Bacteriophage therapy: an analysis of the European regulatory framework and its proposals for amendment

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II. List of Abbreviations

ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File
ATMP	Advanced therapy medicinal product
AMR	Antimicrobial resistance
BMF	Biological Master File
BP	Bacteriophage medicinal product
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
EU	European Union
E. coli	Escherichia coli
FAMHP	Federal Agency for Medicines and Health Products
FDA	Food and Drug Administration
GMO	Genetically Modified Organism
GCP	Good Clinical Practices
GMP	Good Manufacturing Practice
GPP	Good Preparation Practices
GRAS	Generally Recognized As Safe
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IIET	Ludwik Hirszfeld Institute of Immunology and Experimental Therapy
MA	Marketing authorisation

MDR	Multidrug resistant
MHRA	Medicines and Healthcare Products Regulatory Agency
SME	Small and medium-sized enterprise
P. aeruginosa	Pseudomonas aeruginosa
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PTU	Phage Therapy Unit
UK	United Kingdom
US/USA	United States of America
WHO	World Health Organization

1. Introduction

Antimicrobial resistance (AMR) has arisen as one of the most serious threat to global health[1–4]. Specially alarming is the emergence of antibacterial resistance, or resistance to antibiotics. In the EU alone is estimated that 25,000 patients die yearly due to infections by multi-drug resistant (MDR) bacteria[5]. It is expected that the gravity of the problem increases and it is even being claimed that we are entering in a post-antibiotic era where the efficacy of antibiotics will no longer assure the level of control of bacterial diseases that we enjoy today[6,7].Outbreaks of MDR bacteria, as the one from E. coli O104:H4 occurring in Germany in 2011, could become a common event in future, resulting in serious challenges for public health.

The broad use of antibiotics for decades, not only for human but for animal use as well, is the main reason behind the development of resistance by bacteria, that naturally evolve to resist antibiotics[3,8]. This natural process, accelerated by the misuse of antibiotics, is not being counteracted by the current development of new antibiotics[5]. Faced with this reality, the action to prevent a developing global crisis in health care is urgently required, thereby needing the implication and demanding action from health authorities across the world.

Health authorities from all over the globe, led by WHO, are setting strategies to reduce AMR threat[8]. In the EU, measures are based in several approaches, like the promotion of a responsible use of antibiotics, the collection of data, and the fostering of the identification of new medicines[1]. Alternatives therapies or products to “classic” antibiotics are being explored[9].

One of the most promising alternatives in current discussion to overcome the AMR threat is the bacteriophage therapy, or phage therapy, that is, the use of virus that infect bacteria for therapeutic purposes[9,10]. Phage therapy is not a novel treatment, bacteriophages were discovered a century ago, and they have been used for therapeutic purposes in human medicine almost ever since. Especially in countries of the former Soviet Union and Eastern Europe it has a long history of therapeutic use. However, it was never really implemented in western medicine. The main reason therefore was the emergence of chemical antibiotics of broad spectrum, that eventually led to a lack of development and low interest in phage therapy for decades[11–13]. Consequently, there is currently a lack of clinical evidence under current standards that would be required for further acceptance of this therapy[14,15].

The understanding of the interactions between phages and bacteria, as well as phages and the human body, is continuously increasing and cannot be compared with the knowledge back at the time of the first therapeutic use of phages against bacterial infections. Hence, the possibilities to develop bacteriophage medicinal products (BPs) which are effective, safe, and attached to specific quality standards are rising[12]. However, the renewed interest in phage ther-

apy and its possible potential is, among other constraints, confronted with the current regulatory framework, that was not developed considering the unique characteristics of phage therapy[7,12,15].

In contrast to “classic” antibiotics, bacteriophages are highly specific, and have a reduced spectrum, often even restricted to certain bacterial strains. They are also able to replicate themselves in the area of infection, what is crucial for the understanding of their efficacy[12,15]. Bacteriophages are organisms, and as such, they are subject to natural selection as their bacterial hosts are[16]. Even if resistance of pathogenic bacteria against bacteriophages would eventually appear, similarly as against chemical antibiotics, it is expected that new effective bacteriophages would be found relatively quickly[13,17]. In fact, phages are ubiquitous and the most common type of organism in the world, they can be found wherever bacteria are located[9,13], supporting the potential of this therapy.

However, especially the advantageous properties of phage therapy, high specify and flexibility, have limited development potential under the current regulatory framework, as it mainly considers broad spectrum and relatively fixed molecules. Two main therapy possibilities have been proposed and described for development: a personalised, custom-made or *sur-mesure* approach, where the virus or combination of viruses to use are specifically selected for treating a specific patient; and a ready-to-use or *prêt-à-porter* approach, where a virus or combination of them are selected and produced in large-scale for treatment of specific and broadly expanded infective diseases[18].

Up to date, there is no BP commercialised in the EU, and it seems unlikely that any product will reach the market soon. The use of phage therapy is currently limited to named-patient options when the standard treatments failed, and only few SMEs, academic institutions and hospitals are currently investing resources in research and development of this therapy. Authorities, academics, and industry agree on the fact that more clinical evidence is needed for demonstrating that phage therapy is an effective and realistic alternative to antibiotics, what will necessarily need big efforts from all stakeholders as well as higher investments[15]. An inappropriate regulatory framework could expand the time for development of BPs, reduce their life cycle, and discourage investors from risking their resources in development of phage therapy, posing an additional and even unaffordable burden that could prevent phage therapy from being developed and clinically implemented.

2. Aim and objectives

The AMR threat has urged in the search of alternative treatments to antibiotics. Phage therapy is a potential alternative with several regulatory limitations due to its unique characteristics. This master thesis aims to examine the current regulatory status and implementation of phage therapy in the EU, as well as the proposed amendments to the regulatory framework, in order to identify the main regulatory constraints and to envisage a specific regulatory framework for this therapy. Two main therapy options for treatment or prevention of infections in human medicine will be considered: the personalised or *sur-mesure* and the *prêt-à-porter* or ready-to-use.

After describing the main regulatory challenges based on the unique characteristics of phage therapy and the current applicable regulatory provisions, this master thesis will depict the current situation of phage therapy at the EU, analyse and assess the main proposals made for amendment of the regulatory framework for phage therapy, as well as outline and recommend an adapted European framework for phage therapy considering the ready-to use and the customised approaches.

Products derived from bacteriophages, as lysins, or genetically modified phages, are excluded from the scope of this work. Only natural bacteriophages are considered, meaning those obtained in its wild form from different possible sources, used as active substances. The reason of considering only wild type phages is simplification, since an analysis of additional regulations which would apply for GMOs would extend the master thesis.

The efficacy and safety of this therapy will not be discussed in detail, since it is not the purpose of this master thesis to assess the risk/benefit ratio of this therapy.

3. Characteristics of phage therapy

Bacteriophages are viruses, and therefore, very complexes non-living biological entities, consisting mainly of a protein structure surrounding a molecule of nucleic acid. Typically, these viruses bind the specific receptors from the target bacterium and inject their nucleic acid molecule into the bacterial cytoplasm. Then, either their genetic material remains integrated into the host´s genetic material, as a prophage, for an undetermined period of time, replicating horizontally as the bacteria replicate, or it starts replicating soon after entry, using host machinery forming a new generation that eventually will breach the bacterium´s wall and will be released to start a new virulent cycle in other host cells. The first type is known as “temperate” phage, and the second as “lytic” phage. The latter is the one with therapeutic interest, since they cause an immediate effect on bacteria populations and reduce the risk of inducing mutations in bacteria that could help them to develop resistance[11,15].

One of the main characteristics of phages that differentiates them from chemical antibiotics is their specificity. A particular bacteriophage has a reduced host range depending on the complementary receptor that it binds, and can be specific not only to bacterial species level but even to particular strains[9,11]. Another significant difference is that phages can multiply at the site of infection and have a potential for exponential growth as long as the bacterial host exists[9]. They can be isolated relatively easily from the environment and coevolve via mutations as their bacterial hosts do[9,13]. These characteristics give phage therapy unique features to be considered during the development of BPs for clinical use. For example, although the therapeutic use of products containing one phage is not excluded, BPs will generally be developed as cocktails or combination of phages due to their high specificity and to overcome a possible development of resistance against the given BP[11,19].

Another difference with chemical antibiotics has to do with intellectual property. As natural entities, wild type phages cannot be patented. However, methods of manufacturing or specific combinations might offer some possibilities on this respect, even if it might be not provide the level of intellectual property desired by many investors[20–23].

3.1. Classification and definitions

According to Article 1 of the Directive 2001/83/EC, a medicinal product is *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*[24].

A bacteriophage strain in a BP would be considered as an active substance, since every virus strain is *intended to exert a pharmacological, immunological or metabolic action*[24] by lysing the bacteria causing the infection.

As mentioned earlier, phages have a very specific scope, that is, every phage strain is selected based on its capacity to lyse one or several bacterial strains. This led to a negative opinion by a notified body to accept a burn wound ointment (a medical device) combined with bacteriophage as combined medical device-medicinal product falling under the medical device regulatory framework, where the action of the included active substance must be ancillary to the medical device product[25,26], as it is the case of wound ointments containing antimicrobials. The notified body claimed that the phages from that combination product had "targeted action", and therefore its function could not be considered as ancillary[27].

Bacteriophages, as complex biological entities, are undoubtedly biological medicinal products as defined in the Directive 2001/83/EC, since they are a biological substance, or *a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control*[24].

As biological medicinal product, they do not have a specific class as plasma-derived medicinal products or vaccines, which have own documentation particulars and guidances[24,27].

They do not fall under the definitions of ATMP as defined in Article 2 of Regulation (EC) No 1394/2007[28], since they are not a gene therapy medicinal product, a somatic cell therapy medicinal product, or a tissue engineered product.

BPs do not fall under mandatory scope for centralised procedure according to Article 3(1) Regulation 726/2004[29], since they are intended against bacterial infections, unless there is any BP that could be designated as orphan medicinal product. They are however eligible for optional scope from Article 3(2), since there is no authorisation for any BP in any country of the EU and it easily justifiable that any BP is potentially *a significant therapeutic, scientific or technical innovation* or is *in the interests of patients at Community level*.

