Arch. Immunol. Ther. Exp. (2012) 60:161–172
DOI 10.1007/s00005-012-0175-0

REVIEW

Optimizing the European Regulatory Framework for Sustainable Bacteriophage Therapy in Human Medicine

Gilbert Verbeken · Jean-Paul Pirnay · Daniel De Vos · Serge Jennes · Martin Zizi · Rob Lavigne · Minne Casteels · Isabelle Huys

Received: 3 January 2012 / Accepted: 21 February 2012 / Published online: 17 April 2012

Abstract For practitioners at hospitals seeking to use natural (not genetically modified, as appearing in nature) bacteriophages for treatment of antibiotic-resistant bacterial infections (bacteriophage therapy), Europe's current regulatory framework for medicinal products hinders more than it facilitates. Although many experts consider bacteriophage therapy to be a promising complementary (or alternative) treatment to antibiotic therapy, no bacteriophage-specific framework for documentation exists to date. Decades worth of 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 27 EU member states and the US) have not been taken into account by European regulators because these data have not been validated under current Western regulatory standards. Consequently, applicants carrying out standard clinical trials on bacteriophages in Europe are obliged to initiate clinical work from scratch. This paper argues for a reduced documentation threshold for Phase 1 clinical trials of bacteriophages and maintains that bacteriophages should not be categorized as classical medicinal products for at least two reasons: (1) such a categorization is scientifically inappropriate for this specific therapy and (2) such a categorization limits the marketing authorization process to industry, the only stakeholder with sufficient financial resources to prepare a complete dossier for the competent authorities. This paper reflects on the current regulatory framework for medicines in Europe and assesses possible regulatory pathways for the (re-)introduction of bacteriophage therapy in a way that maintains its effectiveness and safety as well as its inherent characteristics of sustainability and in situ self-amplification and limitation.

Electronic supplementary material The online version of this article (doi:10.1007/s00005-012-0175-0) contains supplementary material, which is available to authorized users.

G. Verbeken (✉) · J.-P. Pirnay · D. De Vos
Laboratory for Molecular and Cellular Technology,
Burn Wound Centre, Queen Astrid Military Hospital,
Bruynstraat 1, Brussels, Belgium
e-mail: gilbert.verbeken@mil.be

G. Verbeken · M. Casteels · I. Huys
Department Pharmaceutical and Pharmacological Sciences,
Centre for Pharmaceutical Care and Pharmacoeconomics,
KU Leuven, Leuven, Belgium

S. Jennes
Burn Wound Centre, Queen Astrid Military Hospital,
Brussels, Belgium

M. Zizi
Department of Physiology, Free University Brussels,
Brussels, Belgium

M. Zizi
Section Health of the Division Well-Being
(Belgian Defense Staff), Queen Astrid Military Hospital,
Brussels, Belgium

R. Lavigne
Laboratory of Gene Technology,
KU Leuven, Leuven, Belgium

I. Huys
Center for Intellectual Property Rights,
KU Leuven, Leuven, Belgium

Keywords Bacteriophage · Therapy · Human · European · Regulatory · Legal

Lack of an Adequate European Regulatory Framework for (Natural) Bacteriophage Therapy

The European Directive 2001/83/EC[1] is considered the main code governing medicinal products for human use within the European Union. This piece of legislation was designed to specify the file requirements for the authorization of classical medicinal products (e.g., small chemical molecules). Specific regulatory aspects were included for some types of medicinal products[2] (see Table 1), such as radiopharmaceuticals, herbal medicinal products, homeopathic medicinal products, biologicals (vaccines, toxins or serums) and advanced therapy medicinal products (ATMPs). Historically, herbal medicinal products are at the origin of a large number of commonly used pharmaceuticals and cannot be documented as, for instance, small chemical medicinal products. For ATMP, a separate regulation (No 1394/2007[3]) was established with specific scientific and procedural features adapted to these complex medicinal products.

This paper deals strictly with bacteriophage therapy based on the use of natural bacteriophages in human therapy. Natural bacteriophage therapy uses bacteriophages that are not genetically modified. Natural bacteriophages have been known for decades to be anti-infectious agents that can be used complementary to, or as an alternative for, antibiotic treatment (Abedon et al. 2011; Caplin 2009; Górski et al. 2009a, b; Housby and Mann 2009; Kutateladze and Adamia 2008; Kutter et al. 2010; Monk et al. 2010; Skurnik and Strauch 2006; Sulakvelidze et al. 2001; Thiel 2004). Natural bacteriophages can be isolated from the environment, identified, up-scaled, purified and used as antimicrobial agents (Gill and Hyman 2010; Merabishvili et al. 2009). In view of their potential therapeutic uses, it is imperative that natural bacteriophages be processed according to the appropriate quality and safety standards. However, no such framework detailing the file requirements specific to (natural) bacteriophage therapy products exists today (Shorthose et al. 2010). Therefore, a specific and appropriate quality and safety documentation framework is needed for the application of natural bacteriophages on humans.

[1] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_cons2009/2001_83_cons2009_en.pdf (consolidated version).

[2] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2003_63/dir_2003_63_en.pdf.

[3] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf.

Table 1 Directive 2001/83/EC of the European Parliament and of the Council of 6 NOV 2001 on the Community Code Relating to Medicinal Products for Human Use (consolidated version)

Annex 1
Analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products
Part I: Standardized Marketing Authorization Dossier Requirements
Part II: Specific Marketing Authorization Dossier Requirements
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 authorization applications
Part III: Particular medicinal products
Biological medicinal products
Plasma-derived medicinal products
Vaccines
Radio-pharmaceuticals and precursors
Radio-pharmaceuticals
Radio-pharmaceutical precursors for radio-labelling purposes
Homeopathic medicinal products
Herbal medicinal products
Orphan medicinal products
Part IV: Advanced therapy medicinal products
Gene therapy medicinal products
Somatic cell therapy medicinal products
Tissue engineered products

http://ec.europa.eu/health/files/eudralex/vol1/dir_2001_83_cons2009/2001_83_cons2009_en.pdf

http://ec.europa.eu/health/files/eudralex/vol-1/dir_2003_63/dir_2003_63_en.pdf

In this paper, we investigate whether bacteriophage therapy can be situated within existing European regulatory frameworks. We then summarize possible regulatory pathways at different policy levels. Finally, we reflect on several alternative approaches.

