Comparison between American and European legislation in the therapeutical and alimentary bacteriophage usage

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Abstract. Bacteriophages, though discovered a century ago, still lag behind in the race of antimicrobials due to scarce information about their biology, pharmacology, safety and suitability as therapeutic agents. Although they possess several capabilities of practical utility in medicine, they are still unable to satisfy the regulatory standards set by the regulatory authorities in both United States (US) and European Union (EU). Bacteriophages and their products (lysins) are considered as drugs, therefore they should follow the same route of the chemical drugs in order to achieve regulatory approvals for commercial production and application. However, lack of definitive guidelines and regulations has rendered bacteriophages less attractive to pharmaceutical companies and funding agencies, making it difficult for clinicians and researchers to set up wide scale clinical trials in order to prove efficacy, safety and stability of bacteriophages and their products. In this review, we will discuss the current regulations for developing phages and phage-based products for therapeutic purposes in the US and EU. (www.actabiomedica.it)

Key words: bacteriophages, antimicrobial resistance, regulatory issues, applications of phages

Introduction

Bacteriophages are the most abundant, ubiquitous organism in nature that dwell inside bacteria and manifest dramatic expression in bacterial population dynamics (1). Thus, bacteriophages have the capability to select, occupy, renovate and reshape microbial communities. The estimated phage population is $10^{31}$ and they exist wherever bacteria are present (2). Bacteriophages have the capability of lysing bacteria in both broth and agar cultures (3-5). Since then, this property of phages made them attractive with respect to management and eradication of pathogenic bacteria in humans and animals. The experimentation on using phages in controlling bacterial infections began in 1920s, however this idea soon fell into oblivion due to uncontrolled use, lack of insight into their biology and pharmacokinetics and availability of antibiotics (Penicillin) as method of choice for treating bacterial infections (6-7). However within few years of antibiotic discovery the bacterial species started to become even stronger and developed many strategies against antibiotics collectively termed as antimicrobial resistance. These ‘super bugs’ pose serious threats to the public health across the globe and account for 700000 annual deaths with an increasing trend year after year (8-9).

The rate at which the bacteria evolve and develop antibiotic resistance has raised alarming situation in the world. However, this has led to a decreased interest in research and development of novel antibiotic
compounds for commercial purposes. For instance, in US, 16 new antibiotics were approved by the Food and Drug Administration (FDA) during 1983-1987, and this number was reduced to only 6 between 2010-2016 (10). Consequently there is a global demand of finding new antimicrobials, whereas majority of the big pharmaceutical companies have lost interest in funding new antibiotics, with only two antibiotics approved for commercialization by both FDA and European Medicine Agency (EMA) in the past two decades (10, 11) and carbapenem class of antibiotics being kept as "last resort" due to their deleterious side effects on health. Keeping in view the severity of the situation, a meeting was convened by the United Nations General Assembly on 1st Sep 2016 where the antibiotic resistance was considered "the greatest and most urgent global risk" (12). Consequently, reaching the end of the antibiotic pipeline resulted in a paradigm shift towards finding alternative strategies to combat notoriously resistant bacteria. The world at present is preparing to tackle antimicrobial resistance by finding alternative to antibiotics and this has redrawn the attention to the ‘viral tenants residing in bacteria’ thus reviving the old concept of deploying bacteriophages as predators to pathogenic bacteria in various in vitro and in vivo applications collectively termed as 'phage therapy’ (13).

Phages do not dwell only in all bacterial niches but have evolved mechanisms to combat their resistance strategies that gives them an edge over their hosts and this is what makes them attractive from medicinal and biotechnological point of view (13, 14). In this review, we will discuss the current regulations for developing phages and phage-based products for therapeutic purposes in the US and EU.

American and European legislations on the phage therapy

There are no explicit regulatory guidelines that cover phage therapy and phage-based therapeutic formulations. One of the major concerns is whether phages and phage-based formulations can be classified as 'biological medicinal products (BMPs) as per Commission Directive (2001/83/EC) or as an 'advanced therapy medicinal product’ (ATMP) (Commission Directive 2003/63/EC) (15,16). The European Medicines Agency (EMA) has not approved any phage-based product, therefore it is difficult to say which one these directives should be followed to obtain successful product approval. Since 2011, the phages have been classified as drugs in the US and as medicinal product in EU (17). A medicinal product is defined by EMA as 'a substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action’ (18). A workshop was held by EMA in 2015, in which approximately 60 experts from academia, industry, policy makers and patient organizations discussed practical and regulatory issues in obtaining a licence to develop bacteriophage-based therapies against bacterial infections (18). It was also discussed whether or not the EU Directive 2001/83/EC be applicable to phages or not.

