

Viruses That Can Cure, When Antibiotics Fail...

Verbeken G^{1-3*}, Pirnay JP¹, Lavigne R⁴, Ceulemans C³, De Vos D¹ and Huys I^{2,5}

¹Laboratory for Molecular and Cellular Technology, Burn Wound Centre, Queen Astrid Military Hospital, Bruynstraat, Brussel, Belgium

²Faculty of Pharmaceutical and Pharmacological Sciences, KU Leuven, Herestraat, Leuven, Belgium

³Department of Behavioural Sciences, Royal Military Academy, Renaissancelaan, Brussel, Belgium

⁴Laboratory of Gene Technology, KU Leuven, Leuven, Belgium

⁵Centre for Intellectual Property Rights, KU Leuven, Minderbroedersstraat, Leuven, Belgium

Abstract

Resistance of bacteria to antibiotics just keeps growing. Industry's antibiotic pipeline is running dry. Before the pharmaceutical development of antibiotics, natural bacteriophages (=bacterial viruses) were commercialised and used to kill pathogenic bacteria. This therapeutic application of natural bacteriophages was called "bacteriophage therapy". Today, countries like Poland, Georgia and Russia are still practising bacteriophage therapy. The European Union and "modern" medicine as a whole needs an urgent return of bacteriophage therapy as part of its armamentarium to fight bacterial resistance to antibiotics. This paper reflects on the issue and proposes a European regulatory frame that could fit the re-introduction of bacteriophage therapy without losing sight of safety, quality and efficacy aspects.

Keywords: Antibiotic resistance; Bacteriophages; Bacteriophage therapy; Regulatory; Viruses

Resistance of Bacteria to Antibiotics

The treatment of infectious diseases with antibiotics is becoming increasingly challenging [1,2]. Antimicrobial resistance (AMR) is a serious threat to global public health. In Europe, 25,000 patients die annually from untreatable infections [3-5]. The situation may deteriorate further, as there are only a few drugs left to treat multidrug-resistant bacterial strains and the first strains that are resistant to even these last-resort antibiotics have already emerged [6,7]. Moreover, there is a dearth of genuinely novel antibiotics in the development pipeline despite global efforts by health organisations and political initiatives, including the '10 × 20' initiative of the Infectious Diseases Society of America (IDSA), the 'New Drugs for Bad Bugs' initiative (NDBBI) and the US GAIN Act [5,8-13]. Various proposals have been made to address the problem using novel antimicrobials. One approach seems to be promising and sustainable at the long term and implementable in the near future. That approach is called "bacteriophage therapy", the use of bacteriophages (bacterial viruses) to kill bacteria. Indeed, the use of bacteriophages to kill specific bacterial pathogens without harming the majority of the commensal bacteria has received increasing attention during the past decade [2,14-37]. Since almost a century, bacteriophages, independently discovered by Twort in the UK and d'Herelle in France, have been put forward and are used as antibacterial agents [26]. The principle, set forward by d'Herelle, is using the bacterium's natural predator as weapon against a specific pathogenic bacterium. A single lytic bacteriophage can specifically recognize and bind its host, inject its genetic material and convert the bacterium into a virus producing machine. In a final step of their replication cycle, a large number of progeny bacteriophages are released by breaking down the cell wall, thus killing the host. In this manner, newly formed virus particles are ready for a next round of infection.

Bacterial Resistance to Bacteriophages

Bacteria can develop resistance to bacteriophages [21] through a variety of different mechanisms, including blocking bacteriophage adsorption, inhibiting the injection of bacteriophage genomes, restriction-modification systems, and abortive infection systems [38-40]. In *in vitro* monoculture studies, bacteriophage resistance can

evolve in time frames of hours to days depending on mutation and growth rates. Whether the evolution of bacteriophage resistance *in vitro* is relevant to *in vivo* conditions where bacteria may be replicating more slowly and challenged with a greater set of environmental conditions can be questioned [41]. Bacteriophage mutants more active against the bacteriophage-resistant bacteria can be selected from the environment. Therapeutic bacteriophage banks, as they exist in Georgia and Poland, contain many different natural therapeutic bacteriophages and are regularly updated [42]. In 2015, the first modern "Western" European natural therapeutic bacteriophage bank was opened at the German Leibniz Institute - Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ). Bacteriophages deposited in this special collection of the DSMZ could be of therapeutic interest if further propagated and prepared as new stocks under appropriately controlled conditions prior to their therapeutic application [43]. Naturally evolved bacteriophages, isolated from the environment or the patient's bacteria, can be stored (for later use) in these banks. Patient-tailored bacteriophage preparations can also be developed [42].

