Sustainable implementation of human phage therapy across the EU, EU-JAMRAI-2 conference report

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Abstract

This conference dedicated to the sustainable implementation of human phage therapy across the European Union (EU) took place on the first of March 2024, in Brussels Belgium. Gathering 118 participants from 17 countries, the program covered two sessions: first, an overview of the state of phage therapy implementation across different EU countries, followed by a second session made of two round tables focusing on the current issues regarding manufacturing and quality control for the first one, and the legal framework (national/EU) and fundings for the second one. This one day event included interventions by medical doctors, pharmacists, phage biologists, representatives from the European Institutions (DG santé, JRC, EC…), and representatives from National Drug Agencies of multiple EU countries. Overall, participants agreed that a sustainable implementation of phage therapy across the EU is critical to fight against the rising threat of AMR. Representatives of the EU and National drug agencies were supportive and encourage all the stakeholders (MDs, pharmacists, phage biologist, phage manufacturers) to discuss with them to move the field forward and make phage therapy more easily available to the patients in needs. Notably, one concrete step towards implementation of phage therapy worldwide was taken in the launch of "Phagistry" (https://www.phagistry.org/), the first international, anonymized, retrospective, phage therapy patient registry, created by an international consortium led by Shawna McCallin (Balgrist University, Switzerland).

Keywords: phage therapy; bacteriophages; production; quality control; legal framework; EU

Introduction

This conference, tilted "WP9.4 Sustainable implementation of human phage therapy across EU" was organized as part of work package 9 of the Joint Action on Antimicrobial Resistance and Healthcare Associated Infections (JAMRAI). JAMRAI is a collaborative project built on existing works and initiatives undertaken by Member States and international organizations including OECD, ECDC, WHO Europe, OIE and FAO.

This Joint Action (JA) objective is to survey the best programs across the EU and propose concrete steps to implement best practices to tackle Antimicrobial Resistance (AMR) and Healthcare-associated

Infections (HCAI) in the Member States. Overall, JAMRAI aims at joining forces to define European common policies to fight AMR and control HCAI, in line with the One Health approach.
This one day conference was focused on phage therapy (PT) as a concrete way to tackle the rise of AMR across the EU. It was organized on March 1st 2024 in Brussels, Belgium. It hosted 59 participants on site and 59 online, from 17 countries, including MDs and Hospital Pharmacists, representatives from National Drug Agencies, and representatives from EU agencies (DG santé, JRC, EC, HERA,…). The meeting program was divided in two parts: "Part 1: State of play" and "Part 2: Towards sustainable implementation".

"Part 1: State of play" gave us an overview of PT implementation across different EU countries (Belgium, the Netherlands, France and Germany). After a PT patient testimony by Karen Northshiled, Willem-Jan Metsemakers (UZ Leuven, BE) gave us an MD's perspective on PT, then Jan Dekker (UMC Utrecht, NL) gave us an Hospital Pharmacist' perspective on PT. Followed Sarah Djebara (HMRA, BE) who presented an overview of PT use in Belgium, then Frédéric Laurent (CHU Lyon, Hospices Civils de Lyon, UCBL, FR) talked about the current development of PT in France, while Maria Vehreschild (University Hospital Cologne, DE) summarized the situation regarding PT in Germany. This first part of the conference also included two presentations from EU representatives, the first from Amalia Muñoz-Piñeiro (JRC.F.7), giving an overview of a new report on PT and Phage Biocontrol, and the second one, from Pietro Erba (DG santé), presenting the current EU initiatives/legislations around PT. Of note, this part of the conference also included a presentation by Shawna McCallin (Balgrist University, CH) of "Phagistry" (https://www.phagistry.org/), the first international PT patient registry. This session ended with a presentation about field application of phage biocontrol applied to salmon aquaculture in Norway by Hans Petter Kleppen (ACD Pharma, NO).

"Part 2: Towards sustainable implementation" consisted in two round tables. The first one, chaired by Mathieu De Jode (Belgian Public Health Institute Sciensano, BE), specifically addressed the current issues regarding manufacturing (GMP/GPP, what do we need ?) and quality control (what to test and how?) and included a panel consisting of Frenk Smrekar (JAFRAL, SL), Holger Loessner (PEI, DE), Laure Deligniville (ANSM, FR), Karin Froidbise (FAMHP, BE) and Pieter-Jan Ceyssens (Sciensano, BE). The second round table was chaired by Frédéric Laurent (CHU Lyon, Hospices Civils de Lyon, UCBL, FR) and discussed the legal framework (national/EU) and EU fundings opportunities for phage therapy. Its panel consisted of Jean-Baptiste Perrin (HERA, EU), Alessandra Martini (EC, EU), Jean-Paul Pirnay (QAMH, BE), Daniel Holý (SÚKL, CZ), Nathalie Morgensztejn (ANSM, FR), and Valerie Denux (ANSM, FR).

Part 1: State of play

The conference started with the PT patient testimony of Karen Northshiled, who suffered a polytrauma during the suicide bombing at the Brussels Airport in March 2016. Following multiple rounds of surgeries she was diagnosed with a fracture-related pandrug-resistant *Klebsiella pneumoniae* infection in her left thigh, which was not responsive to classical antibiotic therapies. After 2 years of unsuccessful treatment, a new treatment strategy consisting of a pre-adapted bacteriophage along with meropenem and colistin, followed by ceftazidime/avibactam was used. This salvage therapy results in objective clinical, microbiological and radiological improvement of her wounds and overall condition[1]. During her presentation, Karen Northshiled insisted on how PT changed her life as it was the first treatment that improved her condition after 2 years in the hospital, but also pointed out that such therapy should be more readily available to the patients in needs. She wrote a book about her experience, available in French *"Dans le souffle de la bombe"* and Dutch *"Weggeblazen door de bom"*.