There are several reasons that pose regulatory barriers to the worldwide production and application of phages as alternatives to or at least as supplementary applications to antibiotic. The first and foremost is the lack of awareness and knowledge about phage therapy due to lack of supporting data obtained from clinical trials set up according to national and international ethical standards. Altough countries like Georgia, Russia and Poland have been practicing phage therapy since its discovery there are not regulatory guidelines that can be adapted (19). However in Poland, phage therapy is considered an 'experimental treatment' under the Polish Law Gazette, 2011, item 1634 and article 37 of Declaration of Helsinki (20).

The difficulty of having a uniform regulation is due to the fact that phage therapy does not follow a ‘one size fit for all’ pattern but is rather tailor made according to the needs of the patients. Phage experts have proposed two approaches for phage therapy:

1) Sur-mesure therapy, a tailored therapy matching the individual phages with the pathogen isolated from the patient themselves. The sur-mesure therapy is based on the host-specific nature of phages. This demands the isolation and purification of the target pathogen from complex infections to deploy a potent phage strain capable of causing lysis or elimination of the pathogen from a particular site. However, this is
easy said than done keeping in view of complex bacterial infections in various organs that demands the collection and analysis of biopsy samples (21);

2) Prêt-à-porter model, a polyvalent phage cocktail against a particular type of infection or pathogen (22). Although phage cocktails have been deployed to neutralise pathogenic bacteria in experimental setups the actual number of phage strains available for medical doctors is really scarce. A recent study reports that even if a medical practitioner isolates a specific pathogen the selection of suitable phage is a limiting factor in the application of phage therapy. In fact, when a particular pathogen is screened for active phages the phagogram is often negative indicating the scarcity of available phages (23,24).

Even if a desired phage is obtained the next problem there should be evaluated the safety profile and the absence of side effects. This requires that phages should be isolated, characterized and propagated according to Good manufacturing practice (GMP) standards in the EU thus treating them as industrial phages. However, GMP compliance represents a real challenge and demands extensive financial resources that acts as a huge repelling factor for hospitals and non-profit organizations to sponsors phage therapy (10). Similarly in order to use a phage for Direct human applications in the US, the FDA requires assurance of efficacy and safety backed up by clinical trials data. However before getting to clinical trials special emphasis is given to how phages are isolated, produced and distributed (25), accordingly some of the researchers have proposed that governmental entities such as US National institute for Health (NIH) and its analogues across the world should make phage libraries, collecting, characterizing and maintaining various phages that can be safely deployed to meet the therapeutic demands. Similarly, Universities and institutes can also host such libraries that can allow easy access of phage sample. Setting up of such phage library would ensure that appropriate phage particles are used for medical and therapeutic purposes thus ensuring the safety (26,27).

One of the main challenges is the selection of phage on the basis of their mode of replication. Phages applied in phage therapy should be strictly obligate lytic phages or virulent phages. Lysogenic phages are not suitable for phage therapy because they can integrate in the genome of the target bacteria making them resistant to the lytic phages, carry bacterial genes from one bacteria to another possibly transferring antibiotic or phage resistance genes, transfer genes encoding toxins and virulence factors thus converting the target bacteria into ‘super bugs’ (12,28,29). This is indeed one of the major concerns in obtaining approval of phage-based products for direct human consumption in both US and EU.

