Published online: January 12, 2017

Science & Society

EMBO reports

Regulating phage therapy

The biological master file concept could help to overcome regulatory challenge of personalized medicines

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In a note published in *The Lancet* in December 1915, Frederic Twort described the discovery of an infectious, filterable agent that causes the glassy transformation and eventual killing of bacteria, now identified as *Staphylococcus hyicus* [1]. Two years later, Félix d'Herelle independently described an invisible microbe antagonistic to dysentery bacilli in a note to the Comptes Rendus de l'Académie des Sciences [2]. These two reports are the first published descriptions of bacteriophages, a term coined by d'Herelle, who foresaw the therapeutic potential of these newly identified bacteriolytic agents.

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Yet, phage therapy, despite varying degrees of success during the 20th century, never made it into widespread clinical use owing to the discovery of antibiotics [3]. However, the increasing antibiotic resistance among major pathogens such as *Staphylococcus* or *Mycobacterium* has become a critical public health problem—in the European Union (EU) alone, around 25,000 patients die each year from an infection with drug-resistant bacteria (http://ecdc.europa.eu/en/publications/publications/0909_ter_the_bacterial_challenge_time_to_react.pdf). Although difficult to estimate, the annual global death toll attributable to antimicrobial resistance might range from the hundreds of thousands to as much as millions in the coming decades (https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf). In light of this growing health crisis, phage therapy has attracted renewed interest as an alternative to antibiotics [3].

Regulatory challenges for phage therapy

However, this reemergence raises regulatory concerns. There has been intense discussion on how to classify phage-based therapeutics within the EU's regulatory framework [4–6] with some consensus among Members States' regulatory authorities and the European Medicines Agency that these would be regulated as biological medicinal products [7]. Nonetheless, positions still vary because the current medicinal product regulation is not well suited for this unorthodox therapeutic practice. The key issue is whether phage therapy medicinal products (PTMPs) require a marketing authorization or not.

Originally, the so-called proprietary medicinal products required marketing authorizations under Directive 65/65/EEC on the Approximation of Provisions Laid Down by Law, Regulation or Administrative Action Relating to Proprietary Medicinal Products (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31965L0065&rid=1). Directive 65/65/EEC, which is now obsolete, defined a proprietary medicinal product as "any ready-prepared medicinal product placed on the market under a special name and in a special pack" as opposed to the handmade "medicinal products prepared in a pharmacy in accordance with a medical prescription for an individual patient", usually referred to as magistral formulas. The former, which include any industrially produced drugs, are subject to marketing authorization, whereas the latter are considered to fall outside the scope of European medicine legislation and do not require registration.

This point is relevant for phage therapy because one of the most promising applications is based on the preparation of a cocktail of phages that is specific for each patient and each bacterial infection [6,8]. The infecting pathogenic bacteria isolated from the patient would be analyzed for their sensitivity or resistance against a collection of phages. After determining such a specific "phagogram", the pharmacist would formulate an *ad hoc* preparation of up to a dozen different phages for subsequent administration to the patient. In this scenario, the PTMP is not ready-prepared and, as such, is not a proprietary medicinal product in the meaning of Directive 65/65/EEC. It would therefore fall outside the scope of this original Directive.

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However, in the early 2000s, this Directive was repealed and replaced by Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02001L0083-20121116&rid=1). The older concept of proprietary medicinal product outlined in Directive 65/65/EC evolved and was amended in the Directive 2001/83/EC, which now applies to human medicinal products "either prepared industrially or manufactured by a method involving an industrial process". Ready-preparing is no longer a criteria for determining whether a medicinal product should or should not require registration. Whether tailor-made

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DOI 10.15252/embr.201643250

PTMPs lie within the scope of Directive 2001/83/EC is questionable. Since it is formulated for an individual patient, a PTMP prepared by pharmacist is not intended for large-scale or serial production and, as such, is not prepared industrially. In this respect, the formulation of a customized finished product is still regarded as a preparation of a magistral formula. However, the production of phage stocks as active ingredients fulfills the characteristics of an industrial process, which, ideally, should be manufactured in compliance with the Good Manufacturing Practices (GMP) requirements for active substances for medicinal products. Customized PTMPs are thus situated somewhere between magistral formulas and industrially made medicinal products. This situation raises concerns regarding the appropriate regulatory procedure for licensing customized PTMPs, which are not addressed within the current EU regulatory framework.