The second speaker, Willem-Jan Metsemakers (UZ Leuven, BE), presented his MD's perspective on PT. In his experience, PT could be a potent solution for difficult to treat infections (decades of infection, biofilm, amputation needed…). Indeed, in a new systematic review of a the literature concerning PT safety and efficacy that he co-authored[2], he found that PT can potentially be beneficial in the treatment of difficult-to-treat bacterial infections, and is generally considered safe, via different routes of administration, with a low incidence of adverse events. However, he also insisted that although PT seems a promising strategy in the fight against infections, high quality randomized clinical trials (RCTs) are urgently required. He then presented his team's efforts towards a more sustainable implementation of PT via the development of a standardized multidisciplinary treatment protocol for PT against difficult to treat musculoskeletal infections[3], which lead to the PHAGEFORCE Study Protocol[4].

Then, Jan Dekker (UMC Utrecht, NL) presented "Bacteriophages from a pharmacist' perspective". He was focused on phage preparation, especially by compounding, and started by presenting the 3 different paths leading to a clinically usable phage product (Fig1). In the first path, the phage is a registered commercial product, prepared under GMP (Good Manufacturing Practices). Although classical, this approach would lead to only a limited number of phage being available as GMP certification/production and the RCTs needed to obtained commercial licenses would cost a lot of time and money. Indeed, it was recently estimated that the pre-launch research and development costs of one new drug to be brought to the market were estimated to range from $161 million to $4.54 billion[5]. Additionally, the average development time of anti-infective molecules was found to be 6.4 years[5]. Overall, this time and cost to register, produce under GMP, and obtain market authorization, will constrain phage compagnies to limit the number of licensed phage products, thus limiting the number of patient on which these phages will work.
In the second path, phages are produced under GMP into an active pharmaceutical ingredient (API), which is then prepared by the hospital pharmacist ("compounding") into a compounded product. This allows for a more personal treatment approach as the correct phage API can be matched to the patient needs. However, once again the GMP production, due to its cost and complexity, would surely limits the number of API available to the pharmacist. In the third path, compounding is once again used, but this time to directly prepare a phage into a compounded product, without need for GMP, which would allow for the preparation of personalized phage treatments for any patient, using the "unlimited" pool of natural phages.
In both the second and third path compounding is used: this refers to the ability of an hospital pharmacist to prepared unlicensed product (exempted from the formal licensing requirement) to meet the special needs of individual patients. However, this exceptional procedure is framed by guidelines from the European Pharmacopoeia (Ph. Eur.) which states that the use of an unlicensed preparation involve the area of responsibility of all health professionals involved (*e.g.* the prescribing practitioners and/or the preparing pharmacists) which have a duty of care to the patient receiving the pharmaceutical preparation. Moreover, when considering the preparation of an unlicensed pharmaceutical preparation, a suitable level of risk assessment is undertaken: evaluating the criticality of different parameters relative to the quality of the preparation (*e.g.* quality of active substances, excipients and containers; design of the preparation process; extent and significance of testing; stability of the preparation) and the risk that the preparation may present to a particular patient group.
Based on this risk assessment, the person in charge of the preparation must ensure, with a suitable level of assurance, that the pharmaceutical preparation is: throughout its shelf-life, of an appropriate quality and suitable and fit for its purpose. For stock preparations, storage conditions and shelf-life have to be justified (analytical data, professional judgement, literature references…).
Such preparation usually follows a monograph, and for phage product only the Belgian monograph is available[6] for now, but the BACT working group is currently developing a general chapter for phage to be included in the Ph. Eur.

Finally, Jan Dekker concluded that a sustainable implementation of PT would require a clear placement of PT (*e.g.* a pharmacotherapeutic rationale), a specific roadmap for compounding bacteriophages (*e.g.* in the Ph. Eur.) and of course, the reimbursement of the therapy (phage products are currently often given for free).

The next talk gave us a first overview of a new report on Phage therapy and Phage Biocontrol by the European Joint Research Centre (JRC). This presentation by Amalia Muñoz-Piñeiro started by a brief history of phage use: First medical use in 1919, to treat dysentery in humans (Felix d´Herelle)[7], first use for biocontrol in 1924 to treat *Xantomonas campestris* pv.*campestris* in crucifers (Mallmann and Hemstreet)[8], 1930´s first marketed phage's preparations by big pharma companies (Eli Lilly, Swan-Meyers), and finally the replacement of phages by antibiotics (easier to use and with a wider action spectrum) after World War II[9]. Then she presented the 3 way of applying phages: personalized therapy where one or more phage are specially selected and produced for a given patient; fixed phage cocktails which are prepared in advance and designed to cover one or more bacterial species; phages and antibiotics combinations. Then, she moved on to an overview of PT "advantages" and "weaknesses", which are summarized in Figure 2. Next, she talked about the need of RCTs investigating PT. Indeed, according to the EMA, a medicine cannot be recommended for approval before its efficacy and safety have been proven on the basis of appropriate clinical trials. However, this has been proven difficult for PT as most of its use has been reported as individual case reports, and in which phages are often combined with other antimicrobials. Only few modest size RCTs have been published (including the EU sponsored PhagoBurn trial[10]) and revealed difficulties in patient recruitment, phage product stability, and overall trial design, which limited their conclusions on PT efficacy and safety. A point was made that most registered RCTs currently investigate the use of phage cocktails as stand-alone treatments, while in the clinical practices reported, phages are almost always combined with other antimicrobials (mostly antibiotics). Thus, future RCTs might want to consider investigating phage antibiotics combination rather than phages alone, as this will better inform real world application of PT. Overall, the design of RCTs investigating PT should be tailored to PT distinctive characteristics rather than copying "classical drug" RCT design. The next point concerned the lack of standardization/harmonization concerning phage administration protocols and adverse event reporting, as well as the striking differences in national frameworks around PT (fig3). At the EU level, phage products are considered medicinal products (2011, EC) meaning the same manufacturing requirements, clinical trials, and marketing authorization as antibiotics. However, it was recognized that this framework is not adapted to ad-hoc applications when antibiotics are failing, and new efforts to create "phage specific" frameworks/rules have been started. Indeed, in April 2023 both a Proposal for a new Directive of the European Parliament and Council related to medicinal products for human use – Annex VII mentions "phage containing medicinal product", and a General Chapter on: "Phage therapy active substances and medicinal products for human and veterinary use", were released. In December 2023, the EMA published a Concept Paper on "the establishment of a Guideline on the development and manufacture of human medicinal products specifically designed for phage therapy". Recently, in March 2024, a new general chapter to be published in June in the European Pharmacopoeia titled "Phage therapy medicinal products (5.31)" was pre-released. It provides a framework of requirements for the production and control of phage therapy products and allows a degree of flexibility commensurate with the complex approaches currently employed in this emerging and rapidly developing field. The Bacteriophage Working Party will next work on the general chapter on bacteriophage potency determination.