Another important reason for lack of interest in developing phage therapy from a manufacturer point of view is the evolutionary instability of phages that poses threat to the stability of the phage-based formulations (30). For instance, lytic phages rapidly coevolve with bacterial species thus creating a new phage requiring new clinical trials, new ethical and regulatory approvals thus increasing the overall cost of the product (31). In both US and EU regulations the phages and phage-based products (enzymes) are classified as human therapeutic products and are subjected to the same rigorous implementation procedure like conventional drugs. The FDA and EMA regulations implicate that once a finished medicinal product is registered and approved no further modifications and improvements can be made. This means any changes in the registered and approved products will have to undergo a fresh approval (17,32). Hence, the potentially registered phage preparations cannot be improved in any circumstance after approval whether the change is natural because of evolution or deliberate. Nowadays, given all these difficulties, the prêt-à-porter model is slightly easier to implement. In addition, since phage products are classified as BMPs, their application is not allowed under the “hospital exemption,” as in the ATMPs. This regulation restricts the use of tailored phage therapy for a particular patient (17,25,32).

To further worsen the scenario, there are the intellectual property rights of the finally formulated products. Unlike antibiotics which are chemical compounds and can be patented, phage-based formulations cannot be patented in both US and EU (33). Judges in courts around the world generally decline the patents requested by individuals and firms based on any form of life or their constituents such as DNA or RNA. A historical decision was made by US supreme court in 2013 against issuing the patents for single genes and
gene sequences. The EU however passed a law extending patents to genes isolated from their natural environments but they did not rule out patents for gene sequencing technologies, altered genes, or novel methodologies for using existing genes or organisms for therapeutic purposes (25,34). Allowing patents for single genes or biological organisms would mean that every time a patented gene or organism is used by researchers, money would have to be given to the patent holder. Firms could try to earn profits by creating phages and changing their genome by CRISPR-Cas technology to earn patents according to the aforementioned EU law (25).

Although the development and marketing of phage-based products are currently difficult under the present regulations in both US and EU, the so called ‘compassionate use’ of phage therapy is allowed across EU and US on a case-to-case basis, especially for patients that failed conventional therapies and that are unable to take part in clinical trials (35). Although the EMA provides guiding recommendations each member state implements and coordinates this ‘compassionate use’ of phage therapy according to its own national rules and regulations. Like the article 37 of Helsinki Declaration, the compassionate use of medicines can only be applied if it is helpful in life threatening, chronic and/ or serious problems for which all other available therapeutic methods have failed. This also necessitates that the medicinal products to be used have already been tested and entered marketing authorization application after efficacy and safety studies have been conducted and validated. In France for example the 'Agence Nationale de Sécurité du Medicament et les Produits de Santé (ANSM)', is tightly involved in coordinating ‘compassionate use’ of medicinal products since 2016. ANSM has also created a committee comprising external experts in different fields ‘comité scientifique spécialisé temporaire (CSST)’ for phage therapy. This committee evaluates and discusses the application with the treating physician and sends recommendations to ANSM which then finally decides to approve or reject the request (36).

Fifteen patients have received the compassionate phage therapy between 2006 to 2018, in France and 11 out of 15 were cured immediately. Each application for compassionate treatment is analysed and evaluated by the competent authority. A clinical report is compiled for each application, to help optimise the phage therapy approaches in the absence of an adapted regulatory framework (36,37).

During the past 15 years phage therapy has been revived in laboratories and hospitals and more patients are receiving PT in France, Belgium and Poland to treat cases where existing therapeutic agents failed to provide a cure (37,38).

Also the United States allow the use of phage therapy for special cases. For instance, the case of Professor Tom Patterson, who was infected by a toti-resistant strain of Acinetobacter baumannii in Egypt, was treated by phage therapy after his colleagues received an approval a last resort from FDA (39,25). Moreover, naturally and synthetically modified phages have been used to treat a cystic fibrosis patient infected with a disseminated drug-resistant Mycobacterium abscessus in England (40).

Belgium is now implementing a phage therapy framework that focuses on the magistral preparations (compounding pharmacy in the US) of tailored phage-based medicines. Belgian Minister of social affairs and public health agreed to consider phages as magistral phage formulations (36). The Belgian Magistral Phage medicine framework is expected to be flexible enough to exploit and explore the phages coevolving antibacterial while giving preference to patients safety. This would also avoid stringent production requirements like GMP and would facilitate development of phage-based products for therapeutic purposes (36).