The well-established use as defined in Article 10a from Directive 2001/83/EC is not applicable to phage therapy regardless it has been used for a long time in the EU. This article states that applicant shall not be required to provide results of pre-clinical tests or clinical trials if he can demonstrate through literature the well-established medicinal use with recognised efficacy and acceptable level of safety. Not only the efficacy and safety should be demonstrated according to standards set out in Annex I of this Directive, which is currently not the case for phage therapy, but these data should refer to a specific active substance or specific combination of

substances, meaning a specific phage strain or combination of phages. Thus, the well-established use as defined in Article 10a is not valid for developing phage therapy.

3.2. The quality aspect

Currently there is no monograph in European or national pharmacopoeias for phages or their preparations[30,31]. No specific guidance is currently available either. That brings the question how could be assessed an acceptable quality for BPs.

Although there is no specific guidance for BPs, as biological medicinal product, in general, all standards applicable to these products would apply to them. One significantly relevant due to the manufacturing procedure is the ICH Q5D on *Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products*[30,32]. The manufacturing of a BP basically would require the replication of the selected phage strain/s from a cell substrate, that is, both a cell bank and a virus seed bank would be kept. The guidance from the FDA for *Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications*[33] provides also a good basis for analysis of substrates cells in phage therapy, as well as some indications to virus seeds[30].

The manufacturing process would be handled with a two tiered process, for both bacteriophages and host cells, with Master Viral Seed Banks and Working Viral Seed Banks, and Master Cell Banks and Working Cell Banks respectively[30,31,34].

The quality standards sets in specifications should be in line with the normally accepted for biological medicinal products and described in the ICH Guideline Q6B[35,36].

Host bacteria should be not only identified, but ideally screened in search of prophages or other phage-like elements[37].

Phages characterization should include sequencing and genome analysis, together with a phenotypic analysis. Transduction risk, or risk of transferring genetic material from one bacterium to another, must be also minimised[12,15]. Their efficacy *in vitro* should confirm the host range, the stability of the lysis, as well as other features for a proper phenotypic characterization. For the working lots, which constitute the active substance, should be analysed the absence of bacterial DNA and protein contamination as well as other residues as endotoxins or haemolysins.

Finished products would consist of the purified phage preparation and a carrier depending on the administration route. For example, typically for topical applications it could be a hydrogel or an ointment.

Shelf life for starting material (master seed bank), active substance (working seed bank) and finished product should be analysed following the mentioned guidelines and ICH Q5C[38].

The BP will likely be a combination of several phages, that is, a combination of different active substances. This combination in cocktails have also an implication regarding quality. According to Article 8 (3c), in order to obtain a marketing authorisation (MA) for a medicinal product, qualitative and quantitative particulars of all the constituents of the medicinal product must be submitted. The pertinent standard ICH Q6B[36] specifies that the quantity of a drug substance in the drug product should be determined either by protein content or by potency. That means the proportion of every strain must be defined quantitatively. For a given combination of phages in a BPs, it would be very challenging to determine the potency of a given individual phage, especially if several phages in the cocktail share the same bacterial host.

In case of personalised-approach, the time for manufacturing and quality control till final release would be critical due to the nature of the infection. The Quality by Design approach is a concept that would assist in developing an appropriate system to allow real time release for BPs[30,37].

3.3. The safety aspect

In order to get a MA, the applicant must submit the results of pharmaceutical and pre-clinical tests, as well as clinical trials, as specified in Article 8(3)(i) of de Directive 2001/83/EC[24].

According to Article 10b of the same Directive, in case there were already authorised BPs, either consisting of single phages or fixed combination of phages, a new combination of phages contained in the approved BPs would not exempt from the requirements set in Article 8(3)(i), that is, these results should be provided for the resulting combination, it would only exempt for submission of results for each individual phage[24]. That means that existing individual data developed from one phage or fixed combination of phages would not be sufficient for demonstrating the safety of a new combination of them.

There is no sufficient safety data from clinical trials as required for a MA, but many researchers consider that phages are generally safe according to current uses[11,23,39,40], and that no significant serious adverse events have been described[18,39]. Several bacteriophages preparations are registered in the USA as food additives, having consideration of GRAS for use in meat products for human consumption[41]. The continuous exposure to phages in the environment is a common argument supporting the safety of phages.

Since we are continuously exposed to bacteriophages and only bacteria are targeted by these viruses, safety concerns rely mainly in the occurrence of allergic reactions triggered by high phage concentrations and in the release of toxins after bacterial lysis, the latter shared with chemical antibiotics[13]. There is also safety concern related to phage-associated transfer of genes among bacteria, which could promote the transfer of resistance or toxin related genes[23].

Future studies should confirm the apparent safe profile of phage therapy and address all still open questions related to the safety, both in non-clinical and clinical developments. These questions are mainly concerning the immune response and all factors that have an influence on it, both inherent to the patient, with focus on immunosuppressed patients, as well as to the phage used. It has been observed that identical phages can elicit different levels of antibody responses in patients[19]. Another issue to address is how to deal with multiple infections[13], as the high specificity of phages is a handicap in case of multipathogenic infections. In theory, since phages are more specific than chemical antibiotics, it is also expected that side effects related to disruption of intestinal flora will be lower as in chemical antibiotics[42], although the effect on intestinal absorption is still a matter needing further research. The chosen administration route will also determine the safety profile. As more modern controlled trials phase I/II are performed, more will be known about the safety of phage therapy.

3.4. The efficacy aspect

It is difficult to predict the efficacy of a BP *in vivo* based on data *in vitro*. Pharmacokinetics of phages are complex and interactions bacterium-phage-human body are not yet well understood[15]. Firstly, it is likely that phage therapy applied *in vivo* leads to interactions with the immune system, that could remove rapidly the phages from circulation[11,43] or mask them with inmunoglobulines[44].

The mechanism of action of phages implies that they reply within the targeted bacteria, therefore increasing their concentration in the infected area. That is a unique factor that major implication in dose selection and optimal moment of treatment, firstly, because the complex ecology of bacterium-phage interaction and possible interactions with the immune system do not imply that the highest phage concentration will have the highest killing rate among bacteria, but also because the phase of the infection might have an influence on treatment success[15]. Besides, the response of the immune system, as mentioned, is not yet well understood and may differ among patients[19].

Due to its mechanism of action, and according to population dynamics of bacteria and phages, it is expected that a BP cannot exterminate a whole population of pathogens, but just to decrease their numbers to a level where the immune system is able to eliminate the infection, as shown in animal models[45].

Bacteriophages show a great potential to disrupt and penetrate biofilms[9,11,13]. This might pose an advantage over chemical antibiotics, that generally need high concentrations to inhibit bacterial growth in film colonies[11]. These preliminary results must be still confirmed in clinical applications.

Phage therapy is not only being considered as a unique treatment solution. There are some results suggesting a higher efficacy of phages combined with antibiotics than any of these treatments alone[12,46,47], as well as some results suggesting that previously resistant bacteria became sensitive to antibiotics after application of phages[48,49]. This synergy between phages and antibiotics could open new therapeutical possibilities.

Summarizing, there are many open questions to be addressed to understand the efficacy of phages. Regardless all the literature showing success in the implementation of phage therapy in singular cases or in animal studies, there is clear gap for modern standard controlled studies[15,23]. As new data become available, the efficacy of phage therapy will be better understood.

4. Phage therapy modalities: ready-to-use and personalised

The two therapy options proposed: ready-to-use and personalised, are based in the applicability or development strategy for BPs rather than in the inherent characteristics of phage therapy.

4.1. The ready-to-use approach

The ready-to-use or *prêt-à-porter* approach targets the development of broad use, large-scale uniform BPs, designed for routinary use against specific conditions affecting a significant number of patients[18]. These products can be currently found in the Russian and Georgian markets, sold as oral, topical, rectal, intranasal or conjunctival preparations for prevention and treatment of several infections and even found in pharmacies[18,50]. They often consist of a significant amount of phage strains, with broad indications targeting many bacterial species, but with non-proven efficacy according to current European standards[18,50].

The ready-to-use approach is the one being in focus currently by SMEs researching on phage therapy. These companies are trying to identify unmet clinical needs and to develop BPs to target them, and some of these SMEs have some BPs at early stages of development[19]. Also institutions and academics support the development of this approach with the hope that phage therapy will be extensively used and accepted, making authorities, physicians and the general public used to phage therapy[18,19].

The ready-to-use BPs would need of regular updates to counteract the appearance of resistance against them, but it is also the therapy option that would need fewer adjustments to the current regulatory framework[18]. To the view of European regulators, the current regulatory framework already offers a suitable starting point for this kind of products[14,51]. Since it would not exploit the flexibility that phage therapy may offer, based on the high specificity of phages and the relatively easy discovery of new effective strains, it is considered by many academics as a limited approach that would not exploit all the advantages and flexibility that phage therapy may offer[12,18,52,53].

4.2. The personalised approach

The personalised, custom-made, tailor-made or *sur-mesure* approach targets the use of specific BPs, developed and prepared ad-hoc for an individual patient. It normally requires days to weeks for isolation, identification, testing and application, using either known strains from phage banks or newly isolated phages[18]. These BPs are currently used in the EU in a named-patient basis, mainly in Poland and Belgium[30,31,39].

The personalised approach has been pointed out as the approach having more potential, exploiting all advantages that phage therapy may offer over current antibiotics[12,18,52,53]. Upon isolation of the pathogen causing the infection, it could be confronted to different phages contained in a phage library, and this approach could even be useful in case of bacterial strains for which no effective phage was isolated and characterised at the moment of treatment, or even in case that bacteria evolve and overcome phage therapy during treatment making necessary the fast isolation and application of new phages before the health of the patient is compromised[18].

The personalised modality would have more limitations under the European regulatory framework than the ready-to-use approach[18]. In general, not only for phage therapy, a personalised approach lacks on proper regulatory framework in the EU, as also claimed by many stakeholders from other fields of research and innovative medicinal products[54,55]. The personalised medicine, generally understood only in the context of genomics, is a growing field with regulatory demands by many developers. Specifically about autologous ATMPs, a case comparable to phage therapy, the European Commission states that *it is important that the requirements that apply to autologous products are proportionate and adapted to the specific characteristics thereof,* indicating that setting the requirements as high as for standardised chemical-based medicinal products, concretely batch release certification and manufacturing license, would prevent the development of these treatments[56].