Following was a presentation by Pietro Erbo from DG santé. He started by introducing the new "EU Pharma Strategy" adopted in November 2020, which aims at creating a future proof regulatory framework and supporting industry in promoting research and technologies that actually reach patients in order to fulfil their therapeutic needs. This plan has 6 political objectives: Access, Availability, Affordability, Competitive regulatory framework, Checking environment sustainability, and

Combatting AMR. This plan objective is to address the rapid scientific and technological developments that resulted in new challenges for the system. Indeed, new treatments emerge (*e.g.* personalized medicines) alongside novel approaches and processes and these don't always completely fit within existing laws and regulations. This mismatch can unintentionally create obstacles for innovation, development, production, and even getting approval for these new medicines to reach patients. The current framework is not adapted to novel production technologies or methods (*e.g.* decentralized manufacturing), and this negatively impacts innovation while some innovative products may remain unregulated with negative effect on public health. Then he focused on the AMR related challenges, reminding us that AMR causes 35.000 deaths per year in the EU and amounts to around 1.5 billion euros per year in healthcare costs. Currently, there is a market failure as new effective antimicrobials are lacking, probably due to the high cost of developing a new antibiotic (around 0.5 billion). To tackle these AMR challenges, the EU has launched multiple initiatives including limiting antibiotics use (via prescription, restricted quantities, education…), regulatory incentives with transferable exclusivity vouchers under strict conditions (only novel antimicrobials, full transparency of all funding, obligation of supply, max 10 vouchers in 15 years), financial incentives with procurement mechanisms (HERA), and of course alternatives therapeutic approaches, including PT. One of the challenge of phage therapy implementation in Europe, identified by DG santé, is the lack of distinct regulatory and scientific guidance coupled with scarce clinical and manufacturing experience which are two "issues" feeding each other. It was proposed to address this framework issues via a Proposal for a Directive of the European Parliament and of the Council repelling Directive 2001/83/EC and Directive 2009/35/EC; 2023/0132 (COD), which in its article 28 describes "Adapted frameworks due to the characteristics or methods inherent to the medicinal product". This text states that adapted product regulation can be required if standard regulations are inadequate due to scientific/regulatory challenges. and if unique characteristics/methods positively impact quality, safety, efficacy, patient access, or care. In that case, a proportional to risk and impact, allowing for adaptation, enhancement, waiver, or deferral of requirements can be granted. Waivers/deferrals will be limited, justified, and reviewed regularly, and standard rules still apply except for adapted ones. The Annex VII of this proposal includes "Phage-containing medicinal products, in cases where the medicinal product has a variable composition depending on the specific clinical context."
Finally, the presentation ended with a brief evocation of the EMA concept paper on the establishment of a guideline on the development and manufacture of human medicinal products specifically designed for phage therapy, which was at that time (March 2023) still in public consultation.

Next, Sarah Djebara of the Queen Astrid Military Hospital (QAMH) presented the state of PT in Belgium. She started by reminding that following the classical medicinal product pathway requires to manufactured under GMP, have preclinical studies, Phase I, II and III clinical trials (randomized controlled trials – RCTs) and finally obtain a Centralized Marketing Authorization. Then insisted that this is not only a long and costly process but would not be suitable to the development of PT due to its peculiarities. First, effective PT requires a large number of phages: to target a single bacterial specie you often need a dozen phages, and an increasing number of bacterial species are being targeted, meaning an exponentially growing number of phage being isolated, characterized and produced. For example, in Belgium the overview of all the PT request handled by the QAMH revealed that 249 request were made, overall targeting 31 different bacterial species [11]. Similarly in the US, the San Diego phage therapy center (IPATH) reported 488 requests, targeting 35 bacterial species [12]. Moreover, the number of phages needed further increases when considering the geographical variation (epidemic strains are not the same from one country to another, sometimes even from an hospital to another) and time variation (epidemic strain change overtime). If hundreds of phages are needed for PT, and that phage collections need to be adapted/updated regularly, we can easily understand that getting all of these phages individually through the classical medicinal product pathway (RCTs, GMP…) is essentially impossible. From this reality, the speaker proposed that PT could be developed

in parallel in two different ways: the first path "Licensed Phage Products" would target a few "easy" bacterial species in indications involving large numbers of patients, using commercially viable "broad spectrum" phage cocktails or limited sets of defined phages, produced by pharmaceutical or biotech industries, according to conventional industry standards (*e.g.* GMP). On the other hand, the second path "Personalized Phage Preparations" would target all bacterial species, in all indications, for all patients in need, using personalized phage mixtures selected from an unlimited collection of (pre-adapted) phages, produced by hospitals and academic facilities, according to Risk-benefit based standards (not GMP), see Figure 3.