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Exemptions from registration requirements

In addition to magistral formulas, EU legislation allows for exemptions from the registration requirements of Directive 2001/83/EC. These include compassionate use according to Article 83 of Regulation 726/2004 (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02004R0726-20130605&rid=1), hospital exemption granted to certain advanced therapy medicinal products (ATMP) under Article 3.7 of Directive 2001/83/EC, and compassionate use on a named-patient basis, also referred to as "specials" scheme under Article 5.1. The relevance of these exemptions for PTMP has been investigated, but none proved to be practically applicable [5–7]. According to Article 83 of Regulation 726/2004, compassionate use makes available to a group of patients a medicinal product that is either the subject of an application for a marketing authorization or that is still undergoing clinical trials. PTMPs used in clinical routine do not fulfill these conditions. In particular, owing to the fact that these are tailor-made medicines, these are not intended for a specific group of patients. In fact, phage therapy is a personalized medicine because it delivers a highly specific medicinal product to treat a particular infectious event.

As for the ATMP-related provisions, even though PTMPs might resemble ATMPs in some respects [6,9], they definitely do not belong to this class of therapeutics. As such, they can benefit neither from hospital exemption nor from ATMP-specific exceptions as defined in Directive 2001/83/EC, that is, the possibility of a risk-based approach to determine the extent of quality, preclinical and clinical data required for granting a marketing authorization (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139748.pdf). Lastly, whereas the named-patient exemption could be putatively applied to PTMPs, in practice, it is mostly used to reformulate licensed medicines. Moreover, this scheme suffers from the same weaknesses as magistral preparations—indeed, both provisions are barely detailed in the Community Code and both were disparately transposed within Member States' national legislation. In addition, as it is the case for magistral formulas, products made available through the named-patient scheme may be of variable quality and their risk/benefit balance may be not adequately assessed. Provisions normally required for a proprietary medicinal product, such as GMP compliance, supply of product information including a Summary of Product Characteristics (SmPC), pharmacovigilance monitoring, and so on, are not prescribed in the Community code for this class of medicines and are thus rarely, if ever, met.

Finally, both magistral and named-patient preparations are administered under the direct personal responsibility of the prescriber unless in cases of pharmaceutical malpractice, which then would shift the liability to the pharmacist. But neither is covered by the in-label use as stated in the SmPC. This document, an integral part of the marketing authorization process, provides specific information on the safety and efficacy of a registered medicinal product. It also provides a legally binding framework for prescription: neither the healthcare professional nor the medicinal product manufacturer could be sued for the occurrence of an adverse reaction that had been reported in the approved SmPC. In contrast, if such an incident should occur in the absence of SmPC, the prescriber could be exposed to legal prosecution.

The biological master file

Hence, a novel regulatory framework would be needed in the EU pathway to address the licensing of customized PTMPs. This regulatory process could rely on the concept of a "biological master file", or BMF. The master file procedure already exists for chemical drugs. It can be broadly regarded as the submission for regulatory approval of a stand-alone package covering only part of a dossier, independent of the eventual approval of the full marketing authorization application for a medicinal product. However, the European regulation does not allow a general application of this concept to biological active substances (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129994.pdf). Instead, the current registration procedure of biologics relies on the approval of the medicinal product as a whole. In fact, the BMF concept would thus cover only a part of a biological medicinal product application, for instance related to an active ingredient only, and submitted as a stand-alone package.