To date, only one phage-based product (a phage lysate) against staphylococcal infections is available in market under trade name Stafal®20 (41) in EU. This product was approved by the Czech National Competent Authority, the State Institute for Drug Control as an intended topical treatment for Staphylococcus infections (registration number 59/0149/89-CS) (20). Although phage therapy is successfully being used in EU in the Ludwik Hirszfeld Institute of Immunology and Experimental Therapy of Wroclaw, Poland (42), and Queen Astrid Military Hospital in Brussels, Belgium (43), there is a need of changing European laws that govern the status of phage therapy and registration of phages and phage-derivatives in order to attract big
pharmaceutical companies in investing in phage-based products (22).

**Future perspectives of phage therapy**

Although there is still an unclear picture in both US and EU with respect to regulations governing and pertaining to phage therapy and phage-based formulations including recombinant phage proteins, the future of phage therapy seems promising in this increasing antimicrobial resistance scenario where available antimicrobials are becoming less effective in treating complex life threatening infections. In this regard due consideration is required in selection, preparation and application of phage therapy both as personalised tailored medicine and as a general fit for all medicine. However this requires rigorous clinical trials based on phage formulations prepared according to GMP giving due consideration to individual human rights of safety and wellbeing and informed consent prior the start of the trials.

After the premature termination of the first European randomised controlled phase 1/2 clinical trial termed as ‘PhagoBurn’, www.Phagoburn.eu due to insufficient efficacy, more clinical trials have been launched successfully. Although this trial failed to produce the desired results it was the first of its kind in the EU to use phages purified according to GMP standards and approved by National health regulators (10). Despite of its failure researchers and dedicated institutes designed new projects to address the safety, tolerability and efficacy of purified phage products. For instance in 2017 the German Phage4Cure (http://phage4cure.de/) consortium launched by the four partners (Fraunhofer Institute for Toxicology and Experimental Medicine, ITEM; the Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures GmbH; Charité–Universitätsmedizin Berlin; and Charité Research Organisation GmbH, CRO) aimed to address the safety, tolerability and efficacy of a purified inhaled bacteriophage cocktail prepared according to GMP standards against *P. aeruginosa* causing chronic airway infection (44) and pave the way for clinical applications of bacteriophages in Germany and Western Europe after getting approval from the concerned regulatory authorities (44). In addition to that two other projects are also under way in Western Europe namely PhagoMed and PhagoFlow. The biotech company PhagoMed Biopharma GmbH (https://www.phagomed.com/), based in Vienna, aims to develop phage-based therapies for bacterial infections (45) and is supported by grants and private investments. While, PhagoFlow aims to test magistral prescription of phages in patients having wounds infected by multi-drug resistant bacteria. This project is being conducted at the military hospital of Berlin, together with DSMZ and Fraunhofer ITEM (46). Besides that more trials are in progress including phage therapy for urinary tract infections that has provided encouraging results (47). Besides these European trials, things are changing in the US. The FDA has recently approved the application of a phage therapy centre to conduct clinical trials for intravenous administration of phage therapy in patients with ventricular assist devices infected by *S. aureus* (48).

Keeping in view the flexibility of the Belgian Magistral phage therapy framework, it can be speculated that other EU countries might also adopt it in the near future, anticipating a shared European solution.

In conclusion, easing off the regulations pertaining to commercial development of phage based therapies may provide the biological solution of notorious pathogens such as *Pseudomonas aeruginosa* and *H. pylori*

**Conclusion**

Bacteriophages have a treasure of capabilities that is yet to be explored to its fullest potential in medicine. These obligate parasites provide hopes to several hopeless cases with failed medical therapies. Nevertheless, their production at a commercial scale involves many checks and balances starting from the laboratories where these are isolated to the clinic where these will be applied. To facilitate these procedures regulatory bodies need to play their role, however they need to be assured that the phage-based therapies would achieve Gold standard and would be prepared following GMP and GCP. This ultimately demands highly sophisticated clinical trials across the globe using phage for-
mulations prepared according to the standards set by regulatory authorities.

In this regard, the regulatory authorities should reconsider phage classifications as drugs or medicinal products same as chemical drugs like aspirin. Phages are a form of life and they need to be dealt with separately as compared to the chemical drugs. This also requires social moral and financial commitment on part of physicians, academics, researchers, industries, funding agencies and the governments to nurture, cater and promote a culture of biological control of notorious human pathogenic bacteria. Generous funding both from the public and private sector will be required to prove safety, stability and viability of these bacterial tenants for therapeutic applications.