The classical "Licensed Phage Products" path is developing rather slowly as of 2024 there are still no licensed phage products for human medicine on the market in the EU nor the US. However product have been developed and are being investigated through RCTs. Indeed, a survey of RCTs of phage product done in February 2024 counted 25 trials: 15 active/recruiting, 7 completed, and 3 terminated. 24 were phase 1 and/or 2 and only one was phase 2/3, and was investigating the use of intravesical bacteriophages for treating urinary tract infections in patients undergoing transurethral resection of the prostate. The findings of this trial were underwhelming as it concluded that PT was non-inferior to standard-of-care antibiotic treatment, but was not superior to placebo bladder irrigation, in terms of efficacy or safety[13]. All these trials were also focus on a limited number of indications as only 9 bacterial species were investigated, with 4 species (*P. aeruginosa*, *S. aureus*, *K. pneumoniae*, and *E. coli*) accounting for 80% of the trials.

On the other hand, the second way of PT, Personalized phage preparations, develop quite quickly in Belgium, with over 100 patients treated with unregistered, non-GMP phage products, thanks to a singular national framework: the magistral phage[6]. Indeed, in Belgium phages are isolated by the QAMH then sequenced and analyzed by a government approved laboratory (Sciensano) who certified that the phage genome does not contain any toxin, virulence, AMR or lysogeny related genes. The bacterial production host genome is also analyzed, and its prophage content is determined. Once this genomic "passport" is obtained, the phage is produced into an API (Active Pharmaceutical Ingredient) in clean rooms and the final product batch is once again analyzed by Sciensano, who determined its pH, bioburden, endotoxin level, purity (including prophage content, if any), and titer. The certificate of analysis of the batch is then given to the Hospital Pharmacy that use it to inform the phage API formulation into a magistral preparation for a precise patient, delivered upon prescription. This framework allowed the treatment of over 100 patients in Belgium and 11 other countries using Belgian phage APIs. Recently, the retrospective non-interventional analysis of these first 100 consecutive BT cases (ClinicalTrials.gov ID: NCT05498363) was published[14]. This study observed clinical improvement for 77.2% of the infections, and eradication of the targeted bacteria in 61.3% of infections. Notably, eradication was 70% less probable without concomitant antibiotics use. Finally, 15 adverse events were reported, including 7 non-serious adverse drug reactions. All suspected adverse drug reactions resolved and no correlation between adverse events and a certain bacteriophage product nor administration route could be made. Interestingly, phage pre-adaptation (also referred as phage training) was necessary for 13 treatments. Phage training (multiple passages on the patient strain) has been shown to increase phage efficacy *in vitro*[15] and has also been used in patients[1,14]. Overall, this report show that the Belgian magistral framework allows the production and delivery of safe personalized phage products that ultimately can improve the clinical situation of patients in need.

The next presentation was by Frédéric Laurent (CHU Lyon, Hospices Civils de Lyon, UCBL), who presented the current development of PT in France. He started by reminding us that the history of PT begun in France with the first use of PT in human to treat dysentery in 1919, with phages prepared in the Institut Pasteur (Paris, France) by Félix d'Hérelle. Quickly after, d'Hérelle was in charge of the first commercial production of phages via the "Laboratoire du Bacteriophage". Then the phage production was moved to the Institut Pasteur in Lyon, where phages were prepared for sporadic uses in France during the 1970's. However from the 1990's until 2013, legal changes made PT unavailable. Later, the ANSM (the French drug agency) delivered authorizations for the first modern PT clinical

trial “Phagoburn”, in which the company “Pherecydes” (now “Phaxiam”) investigated the use of lytic phage against *P. aeruginosa* to treat burn patients with infected wounds[10]. Unfortunately, this trial did not gave much insight into PT efficacy, as a problem with the phages stability resulted in patients only getting 10^2 pfu/ml daily instead of the 10^6 pfu/ml initially planned. Additionally to this stability issue, this trial also revealed another unexpected difficulty: patient recruitment. Indeed, across two recruitment periods spanning 13 months, and including 9 burn centers in France and Belgium, only 27 patients were recruited for the trial. These results however did not dismissed PT as a potential solution to the ongoing AMR crisis for the ANSM, and the French agency organized 2 Temporary Specialized Scientific Committee on “Phage therapy”, in 2016 and 2019. These allowed a new scheme for compassionate use of PT in patients with a chronically/seriously debilitating or life threatening disease who cannot be treated satisfactorily with commercially available treatments (according to Article 83 of Regulation (EC) No 726/2004 of the European Parliament and of the Council). For these compassionate use cases, the ANSM requires a clinical documentation of the case, a multidisciplinary advice, a list of treatment options, a phage protocol for administration, a phage susceptibility test, and the informed consent of the patient. The phages used in these compassionates cases were either provided by Phaxiam (phages produced under GMP) or by the QAMH (non-GMP APIs produced following the Belgian Magistral phage monograph). The phages received are formualted in magistral preparations by the hospital pharmacist. Since 2017, the “Phage in Lyon” consortium has treated 59 patients (55 using phages from Phaxiam, and 4 from the QAMH). These cases corresponded to 46 bone and joint infections (BJI), 10 endocarditis/vascular graft infections, and 3 lungs infections.

Recently, the Health Care Strategies branch of the French Health Ministry decided to create a National Multidisciplinary Concertation Meeting dedicated to PT for BJI coordinated by the Hospices Civils de Lyon and Lyon Regional Reference Centre for complex BJI, which started on January 1st 2023. This initiative already resulted of PT being explored for 27 patients, and finally given to 19 patients.

In addition of the compassionate use cases, the “Phage in Lyon” consortium has also started a phase I/II study “PhagoDAIR”, promoted by Phaxiam. This multicentric randomized, non-comparative, double blinded study started in 2022 and will end in 2025. It is currently recruiting patients with prosthetic joint infection (hip or knee) due to *S. aureus*, >3 months after arthroplasty. This study will compare standard of care (SOC) + intra-articular phages (1 injection of 30 ml of 10^{10} PFU) during debridement, antibiotics, implant retention procedure, versus SOC + placebo (NaCl 0.9%). This study already has 9 active centers in France, 4 active sites in Spain, 1 site starting in the Netherlands, and 2 active sites in Germany. At the time of this presentation, 19 patient were already randomized and treated (with a total recruitment aimed at n=64).

