**WRITTEN EVIDENCE SUBMITEED BY DEPARTMENT OF HEALTH AND SOCIAL CARE (DHSC), UK HEALTH SECURITY AGENCY (UKHSA), MEDICENES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA)**

**(PHA0007)**

## Science and Technology Committee Inquiry: the antimicrobial potential of bacteriophages

Written Evidence submitted by the Department of Health and Social Care (DHSC) on behalf of the UK Health Security Agency (UKHSA) and the Medicines and Healthcare products Regulatory Agency (MHRA).

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## Introduction

1. The Department of Health and Social Care (DHSC) welcomes the opportunity to provide evidence for the Science and Technology Committee's Inquiry on the antimicrobial potential of bacteriophages on behalf of the Government. This evidence brings together information from across DHSC and its Arm's Length Bodies including the Medicines and Healthcare products Regulatory Agency (MHRA), NHS England (NHSE), and the UK Health Security Agency (UKHSA). UK Research and Innovation (UKRI) have separately submitted written evidence, which is signposted below.

## Antimicrobial resistance (AMR)

2. The Government is committed to containing and controlling all types of antimicrobial resistance (AMR). Bacterial resistance to treatment, including antibiotics, is the third leading underlying cause of death globally[1]; it is already costing lives, livelihood and resource both within the UK and globally. The exploration and development of new and alternative treatments to antibiotics is central to our approach to tackling AMR. Within the Addendum to the UK's 5-year national action plan on AMR the Government committed to "explore alternative interventions and therapies such as bacteriophages, monoclonal antibodies, virulence factor modulating products and bacterial biofilm inhibiting or resistance materials and modulators or components of host innate immunity."

3. Bacteriophages or 'phages' are viruses that can kill harmful bacteria and are therefore an attractive alternative to traditional antibiotics. Phages have the potential to be useful tool in the fight against AMR and as such, the Government welcomes this inquiry and looks forward to its findings.

## Q1. How well established is the evidence base for phages as an antimicrobial for humans?

4. Phage therapy has been recognised by several public health bodies and funding agencies. There is a wide array of anecdotal evidence to support its use, but a remaining need to strengthen this evidence base, including with randomised efficacy trials and safety data.

5. The predominant use of phage therapy to date has been in compassionate use studies for patients with multidrug or pandrug resistant infections, often in a chronic setting, on a named patient basis.

6. Given the evidence from compassionate use studies and the increase in funded clinical trials and efforts to rationalise and develop innovative protocols for clinical use (e.g. Phages Australia, Phages UK, Phages Innovation Network), there is a clear case for phages' use and development to be seriously considered, including in future Government policy on AMR.

7. Targeted research to identify and address some of the prominent roadblocks in clinical translation of the technology would be merited, especially around regulatory pathways and manufacturing capability, suitable to support licensure. UKHSA support for this research could extend from existing work in this area

[1] Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis - The Lancet

(see paragraph 40) and also through collaborative links with NIHR-funded Health Protection Research Units (HPRUs) at Imperial and Oxford. Further information on the current evidence base and support for research projects in this area can also be found in UKRI's written evidence.

8. The Government is committed to a holistic response to tackle the threat of AMR and, while phages may be an important component of the future therapeutic suite, the potential weaknesses and limitations of phage therapy must also be recognised.

**A. What are their strengths and weaknesses?**

9. Further information on strengths and weaknesses can also be found within the UKRI written evidence submission.

Strengths

10. Phages are an attractive option as they are highly specific for a pathogen of interest meaning that phage therapy can be tailored to meet the individual needs of a patient undergoing treatment. In particular, this specificity avoids any "off target" effects on other bacteria in the microbiome and doesn't propagate resistance in other non-target bacteria.

11. The effectiveness of compassionate-use studies is encouraging, suggesting that phage therapy can resolve even complex and difficult to treat infections in patients with severe disease and may be effective in other clinical settings, if barriers can be navigated.

Weaknesses

12. However, phage therapies either require the use of a cocktail of phages (multiple phages formulated as a single treatment) to cover a range of isolates from a particular species and/or the use of a diagnostic test to confirm that a strain causing an infection is susceptible to the phages being used therapeutically.

13. Resistance to single phages can occur at reasonably high frequency in some cases, though this is partially mitigated by the use of phage cocktails or continued monitoring of susceptibility over time. Rapid phage susceptibility test methods are urgently required to support both the initial selection of phages for therapy and to monitor continued efficacy during treatment.

14. In terms of manufacture, producing phages in high titre or concentration is technically challenging and requires dedicated facilities run by specialist experts.

15. Like other therapeutics, there are also limitations in phages' clinical usage. Phages need to come into contact and be internalised by their target bacteria to be effective, which can be difficult in certain systems, and are likely to have lower penetration and distributions than antibiotics therefore having a lower chance of interacting and killing bacterial pathogens. Some phages may be removed or inactivated by the reticulo-endothelial system and, just like standard antimicrobials, we cannot assume 100% effectiveness against target bacteria.