This phage therapy approach is currently being implemented by hospital and academic institutions, made under a non-profit basis and reaching a very limited number of patients[31,39,57]. These institutions seek a further implementation of phage therapy and a regulatory framework that allows the use of this approach, but since their resources are limited, they would prefer a flexible regulatory framework with requirements they could already fulfil[57,58]. Some authors believe regulators should not do same mistakes as performed by ATMPs in the pasts, as requirement of GMP, because it could discourage the development of phage therapy[58]. This approach is the one facing the most regulatory challenges, especially considering a broad and harmonised use of phage therapy within the EU[14,18].

5. Phage therapy in the EU

The experience with phage therapy in EU countries is rather scarce and limited mostly to Eastern Europe, being Poland the EU country with longer experience in this field. The recent AMR threat has increased the interest of this therapy to other countries, with the remarkable case of Belgium, where institutions and authorities are working to create a more suitable regulatory environment for phage therapy. Today, only some SMEs and institutions in different EU countries are making research in phage applications, which are not limited to clinical uses but that will definitively foster phage therapy using modern clinical standards. The growing interest in phage therapy has also attracted the attention of European authorities, with the EMA workshop on phage therapy as the most prominent example. The increased interest in this therapy and the joined efforts of different stakeholders have led so far to the first modern and broad clinical study for phage therapy, the PhagoBurn project, that will set a basis for future clinical developments.

5.1. Phage therapy in Poland

In Poland, the bacteriophage therapy is being used under national provisions having room under the exception drawn by Article 5 (1) of the Directive 2001/83/EC[24], the named-patient exception (see 6.2), the one leaving out of scope of the Directive the unproven interventions in clinical practices considered in the Declaration of Helsinki[59].

Poland has a long tradition of use of bacteriophage therapy, encompassing several decades. In 1952, the Institute of Immunology and Experimental Therapy (IIET) was founded by Ludwik Hirszfeld and has being playing a crucial role in the development of phage therapy in Poland ever since. In 2005, after the entry of Poland in the EU, the IIET opened the Phage Therapy Unit (PTU) in Wrocław, in order to ensure the continuation of this therapy. PTU functions as a non-profit unit of IIET[39]. The therapeutic protocol is updated and modified periodically with the approval of the bioethical committee. In 2008 some changes were made to the protocol and some other administration routes are being implemented, in particular, the intrarectal and as inhalations of aerosol[39].

The current collection of phages from IIET includes over 500 strains, specific against several species or strains of bacteria, including MDR bacteria[39]. Dozens of patients are treated at PTU yearly in Poland, admitted for treatment in the following cases: the infection was caused by a MDR bacteria; infection persisted despite treatment with targeted antibiotics; in case the qualified specialist considered the applied antibiotic treatment was ineffective; or the treatment with a targeted antibiotic was not possible, for example in case of contraindication[39].

Phage therapy is considered an experimental treatment, which in Poland means diagnostic, therapeutic or prophylactic methods under the Act on the Medical Profession which may be used by a physician for the direct benefit of a patient. This experimental treatment must be new or only partially tested. It may be used only previous written informed consent by the patient and the approval of a bioethics commission, after available treatment has failed or is not possible[39,60]. Several bioethical commissions have approved the use of phage preparations on individual patients, even the regional commission from Lower Silesia request to hospitals willing to use the phage preparations from IIET only to notify the initiation of such treatment[39].

The procedure for preparation of phage formulations against *Straphylococcus* and *Pseudomonas* are under patent protection since 2002 with the US patent number 7232564 B2. Some of the BPs are prepared under GMP principles by IBSS BIOMED S.A.in Kraków[39].

5.2. Phage therapy in Belgium

Since 2007, the Queen Astrid Military Hospital has applied sporadically bacteriophage therapy in patients with antibiotic resistant bacteria, always upon written informed consent[30]. This approach, similarly as the Polish case, have room under the Article 5 of Directive 2001/83/EC[24] (see 6.2).

With the aim of assuring certain quality standards for the phage preparations and to foster the development of this therapy, while avoiding certain high requirements, a further approach is in development, based on the uncertainty of considering BP as a pharmaceutical speciality or magistral preparation[61], and therefore an exception of in accordance to Article 3 exemption for magistral formula (see 6.1). This newly developed approach, the magistral “premium” approach, avoids the requirements of manufacturing under GMP standards, although laboratories preparing the BPs will have some kind of national accreditation[31].

According to the Belgian legislation, the ingredients of a magistral formula must meet the requirements from the European Pharmacopoeia, if not available, those from the Belgian Pharmacopoeia or from another official pharmacopoeia[30]. Since there is no monograph for bacteriophage preparations, an authorisation from the Minister of Public Health previous favourable opinion from the Belgian Pharmacopoeia Commission deems necessary, although it is also possible to use a non-authorised active substance regarded is accompanied with a Certificate of Analysis from a Belgian Approved Laboratory[30].

Due to the big amount of possible individual phage strains which could be involved, and since each of them is considered as an active substance, the magistral formula approach will use the non-approved substance pathway, being the Scientific Institute of Public Health the entity identified as suitable for issuing the certificates of analysis[31]. Due to lack of compendial references, the Certificate of Analysis will be based on a API monograph elaborated by experts

from the Queen Astrid Military Hospital, the Federal Agency for Medicines and Health Products (FAMHP), and the Belgian Scientific Institute of Public Health, which should be used as basis.[31]

Another novelty over the regular magistral formula concept is the involvement of the national competent authority, FAMHP, within the context of the national Scientific-Technical Advice procedure[31].

The procedure would be as follows:

-A physician requests a magistral preparation for a specific patient.

-The supplier, either private company or public institution, prepares the phage APIs for the magistral preparation following the monograph requirements.

-The Belgian approved laboratory performs quality assessment and issues a Certificate of Analysis per API.

-The pharmacist ascertains, based on the Certificate of Analysis, that the ingredients comply with the provisions of the monograph, and prepares the magistral formulation.

This approach, beside setting some standards to improve the existing use of phage therapy in Belgium, is targeting a broader implementation of phage therapy and intends to serve as model for further implementation in other Member States[31,61].

5.3. EMA Workshop

On 8th June 2015 a workshop took place at the EMA with the title "*Workshop on the therapeutic use of bacteriophages*", with participants from the industry, the academia, patient organisations and regulators. The goal of the workshop was to discuss possible issues related to the development of phage therapy for the treatment of bacterial infections[51].

Besides the practical experience presented by scientists from the PTU in Poland and the Queen Astrid Military Hospital in Belgium, also some developments by SMEs were introduced[51].

Physicians advocated for possibilities to develop BPs on an individual patient basis[7], but also companies introduced their interest to develop BPs as fixed combinations to be produced under GMP with the goal of achieving a MA.

Most of the proposals presented in this master thesis were discussed in the workshop: the library approach, the consideration of some exceptions as for influenza vaccine, a hospital exemption similar to ATMPs, the autogenous vaccines and the multi-strain dossier from the veterinary regulatory framework, the homologous-group approach from allergen products, and the Biological Master File.

The conclusion for EMA is that the current regulatory framework is a suitable starting point for ready-to use BPs, and encouraged companies to apply for scientific advice for further guidance[14,51]. The lack of sufficient safety and efficacy data under current standards for clinical trials pose a problem for EMA; that highlights that robust evidence is necessary for further discussion[7].

5.4. PhagoBurn project

PhagoBurn is the name of a project whose objective is the assessment of phage therapy as an alternative treatment for antimicrobial resistance in burn wounds. It is the main clinical study performed so far, being the world first prospective multicentric, randomised, single blind and controlled trial of phage therapy ever performed following GMP and GCP[62].

This trial was designed as a “proof of concept”, in order to assess the safety and efficacy of phage therapy, and will set the basis for further clinical trials for phage therapy under modern clinical trial standards. It started in 2013 and ended in 2017[62].

This trial involved three national authorities: the French ANSM, the Belgian FAMHP and the Swiss Swissmedic. The consortium included two French SMEs, Pherecydes Pharma and Clean Cells, as wells as three hospitals burn units located in France, Belgium and Switzerland. Eight additional hospitals in France and Belgium participated, among other stakeholders. The project was funded by the European Commission through the Seventh Framework Programme.

The main goal of the trial was to assess the efficacy and safety of phage therapy in the treatment of *E. coli* and *P. auruginosa* burn wound infections

Two cocktails were prepared: one with 13 phages against *E. coli* and the other with 12 selected strains against *P. auruginosa*. The preparations were prepared sterile. Testing methods were validated following the standard ICH Q2(R1).

A major issue was to establish the shelf life of the cocktails. It was not technically possible to determine the activity of the cocktail over time or the stability of single strains within the cocktail over time, as there was no method to measure the individual activity or potency of every individual phage within the final cocktail. The problem with the stability even led to a temporary interruption of the trial. Finally, it was taken as acceptable to determine the shelf lives of 6 phages per cocktail and to extrapolate it as a shelf life of the cocktails.

The trial faced other issues as lower recruitment than expected[63], or lower concentration of phages in the final product than predicted. Once of the reasons of the low recruitment was the

low incidence of infections exclusively caused by the targeted pathogens, that is, a low incidence of mono-infections[62], and the reluctance of physicians to treat patients with BPs targeting only one pathogen[31].

As a conclusion for cocktail composition and after the difficulties faced with the stability of the BPs, it was suggested mini-cocktails consisting of 3-5 phages as approach to be favoured over cocktails containing a big number of different phages. Conclusions also highlight the need for better diagnosis methods as critical for determining the efficacy[62].

No definite conclusions on safety and efficacy could be drawn due to the small patient population (25), but PhagoBurn has provided first-hand experience that will outline future design of trials for phage therapy[64].

6. Options and limitations under the current regulatory framework

As BPs are biological medicinal products, with no possible reference to any other approved medicinal product within the EU, and none of the exceptions for particular categories contemplated in the Directive applying, the application must follow Article 8 of the Directive 2001/83/EC[24], that is, a full application including clinical trials.

As justified before, the centralised procedure is not mandatory for BPs, unless some BP is given orphan status, but as innovative therapy and its potential to bring benefit to patients at Community level, the centralised procedure is meaningful for phage therapy.