Can Natural Bacteriophages Used in Anti-Microbial Therapy on Humans be Situated Within One of the Existing Particular or Specific European Legislation Frameworks Governing Medicinal Products?

Bacteriophages are not comparable to standardized chemical medicinal products (Abedon and Thomas-Abedon 2010; Krylov 2011, Payne and Jansen 2003; Pirnay et al. 2011; Ryan et al. 2011). However, it is worthwhile to call to attention a number of particular and specific regulatory

frameworks in European legislation governing medicinal products and analyze briefly where bacteriophages may or may not fit in (see Table 1).

Biologicals

Biologicals are products whose active substance is biological. At first sight and in view of the nature of several approved biologicals, the "biological medicinal product" chapter of the consolidated 2001/83 EC Directive could be considered applicable to bacteriophages given the biological nature of natural bacteriophage products. That is, the active substance of bacteriophage therapy seems to have a biological origin. However, only a few types of biological medicinal products, such as plasma-derived medicinal products and vaccines, have a dedicated specific documentation package defined under the current biological medicinal products legislation. Bacteriophages, thus, probably would not qualify as biologicals.

Homeopathic Products

Products based on homeopathy are also regulated through a specific category under the European consolidated 2001/83 EC Directive. It may seem surprising that these homeopathic "products" can be documented as medicinal products given the difficulty applicants have with proving their products' (even limited) health claims to the competent authorities. Bacteriophage-based therapeutic products are not comparable to homeopathic products. Bacteriophages have the potential to kill bacteria and have a clear, specific antibacterial effect (Bush et al. 2011; Fernebro 2011; Maura and Debarbieux 2011).

Advanced Therapy Medicinal Products

ATMPs are characterized as complex high-tech therapeutic products with technical specificities that require precise legal definitions. The ATMP section of the consolidated 2001/83 EC Directive only covers products for gene therapy, somatic cell therapy and tissue engineered products. In this sense, one could argue that natural bacteriophages are not ATMPs since their nature differs significantly from that of the gene and cell-based therapeutics currently covered by this regulation. Isolation and production technology used for natural therapeutic bacteriophages do not have the same technological complexity as that used for ATMPs, although one could argue that it is also a complex process (e.g., Matinkhoo et al. 2011; Puapermpoonsiri et al. 2010). This fact does not, however, mean that natural therapeutic bacteriophages are the same as ATMPs.

Well-Established Medicinal Products

European legislation considers a medicinal product to be "well established" if data confirm that the product has been used systematically within the European Community for more than a decade. In addition, the available documentation should assess safety and effectiveness and must include an overview of relevant scientific literature. Based on this criteria, one could potentially classify natural therapeutic bacteriophages as "well-established medicinal products" because they were in use long before the European Medicinal Product Regulation came into force and as far back as the early 1920s (Abedon et al. 2011; Bruynoghe and Maisin 1921; Górski et al. 2009a, b; Housby and Mann 2009; Kropinski 2006; Kutter et al. 2010). Regulators could counter, however, that most (but not all) clinical evaluation dealing with bacteriophage therapy was compiled outside the current 27 EU member states (Fortuna et al. 2008; Górski et al. 2009a, b; Khawaldeh et al. 2011; Kutateladze and Adamia 2010; Rhoads et al. 2009; Wright et al. 2009) and that the proven positive clinical effects were not documented by state-of-the-art, Western-standard-controlled clinical trials.[4] For these reasons, this "well-established medicinal product" framework may not entirely apply to bacteriophage therapy either.

Regulatory Pathways for Bacteriophage Therapy as Discussed at Different Policy Levels

The lack of adequate regulatory guidance for documenting safety, quality and effectiveness of natural bacteriophages when used as therapeutics prompted a first attempt to clarify the situation at the European level [European Parliament and European Medicines Agency (EMA)], followed by discussions at the national level.

European Parliament

On 14 February 2011, a Parliamentary Question[5] was sent to the cabinets of two Members of the European Parliament [Ivo Belet (Belgium/PPE) and Catherine Trautmann (France/S&D)] who addressed the Question to the European Commission and Council. Belet and Trautmann began by explaining to the Commission what "bacteriophage therapy" was. Second, they explained what the existing regulatory hurdles are when working with natural

[4] http://www.eortc.be/services/doc/clinical-eu-directive-04-april-01.pdf.

[5] http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+WQ+E-2011-001144+0+DOC+XML+V0//EN&language=CS.

therapeutic bacteriophages in Europe (Pirnay et al. 2011; Verbeken et al. 2007). Then they raised the question of how bacteriophage therapy is currently regulated in Europe and whether the Commission would consider creating an extra documentation box, "Bacteriophage Therapy", under the "particular" European Medicinal Product framework.

On 29 March 2011, Mr. Dalli, the European Commissioner for Health and Consumer Policy, formulated his written answer on behalf of the European Commission[6]: "The EU's legislation on medicinal products does not define specific requirements related to bacteriophage therapy or medicines composed of bacteriophages". In addition, his answer goes on to say, "the Commission considers that the existing regulatory framework as explained above is adequate for bacteriophage therapy without the need for an extra set of documentation for bacteriophage therapy" (see Supplementary Materials Online Resource 1).