Other studies have been presented and are supported by the French Health Ministry but did not launch yet (notably due to the COVID crisis). These include: PhagOS, a phase I/II study evaluating the safety and efficacy of PT combined with standard surgical and antibiotic treatment of hip and knee arthroplasties in adults with recurrent staphylococcal infection; PhagoPied, a randomized, multicenter, double-blind, parallel-group superiority trial, comparing the efficacy of standard treatment combined with PT, versus standard treatment plus a placebo, in *S. aureus* mono-infected foot wounds in diabetic patients; PYOPHANEB, a randomized double-blind placebo-controlled trial looking at nebulized PT for ventilator-associated pneumonia caused by *P. aeruginosa*.

Finally, another initiative promoting PT development in France was initiated by the ANSM: the creation of an integrated public platform for PT, involved in validation of the clinical use for each patient and that work towards the implementation of a public production of phages for clinical use. This project is now undergoing in Lyon where a great ecosystem allows the combination of multiple expertise with 3 reference centers (complex BJI, antimicrobial resistance, and staphylococci), the Institute of infectious agents, and FRIPHARM (Platform for production, research and pharmaceutical innovation). These institutions together aim at producing, from natural phage isolates, 10^{10} PFU/mL of a single concentrated, purified, defined and fully-characterized therapeutic phage with a mastered pharmaceutical process allowing human use. This project has been founded in 2021 for 6 year, by the National Agency of Research, under the name “Phag-One”. It has started by the constitution of

extensive phage banks targeting different priority pathogens (including *S. aureus*, *S. epidermidis*, *E. coli*, and *K. pneumoniae*). Investigations regarding phage production has also been started and the best conditions for optimal phage amplifications are determined in a dedicated L3 lab. Another work package of this project aim to develop and optimize an original process of purification and concentration of phages in compliance with Good Preparation Practices (GPP, equivalent to GMP for French hospital preparations) which would enable fast purification of a reproducible bacterium-free and apyrogenic suspension of therapeutic phages. This process includes treatment of the phage lysate with a DNA nuclease, and tangential filtration and ultrafiltration steps. The final product is filtered sterilized and aliquoted in 1mL glass vials. Quality control for batch release of the final product will include: biological activity (phage titer in PFU/mL), identification (sequencing), opalescence (Ph. Eur. 2.2.1), coloration (Ph. Eur. 2.2.2), osmolality (Ph. Eur. 2.2.35), pH (Ph. Eur. 2.2.3), sterility test (Ph. Eur. 2.6.1), bacterial endotoxin test (Ph. Eur. 2.6.14), particulate contamination: visible particles (Ph. Eur 2.9.20) and Non-visible particles count (Ph. Eur 2.9.19), total proteins (Ph. Eur. 2.5.33), host cell proteins and residual DNA from host cell and vector (Ph. Eur. 2.6.35), hemolytic activity (F756-13 ASTM Standard Practice for Assessment of Hemolytic Properties of Materials), viral contaminants (phage qPCR), residual quantitative analysis of surfactants and chelators (HPLC-MS / MP-AES), residual nuclease research (ELISA). This QC process was approved by the ANSM. Finally the Phag-One project also investigate phage toxicity/tolerance in animals, however this is for now limited to a small number of phage product as the standard study involves the following of 40 rabbits for 28 days and cost around 300.000 euros.

Finally, a list of what would be required at the EU level to further PT development was presented:

- A clear, consistent and stable European juridical framework which would take into account both industrial and public phage production, the specificity of personalized phage therapy, establish clear requirements for human use (ex: toxicity-tolerance study ? limitation on production strains ?...)
- A clear, consistent and stable European QC framework (need to establish clear QC requirement, with the appropriated test/methods, considering phage product specificity).
- Support for a European Network of public producers
- Support for European Clinical Trials in useful indication with personalized phages
- Set up a sustainable economic model for both public and private production, taking into account the waves of MDR infections that is starting and will submerge us in 10 years.

Next, Maria Vehreschild (Goethe University, Frankfurt) presented the PT situation in Germany. Contrary to Belgium and France, most patients receiving PT in Germany do so via clinical trials: PhagoFLow (Feasibility assessment), Phage4Cure (Pseudomonas aeruginosa, bronchiectasis), and international trials such as PhagoDAIR (mentioned previously). This special situation arisen following the stop of PT in the context of individualized treatment attempts (ITA), due to legal and regulatory discussions. PT access via clinical trials has advantages, notably the rapid access to phages after registration and good scalability of this system. On the other hand, this access to PT via clinical trials also has serious limitations: reduced efficacy due to a lack of flexibility (fixed product), available only to frequent bacterial species, and only using phages with broad host ranges, not phages with high host specificity. Then, her presentation continued by exploring two approaches for PT: market authorization as a drug, and individualized phage treatment (personalized approach). Market authorization as a drug presuppose the production according to GMP, and the conduct of RCTs. This a costly and long process which becomes unrealistic for targeting less frequent pathogens, meaning that this approach would only lead to a limited number of products, targeting only a few bacterial species/strains. To overcome some of these limitations, an evolution of the GMP certification process is under discussion with the competent German authorities. Nowadays, GMP certification is issue for single phages and not for a manufacturing facility or formulation, but in the future, GMP manufacturing authorization shall apply to a well-defined type of formulation, that may cover phages that target different pathogens. This change will drastically reduce the cost and time investments for trials, hopefully making them reach a more realistic level. Alternatively, PT via ITA (personalized

approach) offers high efficacy due to its flexibility regarding phage selection and combination. In Germany, 2 requisites are needed for an ITA application: Applicability of article 37 of the Declaration of Helsinki (which states that “In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.”) and, the medicinal product to be used is either registered as a medicinal product in another country or manufactured by the physician according to article 3(2b) of the AMG (Medicines Act). Until recently, Germany could import phages as finished medicinal products from Belgium and used them in ITA. However, due to a change in procedure, Belgium exports are now considered Active Pharmaceutical Ingredients (API) which cannot be used in ITA. As buying finished medicinal products from abroad is currently not a feasible option, PT via ITA has been stopped in Germany. The only solution would be to find a way for German physicians to manufacture phage product themselves, following the article 13 of the Medicine Act on Manufacturing Authorization which states that a physician who directly performs or oversees the manufacture of the medicinal product and personally administers it to a pre-specified patient may manufacture medicinal products without a manufacturing authorization. However this requires a mandatory notification of the local competent authority, which may inspect the manufacturing site with respect to quality management and control, which includes manufacture within a suitable quality assurance system, training and documentation of assisting personnel, requirements for hygiene, premises and equipment, recording of the manufacturing steps and systematic recording and evaluation of defects, deviations or errors. Obviously, all of these quality systems cannot easily be put together by a regular physician wanting to treat a patient with phages. One strategy could be to buy a GMP-produced API from abroad and then have the physician do the formulation into a final medicinal product (following the Medicines Act), but this would be expensive (about 150k € for a GMP-produced API), and treatments would again be limited to a few bacterial species, and the physician should still comply with the stringent quality management and control rules for the final steps of the manufacture. On the other hand, this strategy would make PT more readily available, with a non-decentralized treatment, and a possible reimbursement. Another strategy would be inspired by the Belgian way (magistral framework), and to push this, an effort to build German Personalized Phage therapy guidelines (including manufacturing process) has been started by the German Society for Infectious Diseases, and includes representatives from 19 Medical societies/organizations, 15 national/international experts, and 4 patient representatives. The long-term strategy is that these guidelines replaces GMP for the manufacture of personalized phage treatments and help create a needed PT dedicated legal framework.

Next, Shawna McCallin presented the “Phagistry”, an international PT patient registry. She started by stating that as PT develop across the world, we have seen a new issue arising: the lack of standardization in phage related topics. Indeed, if efforts have been made toward standardization of phage susceptibility testing (ESCMID dedicated group), phage production (Ph. Eur. Bacteriophage Working Party), and phage banks (Phages for Global Health), standardization of PT protocols and their reporting is still lacking. This is a critical issue as most PT cases are individual treatments, reported by different groups all around the world, with a heterogenous level of details, and in various journals. This situation makes the correct aggregation of all of these clinical data almost impossible, thus we lose critical learnings that could inform the design of future PT treatments and clinical trials. To address this issue, an international consortium of phage experts with first-hand experience in PT treatments, phage production and quality control, has designed “Phagistry”, an international PT patient registry. The goals of this project is to provide a PT specific data collection instrument regarding diagnostics, phage production and quality control, phage treatment and its clinical outcomes. The international Phagistry is located in Zurich (Switzerland), it is hosted through REDCap. It stores

anonymized, retrospective core data, which can be provided directly by the participating institutions. Alternatively, national registries can be set up and collect the same data or even use a more extensive data collection tool, which allow the capture of pseudo-anonymous and prospective full data, for local use. The anonymized, retrospective core data are then exported from the national registries to the international one in Zurich, where all data can be agglomerated to facilitate analysis and provide valuable information to support the development of PT guidelines, standardization of treatment protocols, and structure future clinical trials. The data captured by this instrument can be divided in 4 categories: Diagnosis (data regarding patient medical history, details on the indication, the pathogen…), Phages (identity, susceptibility testing, production and quality control), Treatment (protocol, route of administration, dosing, safety, changes made during the treatment, phage resistance), and Outcomes (Microbiological, Clinical, Immunological, Other). The Outcomes data capture has specially been designed to be comparable across indications, contextualized in time, and captures different effects. Overall, this database has been developed to capture most (if not all) pertinent data regarding a PT treatment, in a single and easy to use data collection system. After a long development, and multiple round of testing, "Phagistry" is now ready to be deployed. Visit www.phagistry.org for more information.

The last presentation was by Hans Petter Kleppen from ACD Pharma, about "Phage biocontrol in Norwegian Aquaculture". This company develops bacteriophage-based biocontrol in fish production, and thus has experience on viable development and use of bacteriophage products.
During the hatchery phase of production, multiple sources of infection (both viral and bacterial) can happened, including infection by the bacterium *Yersinia ruckeri* O1 (CC1). Screening for this *Y. ruckeri* infection can be done using PCR on eDNA (environmental DNA), which informs on the infection status at the population level. However, asymptomatic carriers of the infection (infected but clinically healthy fishes) do not release enough bacteria in the environment to be detected by eDNA PCR. Unfortunately, in these asymptomatic carriers, acute and chronical stress can reactivate the pathogen, leading to outbreaks, long after the host has been infected. Operations such as crowding, pumping and handling provoke stress in the fishes which can reactivate the infection. Data collected during fish production showed increased mortality during repeated handling operations, correlated with an increased amount of *Y. ruckeri* detected via eDNA PCR, a mark of an outbreak. To address this problem, ACD Pharma developed Custus®YRS, a biocontrol product based on a phage targeting *Y. ruckeri*. The rational here, is not to treat infected fishes, but rather to use this product to reduce the bacterial population in the environment, thus preventing infection of non-infected fishes. A study[16] assed the efficacy of Custus®YRS in controlling the infection pressure of *Y. ruckeri* in well boat water during transport and freshwater de-licing (operations known to trigger yersiniosis outbreaks). Water sample analyses showed that the phages efficiently controlled the infection pressure of *Y. ruckeri* during the operations and no yersiniosis related mortality was observed after the operations. Additionally, a comparison study looked at two fish groups, both sub-clinical carriers of *Y. ruckeri*, and de-liced with the freshwater treatment "Freshwell", but one group was de-liced in presence of Custus®YRS and the other without. The control group (without Custus®YRS) experienced a typical yersiniosis outbreak whereas the Custus®YRS group had no signs of yersiniosis outbreak and performed similarly to no-yersiniosis reference groups at the same location. The product is currently only available in Norway, but work is underway to make it available in Scotland, Chile and other salmon producing countries as well. The company is also developing another phage based product Custus®MVS, this time targeting the bacterium *Moritella viscosa*. The speaker ended his presentation focusing on the challenges linked to phage product development. First, the complex biology of phage/bacteria interactions makes for complex product development and a need for very close contact between developer/manufacturer and end user. Second, regulation is needed, but there must be a sound balance between "medicinal viability" and "commercial viability". Finally, as phages are fundamentally different from classical antibiotics, when developing a phage product or a regulatory framework for phage, it is essential to start with the risk/benefit analysis.