**Q2. What regulatory approaches have been used by other countries for the use of phages and what lessons can the UK learn?**

**Current UK phage regulation**

16. In the UK, bacteriophages isolated or manufactured with the intention of treating a medical condition are classified as biological medicines and are consequently subject to the Human Medicines Regulations 2012 (HMRs, as amended). In some cases (for instance if genetically modified), phages may also be classified as advanced therapy medicinal products (ATMPs). ATMPs are a class of biological medicines that are subject to both the HMRs and separate legislative requirements.

17. The HMRs set out the conditions for medicines to be assessed in accordance with the criteria of quality, safety and efficacy and for a marketing authorisation (or product licence) to be issued. There are currently no licensed bacteriophage medicines in the UK.

18. The HMRs contains certain provisions for the supply of an unlicensed medicine to address an unmet medical need for named patients only when a licensed product is not available, i.e., “specials” and “extemporaneous preparations”.

**International phage regulation**

19. Bacteriophages are also classified as biological medicines in Europe and regulated under Directive 2001/83/EC (as amended). Similar to the HMRs, the Directive sets out the conditions for medicinal products to be assessed in accordance with the criteria of quality, safety, and efficacy and for a marketing authorisation to be issued.

20. The European Medicines Agency (EMA) held a workshop on the therapeutic use of bacteriophages in 2015. The aim of the workshop was to discuss possible issues related to development of bacteriophage therapies for treatment of bacterial infections.

21. The US Food and Drug Administration (FDA) held a public workshop about the regulatory and scientific issues associated with bacteriophage therapy in 2021.

22. We are aware of several publications that relate to the regulation of phages in Europe. Examples are provided below:
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8023134/
    - https://www.mdpi.com/1999-4915/10/2/64
    - https://pubmed.ncbi.nlm.nih.gov/34801778/
    - https://www.mdpi.com/1999-4915/11/4/352
    - https://pubmed.ncbi.nlm.nih.gov/35456768/
    - https://link.springer.com/protocol/10.1007/978-1-4939-7395-8_19
    - https://www.dgra.de/media/pdf/studium/masterthesis/master_canete_carlos_2018.pdf

23. In Belgium, phage therapies are manufactured as magistral preparations (also referred to as extemporaneous preparations). These are unlicensed medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient. The feasibility of a similar approach could be explored in the UK. The conditions under which extemporaneous preparations are manufactured are not determined by MHRA and MHRA propose that appropriate experts are consulted. The General Pharmaceutical Council regulates pharmacists, pharmacy technicians and pharmacies in Great Britain.

24. MHRA works closely with other international regulators, including through groups such as ICMRA (International Coalition of Medicines Regulatory Authorities). ICMRA produced a statement focused on 'Combatting antimicrobial resistance' which included committing to "*develop processes that facilitate the review of emerging technologies, such as phage therapy and point-of-care diagnostics.*"

25. Currently, bacteriophages can also be manufactured in the UK or imported into the UK as a "special" as long as they meet the requirements for all other specials. However, there are currently no MHRA licence holders in the NHS who are authorised to manufacture phages and quality assurance of imported "specials" is difficult.

**Q3. What opportunities does the UK have for regulatory divergence from the EU on phages, and what would the implications be?**

26. MHRA is responsible for regulating medicines in the UK, including new and existing phage therapies. The MHRA is a sovereign regulator. The Agency will work with stakeholders to ensure that the UK regulation of bacteriophages is risk proportionate, so that UK patients have the fastest possible access to innovative bacteriophage therapies for which quality, safety and efficacy have been shown. If needed, the MHRA could consider new regulatory approaches or pathways.

27. MHRA may rely on EU decisions on medicines until the end of 2023. However, if a medicine meets MHRA's standards of quality, safety and efficacy, and any other applicable requirements, a national marketing authorisation may still be issued even if the EMA has not granted an authorisation for the same product.

**Q4. What are the major barriers and opportunities relating to the development and deployment of phages in the UK?**

Regulatory pathways

28. MHRA recognises the challenges of developing medicines and navigating the regulatory framework which can be complex.

29. MHRA understands that some external stakeholders perceive the requirements for good manufacturing practice (GMP) as a barrier. Good manufacturing practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards that are designed to minimise the risks involved in any pharmaceutical production. While MHRA will assess any

submitted phage therapeutic applications and is willing to facilitate the appropriate regulatory processes, the agency cannot actively seek these applications.

30. The Agency is keen to engage with innovators of new medicines through its Innovation Accelerator and Innovation Office. Support for development programmes can be sought through dedicated scientific advice meetings where challenging aspects of the quality, safety and efficacy of medicinal products can be raised and discussed. In addition, the Innovative Licensing and Access Pathway (ILAP) offers a route for earlier patient access and for the development of medicines that are both regulatory and access ready (MHRA partnership working with Health Technology Assessment bodies such as NICE). MHRA can also provide informal guidance if there are difficulties around understanding the formal classification of a phage technology from a regulatory perspective (Biological medicine versus Advanced Therapy Medicinal Product).

