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Access to bacteriophage therapy: discouraging experiences from the human cell and tissue legal framework

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One sentence summary: Therapeutic natural bacteriophages should not be classified under the medicinal product regulatory frames as they exist today.

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ABSTRACT

Cultures of human epithelial cells (keratinocytes) are used as an additional surgical tool to treat critically burnt patients. Initially, the production environment of keratinocyte grafts was regulated exclusively by national regulations. In 2004, the European Tissues and Cells Directive 2004/23/EC (transposed into Belgian Law) imposed requirements that resulted in increased production costs and no significant increase in quality and/or safety. In 2007, Europe published Regulation (EC) No. 1394/2007 on Advanced Therapy Medicinal Products. Overnight, cultured keratinocytes became (arguably) ‘Advanced’ Therapy Medicinal Products to be produced as human medicinal products. The practical impact of these amendments was (and still is) considerable. A similar development appears imminent in bacteriophage therapy. Bacteriophages are bacterial viruses that can be used for tackling the problem of bacterial resistance development to antibiotics. Therapeutic natural bacteriophages have been in clinical use for almost 100 years. Regulators today are framing the (re-)introduction of (natural) bacteriophage therapy into ‘modern western’ medicine as biological medicinal products, also subject to stringent regulatory medicinal products requirements. In this paper, we look back on a century of bacteriophage therapy to make the case that therapeutic natural bacteriophages should not be classified under the medicinal product regulatory frames as they exist today. It is our call to authorities to not repeat the mistake of the past.

Keywords: bacteriophage therapy; keratinocytes; regulatory; Advanced Therapy Medicinal Products; biological medicinal products; hospital exemption

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INTRODUCTION

Regulation (EC) No 1394/2007 of the European Parliament and of the Council on Advanced Therapy Medicinal Products (ATMP 2007; hereafter referred to as ‘ATMP’ Regulation) was adopted in 2007 and covers products that are based on gene therapy, somatic cell therapy or tissue engineering (ATMP Regulation (EC) No 1394/2007). The ATMP Regulation entered into force in Europe on 30 December 2008. A transitional period was foreseen for ATMPs that were already in the EU market. Products of gene therapy and somatic cell therapy were required to comply with the Regulation by 30 December 2011. Tissue-engineered products needed to comply one year later. The new ATMP Regulation gives EU member states the freedom to authorize the production and use of custom-made ATMPs in hospital settings at the member state level as an exemption to the general obligation to follow the central ATMP marketing authorization procedure. This exemption is called the ‘hospital exemption’.

A hospital exemption can be granted for ATMPs that are prepared on a non-routine basis and are prescribed for individual patients and are applied in a hospital setting and on patients that are treated under the professional responsibility of a medical practitioner. Under the hospital exemption, national requirements on quality, traceability and pharmacovigilance ‘equivalent’ to those required for authorized medicinal products are applicable. Before the publication of the ATMP Regulation, dozens of human cell and tissue products were produced and used in European hospitals. In Belgium, for instance, patients had access to 22 cloaked ATMPs of nine accredited and hospital-based (not-for-profit) human cell and tissue establishments (Pirnay et al. 2013). The safe use of these products was guaranteed by national guidelines as well as by Belgium’s transposition of the European Cell and Tissue Directive 2004/23/EC (ECTD 2004). Human-derived cell and tissue products were, at that time, not considered as medicinal products. Under the new ATMP regulatory framework, only 10 marketing authorization applications for ATMPs have been submitted to the European Medicines Agency (as of 30 June 2013) (Commission Report 2014). Out of these10 marketing authorization applications, only four have successfully completed the procedure and have been granted a marketing authorization by the Commission (ChondroCelect®, Glybera®, MACI® and Provenge®). What happened to the high-quality ‘hospital-produced’ products that were in use before the publication of the ATMP Regulation? Not-for-profit stakeholders were forced to stop using them due to the financial strain linked to their production and market placement. Other stakeholders continue to use these ATMPs despite a legal grey zone and an uncertain future.

In Europe, ATMPs have been extensively researched in a clinical context. Up to 250 distinct ATMPs were reported in the European Clinical Trial Database (EudraCT) during the period 2004–2010 (Commission Report 2014). The majority of research on ATMPs is conducted by Small and Medium Enterprises (SMEs) and entities that operate on a not-for-profit legal basis (70%). Big pharmaceutical companies account for less than 2% of all sponsorships (Commission Report 2014). Despite being financially well-equipped and accustomed to investing in pharmaceutical product development, big pharmaceutical companies do not appear to be interested in developing ATMPs.