Overall, the presentations of the first sessions revealed a wide array of situations regarding phage therapy implementation across EU countries: with Belgium and its unique National framework (Magistral Phage); while France is developing a National Public Phage Production Platform in Lyon, treating patient compassionately and starting clinical trials; and Germany not being able to treat any patients (even under the umbrella of article 37 of the Declaration of Helsinki) due to a lack of GMP produced phage available (a legal requirement in Germany).

Part 2: Towards sustainable implementation

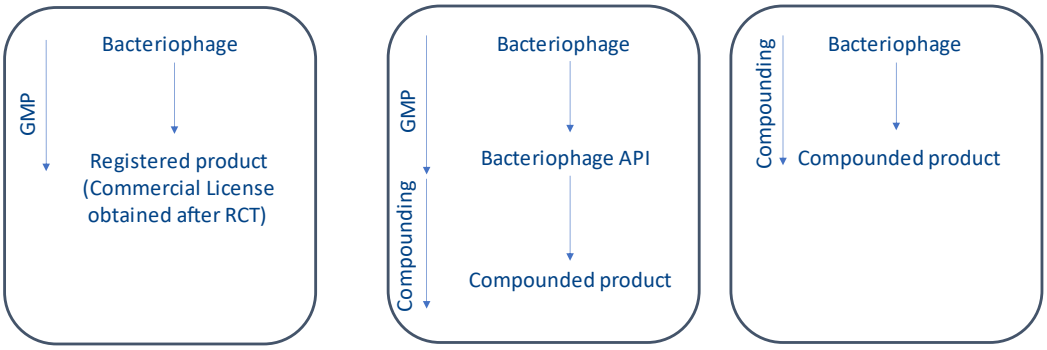
The second part of the meeting consisted in two round tables. In the first one, chaired by Mathieu De Jode (Belgian Public Health Institute Sciensano, BE), panelists Frenk Smrekar (JAFRAL, SL), Holger Loessner (PEI, DE), Laure Deligniville (ANSM, FR), Karin Froidbise (FAMHP, BE) and Pieter-Jan Ceyssens (Sciensano, BE) were ask to discuss manufacturing (GMP/GPP, what do we need ?) and quality control (what to test and how?). Overall a consensus emerge that the lack of clear guidelines regarding the manufacturing process and the quality controls were hampering PT development. However, it was also admitted that a phage specific regulatory framework might be needed as the production of phage is quite different compare to traditional antimicrobials such as antibiotics. Indeed diverse phages would need diverse production strains, with different level of AMR, pathogenic traits, or prophage content, which could mean different level of "danger" associated with the phage product. Concerning the manufacturing of phage under GMP, it was stated that it is possible (and has been done in the past) however the cost associated to a GMP certification of each individual phage product would certainly restrain the development of PT via fixed cocktail only, loosing the efficacy of personalized approaches. Interestingly, it was point out by an expert on GMP that GMP certification can be obtained for a whole manufacturing process/quality system rather than a singular product, meaning that a facility could be GMP certified and the produce every phage product under that certification (which would simplify and reduce cost of the manufacturing process, compare to today's model where each phage needs a separate GMP certification). It was also pointed out that personalized phage therapy could have its own guidelines, with a more flexible safety framework, overall guided by risk-benefit assessment specific to the patient's situation. Specifically on the quality control of phage product, panelist suggested that we could learn from already established guideline for product with some similarities with phages (e.g. recombinant protein produced from bacteria, viral vaccines…) and try to repurpose already validated methods for phage product (e.g Ph. Eur. guidelines on pH, endotoxin…). However we should also put effort in drawing guidelines for phage specific methods (including phage quantification, phage efficacy assays…). Ongoing efforts by the BACT working group in the Ph. Eur. and the "phage susceptibility testing" group of ESCMID are steps in the right direction.

Finally, the second round table chaired by Frédéric Laurent (CHU Lyon, Hospices Civils de Lyon, UCBL, FR) discussed the legal framework (national/EU) and EU fundings opportunities for phage therapy. Its panel consisted of Jean-Baptiste Perrin (HERA, EU), Alessandra Martini (EC, EU), Jean-Paul Pirnay (QAMH, BE), Daniel Holý (SÚKL, CZ), Nathalie Morgensztejn (ANSM, FR), and Valerie Denux (ANSM, FR). Here panelist agreed again that the phage framework might be different for different type of application: patients should primarily be directed to ongoing clinical trials, as these use GMP produced phages and their results are critical to the sustainable development of PT. However patients in critical situation of for which trials are not an options, should also be provided phages in a more personalized phage approach, where more flexibility could be granted around the phage production and quality control. It was stated again that clear rules are needed but that rules could be different between public phage production facility that facilitates personalized phage treatments, and commercial companies that sell a fixed product. Panelists from regulatory institutions

encourage all member of the PT community (biologist, MDs, Pharmacists, private and public actors) to discuss with their local reglementary agencies so they can help the construction of guidelines that would allow safe and feasible PT. Then, the cost associated with phage production and PT was also presented as a limitation of PT sustainable implementation. Indeed today, in most PT treatments, phage are given for free which put financial pressure on the phage manufacturer. Panelist member of different EU institutions insisted that although there is no "PT only funding calls", PT project wouldl qualify in calls regarding "AMR" and "innovative therapeutics" and that PT groups should apply to these to fund their PT projects as the EU institutions generally recognize PT as an interesting solution in tackling the AMR problem.