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In the case of customized PTMPs, one BMF for each individual phage or homologous group of phages could be submitted to and licensed by regulatory authorities. The BMF would cover the industrial aspects of the manufacturing process of the active ingredient and, as such, would also be subject to a licensing procedure and requirements such as submission for approval of a quality module, GMP manufacturing compliance, batch release by a qualified person, and so on. In addition, the BMF could also address safety issues. It is not feasible to compile a complete nonclinical package as normally requested for any finished product, for every customized polyphage

combination. Instead, the safety profiling could be performed for individual phage suspensions and submitted for regulatory review within the framework of a BMF. The finished drug product would then be prepared as a magistral formula and would therefore not fall under medicinal product regulations or require approval by regulatory authorities.

However, such a patient-tailored approach does not fit within the current EU regulatory framework, which is essentially designed for dealing with uniform, large-scale, off-the-shelf medicinal products. In this "prêt-à-porter" framework [10], the responsibility for the safety of a medicinal product and its safe use is distributed between different stakeholders: the prescriber, the pharmacist, the marketing authorization holder, and the regulatory authority. In contrast, the "made-to-measure" approach of a magistral formula prescription puts the liability primarily on the prescriber and the pharmacist, who then face a heavy responsibility. This is not a fair distribution of liability, given that cutting-edge tailor-made medicinal products such as PTMPs are quite unfamiliar to health professionals and that parts of these products would be manufactured by a method involving an industrial process. Setting up a BMF that is subject to approval and is disconnected from the eventual approval of a medicinal product as a whole would introduce duties and responsibilities to the manufacturers of the active ingredient as well as to the regulatory authorities, in terms of both quality and safety aspects.

Implications for personalized medicine

The concept of BMF could also prove valuable in other contexts and other medicinal products. As with any medicinal product, the European regulatory process for biosimilars relies on the approval of a marketing authorization application, which includes a comprehensive quality package as well as the results from nonclinical and clinical studies. However, the extent of the clinical package depends on the comparison between the biosimilar and its reference as determined at the quality level. Thus, the required clinical development can only be designed after the quality comparability exercise has been achieved. Accordingly, instead of submitting the application in a single package, it would make more sense to uncouple the quality comparability exercise from the clinical assessment. The comparability exercise could thus be submitted to the authority within the framework of a BMF procedure. Depending on the outcome of the BMF early assessment, the clinical development could then be optimally designed in line with the licensed quality comparability exercise.

The greatest hurdle for adopting the BMF concept for phage therapy or other personalized therapies is that EU regulation does not support a general application of the master file concept to biological active substances (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129994.pdf). In particular, a master file for an active substance of a marketed drug can include a lot of restricted or confidential information that is not available to the marketing authorization holder. The European Commission argues that, in the case of biologics, the producer of the finished product or the marketing authorization holder needs unrestricted access to information about the early steps of the production process and its control because it is deemed essential for ensuring the quality of the biological active ingredient and the resulting finished product.

This objection could be overcome if the confidentiality constraint was dropped for BMFs to grant the marketing authorization holder unrestricted access to the BMF content. In this respect, it is worth mentioning that two related procedures—the Vaccine Antigen Master File (VAMF) and the Plasma Master File (PMF)—are based on a master file concept and give the marketing authorization holder full access to the master file information (http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2009/10/WC500006407.pdf). However, these apply only to vaccines and plasma-derived medicinal products. Regrettably, extension of this concept to a more general BMF is currently not on the agenda of the Commission, even if this could solve a number of current regulatory issues and ease the regulations imposed on tailor-made healthcare products. We would like to believe that the lawmakers will subscribe to this appeal and agree on appropriate regulations for licensing phage therapy medicinal products, which could not only save many lives from bacterial infections but also become an outstanding example of personalized medicine.

Acknowledgements

The author would like to thank Bernard Couvreur for critical reading of the manuscript and valuable editorial advice.

Conflict of interest

Although the author works for regulatory authorities, the views expressed in this article are his personal opinion. As such, they may not be understood, interpreted, or quoted as being made on behalf of, or reflecting the position of, any agency or institution.

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