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References

1. Hankin EH. L’action bactéricide des eaux de la Jumna et du Gange sur le vibron du choléra. Ann Inst Pasteur (Paris) 1896; 10: 511–23.
2. Twort FW. An investigation on the nature of ultra-microscopic viruses. Lancet 1915; 186: 1241–3.
3. Keen EC. Phage therapy: concept to cure. Front Microbiol 2012; 3: 238.
4. d’Herelle F. Sur un microbe invisible antagoniste des bacilles dysentériques. Comptes Rendus Acad Sci Paris 1917; 165: 173–5.
5. d’Herelle F. Bacteriophage as a treatment in acute medical and surgical infections. Bull N Y Acad Med 1931; 7: 329–348.
6. Fleming A. On the antibacterial action of cultures of a Penicillium with special reference to their use in the isolation of B. influenza. Br J Exp Pathol 1929; 10: 226–36.
7. Chain E, Florey HW, Gardner NG, et al. Penicillin as a chemotherapeutic agent. Lancet 1940; 236: 226–8.
8. WHO. 2018. Antimicrobial resistance WHO. http://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance.
9. WHO. 2017. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/.
10. Luepke KH, Suda KJ, Boucher H, et al. Past, present, and future of antibiotic economics: increasing bacterial resistance, limited antibiotic pipeline, and societal implications. Pharmacotherapy 2017; 37: 71–84.
11. Tacconelli E, Carrara E, Savoldi A, et al. WHO Pathogens Priority List Working Group. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 2018; 18(3): 318–27.
12. United Nations. 2017. PRESS RELEASE: High-Level Meeting on Antimicrobial Resistance. 2016; Accessed Mar 29, 2017.
13. Nair RR, Vasu M, Wielgoss S, et al. Bacterial predator-prey coevolution accelerates genome evolution and selects on virulence-associated prey defences. Nat Commun 2019; 10: 4301.
14. Simmonds P, Aiewsakun P. Virus classification — where do you draw the line? Arch Virol 2018; 163: 2037–46.
15. European Commission. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use (consolidated version: 16/11/2012). In EudraLex—The Rules Governing Medicinal Products in the European Union (Volume 1), Pharmaceutical Legislation: Medicinal Products For Human Use. Available online: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf Commission Directive 2003/63/EC of 25 June 2003 amending.
16. Directive 2001/83/EC of the European Parliament and the council of the Community code relating to medicinal products for human use. Official Journal of the European Union.
17. Verbeken G, Pirmay JP, De Vos D, et al. (2012) Optimizing the European regulatory framework for sustainable bacteriophage therapy in human medicine. Arch Immunol Ther Exp (Warsz) 2012; 60: 161–72.
18. European Medicines Agency (EMA). Workshop on the Therapeutic Use of Bacteriophages. 2015. Available online: https://www.ema.europa.eu/documents/other/therapeuticusebacteriophages-summary_en.pdf.
19. Guo Z, Lin H, Ji X, et al. Therapeutic applications of lytic phages in human medicine. Microb Pathog 2020; 142:04048.
20. Verbeken G, De Vos D, Vancechouette M, Merabishvili M, Zizi M, Pirmay JP. European regulatory conundrum of phage therapy. Future Microbiol 2007; 2(5): 485–91.
21. Colavecchio A, Cadieux B, Lo A, Goodridge LD. Bacteriophages contribute to the spread of antibiotic resistance genes among foodborne pathogens of the enterobacteriaceae family – A review. Front Microbiol 2017; 8: 1108.
22. Pirmay JP, De Vos D, Verbeken G, et al. The phage therapy paradigm: prêt-à-porter or surmesure? Pharm Res 2011; 28: 934–7.
23. Moelling K, Broecker F, Willy C. A wake-up call: We need phage therapy now. Viruses 2018; 10: 688.
24. Bourdin G, Schmitt B, Marvin Guy L, et al. Amplification and purification of T4-like Escherichia coli phages for phage therapy: From laboratory to pilot scale. Appl Environ Microbiol 2014; 80: 1469–76.