The Co-Evolutionary Concept Bacterium/Bacteriophage

Bacteriophage therapy can be defined as the use of exclusively lytic bacterio-specific viruses as antibacterial agents. By setting up a screening system for the circulating noxious bacteria and their respective bacteriophages, it is possible to obtain the right bacteriophage against any emerging pathogen. Any sustainable bacteriophage therapy concept should, based on scientific grounds, fully acknowledge the potentialities of the co-evolutionary aspect of

***Corresponding author:** Verbeken G, Laboratory for Molecular and Cellular Technology, Burn Wound Centre, Queen Astrid Military Hospital, Bruynstraat, Brussel, Belgium, Tel: + 32 2 264 4856; E-mail: gilbert.verbeken@mil.be

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the couplet bacteriophage/bacterium in its ecological environment, *in casu* the human being. Bacteria will inevitably become resistant to bacteriophages, but due to the continuously ongoing “arms race” between the two protagonists, specific bacteriophages able to infect the formerly resistant bacterial strains will quickly emerge [44-49].

European Human Medicinal Products Legislation

For practitioners at hospitals seeking to use bacteriophages for treatment of antibiotic-resistant bacterial infections, Europe's current regulatory framework for human medicinal products hinders more than it facilitates [50]. Although many experts consider bacteriophage therapy to be a promising complementary (or alternative) treatment to antibiotic therapy, no bacteriophage-specific regulatory framework exists to date. Today, bacteriophage therapy is only approved in some former Soviet Republics like Russia and Georgia [21]. In Poland, a recent member of the European Union, bacteriophage therapy is considered an ‘Experimental Treatment’ covered by the Physician Practice Act (Polish Law Gazette N° 28 of 1997) and the Declaration of Helsinki, where other therapeutic options do not exist [2]. In France, therapeutic made-to-order bacteriophage preparations from the Pasteur Institutes (Paris and Lyon) were used until the beginning of the nineties. Historical clinical data on bacteriophage therapy (from Eastern Europe, particularly Poland, and the former Soviet Republics, particularly Georgia and Russia, as well as from today's 28 EU member states and the US) collected during the past decades are not taken into account by European regulators since these data were not collected in compliance with today's Western standards [51]. The current pharmaceutical economic model, implying costly and time-consuming pathways for human medicinal product development and marketing, and requiring strong intellectual property protection, is not compatible with a (possible) smooth re-introduction of traditional sustainable bacteriophage therapy into the European Union. Another major obstacle for the clinical application of bacteriophages is a false perception of viruses as ‘enemies of life’ [52]. Bacteriophages are not straightforward inanimate and stable substances. They are evolvable and natural biological entities. Sustainable bacteriophage therapy legislative frameworks should fully acknowledge the potential of the co-evolutionary aspect of the bacteriophage/bacterium couplet. A specific European regulatory frame with realistic production and documentation requirements, which allows a timely (rapid) supply of safe, tailor-made, natural bacteriophages to patients, is a must [13]. Fundamental changes of mentality in the medical and pharmaceutical environment are essential for a successful re-introduction of bacteriophage therapy into modern Western medicine [53].

Can We Adapt European Legislation to Fit Bacteriophage Therapy?

A suitable European legislative environment for bacteriophage therapy should be developed in collaboration with the competent authorities and responsible political and economic actors. The setting up of credible scientific studies and credible clinical trials needs to be stimulated. Natural bacteriophages are, by definition, “products” in the pharmaco-legal jargon. They are natural, lifelike biological entities. Bacteriophages can be categorized at potentially two (new) classification places under Annex 1 Part III of Human Medicinal Products Directive 2001/83/EC [54]. A first possibility is the creation of a new and specific “Biological Medicinal Products” categorical ranking place under the name “Bacteriophage Medicinal Products” at the same rank level as “Plasma-Derived Medicinal Products” and “Vaccines”. The second possibility can be the creation of a dedicated new category of the Part

III Particular Medicinal Products division. Both proposed new legal frame options are visualized in Table 1 and concern as “products” only the natural exclusively lytic natural bacteriophages.

Another option could be the creation of a new and dedicated Bacteriophage Therapy Directive, outside the existing Human Medicinal Products Directive 2001/83/EC. New legislative frames tailored to bacteriophage therapy should allow an adapted developmental time frame. The development of a “new” natural bacteriophage “product” can in practice happen in a matter of days to weeks [42], in contrast to the time frames applicable to the developing of classical chemical antibiotics. These new or adapted frameworks should also make the tailored use of bacteriophage therapy in hospitals or recognized bacteriophage therapy centres possible. In case the European Union would not actively support, in the near future, the re-introduction of tailored bacteriophage therapy into its Member States, national authorities could regulate bacteriophage therapy at their level. There is an urgent need for bacteriophage therapy centres in view of the increasing antibiotic resistances and its negative consequences. If in the actual pharmaco-economic environment the launch of hospital-based (non-profit) bacteriophage therapy centres should be financially impossible, national governments should support those initiatives and eventually help to develop new pharmaco-economic models. Last but not least, it could be contended that the tailored production and the in-hospital use of a natural therapeutic bacteriophage does not constitute a market placement of this product and, by doing so, places this product and its use outside the scope of the European Medicinal Product Directive 2001/83/EC [55]. Also this argument motivates for the creation of a totally new and specific European Bacteriophage Therapy Directive.

The Moral Issue

The need to introduce an adequate regulatory framework for

Part I	Standardized marketing authorisation dossier
Part II	Specific marketing authorisation dossier
	<ul style="list-style-type: none">• Well-established medicinal use• Essentially similar medicinal products• Additional data required in specific situations• Similar biological medicinal products• Fixed combination medicinal products• Documentation for applications in exceptional circumstances• Mixed marketing authorisation applications
Part III	Particular medicinal products
	<ul style="list-style-type: none">• Biological medicinal products- Plasma-derived medicinal products- Vaccines- Bacteriophage medicinal products• Radio-pharmaceuticals and precursors- Radio-pharmaceuticals- Radio-pharmaceutical precursors for radio-labelling purposes• Homeopathic medicinal products• Herbal medicinal products• Orphan medicinal products- Bacteriophage medicinal products
Part IV	Advanced Therapy Medicinal Products
	<ul style="list-style-type: none">• Gene therapy medicinal products• Somatic cell therapy medicinal products

Table 1: Annex 1 Part III of Human Medicinal Products Directive 2001/83/EC in which the bacteriophage therapy concept could be integrated or classified.

bacteriophage therapy is of course much more than a purely legal issue. It is also and perhaps especially so a moral issue. Indeed, we should never forget that political and economic institutions do not exist for their own sake. They are not ends in themselves. Their core business is, or at least should be, the protection and promotion of human well-being. In that perspective, one cannot escape the conclusion that bacteriophage therapy must be taken seriously by all stakeholders. The pharmaceutical industry, the competent authorities, lawmakers, regulators, and politicians have the moral duty and the shared responsibility towards making bacteriophage therapy urgently available for all patients in need [56]. The pharmaceutical industry has a moral duty to invest in antibacterial therapies like bacteriophage therapy, in view of the social responsibility they need to take. Of equally crucial importance is the role of the competent public authorities to create the appropriate legislative framework to stimulate companies to invest in bacteriophage therapy. Political representatives and lawmakers have an inevitable, logical responsibility to support health care and welfare. The development and production of bacteriophage products in a classical pharmaceutical context (clinical trials, production requirements, marketing authorization procedures...) requires a great deal of time. Patients in need have no time. Therefore, lawmakers and regulators need to design appropriate solutions, on a short term, to buffer for the years needed for companies to develop bacteriophage-based medicinal products. Much more urgent and optimal, legislative solutions need to be created to allow hospitals to adopt patient-oriented and tailored bacteriophage therapy in a legal way for treating those patients that are waiting to be cured today.

Environmental Risks

Bacteriophages are the natural controllers of bacteria in the environment (rivers, soils, plants, animals...). Little is known about the ecological effects that (high concentrations) of bacteriophages in the environment might have on local natural microbial communities. A better and more fundamental understanding of the cost/benefits of resistance to bacteriophage predation and of synergistic effects among bacteriophages in controlling bacterial pathogens will allow for a more informed development and application of treatment, and ideally the prevention of widespread resistance [57-60]. Studying the environmental risk issue is very relevant in relation to the large-scale use of bacteriophages as e.g. bio-pesticides in agriculture. The controlled, tailored, hospital-based use of natural bacteriophages is bound to have little impact on the environment in comparison with the emerging large scale use of bacteriophages in agriculture, cattle breeding and food industry. However, more fundamental as well as applied studies are required for optimizing and safely re-implementing bacteriophage therapy.

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