31. Phage UK is a recently formed body looking to help address questions on how phage therapy could be used and enable a robust clinical pathway to using phages in the UK, mirroring similar work in Australia (Phage Australia). Current expectations are that this is likely to be on a named patient basis initially but may extend to more routine clinical use in the future.

Quality assurance of the proposed product

32. Currently, there are global capacity constraints in any pharmaceutical phage manufacturer with a suitable quality system. Therefore, when faced with an urgent clinical need it is difficult to procure a quality product. Manufacture is often in non-GMP-compliant facilities with unvalidated processes and test methods, and detailed quality assurance knowledge is absent in most NHS institutions.

Supply chain assurance:

33. Adequate supply chain assurance is required, which can be challenging for unlicensed medicines (ULMs) which are imported. Importation requires authorisation from MHRA, and assurance requires expertise from the purchaser (e.g., of cold/ambient chain).

Financial approval:

34. Under current processes, NHS Trusts have to self-fund phages. If this barrier is to be overcome there would need to be:
    - targeted studies using ULMs, co-ordinated to generate sufficient evidence to enable funding and approval of clinical trials.
    - a centralised manufacturing facility set up and licensed in England to facilitate validation, manufacture and testing to ensure the production of phages of a consistent quality suitable for patients.

Health, safety, and containment

35. Phages require proper biosafety hazard classification to understand what level of containment would be required to handle products safely. There are limitations around access to biological safety cabinets and capacity within existing cabinets.

There are further considerations around resource required for decontamination and the resistance from system users in requiring this and other resource.

Usage guidelines

36. Phages are a relatively unique therapeutic. As detailed in the response to question 1, phages have limitations for their clinical usage and will not always be the most appropriate therapy. There needs to be consideration of guidance on usage. This would need to include best practice for phage cocktails, combination phages and antibiotic therapy and decision making on suitability of phages versus antibiotics.

37. There is no dosing knowledge for most phages, so accurate endotoxin levels (indicators for bacteria) are required to safely administer. Decisions on dosing therefore require expert pharmacy and clinical knowledge. Vulnerable patient groups may also be affected by the formulation details of phages, such as their phosphate and magnesium content, before administration. The time required to ascertain this information and undertake quality assurance of ULMs is a barrier in the current therapeutic pathway.

38. There are a number of other areas that should be considered including patient consent, bridging therapy requirements over the manufacturing period, a need for a registry for follow up data if phage therapy is introduced more widely, and administration risks, as phages are often administered via surgery.

**Q5. How well developed is the UK's phages research and clinical trial pipeline and how could it be improved?**

39. DHSC works closely with UKRI to monitor the research and clinical trial pipeline for antimicrobials and alternative therapies.

40. The Government is already delivering research in this field; for example:
    - The Open Innovation in AMR project (NIHR 200658) was awarded to UKHSA to support infrastructure that would enable the development and evaluation of non-traditional therapeutic approaches for AMR, including bacteriophages. Seed projects to evaluate these approaches were supported, working with the University of Liverpool and University of West of England. The infrastructure established within the capital grant continues to be used to support phage research, internally and with external academic laboratories (e.g., University of Southampton, University of Exeter).
    - Ongoing research at UKHSA is focused on the development and evaluation of novel approaches for rapidly assessing phage susceptibility, aiming to support improved selection of phages for treatment, based on evidence that they are effective against a target pathogen. The technology (A fast impedance-based antimicrobial susceptibility test | Nature Communications) has been applied to antibiotics and is being developed for this application with funding from the NIHR Invention for Innovation (NIHR200968). Evidence that this approach works has led to a patent being filed (PCT/GB2021/050694) and additional research funding awarded (BBSRC SoCoBio funded iCASE project, starting October 2023).

41. DHSC will continue to support considerations for improvement to the research and clinical pipeline.

**Q6. To what extent is the UK Government ensuring that phage research and development is adequately funded and supported?**

42. The Government works closely with partners across the research landscape to support research into antimicrobial therapies.

43. UKRI funds a range of research that seeks to develop alternative therapeutics to antimicrobials, including the use of phage therapy. Further information on phage research and development can be found within UKRI's written evidence return.

44. UKHSA has an active programme of work aiming to understand how phages might be used for clinical treatment, the impact of phage resistance as it emerges and exploring rapid phage susceptibility test methods to support future clinical use. Ongoing research focusing on the development and evaluation of novel approaches for rapidly assessing phage susceptibility is being developed with NIHR funding. Additional funding applications to UKRI and other funders will follow publication of the proof-of-concept data.

45. Innovate UK is holding a workshop in early 2023 with attendees with expertise in AMR and/or phages to discuss phage-based therapies. The information gathered from this event will allow the UK to capitalise on its extensive phage expertise and provide novel, effective solutions to the growing global crisis of AMR. It will also serve as the first step towards the UK solidifying itself as a world leader in this area.

**(January 2023)**