Article 2 of the Directive 2001/83/EC defines the scope thereof, including all medicinal products prepared industrially or manufactured by a method involving an industrial process. Some authors have pointed out that this article would leave out of scope BPs prepared for individual patients[27,65], and even have questioned the term "placing on the market"[27].

The current use of BPs in the EU for individual patients is only possible by exclusion from the scope of the Directive 2001/83/EC[24]. Two exemptions in this Directive 2001/83/EC could be referenced as legal basis for treatment of individual patients: Article 3, or magistral formula exemption, and Article 5(1), or "special" named-patient exemption.

Other provisions of the current legislation will be also presented to explore its applicability for phage therapy or their possible impact.

6.1. The magistral formula

The Directive 2001/83/EC[24], through Article 3, leaves out of scope *any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).*

This exemption, transposed in different ways into national legislations[30], was historically made in order to distinguish these magistral formula products from proprietary medicinal products[65], and it allows the physician the prescription of personalised medicinal products which are not available commercially[31].

Under such exemption, a pharmacist may prepare the customised product according to the prescription given by a physician and restricted to one specific patient. The preparation of the product can therefore not precede the prescription. The responsibility lays on the physician, and in the pharmacist to what concerns the preparation and elaboration of the compound.

Since it is transposable into national law, it may be interpreted in different ways. For example, it is not defined either the mixture must be performed by a pharmacist or if it could be performed

under his/her supervision as well, or which specific requirements must fulfil the ingredients used.

It is also not defined what is a pharmacy and which facilities may have, or whether the processes involved in the manufacturing of a phage cocktail could be considered “industrial”.

Although the terms “prepared industrially” or “manufactured by a method involving an industrial process”, that would exclude the product from the scope of Article 3, are not defined, the European Court interpreted in the joined cases C-544/13 and C-545/13 that *such a process is characterised in general by a succession of operations, which may, in particular, be mechanical or chemical, in order to obtain a significant quantity of a standardised product,* and points out stock, wholesale, and large-scale or serial production in batches as characteristics of such method[66].

Concerning “*prepared in a pharmacy*”, the European Court interpreted that the pharmacy preparing the magistral product is also the one supplying it directly to the patients[66].

Additionally to different possible national transpositions of Article 3 exemption, the Article 46b could be differently interpreted as well. It defines quality standards for APIs manufactured or imported into the EU, and could be interpreted either applying to all APIs or to APIs used for manufacturing medicinal products within the scope of the Directive. The Article 46b states as follows:

> *Article 46b*
>
> *Member States shall take appropriate measures to ensure that the manufacture, import and distribution on their territory of active substances, including active substances that are intended for export, comply with good manufacturing practice and good distribution practices for active substances.*

According to Article 46b, APIs manufacturing must comply with GMP for APIs, and this is generally interpreted as applying to any API and not only to those intended for medicinal products within the scope of Directive 2001/83/EC.

For the manufacturing of magistral medicinal products there is no specific requirement at European level, but there is a guidance document from PIC/S known as Good Preparation Practices (GPP) that follows the principles of GMP for such preparations[67].

The Council of Europe issued the Resolution CM/Res(2016)1[68] concerning the quality and basic requirements that magistral formula products should follow. This resolution defines some concepts as “preparing pharmacy” and “dispensing pharmacy”, differently to the interpretation from the European Court, as seen above, that did not make this distinction.

The Council of Europe recommends to national authorities to grant specific licences to pharmacies performing such preparations. The resolution highlights that in some countries, it might

be allowed that companies prepare medicinal products under request of pharmacies, but in that case these companies should have a manufacturing license and full compliance with GMP.

Considering the preparation in a pharmacy, a quality assurance system should be used to prepare the medicinal products, following a risk assessment that classify the products in “high-risk” and “low-risk” preparations, and recommends using GMP as reference for the former and GPP for the latter. The criteria for risk assessment are:

-Type of preparation: lowest for non-sterile cutaneous and transdermal preparations, highest for parenteral.

-Amount prepared annually: lowest for very small amounts.

-Pharmacological effect of the active substance: lowest for mild and highest for very strong. It points out absence of monograph, toxicology, dosage, stability and quality as criteria to assess the assignment of the risk grade.

-Preparation process: highest for aseptic filling.

-Supply: highest for external only, lowest for internal only.

Every section is given with a grade 1 to 5. All of them must be multiplied, and if the result is higher than 100, it is considered a high-risk preparation. There is no further guidance for assignment of risk, but it is easy to imagine that BPs, being biological products, which are provided sterile and with several possible administration routes, would be considered “high risk” preparations.

Since the preparation is done under prescription by a health professional for an individual patient, the prescriber is carrying the responsibility for determining the added value of the preparation over existing approved medicinal products, limiting theoretically to the pharmacist the responsibility to the preparation. Interestingly, the resolution from the European Council states that *a pharmacist should be able to refuse a prescription for a pharmacy preparation if a suitable pharmaceutical equivalent is available on the national market, inform the physician that a suitable pharmaceutical equivalent is available and discuss with the physician if there is a specific need to dispense a pharmacy preparation*.

In summary, this resolution from the European Council, although not legally binding, sets several provisions applicable only through national legislations, which might provide extra details. The magistral formula exception is a non-harmonised procedure across the EU and was not conceived for preparing complex biological medicinal products, but to allow traditional non-industrial preparations to satisfy special patient needs.

6.2. The "special" named-patient exemption

This exemption presented in Article 5 (1) of the Directive 2001/83/EC[24], and states as follows:

> *1. A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.*

The conditions set by this article to skip the general requirements set in Article 6 (obligation of a marketing authorisation) of Directive 2001/83/EC[24] are very restrictive, being applicable only in case of "special need". Otherwise it could conflict through unfair competition with the aim of protecting public health as set by the Directive 2001/83/EC[24], achieved through the harmonisation of provisions relating to medicinal products and the granting of a MA[69,70].

Therefore, it is only applicable in case it is therapeutically justified, as it could result from the lack of alternative treatment or no availability in the market of an equivalent medicinal product. An infection where available antibiotics failed could be clearly considered a case of "special need", as well as allergy or intolerance to available antibiotics.

The health care professional carries personal responsibility for the use of the unauthorised product, as stated explicitly in the Directive.

The Article 5 (1) is the one giving room to the unproven intervention from the Declaration of Helsinki[59], and has been transposed differently into national legislations[30], leaving to interpretation some points, but especially relevant is the delimitation of "special" need. In general, it is to be interpreted as a special and individual clinical need[71], where other considerations as access to cheaper medicinal products must be excluded[69].

It must be originated from a bona fide unsolicited order, that is, as a request from a health-care professional after examination of an individual patient. Advertisement of non-registered products, although not falling under the limitations for advertisement of the Directive 2001/83/EC, could be limited not to undermine the general obligation of obtaining a MA for medicinal products to be commercialised, as well as could be restricted by Member States under their right to limit movement of goods to preserve public health, as ruled by the European Court[72].

The British Authority, MHRA (Medicines and Healthcare Products Regulatory Agency) has issued a guidance that provides more information about the limitation of this Article 5 (1) exception, and illustrates an example of national application. For instance, explains that "*an unlicensed medicinal product should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patients*", and leaves to the prescriber the responsibility for deciding if the conditions of "special need" are met, given as example allergy or intolerance to one ingredient of the licensed medicinal product or inability for the specific administration

form. It restricts the special need to its clinical meaning and not to any economical related need. It sets also some responsibility on the manufacturer as it is expected that documentary evidence of the clinical need is obtained[71,73].

Importation of unlicensed product is not restricted by Article 5(1), and it is therefore open to different national implementations. For example, in the UK, a specific license for the importer as Manufacturer´s "Specials" License is required in order to import unlicensed products from countries other than EU members, Norway, Iceland or Liechtenstein, while only a Wholesale Dealer´s License is required for importing from mentioned countries. A notification to MHRA must be done 28 days prior import.

When it comes to bacteriophage products, the different interpretations of this Article 5 (1) provisions would prevent a same approach for phage therapy across the EU, but it is the main exemption that can be currently used in the EU for treatment of individual patients with phage therapy if the conditions are met.

6.3. Further possibilities under Article 5 "specials"

Article 5 of Directive 2001/83/EC[24] contemplates other option for which a non-authorised medicinal product could be used.

> *2. Member States may temporarily authorise the distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.*

This Article might allow a broad use of BPs in case of a MDR strain epidemy, as the one occurred in Germany with E. coli O104:H4.

The paragraph 3 establishes that Member States shall lay down provisions to limit the civil or administrative liability for any consequence resulting for the application of non-authorised medicinal products in response to the suspected or confirmed spread of a pathogenic agent, relieving health professionals and manufacturers from this responsibility.

There is no use of phage therapy made under this exemption, but if phage therapy gets consolidated, it is not unlikely that this exemption will be used to stop an outbreak of a MDR pathogen.

6.4. Compassionate use

Often the term "compassionate use" is used for any authorised use of an unlicensed product under the "specials" exceptions covered under Article 5 of 2001/83/EC, but it must not be confused with the one described in this chapter.

Compassionate use is a possibility through which a non-approved medicinal product could be used for a group of patients as an early access option, as pointed out in the Regulation 726/2004[29].

> *Article 83*
>
> *1. By way of exemption from Article 6 of Directive 2001/83/EC Member States may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and (2) of this Regulation available for compassionate use.*
>
> *2. For the purposes of this Article, 'compassionate use' shall mean making a medicinal product belonging to the categories referred to in Article 3(1) and (2) available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorisation in accordance with Article 6 of this Regulation or must be undergoing clinical trials.*

This provision is addressed for medicinal products on review (for which an application was made) or with ongoing clinical trials, which belong to the mandatory or the optional scope of the centralised procedure, that is, which are undergoing review at the EMA or that are intended to do so, leaving for national interpretation to which extend the "ongoing clinical trials" applies. Besides, this exemption applies only for groups, not for individual patients, and can be made exclusively in a non-profit basis. These conditions could be similarly transposed in national laws to broaden the scope to medicinal products undergoing review at national authorities.

