworks.*

"The results of the pilot shall be evaluated by the European Medicines Agency (EMA) in collaboration with national competent authorities, with recommendations provided for the full implementation of phage regulatory provisions beyond the pilot phase."

Justification:

- The regulatory sandbox is intended as a "controlled environment [to] facilitate development and authorization of innovative products". Phage therapies – especially personalized phage treatments tailored to individual patients' infections – exemplify products needing this flexibility. Under current rules, conducting traditional large trials or meeting fixed CMC requirements for each bespoke phage mix is impractical.
- By explicitly referencing phage products in Article 113, we signal that phage therapy qualifies for sandbox consideration due to "scientific or regulatory challenges" (e.g. each patient's infecting bacteria may require a different phage). The sandbox can provide "targeted derogations" from standard rules, such as allowing adaptive trial protocols or n-of-1 trials with pooled data, while still under authority supervision
- This approach has precedent: Belgium has effectively created a phage therapy framework by treating personalized phages as magistral (compounded) preparations. In Belgium, phages are prepared per prescription in a pharmacy with quality oversight, bypassing full pharmaceutical marketing authorization. This "magistral phage" model – allowed under national law – provides production and handling flexibility (e.g. not forcing strict GMP) for personalized phages. The sandbox amendment would let the EU emulate such successful models in a harmonized way. For example, a phage sandbox could permit a phage bank and quick release of certified phages for compassionate use – concepts already suggested by experts to overcome regulatory hurdles.
- By integrating this into EU legislation, personalized phage therapy can be developed under close monitoring without having to fit squarely into the traditional one-size-fits-all trial paradigm. The sandbox would still require a plan ensuring patient safety and science-based oversight (as per Article 113 and 114). This balances innovation with protection: it "allows testing of innovative approaches in a time-limited, supervised setting". As a result, promising phage treatments (for example, emergency use of phages in life-threatening infections) could reach patients faster, generating data for broader authorisation. Successful outcomes from sandbox trials can then inform full EU approvals. This adaptive pathway is crucial since "phage therapy may not fit within traditional drug regulations" and calls have been made to create specific regulatory approaches for it. The sandbox amendment answers that call within the existing legislative structure.

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4. Streamlined Updating of Phage Cocktail without Full Reauthorization

Amendment to Regulation – Variation Provisions (Article 47 or new Article)
Introduce a provision to treat certain phage-cocktail updates as variations of the marketing authorization (rather than entirely new MAs):

Article 47(x) (new) – Phage Cocktail Updates: *For an authorized medicinal product that consists of a combination of bacteriophages ("phage cocktail"), the addition or replacement of a phage in the product's composition shall be considered a variation of the marketing authorization, not a new marketing authorization, provided that:*

a) *the new phage is of equal or narrower host range purpose (targeting the same pathogen group) and meets quality and safety criteria established for the product;*
b) *the marketing authorisation holder supplies data demonstrating that the overall safety, quality, and efficacy of the updated phage cocktail is maintained or enhanced;*
c) *in case of genetically engineered phages, an assessment is made to ensure compliance with relevant GMO safety requirements (in line with Directive 2001/18/EC Article 5 and related legislation).*

The Commission is empowered to adopt delegated acts specifying conditions and guidelines for such phage-cocktail variations, drawing on principles applicable to vaccines and other biologicals where strain updates do not require full reauthorisation.

Justification:

This amendment creates a regulatory pathway for updating phage products efficiently, reflecting the reality that phage cocktails may need periodic modification to remain effective (for example, if bacteria develop resistance to one phage, a new phage is substituted).

Currently, adding a new phage could be treated as a new product, since each phage is an active substance requiring review. That is a "major regulatory issue" and would severely slow down improvements to phage therapies. The proposed change ensures such updates are handled as variations to the existing authorization, leveraging existing data. This concept parallels how influenza vaccine strain updates or COVID vaccine variant updates are managed via variation procedures rather than brand-new authorizations, due to established manufacturing processes and prior safety profiles. It is also consistent with the draft Directive's recognition that marketing authorizations may be varied after approval to account for scientific and technical progress.

By tailoring variation rules to phage cocktails, we maintain regulatory rigor (each change reviewed by authorities) but avoid unnecessary duplication of full dossiers. The amendment calls for delegated acts to detail conditions – for example, requiring comparability studies or minimal clinical data for the new phage akin to how biotech products are handled.

Distinguishing natural vs. engineered phages: Natural (wild-type) phages might be added based on phenotypic and genomic characterization, whereas engineered phages (which might include added lysin genes or other modifications) will undergo an extra level of scrutiny

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for environmental and safety aspects. The text explicitly links to existing GMO provisions: the Regulation already coordinates with GMO rules (see Recital 150 of the proposal, noting that medicinal products containing GMOs follow medicinal law if certain criteria are met). Our amendment ensures engineered phage substitutions are reviewed in light of GMO biosafety, but without forcing a completely separate licensing process under GMO law if they remain within the medicinal product's scope. This maintains consistency with the principle that authorized medicinal products containing or consisting of GMOs are exempt from separate GMO release authorizations (Directive 2001/18/EC Article 5).

Overall, the streamlined process will be "aligned with existing frameworks for biologicals and gene therapies" in that it uses variation procedures and delegated acts to handle changes. It acknowledges the unique nature of phage cocktails that may require updates, while ensuring safety and efficacy are not compromised. The flexibility is supported by scientific consensus: experts note that requiring full reapproval for each phage is impractical and have called for regulatory adaptations for phage therapy.

The European Pharmacopoeia has even adopted a new chapter (5.31) on phage therapy products that "*allows a degree of flexibility… in this emerging and rapidly developing field*" edqm.eu – our amendment translates that principle into regulatory practice. By handling phage additions as variations, patients can benefit more quickly from improved phage cocktails (addressing resistance or new bacterial strains) without undue delay, all while regulators retain oversight through a streamlined variation review instead of a full marketing authorisation process.

Sources:

- **Draft Regulation on medicinal products (2023)** – Recitals (77)-(80) on priority antimicrobials; Article 40 on transferable vouchers; Chapter IX on Regulatory Sandboxes (Articles 113-114)
- **Draft Directive on medicinal products (2023)** – Recitals on priority antimicrobials and variations; Definition of magistral preparation/hospital exemption.
- **Faltus, T. (2024). "The Medicinal Phage – Regulatory Roadmap for Phage Therapy under EU Pharmaceutical Legislation."** – Explains current legal classification of wild-type vs. genetically modified phages and calls for coherent integration of phage therapy into pharma law.
- **Vázquez et al. (2022). "Essential Topics for Regulatory Consideration of Phages: A Perspective from Spain."** – Describes regulatory hurdles: each phage currently needs approval; suggests phage banks and adapted frameworks. Notes Belgium's magistral phage model as a successful flexible approach and emphasizes that phage therapy is scientifically ready for a supportive regulation.
- **European Pharmacopoeia Chapter 5.31 (2024)** – Provides quality standards for phage therapy products with flexibility for complex phage mixtures edqm.eu

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About PhageEU

Phage EU is a coalition of likeminded stakeholders who represent phages in industry, the scientific community and civil society. We want to realise the full poten0al of phages in Europe. https://phageurope.eu

Contact

Margareta Przybyla, PhageEU Secretary General, mprzybyla@phageurope.eu, Tel: 0032 476 591 091