The Burn Wound Centre of the Queen Astrid Military Hospital (Brussels, Belgium) has been a European pioneer in the defined production of human epithelial skin cultures (keratinocytes) for use on acute and chronic skin wounds for nearly 30 years. Since 1987, the center has successfully treated more than 1000 patients with keratinocyte-based grafts. As the Belgian definition of an ATMP hospital exemption has not yet been articulated, the center continues its work within the framework of the European Tissues and Cells Directive 2004/23/EC (ECTD 2004). Arguably, the hospital should stop producing keratinocytes for clinical use since it does not have a medicinal product production license, it does not have a pharmaceutical production environment and it does not have a pharmaceutical marketing authorization license for keratinocytes produced on its premises. Due to this situation, the center is forced to continue its work in a legally grey zone at the mercy of the National Competent Authority. Important is that the European Commission has now advised the European Parliament to create a more favorable environment for ATMP developers working in an academic or non-for-profit setting (Commission Report 2014). However, it is unlikely that this advice will result in immediate action.

Patients in the Burn Wound Centre of the Queen Astrid Military Hospital (Brussels, Belgium) are not only treated with cultured keratinocytes. They are, since 2007, also sporadically treated with natural bacteriophages, under the umbrella of Article 37 of the Helsinki Declaration (WMA Declaration of Helsinki 2013). Antimicrobial resistance in bacteria is, also in the Burn Wound Centre, an increasingly serious threat. New initiatives to tackle the problem of antibiotic resistance are urgently needed. One promising solution is the therapeutic use of natural bacteriophages—the viruses of bacteria—to treat bacterial infections. When discovered in the early 20th century, bacteriophages were immediately applied in medicine (bacteriophage therapy) with variable success. After World War II, Western industry and policymakers preferred antibiotics, which at the time had obvious advantages in terms of breadth of coverage and ease of production and patentability, and bacteriophage therapy was pushed into the background.

Today, bacteriophage therapy is again put forward as a potential way to address the current antibiotic crisis. Regulatory parallels can be seen between the regulation history for human keratinocyte-based grafts and that of natural therapeutic bacteriophages. Natural bacteriophages have been used for therapeutic purposes in humans for almost 100 years. Today, Europe classifies therapeutic bacteriophages as human medicinal products to be regulated through the classical human medicinal product frameworks (Parracho et al. 2012). We urge regulators ‘not’ to repeat the regulatory mistakes of the past. To maximally exploit the advantages bacteriophages have over conventional drugs, it is important that sustainable bacteriophage products are not submitted to the conventional long medicinal product development and licensing pathway. There is a need for an adapted framework, including realistic production and quality and safety requirements, that allows a timely supply of bacteriophage therapy products for ‘personalized therapy’ or for public health or medical emergencies (Pirnay et al. 2015). All stakeholders should be aware that they have a moral duty to proceed fast within their respective domains of responsibility in countering bacterial antibiotic resistance (Verbeke et al. 2014a,b). We are convinced that opting for a local, patient-specific approach will allow us to strike the right balance between the obligation to protect the patient from unnecessary risks on the one hand and the obligation to offer the best possible medical attention to the patient on the other. Flexibility (at all levels) is a basic requirement for success in this endeavor.
THE BELGIAN MINISTRY OF DEFENCE’S HISTORICAL ATMP EXPERIENCE