Since there are no BPs under review at EMA or national authorities, and only few clinical trials ongoing or planed, where even PhagoBurn is considered a "proof of concept" trial, the compassionate use option seems unlikely to be used by applicants to allow early access to bacteriophage therapy in a short term. Nevertheless, as more BPs start clinical trials, this provision becomes a more feasible option for early access to BPs, especially in case of an outbreak of MDR pathogens.

6.5. Orphan designation

A BP indicated against a MDR infection could eventually meet the requirements for orphan designation.

Orphan medicinal products are targeting life-threatening or chronically debilitating conditions affecting not more than five in ten thousand persons in the EU at time of application (approximately 250,000 patients). Another requirement is that there is no satisfactory method against that condition or that the medicinal product will be of significant benefit, as specified in the Regulation (EC) 141/2000[74].

These medicinal products need approval through centralised procedure and are exempted from providing complete non-clinical and clinical data. Other benefits from orphan designation are fee waivers, protocol assistance and 10 years market exclusivity[74].

The application to obtain orphan designation can be submitted at any stage of the development process before the application for MA, and must be accompanied by the proposed indication and the justification that the criteria for orphan designation are met. If the designation is granted by the European Commission, the sponsor must submit yearly reports on the stage of development and the medicinal product enters the register for Orphan Medicinal Products[74].

The orphan designation given to a product will be removed if criteria for designation are no longer met and at the end of the market exclusivity. This market exclusivity may be reduced to six years if, at the fifth year after being granted MA, it is established that the product is sufficiently profitable or the conditions for orphan designation are no longer met. A MA may be granted to a product with same indication if the product is safer, more effective, or otherwise clinically superior to the one with orphan designation[74].

6.6. The variation regulation

Although there is currently no BP authorised in the EU, the variation regulation is very relevant for BP developers to evaluate post-market possibilities with respect to notification of variations and line extensions of a hypothetical BP.

If the BP is a cocktail of phages, as it is likely to be, any modification on the composition in this combination, as an addition, removal or replacement of a phage strain could not be performed as extension of the MA or as variation. That is, any modification on the composition would be only possible through a new application following Article 8 of Directive 2001/83/EC leading to a new MA.

Annex I (1) (c) of Regulation 1234/2004[75] states as possibility for extension of an existing MA for a biological product the *replacement of a biological active substance with one of a slightly different molecular structure where the efficacy/safety characteristics are not significantly different*. Therefore, the replacement of one phage by another with improved efficacy to overcome the development of resistance by bacteria, even if they are very close genotypically and phenotypically, would fall out of scope of line extension, since an improvement of the efficacy is targeted. That means that any kind of change in a phage strain of a cocktail will trigger a new marketing application.

A change of the cell substrate used to replicate the phage would request a line extension, provided the *efficacy/safety characteristics are not significantly different*. Other typical modifications requiring a line extension are changes in the strength/potency, pharmaceutical form or route of administration.

Significant potential variations for BPs that would be considered as type II (major) variations are the addition of a new therapeutic indication or significant changes in summary of product characteristics. That could be the case if some phage or combination of phages turns to be effective against another bacterial infection, not to be excluded even provided the high specificity of phage therapy The variation type II for a new indication would be confronted with the fact that the new indication (a different bacterial species or strain as considered for MA) would also require a new cell substrate in a normal case, triggering a line extension according to the current provisions of Regulation 1234/2004.

A major variation type II has an assessment period of 60 days, that may be reduced in case of urgency or prolonged till 90 days in the mentioned case of addition of an indication[75]. There are some cases where a change of active substance does not trigger a new MA and is assessed as a variation type II. Within medicinal products for human use, the only exception is the change of active substance for the human influenza vaccine for the annual update, assessed as a variation type II. Within the medicinal products for veterinary use, the exceptions consider replacement of a strain for the vaccine against equine influenza and several variations concerning vaccines against avian influenza, foot-and-moth disease and blue tongue, to be further described in “multi-strain dossier” section (see 7.4).

7. Proposals to amend the current regulatory framework

Several proposals have been made to adapt the current regulatory framework so that it fits the unique characteristics of phage therapy, as well as it may exploit all potential advantages of this therapy. Some of these proposals are based in existing approaches for specific medicinal products, either in the human or in the veterinary regulatory frameworks. Others are novel or were not proposed for bacteriophages in particular, but for other personalised therapies.

7.1. Hospital exemption

Regardless BPs are clearly not ATMPs, it has been proposed the establishment of a hospital exemption for bacteriophage therapy, either by including bacteriophage products as an specific category of ATMPs, or preferably, by creating an specific phage therapy hospital exemption[27,76].

A hospital exemption as defined in Article 3 (7) of Directive 2001/83/EC[24] exempts certain ATMPs from MA, but poses some differences over the two analysed exemption possibilities of magistral formula and the named-patient Article 5 approach, as the explicit fulfilment of specific quality standards and the restriction to import. The hospital exemption does not explicitly require “special need”.

Article 3 (excluded scope from the Directive) states as follows:

> *7. Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is 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, in order to comply with an individual medical prescription for a custom-made product for an individual patient.*
>
> *Manufacturing of these products shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.*

The hospital exemption was introduced in the Regulation 1394/2007 for ATMPs[28], together with other specific provisions for ATMPs as the risk-based evaluation approach, all intended to provide a suitable framework with a growing potential and great complexity[28]. The hospital exemption was conceived as there were already ATMPs on some European markets being used and developed in hospitals and by non-profit entities when the Regulation was issued. It considers only *non-routine* manufacturing and use to an *individual patient*, leaving to national

authorities the assessment and approval of products falling under this exemption The interpretation of the “non-routine” manufacturing and even the purpose of such an exemption has been differently interpreted by national authorities[77], being one discussion topic either the hospital exemption should be seen as a permanent regulatory pathway or just temporary until a full MA can be granted.

The European Commission has shown concern about the implementation of the hospital exemption for ATMPs and the possible unfair competition that it might cause by products not getting centralised approval, and has suggested more clarification and amendment thereof[56].

The hospital exemption does not free from fulfilling state of the art quality requirements, and therefore makes necessary the fulfilment of GMP standards. This provision of the exemption should not only assure a high level of quality and safety for ATMPs produced under the hospital exemption, but limits a possible unfair competition from ATMPs going through centralised procedure and those limited to hospital exemption, as well as to promote the free movement of ATMPs within the EU[56].

The hospital exemption, made to fit the needs and the reality of ATMPs, explicitly limits the use of ATMPs nationally approved within the country of manufacturing. Although it does not explicitly limits its use to unmet clinical needs, it is generally expected a justification for the use of the product for getting national hospital exemption authorisation[77].

Although a hospital exemption applicable for biological medicinal products in general or to bacteriophage therapy in particular has been proposed, it has been also highlighted the difficulties that hospitals working with phage therapy would have in order to comply with GMP requirements[76].

7.2. The homologous group concept

Within the allergen products regulations there is an useful concept that could be applicable for phage therapy: the homologous group concept[30]. In the Guideline on Allergen Products[78], *since it is impossible to determine all relevant parameters for the allergens within a given extract or a defined allergen extract mixture*, some criteria are set in order to extrapolate data from different substances that can be included within the same homologous group.

The homologous group replaces the taxonomic family concept proposed by the *Note of Guidance on Allergen Products*[79] that set the basis for extrapolation of data from different active substances for industrially manufactured allergen products back in 1996.

The extrapolation of data for similar or evolved bacteriophage strains, specially concerning quality and safety, could be a useful tool for certification of BPs. As in the allergen guideline, a taxonomic classification of phages could not be sufficient, a phenotypical characterization has

been also pointed out as relevant specially concerning the safety and quality[30], as shown in the quality aspect section (see 3.2).

The extrapolation shall be limited to defined and scientifically justified groups. The grouping is based in four criteria which should be fully fulfilled[78]:

-Comparable physiochemical and biological properties of the source material.

-Cross-reactivity/structural homology of the allergens.

-Identical formulation of the finished products.

-Identical production process of the allergen extract and of the finished product.

Quality, safety and efficacy data can be extrapolated to a limited extend from the representative source to the other members within the group. Detailed safety studies are only requested for the representative allergen, while post-marketing safety data must be submitted from any of the group members[78].

The extrapolation of efficacy data from one representative to the other members of the homologous group is not possible in case of different route of administration[80].

For combination of substances belonging to two different homologous groups, the applicant is advised to request scientific advice[80].

So far, defined homologous groups belong to plant or animal kingdoms, often grouped as species, genus, families or subfamilies[78].

In the case of phages, most of the already used or expected to be used belong to three families within the order Caudovirales: Myoviridae, Siphoviridae and Podoviridae[13]. They are all tailed viruses with a double-stranded DNA from 15 to 500 kilobase pairs within an icosahedral protein capsid and with a variable tail, which might be contractile (Myoviridae) or not, short (Podoviridae) or long (Siphoviridae), and that interacts with the host bacterium surface. The tail, as part interacting with the bacterial host, is critical for the efficacy of the given strain, but the head of the virus should not have a big effect on the efficacy. Concerning the safety, future studies may confirm that the structural diversity of phages do not to prevent a relatively high homogeneity in the safety profile of all therapeutically significant phages.

7.3. The autogenous vaccines approach

The autogenous vaccines approach is a concept from the veterinary regulatory framework that could be used as a basis for specific BPs provisions.

The autogenous vaccines are veterinary medicinal products excluded from the scope of the Directive 2001/82/EC and which are defined in Article 3(b) as *inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals from a holding and used for the treatment of that animal or the animals of that holding in the same locality.* Besides, Article 4 allows to Member States to leave out of scope "non-inactivated" immunological veterinary medicinal products as well, for the same purpose as described in Article 3(b)[81].

This approach is addressed to one particular infectious event, being then comparable to phage therapy in that aspect, but in others differs, as the veterinary use versus human use, and in the mechanism of action[30].

Since it falls out of scope of the Directive 2001/82/EC, it may be applied in national regulations in different ways. In France, where a regulatory framework for this approach is well defined, the Authority grants an authorisation to a qualified person or establishment with a qualified person, and performs inspection to them[30].

In France, autogenous vaccines must be prepared according to specific "Good Preparation Practices", the prescription must be made by a veterinarian, who assumes a similar responsibility to an off-label prescription, and adverse events or lack of efficacy must be reported by the prescriber through a pharmacovigilance declaration[30].