European Medicines Agency Innovation Task Force

The European Commission's, thus, did not clarify how the existing regulatory framework (which it characterized as "adequate") should be interpreted in view of bacteriophage therapy. Clarification was sought at the level of the EMAs Innovation Task Force (ITF). The ITF is tasked with facilitating the informal exchange of information and providing guidance in the early stage of medicinal product development (see Box 1 of Appendix). A request for a Briefing Meeting was submitted to the ITF, supported by specific briefing documents (Merabishvili et al. 2009; Pirnay et al. 2011; Verbeken et al. 2007). The objectives of the meeting were to clarify bacteriophage therapy's classification, to identify the type of documentation needed to launch clinical trials testing natural therapeutic bacteriophages and/or to get marketing authorization and, finally, to discuss a two-way regulatory route for bacteriophage therapy, as described by the author(s) (Pirnay et al. 2011). In short, the "two-way regulatory approach" differentiates between the industrial development of uniform bacteriophage products meant for uniform market placement[7] and the tailor-made production of patient-specific natural therapeutic bacteriophages.

On July 12, the authors' delegation (6 experts, hereafter called "the delegates") met with the ITF (13 experts) and discussed the current situation and certain specific aspects. Subsequently, the final opinion was published by the ITF in the Briefing Meeting Report,[8] reflecting the opinions of the members of the ITF and of the contributing experts. These opinions should be interpreted as a preliminary set of scientific considerations related to the information presented.

Point of View of the Delegates

Working with natural bacteriophages in a non-profit hospital environment contrasts with industrial approaches to the preparation of bacteriophage-based products in that the latter prioritizes regular market authorization while the former does not. Bacteriophage therapy should be understood as a "therapy concept". Bacteriophages and bacteria co-evolve in a dynamic system. Taking this reality into account is crucial if the full sustainable potential of bacteriophages in therapeutics is to be actualized. Industry actors may pursue uniform market placement of bacteriophage cocktails for economic reasons, but this diverges from the idea and practical aspects of bacteriophage therapy itself, which is based first and foremost on a tailor-made patient approach. Additionally, securing intellectual property (IP) protection for tailor-made natural bacteriophages, while likely possible, is far from simple. Phages are widespread and the therapy has existed for years. One can thus anticipate broad patent claims covering production processes, intended (new) uses and the phages themselves. However, such broad patent claims are weak and easy to circumvent. Weak IP protection makes the task of attracting venture capitalists difficult, which means developers of tailor-made natural bacteriophage therapies often lack the financial resources necessary to pursue costly regulatory pathways. The "reusing" or "refitting" of [non-good manufacturing practices (GMP) but carefully developed and delineated] production process developed in the authors' previous study (see Box 2 of Appendix) (Kutter et al. 2010) raises an important regulatory question. Do production processes approved for similar products satisfy EMA regulators and adhere to the necessary safety and quality standards (Merabishvili et al. 2009)?

Final Opinion of the ITF

Medicinal Products

Since the pathway for developing a medicinal product is specific to each indication and each product, the ITF advises applicants to submit, free of charge, a request to have EMA scientific services investigate a specific proposed bacteriophage product's "eligibility" to be classified

[6] http://www.europarl.europa.eu/sides/getAllAnswers.do?reference=E-2011-001144&language=CS.

[7] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726_cons/reg_2004_726_cons_en.pdf.

[8] ITF's Opinion, Briefing Meeting Report, EMA/642573/2011, 22 July 2011, available on request to the author of correspondence.

as a medicinal product.[9] The EMA then evaluates whether that product is a medicinal product based on the description of the active substance, the manufacturing process, the production process, the mechanism of action and the intended clinical application. The European Commission is consulted during that process. At the moment of submission, a product-specific website with a description of the information to be submitted is created, the information is then submitted by the applicant and the EMA consult its experts.

Biologicals or ATMPs

If bacteriophage-based products are considered medicinal products, they will likely be classified as biological medicinal products. In general, a bacteriophage-based product is not considered an ATMP in light of the current, highly specialized ATMP Regulation. This holds unless the Scientific Committee changes its opinion and the European Commission interprets the legislation to include a particular bacteriophage-based product. The ITF does not anticipate this, but this does not preempt the decision (should there be one) made by the Commission and the Scientific Committee.

Dossier Requirements

The specific regulatory requirements necessary for bacteriophage therapy approval are evaluated on a case-by-case basis and are determined by the specific characteristics of the product and its intended use and hence not on the product as such. The quality and safety data presented in the authors' study (Merabishvili et al. 2009; Kutter et al. 2010) were considered to be basic. However, these data could be part of an Investigational Medicinal Product Dossier (IMPD) when launching clinical trials. Additionally, an EMA's Scientific Advise (SA) procedure could also be requested to seek advice on medicinal product development. All information related to SA requests is also available on the EMA website.[10]

It is notable that the EMA explicitly acknowledges efforts to develop tailor-made bacteriophage products. But SA's are still needed for each particular bacteriophage-based product based on a review of the full package submitted in a separate SA procedure. Each natural bacteriophage-based product must prove to be safe, with a suitable dosage and with evidence of clinical significance.

European regulators currently emphasise "Quality by Design", where one designs the critical parameters that form the core of the product before moving forward with development or marketing authorization. One can decide to apply for a product classification (as described above) to get an idea of how the product is positioned and based on this information, can then consider various elements of the product's Marketing Authorization options. One element to consider, for instance, is the production process. The EMA has sufficient insight into what elements may be important for a particular product. It has extensive experience with the manufacturing process, disease frequency and conditions to target (for example for an orphan drug designation), and SA on the quality aspects relevant to these defined elements is also available. The "quality by design" approach could potentially be very useful, but would require some modelling and simulation exercises (especially in view of co-evolutionary aspects). It could nonetheless be particularly critical to defining the key parameters for production processes or manipulations, which could then provide the basis for further development.

Evolving Products

Bacteriophages are not considered unique as "evolving" products. The EMA has handled precedents in this respect, for instance, living cell preparations and the flu vaccine. Every 1–2 years, the recommended strains for the seasonal flu vaccines are reviewed to investigate whether an adaptation is needed to accommodate for the flu strain(s) that will likely appear in the next season. The launch of a new vaccine needs to be supported by facts and data and an appropriate risk management strategy for the product. Likewise, bacteriophage product for a given indication and produced according to a given manufacturing process could also be updated every 1–2 years. While natural bacteriophage therapy is an unprecedented particular case, the EMA has dealt with similar products before, which suggests that it would be able to handle natural bacteriophage therapy as well.