The Queen Astrid Military Hospital established a human keratinocyte production unit in the late 1980s. Its principal goal was to produce autologous keratinocyte sheets (see Fig. 1A) for immediate use on critically burnt patients (mostly civilians). The launch of this production unit (staffed primarily by biologists performing their obligatory military service at that time) was successful and the first patients were grafted in 1987. The technique for growing keratinocytes was referred to as the ‘Reinwald and Green’ technique (Atiyeh and Costagliola 2007). Over time, the technique has been optimized. Keratinocytes can now be grown in totally defined and animal-component-free culture media, without the additional use of animal fibroblasts feeder layers (see Fig. 1B). This defined production protocol was published open access (without patent protection) in 2012 (De Corte et al. 2012). Figure 2 illustrates the timeline related to this project (see Fig. 2). Alongside culturing autologous cells, donor keratinocytes for allogeneic use are also grown. The cultured keratinocytes can be cryopreserved for later use (see Fig. 3A). Keratinocytes can be applied under the form of a sheet or under the form of a spray (see Fig. 3B). It is also possible to generate cultures using adult skin or from neo-natal foreskin donations. The keratinocyte bank of the Queen Astrid Military Hospital became ISO 9001 certified in 2008. The hospital works in compliance with the European Tissues and Cells Directive 2004/23/EC (ECTD 2004) and the keratinocyte bank is compliant with specific Belgian regulation and guidelines as defined by the Belgian Health Authorities and advised by the Belgian Superior Health Council. In addition, the hospital’s keratinocyte bank is licensed by the Belgian Federal Public Service for Health, Food Chain Safety and Environment. Initially, the keratinocyte bank was inspected (in view of the prolongation of the licenses) by the Belgian hospital inspection authorities. Inspection duties later transferred to the pharmaceutical inspection authorities, the Belgian Federal Agency for Medicinal and Health Products (FAMHP). The use of keratinocytes for treating burn wounds or chronic skin wounds was (and still is) reimbursed by the Belgian social security system (after having documented the efficacy) at a (not-for-profit) production cost.

In 2012, at the end of the transitional period of the ATMP Regulation, the hospital received a letter from the Belgian National Competent Authority (FAMHP) that these cultured keratinocytes had been reclassified, effective immediately, as medicinal products for human use and thus to be produced and placed on the market as if they were human medicinal products. Keratinocytes are cultured currently in a ‘controlled...
environment’ (GMP air quality Class A in a minimum Class D background). Halting production at the center meant ceasing all keratinocyte-based treatments, since no equivalent products for keratinocytes are currently available on the market. Faced with this situation, the Belgian Ministry of Defence had no other choice but to invest €5.3 million in a cleanroom facility for GMP (keratinocyte) production. The authors are convinced that this investment only increases production costs and, again, will not increase the quality and safety of the final products.

GLEANING LESSONS ON THE (RE-)INTRODUCTION OF NATURAL BACTERIOPHAGE THERAPY IN EUROPE

Parallels can be seen between the regulatory history of keratinocytes and current developments in the re-introduction of (natural) bacteriophage therapy. Europe recently classified natural bacteriophages, used as therapeutics, as human medicinal products (Parracho et al. 2012). This classification will impact access for patients in a way similar to how the ATMP Regulation impacted patient access to cultured keratinocytes. Therapeutic use of natural bacteriophages (on humans) goes back for almost 100 years (Kutter et al. 2010; Reardon 2014). Since 2007, the Burn Wound Centre of the Queen Astrid Military Hospital sporadically applies bacteriophage therapy in patients infected with antibiotic-resistant bacteria. The first therapeutic use of bacteriophages in the center was conducted in a small clinical trial (Rose et al. 2014) in which bacteriophages were sprayed on the patients’ wound bed (see Fig. 4A). A total of 10 bacteriophage applications were performed on nine patients. This trial was approved by the Leading Medical Ethical Committee of the University Hospital of the Free University of Brussels (UZ Brussel). After the trial, patients in the Burn Wound Centre continued to receive sporadic spray-based and drain-based treatments with natural therapeutic bacteriophages (see Fig. 4B). These treatments were performed under Article 37 of the 2013 Helsinki Declaration (WMA Declaration of Helsinki 2013). All patients (or their legal representative) signed an informed consent document. Protocols for the production of natural therapeutic bacteriophages...
have been increasingly optimized much as keratinocyte production protocols have been optimized over the years. The results of these efforts were published open access (without patent protection) in 2009 (Merabishvili et al. 2009).

In-house bacteriophage production activities at the hospital are actually not performed in a pharmaceutical GMP environment and the produced natural bacteriophage cocktails are not compliant with the Belgian Medicinal Product Legislation (BMPL 2014). Bacteriophage cocktail BFC1 (see Fig. 4C) contains two different bacteriophages against Pseudomonas aeruginosa (see Fig. 4D) and 1 phage against Staphylococcus aureus.

