PHAGE FUTURES EUROPE

# Phage commercialization from a European perspective: a recap of Phage Futures

An in-depth look at what was discussed at Phage Futures EU taking place in Brussels, Belgium Sept 25-26, 2019
Written by **Jessica Sacher**, Co-Founder of Phage Directory.

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I attended Phage Futures Europe in Brussels, Belgium Sept 25-26, 2019. It was an incredibly informative two days, and I've put together an overview of my main takeaways, made comparisons with the first Phage Futures event (January 29-30,  2019 Washington D.C), and given some examples of what was discussed.

There was a great mix of perspectives across the spectrum of translational phage research and commercialization. This meeting was especially noteworthy because it brought in significant attendance from European health regulators, both at the European Union level and at the national level (Germany, France, Belgium).

## Clear that the phage therapy field is moving rapidly

Compared to the January Phage Futures meeting in the USA, which was one of the first phage therapy conferences in recent years with a predominantly commercial focus, the level of discussion during Phage Futures Europe gave the feel of an already more mature field. Companies that presented at both meetings demonstrated substantial progress compared to January's meeting, with **new disease indications explored, clinical trial design discussed in greater detail, new concepts like applying AI and machine learning to phage therapy debated, companies announcing their investment in in-house GMP facilities,** and much more. It is still not clear, however, how companies can commercialize phage and make a profit. There is a clear need for domain expertise in clinical microbiology, microbiology, phage biology and genetics in general for this field to move forward, and for commercial collaboration with academic institutions who are doing fundamental research.

## A unique perspective to kick off the conference: clinicians who want phage therapy for their patients

The conference began with perspectives from clinicians, such as **Ard Struijs from Erasmus MC in Rotterdam,** Netherlands, who talked about his first phage therapy patient (himself) and his years-long battle (still ongoing) with his hospital to bring phage therapy to his patients.

He discussed how his colleagues have been resistant, since they didn't learn about phages in their training. "People say, 'if phages are as good as you say, we'd have heard of them a long time ago'", he said, emphasizing a need for controlled clinical trials if more physicians are to get on board. He also shared his experience that, paradoxically, safety trials have been hard to get approved, since hospital safety councils haven't seen enough safety data for phages.

**Ran Nir-Paz, a clinician at the Hadassah Medical Center** in Jerusalem, Israel, talked about his group's experience treating patients compassionately, emphasizing that phage manufacturing for clinical use is extremely complicated, and stating that improving access to clinical-grade phages is paramount. He was optimistic, though, stating "the road to phage therapy is long and winding, but we need to take it".

> **We need a good structure and platform to follow up on treatments, like a clinical trial that tracks side effects. Clinical trials need to be run in a flexible way.**
>
> Patrick Soentjens
> Tropical Medicine in Antwerp

**Patrick Soentjens, a clinician at the Institute of Tropical Medicine in Antwerp, Belgium,** talked about regulatory challenges, emphasizing that "there's quite a good base for phage therapy, but from a regulatory standpoint it's not a good medical product". He discussed how we need an adaptive framework that allows phages to change during treatment. "If we produce them GMP, there will always be a big hurdle; we need a good structure and platform to follow up on treatments, like a clinical trial that tracks side effects.

Clinical trials need to be run in a flexible way.

> **The road to phage therapy is long and winding, but we need to take it.**
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> Ran Nir-Paz
> Hadassah Medical Center

## Large, well-designed clinical trials: a nearly universal holy grail

Certain topics were consistent with those raised at the last meeting; namely, the fact that large, well-designed, randomized, controlled clinical trials are required and generally universally demanded for phage therapy.

Similarly to the last Phage Futures meeting, there was substantial discussion of why past clinical trials haven't been successful (this time **Harald Brussow, who ran the Nestle E. coli diarrhea trial,** gave a detailed analysis of the challenges they experienced and how the field can learn from them).

**Challenges included:** isolating the right phages that can lyse the pathogens causing the problems, evaluating phages for undesired genes, preparing pure enough phages, storing the phages as long as needed without losing activity , convincing investors to back phages when phage patents can be easily circumvented, getting ethical approval for testing phages in a trial (much more documentation and supplementary safety trials required than expected, added years and extra costs to the process), predicting pharmacokinetics and pharmacodynamics of phages, enrolling enough of the right patients, showing a benefit of phages when they must be compared to standards of care that normally work well (antibiotics), understanding which pathogen is actually causing the disease you're treating, etc.

**His advice:** clinicians and clinical microbiologists need to work together to get a good understanding of how phages work in vivo before starting trials.

As a step in the right direction, **Associate Professor Ruby Lin** mentioned that they recently conducted n=14 compassionate use series using a GMP-purified phage cocktail to treat severely ill patients (sepsis and infective endocarditis cases) as an adjunct to standard antibiotics. As this was as single arm, open-label, uncontrolled study, emphasis on randomised clinical trials in the future was discussed.

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## Missing phage fundamentals

A concept that came up repeatedly was that there are holes in the foundation of phage understanding, and we may not know enough to even design clinical trials that would be successful.

Several speakers and attendees (especially regulators) acknowledged that in vivo understanding of phage biology was lacking.

For example, we know little about how phages behave in cocktails, whether they should be used sequentially or all together, which antibiotics they should be used with, what the downstream effects of resistance are, what inactivated phages do in a living system, etc. We don't understand how they interact with the immune system (though we heard several presentations on progress being made toward this), and we don't understand much about where phages go in the body or how they are cleared.

Several people raised the issue that animal models for phages are unreliable due to different innate and adaptive immune responses, and should be avoided in favour of human trials.

## Choosing the right disease indication

There was substantial discussion about how trials should be designed to improve a trial's chance of success.

One factor was the importance of choosing an indication wisely; UTIs, diabetic foot ulcers, and ear infections were emphasized as being smart choices for ensuring successful trials, based on being well-understood from an etiology standpoint and easy to access with phages.

On the other hand, the point was raised that even seemingly simple indications like diabetic foot ulcers can be complex, multispecies indications. As well, much more complicated indications have been successfully treated compassionately as of late, such as systemic and heart valve infections.

In addition, the indications discussed as being next on the list for clinical trials include complex, multi-species, chronic indications like IBD, acne, respiratory diseases, and even vaginome editing. Therefore, it seems that there is still no consensus on the "best" choice of indication for demonstrating effectiveness of phage therapy.

## Personalized vs. fixed cocktail approach

In almost any phage therapy discussion, the personalized vs. fixed cocktail question is inevitably raised, and it was naturally discussed at length at this meeting.

Voices from both camps were heard, and convincing data was shown to back both strategies. Two companies pursuing personalized phage medicine (**Adaptive Phage Therapeutics and Vesale Pharma**), and several others pursuing a fixed cocktail approach (PhagoMed, Technophage, BiomX, etc.) were featured as speakers and panelists.

Some believe the two models are not mutually exclusive, but rather, each have their merits, and situations exist where each might be better suited. It was not clear which would be the easier path from a regulatory standpoint, but the fixed cocktail approach appeared to be favoured by (or at least more familiar to) the regulators present.

The personalized vs. fixed cocktail debate also centered around logistics. It was acknowledged that while it's clear how the personalized approach works for single patients, it's less clear how it can logistically work for thousands.

Backers of the personalized approach emphasized that their approach involves developing a companion diagnostic to rapidly determine which phage to use on each patient, and improving the speed of this process is a major current focus. **Greg Merril of Adaptive Phage Therapeutics** described the plate reader system they've developed (essentially doing the work of a high-throughput phagogram). In 8 hours, they have good phage predictive capacity (this is down from 48 hours). In the future, they want to replace this diagnostic with an AI-informed system to match therapeutic phages with a patient's strain much more rapidly.

## To engineer or not to engineer?

Another frequent debate, whether or not to engineer phages for therapy, was also raised. Both opinions were represented, and it seems that there are beginning to be more "in-between" answers.

**PhagoMed** spoke of how it "breeds" its phages, rather than engineering them, Ronen Hazan of the Hebrew University of Jerusalem talked about "training" phages, while N**aomi Zak of BiomX** discussed how they use engineered bacterial strains to propagate natural phages. **David Harper of Evolution Biotechnologies** made the point that engineering phages is overkill when there are already effective phages in nature. Conversely, the point was raised that engineering may help improve phage patentability.

## To treat the patient or collect the data? Or why not both?

It was stated several times that we don't as a field do an adequate job of collecting and compiling the data we generate about patients (eg. compassionate use case data).

On one hand, this is specifically not allowed by the FDA (though it does not appear to be as clearly disallowed in Europe), as compassionate use is strictly for the benefit patient, not for the scientist. And yet, several presenters and audience members suggested we start collecting, compiling and learning from compassionate use data (and some have started).

For example, **Alexandra Petrovic Fabijan of the Westmead Institute for Medical Research** in Australia presented data on the 14 sepsis/endocarditis patients they successfully treated using Ampliphi (now Armata)'s Staphylococcus aureus phage cocktail.

She mentioned their group's work toward phage biobanking, where clinical samples during phage therapy are characterised (whole genome sequencing, transcriptome, and phage susceptibility test data) and archived for future research. She described how their group has gleaned new insights into common human immune responses to phage therapy from analyzing data collected in this way.

## GMP phage manufacturing is challenging, expensive, and required

The challenges associated with GMP (Good Manufacturing Practices)-level manufacturing of phages were discussed repeatedly at the meeting.

Essentially, most European countries require GMP-produced phages even at the compassionate use level (unlike in the US, which has more relaxed requirements for compassionate use and early stage trials), and yet GMP phage production is costly, and there are limited service providers of GMP-level phages.

Several presenters addressed the fact that globally, very few (~under 5) facilities have GMP phage-producing capacities. One of these is JAFRAL, a Slovenian company (one of the event sponsors). **JAFRAL's CEO, Frenk Smrekar,** spoke about how JAFRAL can both provide GMP phages as a service, and can also help companies set up in-house facilities.

Several companies present, such as **BiomX, Technophage, and Adaptive Phage Therapeutics**, stated that they've invested in their own in-house GMP phage manufacturing facilities (and at least one of these had JAFRAL help them set this up). The actual cost of GMP setup was not discussed, however.

**Most European countries require GMP-produced phages even at the compassionate use level**

## Phage therapy is on the radar of European regulators

This meeting was exceptional based on the number of representatives of health regulatory agencies who attended and presented. **Eric Pelfrene of the EMA (European Medicines Agency)** gave a detailed, critical breakdown of the hurdles and gaps that developers need to address. While his words and tone suggested that he believes phage therapy has a long way to go (i.e., animal data, clinical trial route), several attendees reported feeling pleased to hear from the EMA in such length about phage therapy at all, and were impressed that a representative of the EMA had dug so far into the evidence for phage therapy and the gaps that exist. It seems clear that they cannot ignore the increasing number of phage therapy treatments through the compassionate use route. Hearing from the EMA seemed to provide reassurance that phage therapy is finally being taken seriously as an antimicrobial strategy by European regulators, which was reflected in Eric Pelfrene's admission that "10 years ago, we could not have imagined we would be sitting here today to discuss regulatory aspects of phage therapy". human trials.

> **10 years ago, we could not have imagined we would be sitting here today to discuss regulatory aspects of phage therapy**
>
> **Eric Pelfrene**
> European Medicines Agency

## Germany and France taking steps toward implementing Belgium's magistral phage framework

This meeting also brought in national perspectives on phage regulation: members of Belgian, German and French national health authorities were present. In addition to regulators in Belgium, which recently approved the "magistral phage" framework, regulators from Germany and France spoke about their views on phage therapy.

Overall it seemed that both countries are open to phage therapy, and are in the process of implementing versions of Belgium's magistral phage framework (though treating physicians may not agree to the same treatment regime as the one in Belgium). Regulators from all countries, including Belgium, still maintain that clinical trials are of high importance for phage therapy to become a reality for the mainstream.

## Verifying phage safety in Belgium: Sciensano grants phages genetic passports

**Pieter-Jan Ceyssens of Sciensano,** Belgium's federal public health institute, explained how Sciensano characterizes and approves phages submitted as active pharmaceutical ingredients to be used in magistral preparations. Once approved, a phage gets a genetic passport, and then can be used by pharmacists following prescription by a physician. This is still a relatively new practice, as the magistral phage framework in Belgium has only been around a couple of years, but it was made clear that phages are now actively being evaluated and that this system appears to be functioning.

## Verifying phage safety in the US: US Navy works toward a pipeline for assessing phage genetics

**Matthew Lueder of the US Navy's BDRC** describes how he and his colleagues have developed steps to be taken to characterize a phage genetically, which can give a readout about each phage's likely safety for phage therapy.

**Adaptive Phage Therapeutics,** the company commercializing the Navy's phage library, appears to have incorporated this pipeline into its processes. It seems that the data generated will be provided to the FDA to create Drug Master Files for each phage

## AI and machine learning now being applied to phages

Applying AI and machine learning to the phage field is a new frontier garnering rapid enthusiasm (as well as skepticism). This concept was mostly discussed in the context of being able to more rapidly predict phage-host interactions, but using it to detect problematic genes, receptors and phage lifestyle was also discussed. It seems that this technology will likely be of most importance to companies and phage therapy centers using personalized phage therapy, since in silico predictions could reduce the time it takes to screen phages for activity.

**Miguel Barreto-Sanz** spoke about how his company, **Phages4A,** is training algorithms to do phage-host prediction, and **Greg Merril of Adaptive Phage Therapeutics** spoke about how his company plans to integrate this type of technology with its companion diagnostic to speed up the process of matching.

The audience peppered both Miguel and Greg with many questions, and it was clear that this topic is garnering both excitement and skepticism among those in the phage field.

## What is the value of a phage?

At this meeting, there was an interesting leap that was made: substantial discussion at one of the round table sessions revolved around how to assign value to phages. How much should it cost to buy or license a phage? Where does the value lie: in the phage itself, or in the work that goes into characterizing it, the data generated, the knowhow of how to use the phage, etc.?

Diverse perspectives were put forth, with some feeling that phages should be patent-protected before their genome sequences are published, and others feeling that phage patenting is unlikely to be useful or valid. One perspective was that phages have no inherent value, but rather that the value is in properly matching them to a pathogen or situation.

Most agreed that phages shouldn't be free, but questioned at what point a company should pay for a phage. Should companies pay when a phage is used in a final drug, or upon receiving a sample of the phage to begin testing? Some agreed that the way a phage is used should influence its value, but overall it was clear that the value of a phage is a question with many interpretations.

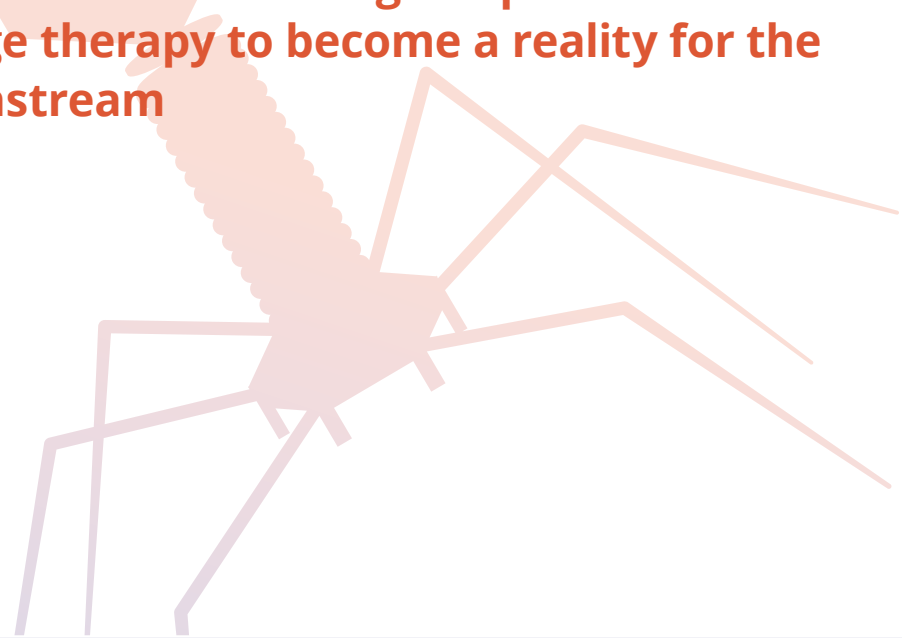
## What is the value of phage banks?

Another interesting conversation was about the value phage banks/ repositories should provide.

**Christine Rohde of the DSMZ,** which comprises a public phage repository, spoke about how researchers want phage repositories to exist, but they don't appear to want to deposit their phages.

Some participants expressed frustration that phage banks sometimes collect but limit distribution of phages. Some felt that central phage banks were important, while others felt that a distributed phage collection network might be more cost effective. There was no consensus on how sustainable a phage bank would be.

## Clinical trials are of high importance for phage therapy to become a reality for the mainstream



## Concluding remarks

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## Learn more: check out Phage Futures' social media archives!

Phage Directory provided live coverage of Phage Futures Europe through a custom live feed, view here. Additionally, the Twitter hashtag **#phagefutures** was used by many throughout the event.

Read Tweets from the event here.

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