Similarly, in Spain, the establishments elaborating these vaccines will have authorisation from regional authorities for handling with animal pathogens and can only deliver these products to the veterinary or to the affected establishment, always prior veterinary prescription. Non-inactivated vaccines must be manufactured following equivalent principles to GMP. Establishments manufacturing these preparations must report at least quarterly to regional authorities the amount of autogenous vaccines manufactured, the destination establishment/owner of the animal, and the prescriber[82].

This approach shares with the personalised approach of phage therapy the fact that the medicinal product is prepared from a sample of the infecting pathogen taken from the patient. In phage therapy, nevertheless, the sample taken would not be used as a base for the active substance but as cell host for replication of the phage or phages that prove effective against it.

7.4. The multi-strain dossier

The multi-strain dossier which is currently used for certain vaccines for veterinary use has been proposed as refence for a flexible approach that would be more suitable for BPs[30]. This concept is introduced in the Title IV in Annex I of the Directive 2001/82/EC[81], amended through Directive 2009/9/EC[83].

> *B. MULTI-STRAIN DOSSIER*
>
> *For certain immunological veterinary medicinal products (foot-and-mouth disease, avian influenza and bluetongue) and by derogation from the provisions of Title II, Part 2 Section C on active substances the concept of the use of a multi-strain dossier is introduced.*
>
> *A multi-strain dossier means a single dossier containing the relevant data for a unique and thorough scientific assessment of the different options of strains/combinations of strains permitting the authorisation of vaccines against antigenically variable viruses.*
>
> *Scientific guidelines for the submission and evaluation of multi-strain dossiers shall be adopted by the Agency. The procedure for the submission and evaluation of multi-strain dossiers shall follow the guidance published by the Commission in* The rules governing medicinal products in the EU, Volume 6B, Notice to Applicants.

This exception was created for veterinary vaccines needing frequent adjustments, in order to *ensure that the most effective measures can be taken swiftly by the Community against the incursion or spread of epizootic disease*[83].

The guideline for multi-strain dossiers explicitly excludes from the scope the use of this approach in response to an emergency situation, and it also excludes life vaccines[84,85].

The multi-strain dossier is also complemented by specific provisions in the Regulation 1234/2008/EC[75], which considers the *replacement or addition of a serotype, strain, antigens, or a combination of serotypes, strains or antigens* as major variation type II, and exclude these variations from line extension or new MA requirements.

Concerning the qualitative and quantitative particulars that must be specified according to Article 8 (3) of the Directive 2001/83/EC[24] or to Article 12 (3) of the Directive 2001/82/EC[81] (the equivalent article in the veterinary directive), the multi-strain dossier guideline states that the maximum number of active substances to be included in the formulation must be defined by the applicant, and, if there is no fixed amount targeted for each of them, the minimum and maximum quantities of each should be specified[84,85].

This concept allows an approval based on a core dossier for which addition or replacement of active substances does not require a full submission, but it is individually assessed following some principles as described in the guideline[84,85]. The applicant can then keep a single dossier containing multiple vaccine strains, to which an addition or replacement of strains can be done

via amendment of the multi-strain dossier. These amendments are assessed as type II variation, that is, in a 60 or 90 days period. And not only allows to add another strain to the approved eligible strains for the final product combination, it allows as well to change the maximum amount of strains to be included in the final product[86].

For each antigen to be included in the multi-strain dossier a full set of quality data must be provided. All strains to be included must be prepared following the same method of preparation, to which deviations must be explained and justified. Other tests must be provided for every strain separately, as complete inactivation. Same test methods for all strains must be preferably the same, any deviation must be explained and justified, and a specific validation of these methods for each strain will normally be required. A validated potency test must be specified for each strain. This is important since the potency of the individual strains must serve as basis for assessment of the potency of the final product, since this cannot be established as it is usual for this kind of products, due to the combined action of different strains in the final product.

The quantity of the excipients should be the same regardless the amount and identity of the used strains, and the volume of one dose may also not differ.

7.5. The Biological Master File

Fauconnier proposed a solution based on the Biological Master File (BMF) concept as an approach to address the customised application of bacteriophage therapy[65]. According to this concept, specific information about an individual phage or homologous group would be provided as active substance, to be added to the BP dossier. The BMF should cover the manufacturing aspects, and possibly address the safety as well.

The concept of the BMF is based in the Active Substance Master File (ASMF) already in place with the purpose of keeping intellectual property[87]. The principle of this concept is that a standalone package containing information only about the active substance is submitted an evaluated, being part of the information restricted to the MA applicant for the medicinal product as a whole.

The concept to be taken from the ASMF would be then the evaluation of an individual package that in the case of a BP would correspond to a specific bacteriophage strain that would be consider as an active substance. Since the most likely application of BP would be a combination of different phages, that is, different active substances, the inclusion of new strains would need assessment.

The assessment would be made mostly based on quality but ideally would consider safety as well. Some criteria should be considered by inclusion of specific strains, as detailed in the homologous group concept.

Similar approaches to this concept exist already, the Vaccine Antigen Master File[88,89] and the Plasma Master File[90–92], which are based under the principle of stand-alone packages which have later on reflection in approvals of different products. The multi-strain approach is also based in a stand-alone assessment of a specific active substance. With the BMF, the focus is on the active substance, and the use of the new assessed phage could be considered for different already existing BPs.

7.6. Certification of libraries

Cooper et al (2016)[93] proposed an alternative licensing way by creation and approval of phage libraries as a long-term possibility for phage therapy. These libraries would contain efficient phages against the most severe pathogen bacteria. Existing phage banks could be used, but new phages would be continually added.

The phages in the library would be at least characterised *in vitro*, but phages not performing good would not be discarded, since they could turn out useful with future pathogen strains or perform better *in vivo* than expected initially.

This approach pursues the assembling of potentially effective phage cocktails from well characterised phages already fulfilling predefined standards, in order to shorten the time and requirements for implementation of the given effective combination. This approach has nevertheless no precedent in the current regulatory environment[93].

7.7. The manufacturer statement

The manufacturer statement is a concept coming from the medical device framework. In this framework, customization of products is usual and have led to a further definition of tasks and responsibilities for such personalised devices. The regulatory framework for medical devices is even seen as an instrument for support of personalised medicine[94], and it has already been proposed for regulation of slightly modified oligonucleotides for personalised medicine[95].

According to Directive 93/42/EEC[26], a custom-made device is defined as *any device specifically made in accordance with a duly qualified medical practitioner's written prescription which gives, under his responsibility, specific design characteristics and is intended for the sole use of a particular patient.* The new Regulation 2007/745[25] for medical devices defines it as *any device specifically made in accordance with a written prescription of any person authorised by*

national law by virtue of that person's professional qualifications which gives, under that person's responsibility, specific design characteristics, and is intended for the sole use of a particular patient exclusively to meet their individual conditions and needs.

Although the prescriber is responsible for the specific design characteristics, the manufacturer is sharing obligations in form of a statement, that must contain, beside the information of the manufacturer and unequivocal reference to the specific patient and the prescriber, the specific characteristics of the product as indicated in the prescription, a statement that the device conforms to the general safety and performance requirements set out, and if applicable, which safety and performance requirements have not been fully met together with the grounds[25,26].

In the current guidance for clinical evaluation of medical devices[96], custom made devices are considered “breakthrough products” and it is regarded that *in exceptional cases, major benefits may justify relatively high levels of uncertainty, and access to the market may be granted on the basis of limited clinical evidence*. The evaluator is advised to assess whether devices *deliver clinical benefit to patients for medical conditions that are life threatening, or cause permanent impairment of a body function, and for which current medical alternatives are insufficient or carry significant risks*.

8. Discussion

8.1. The ready-to-use approach

The ready-to-use or *prêt-à-porter* approach is, according to literature, a limited approach that would not exploit all the advantages and flexibility that phage therapy may offer[12,18,52,53], but it is also the approach that require the fewer adjustments to the current regulatory framework.

The development of a ready-to-use BP could follow the current regulatory framework as a biological medicinal product. In fact, as shown in the EMA Workshop, the current position of European regulators is that the regulatory framework is suitable for development of these BPs and have advised developers to get assistance from EMA during the development phases[14].

No ready-to-use BP has been commercialised in the EU market, but they can be found in Russian and Georgian markets[18,50]. However, these products have often unclear indications and their efficacy has not been proven according to European standards, and therefore could not be generally used as a base for the ready-to-use approach to be developed at the EU. Nevertheless, they show some features that may inspire this concept, as the easy access and the targeting of several bacterial species. A broad use of phage therapy is still difficult to imagine, and current efforts are mostly addressed to diseases with lower incidence and MDR bacteria.

BP developers are following the approach of preparing cocktails with several phage strains to restrain a possible fast appearance of resistance to the BP. If several bacteria are to be targeted, the number of necessary phages for the cocktail multiplies, to assure both a broader spectrum and a long-standing efficacy. However. this approach does not guarantee a long enough life cycle of the product if “updates” are not performed[18,64]. These updates, which are currently not even triggering a line extension, but a new marketing approval application, should be accepted as a variation as it is accepted in influenza vaccines in order to prolong the expected life cycle of a MA.

Given a hypothetical approved BP with several well characterised phages, which, after being available on the market for several years and, and as shown in the post-marketing monitoring, is losing efficacy against the targeted bacteria, a flexible procedure to maintain it effective deems necessary. The maintenance of the efficacy of this BP could imply the addition and/or replacement of some phages from the preparation. Any of these replacements or additions would directly trigger the need of a new MA under the current regulatory framework.

Only a slight change of the phage strain could currently be attempted under line extension. Since the ability of the phage to infect and lyse a defined bacterium is directly dependant on the interaction phage tail-bacteria receptor, it not difficult to imagine that a slight change in the

molecular structure could be the cause of an improved or regenerated efficacy. With a broad interpretation of “slightly different molecular structure”, it could be considered a line extension, provided it is justified that the change is performed in order to keep the efficacy of the BP and not as an improvement. Searching for a close enough phage would be deemed as unfeasible task, considering that phages are extremely diverse and that the screening methods are based in titration against potential host bacteria, and not based on similarity to previously characterised phages. Besides, it more than questionable targeting a similar efficacy (to the initial efficacy) if an improved efficacy is achievable. And that would be only to be able to apply for a line extension, which would require a lot of resources in comparison with a change notification. Even being open in that interpretation of slight change in active substance, it is noticeable how unsuitable is the current Regulation 1234/2004 for addressing expected and needed variations in phage therapy.