Procedure

Authorization of a medicinal product follows either a centralized, decentralized, or mutual recognition procedure, depending on the product's categorization. For a biological medicinal product, authorization processes are not homogeneous between EU member states, as applicants may opt for a national rather than European procedure and national procedures can differ from country to country. However, the product's quality, safety and efficacy must be

[9] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&mid=WC0b01ac05800ba1d9&jsenabled=true.

[10] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800ba1d9.

demonstrated in all procedures. ATMPs can only be authorized via the centralized procedure.

Personalized Medicine

One possible method for using phages in patient treatment could be to provide a first injection of natural bacteriophages geared toward attacking a broad bacterial infections problem. This would then be followed by a treatment with a specific (personalized) set of bacteriophages, selected and applied to the patient to combat an emerging additional problematic bacterial strain specific to that patient. Tests should be performed before administering the second batch of personalized bacteriophages. The best way to use bacteriophages—and this is where it becomes especially personalized—would be to take the original bacteriophage (to which resistance emerged) and let it evolve (in vitro), in parallel with the patient's infecting strain, that is, to use the bacteria-phage dynamics to actually evolve a phage. Although it complicates matters, it exemplifies the real power of this approach. This approach is considered comparable to some therapies using autologous cells that are manipulated ex vivo and then returned to the patient. There is a particular need for critical dialogue with EMA Scientific Committees on this topic. However, in the case of bacteriophage therapy, the target is not a human cell but a bacterial cell. There are millions of bacteria and phages living in and on the human body. The question thus arises as to whether bacteriophages can be considered "human body material". If so, bacteriophages would be covered by the European Human Cells and Tissue Directive.[11] However, no real answer has been provided on this question.

Although bacteriophages differ from conventional biological products and an adaptation of the current legislation is urgently needed, regulators like the EMA stress that they do not make new rules; they only apply existing regulations. It is the view of the ITF that a new regulation cannot be "invented" by regulators.

Actions Proposed by the ITF

First, a request could be submitted to the Committee for Medicinal Products for Human Use to investigate the eligibility of a particular phage-based product.[12] If bacteriophage therapy could be used for an orphan indication, an application for Orphan Designation could be considered, making use of specific incentives in the law such as protocol assistance and fee reductions. Second, the option remains to apply for EMA scientific advice to delineate a clinical development strategy as well as specific protocols and models of how to prepare the product and the precise use of bacteriophages, for instance, whether to use a fixed cocktail or a fixed cocktail complemented with personalized bacteriophages. Overall, the clinical development of bacteriophage therapy needs to show that phage products are safe (Phase I), that the proposed dose will be the most effective one (Phase II) and that in clinical trials (in which bacteriophages are applied exactly as they will be used in practice) the therapy shows efficiency, taking into account the "appropriate indication" and "clinical end point" (Phase III).

National Competent Authority

Following the opinion of the ITF at EMA, a discussion took place with the Belgian Competent Authority, the Belgian Federal Agency for Medicines and Health Products (FAMHP), which, though unofficially, expressed the following view:

Medicinal Products

In line with EMA, natural bacteriophages used as therapeutics are considered medicinal products, based on their nature and intended use.

Biologicals or ATMPs

In addition, bacteriophages are seen as biological medicinal products that can be commercialized via a national regulatory procedure. However, these natural bacteriophages are not considered as ATMPs. This was the conclusion reached at a consultation by FAMHP of EMA's Committee for Advanced Therapies. This standpoint has specific consequences for hospital-based therapies. The ATMP Regulation as such is a *lex specialis* which introduces additional provisions to those laid down in Directive 2001/83/EC. The scope of the ATMP Regulation is to regulate the authorization of ATMPs intended to be placed on the market in European Union member states, either prepared industrially or manufactured by a method involving an industrial process, in accordance with Directive 2001/83/EC. ATMPs are excluded from the scope of the European ATMP Regulation if they are prepared on a non-routine basis according to specific quality standards and used within the same member state in a hospital under the exclusive professional responsibility of a medical practitioner and an individual medical prescription for a custom-made product for an individual patient. This

[11] Directive 2004/23/EC of the European parliament and of the council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

[12] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&mid=WC0b01ac05800ba1d9&jsenabled=true.

exclusion is called the hospital exemption. The precise interpretation of the definition of hospital exemption is left to the National Competent Authorities. For instance, the (national) definition of "non-routine use" can be different in each member state. However, the member states have to ensure that relevant community rules related to quality and safety are not undermined. This national procedural pathway for hospital exemptions could be of interest to hospitals working with their own tailor-made natural bacteriophage therapies. However, since the ATMP framework is not considered to be relevant by the EMA and Belgian regulators when positioning natural bacteriophages, the hospital exemption procedure cannot be applied to bacteriophage therapy and therefore hospitals interested in bacteriophage therapy cannot benefit from this hospital exemption.

File Requirements

At the national level (FAMHP), the possibility of obtaining an "early phase" clinical trial status for bacteriophage therapy could be considered. It should be pointed out that, at present, obtaining an authorization to produce IMP's (Trouet et al. 2007) may be an impossible burden for hospitals. It is even questionable as to whether a full authorization is always needed for the limited IMP production that is required for a phase I clinical trial, for instance. At this level, as at the European level, there is a need for a pragmatic approach.[13]

Actions Suggested by the National Competent Authority

A reduced IMPD could be submitted for evaluation, and interactions with the National Competent Authority concerning the content of the application could be initiated in a constructive and open-minded way.

Reflection by the Authors

Theoretically, the proposal to opt for a full market authorization via a simplified procedure at the National Competent Authority appears feasible. However, this proposed approach lacks an awareness of the specific "personal medicinal character" of natural bacteriophages and reflects only a (classical) medicinal product development approach. Today, there is no legal definition for "Personalized Medicine" and most preparations intended for use as "personalized medicinal products" are not really "personal", meaning that they are produced for a very small patient population and not for one patient as such.

Hospitals willing to use bacteriophage therapy in clinical practice, working independently from industry in a non-profit setting and using tailor-made phage products to treat patients, are not necessarily interested in obtaining marketing authorization and IP protection. Moreover, a stringent marketing authorization approach, even with simplified procedures, is nearly impossible for hospitals to manage to date. In addition, in view of the enormous challenges related to rapidly progressing bacterial resistance, a product development process that takes many years does not seem to be the best way forward.

Belgian and UK Notified Bodies

Given the opinions expressed by European and national regulators and given that uncertainties remain regarding the appropriate regulatory pathway for a natural bacteriophage-based product, it is worth considering whether such a product could fall under the Medical Device framework. To find out whether such an approach would work for bacteriophages, a burn wound ointment that is actually on the market as a medical device was supplemented with natural bacteriophages. In fact, the antimicrobial component of the burn wound ointment (in this case an enzyme) was replaced with natural bacteriophages.

In May 2011, a request for opinion was submitted to a Belgian Notified Body (SGS) authorized to certify medical devices for market placement. SGS Belgium forwarded the question to their London office, and this SGS London office contacted the UK Competent Authority, the Medicines and Healthcare Products Regulatory Agency.

Medical Devices Framework and Current Applications

Directive 2001/83/EC defines a medicinal product as "any substance or combination of substances presented as having properties for treating or preventing disease in human beings or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis". According to the Medical Devices Directive 93/42/EC,[14] medical devices support the restoration, correction or modification of physiological functions as described above, rather than being the cause of it. Some medical device manufacturers drop the primary therapeutic claim for the proposed product so that this product can be covered by the Medical Devices Directive 93/42/EC. In light of the above, it seems useful to consider whether bacteriophage therapy

[13] http://www.pharma.be/assets/files/2309/2309_1295209549827530 81.pdf?bcsi_scan_3c79e7817cdc4fd7=0&bcsi_scan_filename=2309_ 129520954982753081.pdf.

[14] Council directive 93/42/EEC of 14 June 1993 concerning medical devices (consolidated version).

can be covered by the Medical Device Directive. Under current practice, for instance, as long as a burn wound ointment only moistens and protects a wound bed (primary claims), these ointments are considered to be medical devices, even when they contain antimicrobials that keep the ointment aseptic.

Opinion of the UK Notified Body

Adding natural bacteriophages to a burn wound ointment would turn a medical device (such as the ointment described above) into a medicinal product, based on the fact that phages have a "targeted action".

Reflection by the Authors

It is true that phages have a targeted action when considering a tailor-made use of bacteriophages for treating specific infections on defined patients. However, in theory, uniform bacteriophage cocktails could be placed on the market as medical devices, without claiming any primary therapeutic effects, circumventing the current and usual medicinal product regulation. This cannot be the intention of regulators. Therefore, the preferred route is the creation of an adequate regulatory framework for therapeutic natural bacteriophages.

Alternative Regulatory Approaches

During the consultations at different regulatory levels, certain specific concepts and types of product status were mentioned that are useful to investigate in greater detail.

Medicinal (Whole) "Animal" Product Status

It is worthwhile to consider whether bacteriophages can be regarded as "whole animals" (as mentioned in Art. 1 of the consolidated Directive 2001/83/EC), such as larvae (medicinal maggots used, for instance, in debridement of wounds) and leaches (medicinal leaches used, for instance, in the stimulation of vascularization after amputation), all of which are present on the European market for therapeutic use. Some of these types of products are regulated via the current European medicinal products regulation. Product files have been compiled and licenses have been granted in that area, and in some cases, such "animals" have even been GMP produced. In practice, some manufacturers of these "whole animal" products try to avoid the full GMP requirement in a way similar to that described above in the medical device section. For instance, manufacturers put their animals in a dressing and call this dressing a "biosurgical wound dressing". The animals (e.g., maggots) are "aseptically cultivated/raised". Preparations are available by prescription only and are individually produced for a specific patient.[15] Indeed, such a situation is preferable and compatible with bacteriophage-based therapy. However, defining a natural bacteriophage as a "whole animal" is somewhat far-fetched.

Magisterial (Compounded) Preparations

During the GEEPhage 2011 meeting (March 2011),[16] the French Competent Authority explained that the pathway that regulates magisterial hospital preparations could perhaps provide a regulatory gateway for hospitals that have the intention to use, in-house, home-made preparations of natural bacteriophages on a non-routine basis and in a patient-tailored manner.

Under Belgian legislation, certain specific considerations need to be taken into account. First, if the bacteriophage cocktail is not authorized to enter the European market, a "product monograph" must be compiled. Specifically, this means that a documentation and description of the identity, the purity and the properties of the natural bacteriophage preparation must be provided. This monograph must be submitted for evaluation to the Belgian Pharmacopeia Commission. The bacteriophage preparation as published by Merabishvili et al. (2009) is considered as "crude material" by regulators. To be considered as a magisterial preparation, the preparation must be produced under GMP. After a positive answer from the Pharmacopeia Commission, the microbiological lab of the particular hospital can be licensed by the necessary Belgian Minister as a supplier of "crude materials". Only then may a pharmacist at the respective hospital use that particular bacteriophage cocktail as a component for magisterial preparations. It is clear that this pathway is not adapted to hospitals that do not have the ambition, intention, or financial resources to place a product on the national or European market.

Medicinal Products without Marketing Authorization: "Compassionate Use"

Medicinal products that are not (yet) authorized to enter the European market can be used on patients when this use is covered by compassionate use programmes, regulated at the national level. Compassionate use programmes are meant for patients with chronically or seriously debilitating diseases or for patients whose disease is not considered to be treated satisfactorily with an authorized product (Dodds-Smith and Valverde 2009). As tailored bacteriophage

[15] http://www.biomonde.de/English/protected/bio_produkt.html.

[16] http://geephage.org/bacteries/.

cocktails (Merabishvili et al. 2009) are in fact not in the pipeline to obtain European marketing authorization, the compassionate use pathway seems untenable yet still possible. On the other hand, compassionate use programmes would definitely be relevant to potential uniform bacteriophage preparations that are currently involved in marketing authorization procedures.

The Declaration of Helsinki is particularly relevant for medicinal products not intended for placement in the European market under license. Paragraph 35 of the Declaration of Helsinki[17] states the following: "In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health, or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available".

Taking this paragraph into account, natural tailored bacteriophages can be used on patients in need when the Helsinki conditions are fulfilled. This is what is sporadically done in Europe at the moment, for instance, at the Queen Astrid Military Hospital in Brussels, Belgium. Due to its "exceptional" character, the Helsinki procedure is not a regulatory procedure with the potential to introduce bacteriophage therapy into modern medicine in any widespread, sustainable sense.

National Legislation Defining Exemptions

Some countries have published national legislation to regulate certain specific products or techniques made available in the country in a non-profit setting. In Poland, phage therapy is considered an experimental treatment. Experimental treatment occurs when a physician introduces new or only partially tested diagnostic, therapeutic, or prophylactic methods for the direct benefit of the person being treated. In contrast, an investigational experiment has the primary purpose of broadening medical knowledge. Two basic items are prerequisites for experimental therapy in Poland: (a) the written informed consent of the patient and (b) approval by an institutional review board (bioethics commission). Furthermore, experimental therapy may only be applied by a qualified doctor and when other available treatment has failed.[18] In Poland, this type of treatment is also covered by the Helsinki Declaration (Kutter et al. 2010; Letkiewicz et al. 2010).

In the Czech Republic there is an (reimbursed) anti-staphylococcal bacteriophage product (lysate) on the market under the trade name Stafal.[19] Stafal was approved for market placement by the Czech National Competent Authority, the State Institute for Drug Control. The product is an anti-staphylococcal phage lysate intended for topical use (registration number 59/0149/89-CS).

When considering clinical trials, the type of exemptions listed above may favour small (to very small) investigator-driven trials, allowing clinicians to conduct pilot studies without the full burden of commercial regulation. However, it is uncertain as to whether bacteriophage therapy would be covered by such exemptions, and even so, bacteriophage therapy would not be covered in a harmonized manner across Europe. Again, there is a need for an adapted framework for defining (natural) bacteriophage therapy at the European level. Member states are forced to try to find solutions at the national level because there is no adequate European framework.

Grey Areas

Aside from bacteriophages, there are some other products that could be called "grey area" products. This means that it is not always clear whether a certain product has to be classified as a medicinal product, as a food supplement (see Box 3 of Appendix), as a cosmetic, as a biocide, as a nutrient, or as a product for regular consumption. The regulatory pathway for each of these categories differs considerably.

In a sense, a natural bacteriophage preparation could also be considered a "grey area" product. As yet, it is unclear whether a bacteriophage-based preparation is really a medicinal product. Some member states have installed a specific commission at their national regulatory authority to tackle "grey area" products. For instance, in Belgium, a "Mixed Commission" is in place that decides on the classification (or not) of a particular "grey area" product as a medicinal product. When the commission decides that a specific product is a medicinal product, the medicinal product regulatory framework (Directive 2001/83/EC) has to be applied. Thus, for "grey area" products, the national competent authorities at the member state level decide whether such a product is a medicinal product, after consulting other relevant stakeholders. They can take European precedents into account and they can, of course, also consult the European Competent Authorities.

If this Mixed Commission were to decide that tailored natural bacteriophages are indeed medicinal products, the question arises as to how Directive 2001/83/EC

[17] http://irb.sinica.edu.tw/declaration%20of%20helsinki%20(2008).pdf.

[18] arts. 29/1, 21/2, and 21/3 of the Polish law on the physician's profession.

[19] http://www.sevapharma.cz/file/Stafal_EN.pdf.

(Consolidated) would then be applied, taking into account its scope. Indeed, Article 2 of the Directive explains that the rules shall only apply to "medicinal products for human use intended to be placed on the market in the European Member States and are either prepared industrially or manufactured by a method involving an industrial process". "In cases of doubt", the Directive mentions, "where, taking into account all its characteristics, a product may fall within the definition of a "medicinal product" and the definition of a product covered by other Community legislation, the provisions of Directive 2001/83/EC shall apply". In addition, the Directive shall also apply to medicinal products intended only for export and to intermediate products. In view of these wordings, "home-made" and "in-house-applied" natural bacteriophage cocktails such as bacteriophage preparations do not seem to be captured by the scope of the Medicinal Products Directive, since such cocktails are not intended to be placed on the market in the European member states. Indeed, everything depends on what the legislator takes "placing on the market" to mean. Informal contacts with EMA and the Belgian National Competent Authority determined that even the in-house application on one patient of an in-house-prepared product could be considered a market placement. However, to date no legal argumentation for this position has been made available, and no such interpretation seems likely to be implemented, especially if this service is not publicly advertised. Nonetheless, it is important that the issue be clarified.

Conclusions

The authors are convinced that products for bacteriophage therapy deserve their own regulatory framework in Europe. Various pharmaceutical products different from the classical chemical molecules already have a proper framework designed under the Medicinal Products Directive 2001/83/EC (see Table 1). Natural bacteriophages are products that proved to have a well-established medicinal use in Eastern Europe and the former Soviet republics. They could be considered a type of Particular Medicinal Products, to be defined under a separate (dedicated) chapter in Annex 1 of the Directive. Alternatively, the optimal framework could be one dedicated specifically to bacteriophage therapy, alongside the present Medicinal Products Directive 2001/83/EC. As regulatory frameworks for other medicinal products have been introduced via particular Directives in the past, a new Directive for bacteriophage therapy could be a suitable solution. This new Bacteriophage Directive could then be called "Directive concerning the Therapeutic use of Natural Bacteriophages". This "new" adapted regulatory framework should certainly also include adequate timeframes, since the actual timeline for a classical drug approval is of the order of months/years/decades while the development of a "new" natural bacteriophage product can happen in a matter of days/weeks. Regulators at the competent national or European authorities (like EMA or FAMHP in Belgium) understand the potential of bacteriophage therapy. However, they cannot change or adapt any legislation. A collective lobby at the European political level could be an option for securing a vote of the European Parliament to adapt the actual European medicinal product regulatory framework. At the international level, dedicated bacteriophage therapy symposia such as the recent Phage 2011 meeting[20] are important at the scientific and technical-industrial level, but additional encounters and meetings are needed as platforms for increasing awareness at the political as well as at the public opinion levels. Classical pharma-symposia should start to integrate bacteriophage therapy issues into their programmes. For this reason, initiatives led by non-profit organizations like GEEPhage, P.H.A.G.E.[21] and PHAGESPOIRS[22] can play an active and primary role for change, particularly because these organizations were created to support bacteriophage research and therapy to the benefit of all patients. As foci of patient support efforts, these organizations play an important role in the creation of greater awareness among competent authorities (regulatory implementation) and policymakers (voting regulation).

Acknowledgments The authors would like to thank Professor Carl Ceulemans from the Military Higher Institute of Defence (Chair of Philosophy, Faculty of Social and Military Sciences, Royal Military Academy, Brussels, Belgium) for his honest, coherent and beneficial interactions concerning the re-introduction of phage therapy in routine clinical settings.

Conflict of interest The authors have no potential conflicts of interest directly relevant to the content of this manuscript.

Appendix

Box 1 Innovation Task Force (ITF)

The "Innovation Task Force" of the European Medicines Agency (EMA)[23] is a multidisciplinary group of scientific, regulatory and legal experts set up at the EMA to provide a forum for early dialogue in the form of "briefing

[20] http://www.libpubmedia.co.uk/Conferences/Phages2011/About.htm.

[21] http://www.p-h-a-g-e.org/Home.html.

[22] http://translate.google.be/translate?hl=nl&sl=fr&tl=en&u=http%3A%2F%2Fphagespoirs.unblog.fr%2F.

[23] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&mid=WC0b01ac05800ba1d9&jsenabled=true

meetings". The scope of the briefing meetings covers regulatory, technical and scientific issues arising from innovative medicines development, new technologies and borderline products. Within 60 days of receipt of a valid request, the ITF arranges free-of-charge briefing meetings to facilitate the informal exchange of information and the provision of guidance early in a development process. The scientific discussions are led by experts from the European Medicines Agency network, working parties and committees, where the best available scientific expertise is represented. Briefing meetings are meant to complement and reinforce existing formal regulatory procedures (e.g., ATMP classification, ATMP certification, designation of orphan medicinal products, etc.).

Box 2 Quality and safety evaluation criteria bacteriophage cocktail BFC1 (Merabishvili et al. 2009)

Characterization of the bacteriophages:

- Determination of the morphotype
- Complete DNA and proteome analysis (confirm absence of lysogeny and toxin genes)
- Testing host bacteria used in production for absence of (lysogenic) phage (mitomycin test)

QC tests performed by qualified accredited laboratories:

- Phage titer (agar overlay method)
- pH (according to EP)
- Cytotoxicity (ISO10993-5)
- Pyrogenicity (10 ml/kg rabbit, according to USP)
- Sterility (according to EP)
- Confirm morphology and activity towards targeted bacteria (transmission electron microscopy)

Box 3 Bacteriophages introduced into the food chain: some reflections

As a regulatory pathway, legislation for food supplements was investigated. In the US, the Food and Drug Administration (FDA) approved the use of Listex natural bacteriophages for the decontamination of foods.[24] Additionally, in the Netherlands and Switzerland anti listeria bacteriophages are in use for food products.[25] Current practice in the US for bacteriophage-based products is that such products are evaluated 'case-by-case' and finally approved (or not) under the US GRAS regulation (Federal Regulation of Substances Generally Recognized As Safe). In the US, foods and drugs are administered by one competent authority, the FDA, which is a federal structure without an equivalent in Europe. In Europe, the European Medicines Agency (EMA) and the European Food Safety Authority (EFSA) are two separate structures, probably explaining why it is a bigger step from food to medicinal products in Europe than it is in the US. However, in 2008 the European Commission (DG Health and Consumers) asked the EFSA to provide technical assistance in relation to the use and mode of action of bacteriophages on food of animal origin (Question No EFSA-Q-2008-400[26]). The scientific opinion of the EFSA panel on biological hazards was endorsed on 22 April 2009. The EFSA panel concluded that some bacteriophages, under specific conditions, have been demonstrated to be very effective in the targeted elimination of specific pathogens present on meat, milk and products thereof. The panel, however, could not conclusively find that bacteriophages could protect such products when re-contamination of the decontaminated products occurs. The panel also proposed that a "case-by-case" evaluation of presented phage products is necessary. This European approach is comparable to the US (GRAS) approach, which is in fact a positive evolution.

Surprisingly, however, some (pro-biotic) food-products define health claims in their dossier without being registered as medicinal products (for example, Actimel[27] and Yakult[28]). These types of products, by definition, also contain natural bacteriophages. It is questionable whether these health claims are evidence-based. In any case, the issue is hot in Europe, especially because Europe recently refused to accept some of the health claims related to specific products based on lack of evidence.[29],[30] Recently, an international workshop on the topic was organized in Brussels[31] entitled "how to design studies to prove the claimed health effects of these food products". Obviously, this field is moving quickly as well.

References

Abedon ST, Thomas-Abedon C (2010) Phage therapy pharmacology. Curr Pharm Biotechnol 11:28–47

Abedon ST, Kuhl SJ, Blasdel BG et al (2011) Phage treatment of human infections. Bacteriophage 1:66–85

Bruynoghe R, Maisin J (1921) Essais de thérapeutique au moyen du bacteriophage du Staphyloccoque [therapeutic trials using bacteriophage of *Staphylococcus*]. CR Soc Biol 85:1120–1121

[24] http://www.prnewswire.com/news-releases/fda-extends-gras-approval-listextm-to-all-food-products-57761742.html

[25] http://www.micreosfoodsafety.com/images/USDA-23-2011-1.pdf

[26] http://www.efsa.europa.eu/en/scdocs/doc/1076.pdf.