Overall this meeting exposed an irregular development of PT across EU countries, with some treating a lot patients with non-GMP products via a magistral framework, while other initiated different RCTs, and some could not even use PT at all. A large consensus of this meeting was that PT has real clinical value, and is overall safe (even when using non GMP phages). A lot of participants also agreed that two ways of PT could/should coexist: one that follow a classical drug path (GMP, RCTs, market authorization) which would provide fixed product for frequent the most frequent indications, and one with a more flexible framework (magistral, or other risk-benefit based system) dedicated to personalized PT, which could provide potentially any phage for any type of indications. Members of national regulatory agencies and of EU institutions were actually quite supportive of the development of PT as they recognize the growing number of patients that could benefit from it. They were also recognized PT specificities and that a phage specific framework should be developed through discussion between them and all the PT actors.
At the end of the conference, the general feeling was hopeful for the future of PT implementation in the EU, as the road ahead looks shorter and clearer every year.

Figures



(+) No need for additional framework
(-) Cost/time needs both GMP and license
(-) Limited product availability
(-) Limited patient population

(+) No need for license
(+) Personalized PT
(-) But only if the needed phage API is available
(-) Cost/time needs for GMP
(-) Need additional phage specific framework

(+) No need for license
(+) No need for GMP
(+) Personalized PT
(+) Potentially "Unlimited" treatment options
(-) Need additional phage specific framework

Figure 1: The 3 different paths leading to a clinically usable phage product.

Advantages	Weaknesses
Highly host specific (no off target, no dysbiosis)	Highly host specific (extensive phage testing via phagogram is needed before treatment)
Auto-dosage / short life (15-30 min)	Bacterial resistance to phages implies regular update during treatment
Isolation from the environment allows fast response	Temperate phages are possible reservoir of antibiotic resistance and toxin genes
Pre-adapted ("trained") *in vitro* or even engineered phage to increase phage efficacy and/or host range	Phages require direct contact with bacterial cell
Bacterial resistance to phages can be tackled via phage adaptation/training	Pharmacodynamics and pharmacokinetics of phages are still poorly understood
Phages cocktails can have broader action spectrum allowing fast response to a acute health crisis (food borne disease outbreaks, bio-threats, …)	Long term-effects ? Further studies needed
Several routes of administration	*In-vitro* and *in-vivo* activity are not always correlated
Safe to use (more studies needed, nevertheless)	Quality and safety need to be supervised by an independent expert laboratory

Figure 2: Advantages and Weaknesses of phage therapy, according to a new report of the Joint Research Council.

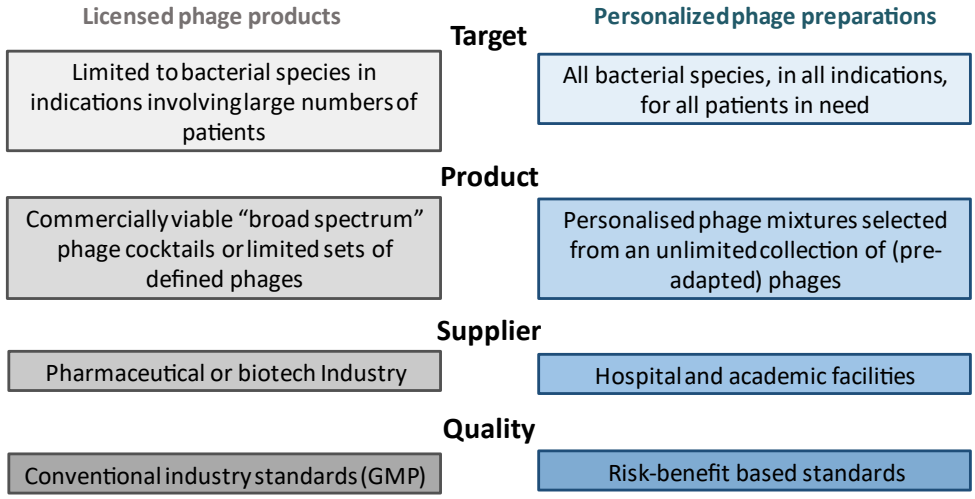


Figure 3: Two visions of PT, Licensed phage products and Personalized phage preparations.

Country	Legal Framework	Description
Belgium	Magistral Preparation (guided by a National Pharmacopoeia Monograph)	Under direct responsibility of medical doctors and pharmacists, the production of phage APIs is authorized following a national pharmacopoeia monograph. Each phage lot need a certificate of analysis from a government approved laboratory (Sciensano).
France	Compassionate Use (of an unauthorized experimental drug)	The national drug agency (ANSM) grants a "limited use authorization" for a single patient in therapeutic failure, after evaluation by an expert committee.
Germany	Helsinki declaration + Magistral Preparation (need to comply with GMP requirements for medicinal products)	The Art 13(2b) of German Medicinal Products Act, allows MDs/Pharmacist to prepare medicinal products without license under their professional responsibility (need to be GMP compliant). Note that this prevision has not been used in practice (no patient treated with GMP phages produced by a MD/Pharmacist).

Figure 4: The different national frameworks allowing PT use in presenting EU countries.

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