There is a precedent in the human medicinal product regulatory framework considering a change of active substance as a variation of the MA: the yearly update of the influenza vaccine, considered as a type II variation. However, a major difference with the influenza vaccine variation is the amount of active substances that could be expected from BPs. While the change of the influenza antigen is a replacement of an active substance by another, the number and proportion of phages in a BP could be significantly high, although recent experiences from PhagoBurn recommend using cocktails with very few strains, three to five. Regulators could argue that changing the antigen in influenza vaccines is not comparable to remove, add or replace one or several different phages to the established BP, since the variability expected in one virus type (influenza) is not comparable to the consideration of different virus types (phages), which may even have significant differences taxonomically and phenotypically, despite the totally different mechanism of action and purpose of vaccines and phage therapy.

The homologous group concept could be useful in case of reluctancy from authorities to create the same exemption for BP as for influenza vaccine concerning variations. The application of the concept of homologous group as applied for allergen products would not relieve from the need for new marketing application by making amendments to the MA, but it could be adapted to a context of variations. In allergen products, the homologous group was not conceived n in the context of variations but as a way to demonstrate safety and efficacy for new applications based on existing data from homologous allergens.

If the homologous group concept was accepted in the context of variations, certain changes in active substances would not trigger new MA applications. It should be assumed that the homologous groups contained in the approved BP would have to be the same as in the modified BP, and it would depend on the amount of selected homologous groups.

The main problem for implementing the homologous group concept is the different characteristics of BPs with respect to allergen products. While in allergen products the homologous group is based on the assumption that substances sharing a lot of similar features have also a similar safety and efficacy profile, in phage therapy, very similar phages could have a totally different efficacy profile, in that would be actually desirable, as the goal of phage therapy is to find the most effective phage against a given pathogen.

A suitable regulatory framework could also be supported in the multi-strain dossier approach, and some of conditions of multi-strain dossiers could apply. For example, all phages should be prepared following the same method, and the content in excipients should not vary. The maximum amount of strains would be also defined up-front by the manufacturer[84,85].

It could be argued that, from the point of view of safety, the risks accepted on veterinary use for three specific animal diseases with inactivated vaccines cannot be compared with the risk of using different phages, which are active entities, on humans. Future studies should address and may confirm that the safety is not dependant on the specific phage strain as long as some criteria are established. That is, if the manufacturing process is the same, quality issues could be mostly excluded from the safety question. Other safety concerns related to the use of phages could be excluded via *in vitro* and *in silico* analysis, and further clinical experience could drive to the conclusion that the safety profile of different phages is similar and that a possible benefit by using a new strain outfits the risks.

About the stability of a hypothetical cocktail, the approach in the multi-strain dossier is more restrictive than the approach used in PhagoBurn, where only data to 6 out of 12 or 13 phages were provided and extrapolated to the two final BPs used in the trial[62]. According to the multi-strain dossier guidance, all possible strains should have stability data, and the extrapolation to the combination of them would correspond to the strain with shortest shelf life[84,85]. Therefore, stability principles set in the multi-strain dossier seem also applicable to phage therapy.

In contrast with many other products made by combination of active substances, different phages can be produced by relatively similar methods, so it is not difficult to imagine that a same manufacturer or holder of a multi-strain dossier could integrate new phages using the same methods, including protocols for replication and preparation of cell banks and phage seed banks. Nevertheless, an open point for discussion would be the demonstration of a similar potency of the new strain. In fact, it is not possible to estimate with accuracy the potency of a singular phage strain within a product containing several phage strains targeting the same bacterial host.

In summary, to include the addition, removal of replacement of phages from a BP as variation type II, preferably supported by the homologous group and multi-strain dossier concepts, would increase the viability of BPs in the long term. Developers would be confident that they

could market a BP with a long life cycle that would enable return and profitability. Ideally, this change of the variation regulation would be accompanied by the introduction of a multi-strain dossier for BP, allowing different combinations of strains, but this is not strictly necessary in order to have a regulatory framework that facilitates the development of ready-to-use BPs.

The addition or replacement of strains should not be the only change in the variation regulation to be performed. Currently, a change of cell substrate for developing a biological medicinal product would trigger a line extension. That would prevent the use of classified and well characterised phages that are effective against newly discovered bacterial strains, since the host bacterium for replication of phages is usually the target bacterium. This requirement contrasts with the change of indication, necessary to broaden a MA for a new infecting pathogen, that would only require a variation type II.

Another source of uncertainty that prevent bigger investments in phage therapy has to do with patent protection. The market protection granted for orphan designation could be worth considering for specific indications which have, at least at the moment, a low incidence. Nevertheless, this might provide some guarantee in early stages of phage therapy implementation, but if phage therapy aspires to become an alternative or auxiliary treatment to antibiotics and have a broad, only the mentioned protection of manufacturing methods or certain combinations of phages seem possible.

Some authors have mentioned the outbreak of E. coli O104:H4 as a situation that could have been alleviated with a well-established phage therapy[13,22,23]. As we have discussed, the ready-to-use approach is the one having more possibilities to expand the use of phage therapy, but it is questionable if it could help preventing or treating such outbreaks. Only in the unlikely case that a hypothetical approved BP is effective against a newly outbreaking pathogen, it could turn out to be useful. In case of implementation of changes to the Regulation 1234/2004 to enable change of strains as variation type II, even with fully adoption of a multi-strain model, it would be doubtful that a ready-to-use BP would restrain the spread of a fast spreading infecting strain, considering the assessment time for amendments of a MA.

It is to notice how the multi-strain dossier, one of the proposals for phage therapy which is currently used for veterinary applications and only for three very specific animal diseases, excludes explicitly the use of this approach in emergency situations[84,85]. However, in the veterinary regulatory framework the autogenous vaccine may cover that gap. Similarly, in phage therapy, the ready-to-use approach may not be sufficient to exploit all the advantages that phage therapy could eventually demonstrate.

Although this approach would not fully exploit all the potential that phage therapy might have, it is crucial to develop a specific regulatory framework in this direction in order to increase the use and the available data for phage therapy. If phage therapy turns out to be a sustainable

and efficient alternative to antibiotics, a ready-to-use approach, sustained in a slightly modified regulatory framework, could allow an extensive use and a lower dependency to antibiotics.

8.2. The personalised approach

The custom-made approach has been pointed out as the one having more potential and the one exploiting all the advantages that phage therapy has over current antibiotics[12,18,52,53]. The customised use of phage therapy is currently taking place mostly in Belgium and Poland, by hospital and academic institutions in a non-profit basis. This application of phage therapy is possible under the exceptions set out by the Directive 2001/83/EC, which are very restrictive and do not support a broad personalised use of phage therapy.

Although preparing a customised BP requires a minimum amount of days for isolation, identification, testing and application, its advantage over a ready-to-use BP lays on the high specificity of phages to concerned infecting strains. As seen during PhagoBurn, infections are often caused by several bacteria, so cocktail targeting only one pathogenic species or a fixed combination of pathogens might not be sufficient. This would apply also for a fixed combination of phages in a cocktail to be used against a diverse and not predicted combination of infected bacteria.

Interestingly, some ideas for a phage-specific framework are based in the ATMP Regulation. The ATMP Regulation was intended to provide a suitable regulatory framework for a set of products with great diversity, setting clear requirements, but on the other hand giving some flexibility through the risk-based evaluation approach and the hospital exemption. The risk-based evaluation approach intends to allow flexibility to the assessment of ATMPs based on their high heterogenicity. It is therefore not applicable to phage therapy, where BPs share a same mechanism of action and principles, but the hospital exemption for ATMPs is meaningful as applicable proposal for phage therapy.

The hospital exemption was established in order to allow the use of ATMPs under certain conditions, considering this kind of products had been already used under national provisions, and enabling to some institutions to keep treating their patients mainly as done before, while demanding “specific quality standards”. It has also become a way to use new ATMPs without following the centralised procedure, and it is in discussion if hospital exemption as conceived so far allows unfair competition, making possible for some products to be placed on the market avoiding the high requirements and investments that require a central application[77]. The interpretation of the hospital exemption at national level is also a source for different implementations, and depending on the country, the hospital exemption is seen as a transitory path for adapting to new requirements or as a permanent way to have ATMPs on the market without applying to EMA. Even the European Commission has warned about the misuse of the hospital

exemption to skip market authorisation and have called for a clarification of terms in order to allow harmonization within the Union[56]. It seems therefore unlikely that any solution for phage therapy could go in this direction, based in the different backgrounds of ATMPs and BPs.

Besides, a hospital exemption for phage therapy would probably not encourage the European spread of this therapy. In fact, the current use of phage therapy in the EU is done in the context of unmet clinical need of individual patients at small research institutions and hospitals. That is, these criteria are mostly covered by the Article 5(1) exception of Directive 2001/83/EC, the only significant change would be the removal of the “special need” criterium. In the praxis, it is very unlikely that such an exemption would bring phage therapy to more patients, since no national permission is generally granted to hospital exempted products for which there is an available authorised product, and even if such a permission is granted, too much responsibility would be assumed by the prescriber of phage therapy to justify its use over existing approved medicinal products.

A good opportunity for development of phage therapy at European level is the approach recently implemented in Belgium, the magistral “premium” formula. One of the aims of this Belgian approach is to set a basis for BPs manufactured under minimum acceptable quality and safety standards. The inclusion of a monograph into the Belgian Pharmacopoeia is already a significant step, as it offers a quality standard to be referenced in the whole EU.

The magistral “premium” formula as proposed in Belgium is based in Article 3 exemption (magistral formula) and aims to overcome some high requirements as would be set by Article 5 (1), with the hope that it could serve as a model for a further implementation of phage therapy at European level and increase the use of phage therapy.

The “special need” requirement of Article 5 (1) is not explicitly stated in Article 3 exemption, but Article 3 was conceived for non-industrial preparations to make possible for prescribers to provide personalised preparations for particular needs of their patients. The “special need”, or therapeutic need, is therefore present. The lower requirements by using Article 3 instead of Article 5 (1) is that under the latter, “medicinal product” definition applies and similar quality requirements as for those with granted MA are expected.