25. Anomaly J. The future of phage: Ethical challenges of using
phage therapy to treat bacterial infections, Public Health Ethics 2020; 13 (1): 82–8.
26. Rohde C, Wittmann J, Kutter E. Bacteriophages: A therapy concept against multi-drug-resistant bacteria. Surg Infect (Larchmt) 2018; 19: 737–44.
27. Sybesma W, Rohde C, Bardy P, et al. Silk Route to the acceptance and re-implementation of bacteriophage therapy-Part II. Antibiotics 2018; 7: 35.
28. Abedon ST. Lysis from without. Bacteriophage 2011; 1: 46–9.
29. Loc-Carrillo C, Abedon S. Pros and cons of phage therapy. Bacteriophage 2011; 1: 111–4.
30. Brives C, Pourraz J. Phage therapy as a potential solution in the fight against AMR: obstacles and possible futures. Palgrave Commun 2020; 6: 100.
31. Koskella B, Brockhurst MA. Bacteria-phage coevolution as a driver of ecological and evolutionary processes in microbial communities. FEMS Microbiology Rev 2014; 38: 916–31.
32. Maciejewska B, Olszak T, Drulis-Kawa Z. Applications of bacteriophages versus phage enzymes to combat and cure bacterial infections: an ambitious and also a realistic application? Appl Microbiol Biotechnol 2018; 102(6): 2563–81.
33. Brüssow H. What is needed for phage therapy to become a reality in Western medicine? Virology 2012; 434: 138-42.
34. Pirmay JP, Verbeken G, Rose T, et al. Introducing yesterday’s phage therapy in today’s medicine. Future Virol 2012; 7: 379-90.
35. Patey O, McCallin S, Mazure H, Liddle M, Smithyman A, Dublanchet A. Clinical indications and compassionate use of phage therapy: personal experience and literature review with a focus on osteoarticular infections. Viruses 2019; 11: 18.
36. Pirmay JP, Verbeken G, Ceyssens PJ, et al. The magistral phage. Viruses 2018; 10(2): 64.
37. Djebara S, Maussen C, De Vos D, et al. Processing phage therapy requests in a Brussels military hospital: lessons identified. Viruses 2019; 11: 265.
38. Gorski A, Jonczyk-Matysiak E, LusiakSzelachowska M, et al. The potential of phage therapy in sepsis. Front Immunol 2017; 8: 1783.
39. Kasman LM, Kasman A, Westwater C, Dolan J, Schmidt MG, Norris JS. Overcoming the phage replication thres-
old: a mathematical model with implications for phage therapy. J Virol 2002; 76: 5557-64.
40. Dedrick RM, Guerrero-Bustamante CA, Garlena RA, et al. Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant Mycobacterium abscessus. Nat Med 2019; 25: 730–3.
41. Dvořáková M, Růžička F, Benešík M, et al. Antimicrobial effect of commercial phage preparation Stafal® on biofilm and planktonic forms of meticillin-resistant Staphylococcus aureus. Folia Microbiol 2019; 64: 121–6.
42. Miedzybrodzki R, Borysowski J, Weber-Dabrowska B, et al. Clinical aspects of phage therapy. Adv Virus Res 2012; 83: 73–121.
43. Jenns S, Merabishvili M, Soentjens P, et al. Use of bacteriophages in the treatment of colistin-only-sensitive Pseudomonas aeruginosa septicaemia in a patient with acute kidney injury—a case report. Crit Care 2017; 21: 129.
44. Poole K. Pseudomonas aeruginosa: Resistance to the max. Front Microbiol 2011; 2: 65.
45. PhagoMed. Available online: http://www.phagomed.com/2018/08/28/viruses-against-bacteria/
46. Geförderte Projekte des Innovationsausschusses zur Förderbekanntmachung Versorgungsforschung vom 20.Okto-
ber 2017, PhagoFlow (page 25). Available online: https://innovationsfonds.g-ba.de/downloads/media/112/1/5/Liste-ge-
foerderter-Projekte-VSF-FBK_20-10-2017.pdf.
47. Ujmajuridze A, Chanishvili N, Goderdzishvili M, et al. Adapted bacteriophages for treating urinary tract infections. Front Microbiol 2018; 9: 1832.
48. UCSD. Center for innovative phage applications and therapeutics. https://medschool.ucsd.edu/som/medicine/divisions/idgph/research/center-innovative-phage-applications-and-therapeutics/Pages/default.aspx. Accessed January 14, 2019.