[27] http://www.efsa.europa.eu/en/efsajournal/pub/1903.htm.

[28] http://www.efsa.europa.eu/en/efsajournal/pub/1860.htm.

[29] http://www.efsa.europa.eu/en/press/news/110728.htm.

[30] http://www.telegraph.co.uk/health/healthnews/8074182/Probiotic-drinks-do-not-aid-health-Europe-says.html.

[31] http://www.healthclaims.eu/

Bush K, Courvalin P, Dantas G et al (2011) Tackling antibiotic resistance. Nat Rev Microbiol 9:894–896

Caplin J (2009) Bacteriophage therapy: old treatment, new focus? Microbiologist 10:20–23

Dodds-Smith I, Valverde S (2009) The supply of unlicensed medicines for individual patient use. In: Griffin JP (ed) The textbook of pharmaceutical medicine, 6th edn. Wiley-Blackwell, West Sussex, pp 331–346

Fernebro J (2011) Fighting bacterial infections-future treatment options. Drug Resist Updat 14:125–139

Fortuna W, Miedzybrodzki R, Weber-Dabrowska B et al (2008) Bacteriophage therapy in children: facts and prospects. Med Sci Monit 14:RA126–RA132

Gill JJ, Hyman P (2010) Phage choice, isolation, and preparation for phage therapy. Curr Pharm Biotechnol 11:2–14

Górski A, Miedzybrodzki R, Borysowski J et al (2009a) Bacteriophage therapy for the treatment of infections. Curr Opin Investig Drugs 10:766–774

Górski A, Targońska M, Borysowski J et al (2009b) The potential of phage therapy in bacterial infections of the eye. Ophthalmologica 223:162–165

Housby JN, Mann NH (2009) Phage therapy. Drug Discov Today 14:536–540

Khawaldeh A, Morales S, Dillon B et al (2011) Bacteriophage therapy for refractory *Pseudomonas aeruginosa* urinary tract infection. J Med Microbiol 60(Pt 11):1697–1700

Kropinski A (2006) Phage therapy—everything old is new again. Can J Infect Dis Med Microbiol 17:297–306

Krylov V (2011) Use of live phages for therapy on a background of co-evolution on bacteria and phages. Int Res J Microbiol 2:315–332

Kutateladze M, Adamia R (2008) Phage therapy experience at the Eliava Institute. Med Mal Infect 38:426–430

Kutateladze M, Adamia R (2010) Bacteriophages as potential new therapeutics to replace or supplement antibiotics. Trends Biotechnol 28:591–595

Kutter E, De Vos D, Gvasalia G et al (2010) Phage therapy in clinical practice: treatment of human infections. Curr Pharm Biotechnol 11:69–86

Letkiewicz S, Międzybrodzki R, Kłak M et al (2010) The perspectives of the application of phage therapy in chronic bacterial prostatitis. FEMS Immunol Med Microbiol 60:99–112

Matinkhoo S, Lynch KH, Dennis JJ et al (2011) Spray-dried respirable powders containing bacteriophages for the treatment of pulmonary infections. J Pharm Sci 100:5197–5205

Maura D, Debarbieux L (2011) Bacteriophages as twenty-first century antibacterial tools for food and medicine. Appl Microbiol Biotechnol 90:851–859

Merabishvili M, Pirnay JP, Verbeken G et al (2009) Quality-controlled small-scale production of a well-defined bacteriophage cocktail for use in human clinical trials. PLoS One 4:e4944

Monk AB, Rees CD, Barrow P et al (2010) Bacteriophage applications: where are we now? Lett Appl Microbiol 51:363–369

Payne RJ, Jansen VA (2003) Pharmacokinetic principles of bacteriophage therapy. Clin Pharmacokinet 42:315–325

Pirnay JP, De Vos D, Verbeken G et al (2011) The phage therapy paradigm: prêt-à-porter or sur-mesure? Pharm Res 28:934–937

Puapermpoonsiri U, Ford S, van der Walle CF (2010) Stabilization of bacteriophage during freeze drying. Int J Pharm 389:168–175

Rhoads D, Wolcott R, Kuskowski MA et al (2009) Bacteriophage therapy of venous leg ulcers in humans: results of a phase I safety trial. J Wound Care 18(237–238):240–243

Ryan E, Gorman S, Donelly RF et al (2011) Recent advances in bacteriophage therapy: how delivery routes, formulation, concentration and timing influence the success of phage therapy. J Pharm Pharmacol 63:1253–1264

Shorthose S, Bird & Bird LLP (2010) Guide to EU pharmaceutical regulatory law. Wolters Kluwer, Alphen aan den Rijn

Skurnik M, Strauch E (2006) Phage therapy: facts and fiction. Int J Med Microbiol 296:5–14

Sulakvelidze A, Alavidze Z, Morris JG Jr (2001) Bacteriophage therapy. Antimicrob Agents Chemother 45:649–659

Thiel K (2004) Old dogma, new tricks—21st Century phage therapy. Nat Biotechnol 22:31–36

Trouet C, Gobert M et al (2007) Investigational medicinal products. In: Clinical trials in Belgium: the Belgian implementation of the European Clinical Trials Directives. An operational guidance, 2nd edn. Intersentia, Antwerp

Verbeken G, De Vos D, Vaneechoutte M et al (2007) European regulatory conundrum of phage therapy. Future Microbiol 2:485–491

Wright A, Hawkins CH, Anggard EE et al (2009) A controlled clinical trial of a therapeutic bacteriophage preparation in chronic otitis due to antibiotic-resistant *Pseudomonas aeruginosa*; a preliminary report of efficacy. Clin Otolaryngol 34:349–357