By avoiding the requirement of manufacturing under GMP standards, the magistral premium approach sets the standards for these BPs lowers as for those ATMPs manufactured under the hospital exemption, which must be manufactured under GMP standards. This exemption cannot be justified based on the lack of resources by institutions or SMEs that are currently involved in phage therapy. Even though phage therapy could eventually be considered as generally safe, a manufacturing under GMP standards is essential to guarantee the quality and safety. Besides, as generally interpreted under Article 46b of Directive 2001/83/EC, the APIs

must be manufactured within the EU under GMP requirements for APIs, including the APIs to be used in a magistral formula.

Nevertheless, the magistral formula approach is a good start that will provide more data for phage therapy and set some quality standards to be used at European level, although it is unlikely that other countries will take similar measures as those set in Belgium, at least in the short term. The interpretation of Article 3 is not equivalent among members states and an approach following Article 3 can obviously not replace a suitable framework for phage therapy in the long term, if phage therapy is to be implemented and considered a sustainable alternative to classic antibiotics.

As a specifically solution for a personalised phage therapy, the certification of libraries approach could be envisaged in the praxis through the application of some basic compendial standards, as those to be set by the Belgian magistral premium formula approach, plus a manufacturing process of the BPs under GMP requirements. The certification of libraries could be complemented with the BMF approach, being a BMF made available for every phage contained in the library, that could be reviewed by competent authorities prior use or in post-market requests, as exemplary samples, if this approach proves to guarantee the quality, safety and efficacy of final products.

The manufacturer statement as conceived in the medical device regulatory framework is useful in the context of personalised approaches as it distributes the responsibility of the stakeholders involved, relieving the prescriber from the whole responsibility and giving the manufacturer some of it. The manufacturer statement applied for BPs should resemble a Summary of Product Characteristics, in which basic information on the safety product is given. Of course, since a personalised product would have unique features, many of the statements would be general to a product category, to be defined following criteria as same homologous group, same administration route, etc. This information could be shared by products being manufactured from the same library, that would be accredited as fulfilling some “essential principles”.

A multiple-strain dossier, which could be the basis of a flexible BP, would be attached to the same fixed information that would be contained in the manufacturer statement, together with some variable information specific to the BP manufactured for the individual patient. Pharmacovigilance information resulting from the use of the BP in an individual patient would be added to the multi-strain dossier.

The autogenous vaccine approach from the veterinary framework, although useful as it is addressed to a very similar case, it is not applicable without performing significant changes in current regulations and it would require the demonstration of a very low risk by using BPs, as well as it does not provide a harmonised implementation across the EU. In the case of personalised phage therapy, intended for human use, the safety concern should be minimised by a

manufacturing process that guarantees no rests from the host bacterium or its genetic material, as well as by the fact that in a customised approach the receptor of the BP is the source of the bacterial host, and would not be intended to other patients.

A challenging issue would be the batch release in a relatively fast period of time, since the life of the patient could be compromised. Efforts targeting a real-time release of batches provide a solution on that respect[30], reinforced by GMP manufacturing process and characterization and incorporation into the library of the phage even afterwards. It would not be easy for hospitals to comply with all these requirements, but efforts could be centralised and some hospitals or institutions could specialise and provide finished BPs to other requesting hospitals or clinics.

As a result of applying all useful approaches, a personalised system would look like this:

-Public or private stakeholders willing to manufacture personalised BPs would have a GMP certificate.

-Manufacturers of personalised BPs would keep a phage library, and one or several multi-strain dossiers, generally considering route of administration and homologous groups.

-Following a prescription, either directly by the physician or addressed through a hospital, the manufacturer would prepare a BP using samples of the pathogen from the patient.

-The manufacturer would issue a statement that would contain quality related information to the batch and general information associated to the multi-strain dossier. The manufacturer would deliver the personalised BP together with the statement.

-Manufacturers would update their multi-strain dossier and would update authorities periodically with these updates as well as with pharmacovigilance data.

The main challenge of this approach would be the extrapolation of the data within a multi-strain dossier, that would be mainly focused on the administration route, but that would be problematic if the selected phage strain or strains belong to a different homologous group as the one present in the dossier.

Stability would be a critical parameter not possible to verify associated to real-time release, but less critical if it is considered a fast application to the patient.

In the praxis, the manufacturers might keep several multi-strain dossiers related to different routes of administrations and containing all defined homologous groups, still to be defined.

Although this process would have high manufacturing costs in comparison with a hypothetical hospital exception, the holding of libraries and multi-strain dossiers could assure access to many patients and attract SMEs or bigger companies to manufacture BPs. Since the intellectual property about BPs would not play a role in such a personalised-approach, the appeal for

private investors would result from keeping diverse libraries and GMP certification, assuring them profitability.

A development in this direction could easily enable phage therapy to answer effectively to an outbreak of a bacterial infection, since it would just require the preparation of a BP for targeting the specific pathogen in a bigger scale as for one patient.

The custom-made BP, or *sur-mesure*, is according to some authors the approach that would allow to phage therapy to reach its full potential[12,18,52,53]. Provided bacteriophages can be found everywhere and that they have being coevolving with bacteria, it seems possible to find and isolate phage strains against any possible MDR bacteria[13,17]. A well-established phage therapy should allow to find also a suitable dossier-based BP to incorporate the new selected effective strain to it.

The European regulations contain several provisions than allow personalised use of medicinal products in a limited way, and some efforts might be made in order to accommodate personalised medicine in general. A similar level of protection for public health could be expected for personalised BPs as for autologous ATMPs, to which the European Commission has acknowledged the need for adjusted and flexible requirements for fostering their development[56]. Therefore, some regulatory flexibility could be also expected for a personalised phage therapy. The efforts made today in order to broaden for personalised medicine, especially for ATMPs, should be used as well for phage therapy to create a suitable regulatory framework for the personalised approach.

Regardless the potential that phage therapy could have under such personalised approach, the reality is that much information is still needed on safety and efficacy of phage therapy in order to build a system that would guarantee a favourable risk/benefit ratio for a personalised approach. As any personalised medicinal product, their scope of use would mainly target unmet clinical need, limiting its potential use, but extremely useful for societies facing emergence of MDR bacteria. A personalised approach would also benefit from a broad implementation of the ready-to-use approach, since more safety and efficacy data would be available, as well as the knowledge and the awareness about phage therapy would increase among all the stakeholders involved in the health system.

9. Conclusion and outlook

The current regulatory framework for BPs did not consider medicinal products with the characteristics that phages have and cannot be considered suitable for phage therapy. A non-suitable regulatory framework has been highlighted as one of the main constraints that could prevent the further development of phage therapy under current existing standards.

BPs are biological medicinal products, but there are not specific guidelines or quality standards for phage therapy at European level. The potential of phage therapy lies on its flexibility. While it is becoming every time more difficult to find new antibiotics, the ubiquity and diversity of phages assure a virtually unlimited source for new medicinal products. Provided a balanced benefit-risk profile, these advantages should be enhanced within a suitable regulatory system, and not constrained.

Phage therapy is used today at the EU only in a named-patient basis using existing exceptions from Directive 2001/83/EC. This therapy is enjoying more interest as an alternative or complement to antibiotics, and several SMEs and institutions are having the lead generating data that should set the basis for a broader implementation of this therapy. Some steps have been made at the EU in order to bring closer different stakeholders and to propose solutions for improvement of the regulatory framework, but no changes are planned at the moment by regulators.

Lack of valid data and strong evidence is the main pointed reason not to perform changes to the current regulatory framework to adjust it to phage therapy peculiarities, and it is also a handicap to establish and define specific suitable provisions for phage therapy. All stakeholders agree that more data are necessary before phage therapy is considered as a real alternative or complement to antibiotics, but under current conditions, development is slow, and to develop BPs that could reach the European market will demand much time and major investments. In these conditions, a non-specific regulatory framework sets an extra obstacle for development of phage therapy.

Few adjustments in the current legislation deem necessary and should provide more certainty to BP developers and encourage the development of phage therapy, at least with respect to a ready-to-use approach. Basically, a change in the variation regulation, to allow change of phage strains, would guarantee the feasibility and sustainability of BPs composed of several strains, or phage cocktails, that would require updates to maintain their efficacy over long life cycles. There are precedents in the human and veterinary legislation allowing changes concerning the active substances. Some concepts as the homologous group and the multi-strain dossier could be helpful for developing specific provisions for ready-to-use BPs.

A personalised solution seems more difficult to conceive and to implement, and the customised application of phage therapy will likely be handled in coming years through the limited named-

patient exceptions to MA considered in the Directive 2001/83/EC. The magistral “premium” formula approach sets an important start point but it is hardly extensible to other EU countries. Some existing proposals might help to envisage a customised model that could have a positive benefit-risk ratio. Additionally, the customised approach could benefit from a higher demand on flexible approaches for other personalised treatments, as well as from a ready-to-use approach that could contribute to increase awareness in the authorities, developers, health professional and general public, while incrementing the safety and efficacy valid data under current state of the art procedures.

10. Summary

After many decades of scarce use in EU countries, phage therapy is having a revival due to the emergence of MDR bacteria and the need for alternative treatments. More data are urgently needed to provide evidence that phage therapy is a credible therapeutic alternative or complement to chemical antibiotics against bacterial infections. The existing regulations for biological medicinal products in the EU, which were not conceived considering the unique characteristics of phage therapy, do not provide an optimal regulatory framework that would promote the development of this therapy and all the potential advantages that might offer against bacterial infections. At the moment, phage therapy is being used in Europe only in a named-patient basis under national provisions out of the scope of Directive 2001/83/EC. Several proposals have already been made in order to amend the existing European regulatory framework, mainly considering two approaches: a ready-to-use bacteriophage product, and a customised approach. This master thesis analyses the different proposals and their applicability for establishing specific regulatory provisions for phage therapy. The ready-to-use approach has bigger chances to bring some bacteriophage product in the market in coming years and would benefit from some minor changes in regulations, especially considering variations. The customised approach would require further amendments and is less likely to have a specific regulatory framework at EU level in a short term, but it should benefit from the developments of the ready-to-use approach and specific national strategies that will generate necessary data for the benefit-risk assessment of this model.

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Neuwied, 7. September 2018

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