Within the European medicinal product frame, natural bacteriophages are classified as ‘Biological Medicinal Products’ (BMPs). This classification is disadvantageous for the option of phage therapy because the BMPs’ legal framework does not provide for a hospital exemption procedure, as it does for ATMPs. Big pharmaceutical companies are no longer interested in investing in the development of small-spectrum antibacterial products (Blaser 2014). The Queen Astrid Military Hospital does not experience the Medicinal Product Legislation as an adequate tool for bringing natural therapeutic bacteriophages to patients in a sustainable and tailored way (Verbeken et al. 2014b; Pirnay et al. 2011; Huys et al. 2013). Hospitals working under a yet-to-be-defined BMP ‘hospital exemption’ should have access to a specific European Bacteriophage Therapy Legislative Frame that guarantees quality and safety for also these therapeutic bacteriophage products.

Fecal microbiota transplantation

Another innovative and unorthodox but effective microbiotic therapy in the fight against resistant infections is fecal microbiota transplantation (FMT), which has to cope with similar regulatory hurdles. In May 2013, the US Food and Drug Administration (FDA) announced that it would begin regulating human feces for transplantation as a ‘drug’ (de Vrieze 2013; Smith, Kelly and Alm 2014). Where the FDA uses the term ‘drug’, Europe uses the equivalent term ‘medicinal product’. The FDA reasoned that this would make FMT safer by providing oversight, standardizing therapy and, eventually, encouraging development of commercial drug products. FMT has been effective in cases of treatment-resistant Clostridium difficile infection (van Nood et al. 2013), a killer of 14 000 patients in the USA each year. In general, antimicrobial resistance is estimated to cause at least 23 000 deaths per year in the USA and 25 000 deaths per year in Europe, as indicated by the AMR Control Report 2015 (AMR Control Report ECDC/EMA 2009; CDCP 2013; 2015).

At a public meeting that month organized by the FDA and the US National Institutes of Health (NIH), patients and representatives of the Centres for Disease Control and Prevention (CDC) and several professional medical societies voiced concern about restricting access to care. Six weeks later, the FDA revised its position. The agency decided, for the time being, not to enforce Investigational New Drug (IND) requirements for the treatment of recurrent C. difficile infections. This compassionate exception is now enabling many patients to receive much-needed care. Whether and when the therapeutic potential of FMT is realized will depend on how FDA and other agencies regulate the future therapeutic use of stool. Treating stool as a drug imposes strict patient-protection requirements but it significantly limits access to care. Reclassifying stool as a tissue product or giving it its own classification, as the FDA does for blood, would keep patients safe, ensure broad access and facilitate research. We urge European regulators to do the same for natural bacteriophages.

Discussion and conclusion

Today’s European Medicinal Product Legislation needs to be reworked to ensure the sustainable larger scale (re-) introduction of natural bacteriophage therapy in Europe. Defining a hospital exemption under the actual Biological Medicinal Product Legislation is crucial to this effort. This new hospital exemption needs to target the ‘in-hospital’ use of natural bacteriophages, tailored to the patient’s needs and taking into account the evolutionary aspects of what natural bacteriophage therapy really stands for. Hospitals that have obtained the hospital exemption status should have access to tailored and bacteriophage-specific quality and safety guidelines. Efficacy and safety of the treatments needs to be documented (Kazmierczak, Górski and Dąbrowska 2014) but not necessarily in the format of a clinical trial which exists for the testing and development of new medicinal products. Specific quality and safety requirements should be elaborated to guarantee patients’ safe access to efficient bacteriophage therapy products and to facilitate research. An important contribution into this direction has been made by the bacteriophage consortium P.H.A.G.E., by publishing a consensus report on Quality and safety requirements for sustainable phage therapy products (Pirnay et al. 2015).

We sincerely hope the arguments put forth in this paper can contribute to effective regulation of bacteriophage therapy within existing regulatory frameworks. Should that fail, a final strategy could be to contend that the tailored use of natural bacteriophages produced in-hospital for use on its own hospitalized patients does not constitute a market placement of that product. Such an interpretation places production of bacteriophages outside of the scope of European Medicinal Product Directive 2001/83/EC (EMPD 2001; Title II; Scope; Article 2; 1) and would render European Medicinal Products Legislation irrelevant to the use of natural bacteriophages inside the hospital on its own patients. A specialized law firm studied this issue in detail and supported this position (Bredin Prat Lawyers Office 2012). Meanwhile, it is possible to revise the actual medicinal product regulatory status of natural therapeutic bacteriophages, allowing compassionate use analogous to the US FMT issue (Smith, Kelly and Alm 2014).

In view of the fact that bacteriophage therapy requires an approach tailored to the patient’s needs, new policy visions from personalized medicine could inspire the debate about bacteriophage therapy introduction.

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References


WMA Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects.