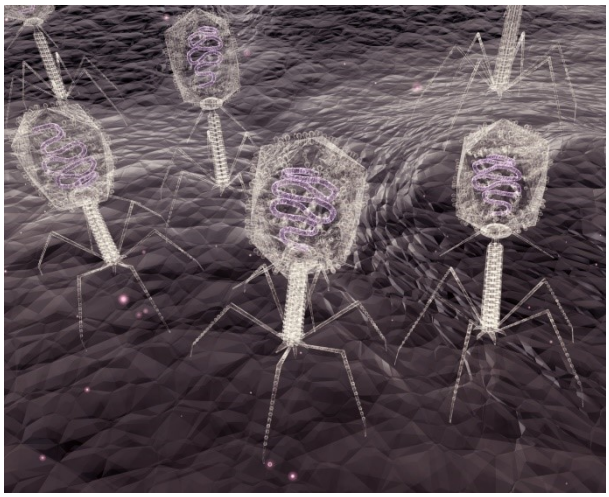
SCIENCE AND TECHNOLOGY BRIEFINGS
PARLIAMENTARY OFFICE FOR SCIENTIFIC AND TECHNOLOGICAL ASSESSMENT

Briefing 24

March, 2021

No. 3942 ASSEMBLÉE NATIONALE - No. 425 SÉNAT

Phage therapy: the medicine of yesterday and tomorrow



© iStock_Aunt_Spray

Summary

- *First discovered more than a century ago but having since become somewhat obsolete, bacteriophages are now attracting a great deal of attention as a means of treating infections caused by antibiotic-resistant bacteria.*
- *However, French medicine does not recognise any bacteriophage-based treatments and phage therapy is only used for experimental and compassionate purposes. This is mainly due to the fact that an economic model and legal framework for this type of treatment has not yet been established in France.*
- *With patients and carers eager to find a solution to multidrug-resistant bacterial infections, often with serious health consequences, there is a strong argument for a policy to promote phage therapy and develop new methods of producing phages for personalised medicine.*

Mrs. Catherine Procaccia, Senator
Vice-President of the Office

Since the middle of the 20th century, antibiotics have been an extremely **effective** and **inexpensive solution in the fight against bacterial infections**. However, with an increase in multidrug-resistant bacteria (MDR bacteria),[1] and with little progress being made in the search for new antibiotics,[2] it is now time to look for solutions that go beyond antibiotic treatment.

Discovered by both the English bacteriologist Frederick Twort in 1915 and the French-Canadian biologist Félix d'Hérelle in 1917, bacteriophages, also known as "phages", are **viruses that are naturally found in bacteria**, which can infect them, multiply within them and eventually kill them. This means that they can be used to treat bacterial infections.

Although phages are the most abundant organisms in the biosphere, they have **limited specificity with respect to their bacterial target** and therefore have a much smaller effective range than antibiotics.[3] A phage is generally only effective on a single bacterial species and sometimes only on a few strains of that species.

After a short period of success between the 1920s and 1940s, phages were soon replaced by antibiotics, which were easier to use, more stable and capable of targeting a wider range of bacteria with just one product. Phage-based pharmaceuticals were produced in France until the 1970s and were listed in the Vidal dictionary up until 1976.[4] But only the former Soviet Bloc countries such as Poland, Russia and Georgia (all close to the Eliava Institute in Tbilisi) still recognise and use bacteriophages, which are available in pharmacies without a prescription. This is mainly due to the fact that these countries had limited access to antibiotics during the Cold War.

Given the continuing lack of treatments for patients infected with MDR bacteria, we must now turn to phages to find new solutions.[5]

Phages, viruses in bacteria

• *Composition and structure of phages*

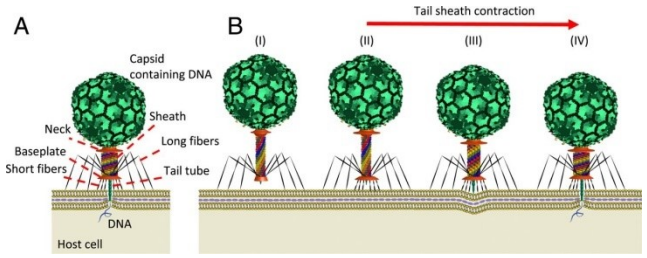
Phages are found in large numbers[6] and in many different varieties[7] throughout the natural environment. They are easily found in aquatic or moist environments, including fresh water, salt water, sewers, and soil. They play a major role in balancing bacterial ecology.

They are composed of nucleic acid, which contains their genetic information, in the form of DNA or RNA, and proteins that form the phage capsid shell, to protect the DNA or RNA. The majority of known phages contain double-stranded DNA.

They come in many different forms. Their size can vary from a few dozen to several hundred nanometres. Their genome can contain anywhere between 18 and 400,000 genes.

They are equipped with a means of **attaching themselves to the target bacteria** (often a tube-like appendage for "caudate" phages) and injecting their genetic material into the bacteria.

Illustration: a T4 phage[8]



• *How phages infect bacteria*

When a phage reaches its host bacterium, it attaches to its surface and injects its genome by puncturing the bacterial wall. Then, there are two possible infection cycles: the lytic cycle and the lysogenic cycle.

The lytic cycle is the one that is used for phage therapy: lytic phages, also known as "virulent" phages (the most common forms found in the environment), hijack the host bacterium's cellular machinery. They then replicate the injected DNA within the bacteria and use the bacteria's metabolism to produce new phages at an exponential rate. This process eventually kills the host bacterium and releases a large number of phages that can attack identical neighbouring bacteria.

The lysogenic cycle, or lysogeny, is triggered by phages known as "temperate" phages. The phage DNA first integrates into the bacterial chromosome and the bacteriophage replicates passively during cell division, thus transforming the bacterium into a genetic reservoir for the phage. The genome in its dormant state is known as a "prophage" and can represent up to 20% of the host bacterium's genome. It becomes "active" when the bacterium experiences some kind of deficiency and then enters the lytic cycle. Temperate phages also have the disadvantage of being able to modify the host bacterium by providing additional virulence factors (as in the case of the Panton-Valentine toxin introduced into Staphylococcus aureus).

■ The therapeutic potential of phages

Phages are already used in non-medical applications. For instance, lytic phages are used as an antibacterial treatment in the food industry (e.g. the use of Phage P100 to control Listeria monocytogenes). They can also be used for water treatment and processing.

But recently, their use in the medical treatment of serious bacterial infections in humans (as well as in veterinary medicine) has been re-examined[9] to respond to cases where antibiotic treatment has proved ineffective, but also to reduce the use of antibiotics or simply to treat certain bacterial infections more effectively (i.e. acne).

In theory, phage therapy has many advantages:

- **fast treatment**: a single dose is enough to destroy a whole colony of bacteria, thanks to the multiplication effect of the phages acting against the bacteria;

- **no side effects**: by destroying the target bacteria, the phages also disappear once the bacterial infection has been treated;

- a highly targeted treatment: phages attack only the target bacteria and **do not affect the patient's entire microbiome.[10]**

Phages also have the ability to attack the **bacterial biofilm[11]** that forms on surfaces, such as prostheses, and which is resistant to conventional antimicrobial agents such as antibiotics. Using phages on bacterial biofilm can then make an antibiotic treatment more effective. **This means that phage treatment and antibiotic treatment can be combined.**

Phages have great potential for use in the medical field: they can be used to treat a wide range of infections, such as chronic prosthetic joint infections (PJI), respiratory infections (pneumonia), urinary tract infections, gastrointestinal infections and even skin infections (e.g. from burns) caused by MDR bacteria such as *Pseudomonas aeruginosa* (P. aeruginosa), *Staphylococcus aureus* (MRSA), *Acinetobacter baumannii* (A. baumannii) and *Escherichia coli* (E. coli).

However, phages are ineffective in treating intracellular bacterial infections since they are unable to reach them inside the eukaryotic cells.

■ Limited but promising phage trials in France

Faced with drug-resistant bacterial infections, last-chance phage-based **experimental treatments** have been initiated for patients with a vital and/or functional prognosis (i.e. amputation) and have given good results.[12] But this is only for compassionate use[13] and involves very few patients.[14] This is not a routine form of treatment.

The use of phage treatment involves several different stages:

- Since phage therapy is a precision therapy, as phages are used to target certain bacteria and not others, the process starts by **identifying** one or several phage(s) that are capable of destroying the target bacteria (phagogram) from a library of available phages.[15]

- Next, the effective phages need to be **produced and purified** to provide a stable solution. This step is not technically complicated. However, since no phages are available in pharmacies and none are currently recognised as medicinal products, this step can take several weeks, making it impossible to use phages for urgent cases. But

since only a small amount of the phage produced is needed for treatment, the rest can be stored for a year, or more, and used for other patients if needed.

- Finally, **the phages are administered to the patient** in such a way that the phage is not destroyed before reaching its target bacteria. This can be done through direct contact during surgery (local application, *in situ*) or intravenously (IV).

This process is currently being carried out in France on a purely experimental basis, as there are no phage-based medicines with marketing authorisation (MA) and therefore no standardised products available to healthcare professionals.

■ Restrictive regulations

Phages are **legally considered to be medicinal products** and, as such, are subject to European and national legislation governing their release onto the market following an assessment of their benefits and risks. This means that the process of approving phage-based pharmaceuticals involves costly clinical trials.[16] The trials have to be conducted using standardised products that comply with "**good manufacturing practices**" (GMP) guidelines, and this certification alone is quite expensive.

These trials also need to produce controllable and quantifiable results. However, the individual nature of these treatments makes it difficult to prove their effectiveness through randomised controlled trials (RCTs).[17] Therefore, we need to use a more sophisticated method to prove their effectiveness.

■ The absence of an economic model

Phages are of little interest to major pharmaceutical companies (Big Pharma). As biological, living agents, they cannot be patented as such. Only the process of selecting and preparing phages and phage cocktails can be patented. Unlike chronic disease medications, they have an immediate effect and are not intended for long-term use. The highly individual nature of the treatments, owing to the phages' limited range of effectiveness, makes mass production practically impossible. As a result, only a few small companies are venturing into what is perceived as a potential "niche market". In France, the company Pherecydes Pharma plans to launch a clinical trial in 2021 using phages to treat staphylococcus aureus on prostheses. A previous trial launched in 2015 to assess the effectiveness of phage therapy for burn wound infections (Phagoburn) produced disappointing results.[18]

Due to the lack of products developed according to industrial quality standards (GMP), experiments on phage therapy are now mostly conducted using academically produced pharmaceutical compounding preparations.[19] However, the small number of cases treated and the non-standardisation of products do not provide sufficient evidence of the efficiency and safety of phage-based preparations, even if, in theory, they appear to be useful and without risk for patients.

■ The overriding factor: meeting patients' expectations

Patients and their families are becoming increasingly aware of the need for access to a more comprehensive range of treatment options. Faced with the failure of conventional antibiotic-based treatments, patients suffering from life-threatening or debilitating drug-resistant infections **are now turning to phage therapy**. The fact that phage therapy is **already practiced in other countries**, in the former Soviet Bloc for example, and that the expected benefits of these treatments appear to be relatively low-risk, makes phage therapy all the more attractive. Some patients are willing to go abroad, namely to the Eliava Institute in Tbilisi, to gain access to the phage cocktails used in those countries.

However, this medical tourism makes it virtually impossible to scientifically measure the effectiveness of phage therapy, since the exact substances administered and the records of each patient are unknown, and it places a significant financial burden on the patients concerned.

Therefore, a framework needs to be created to encourage organised phage therapy in France, and the results need to be scientifically monitored; otherwise, patients will continue to seek this type of treatment elsewhere.

■ Building a framework for the development of phage therapy in France

The French National Agency for the Safety of Medicines and Health Products (ANSM) set up a temporary specialised scientific committee (CSST) in 2016 and another in 2019 to examine the benefits of phage therapy. Three hospital-based clinical research programmes were also approved.[20] Phage therapy is now being considered as a serious option for combating antibiotic-resistant infections, one that is worthy of public funding.[21] But as other countries invest in phages,[22] France has yet to establish a serious development strategy, and the teams experimenting with phage therapy, who rely on other European countries (e.g. Switzerland and Belgium) for their phage supplies, are encountering some major obstacles.

- *A stronger research framework*

The first step in phage development is to gather massive amounts of medical information that **prove their effectiveness and lack of side effects.** Since phages can be used in a wide variety of cases and are themselves very varied, the limited number of existing clinical trials is not sufficient to collect the relevant data. The teams using phages in their experiments must be able to compare

their results and standardise their protocols. A register tracing their experimental use could provide a record of these experiments and thus contribute to the relevant therapeutic indications.

The research framework should also allow for the **analysis of possible problems regarding the loss of phage efficacy due to co-evolution with the target bacterium**. It is important to avoid the mistakes made with antibiotics, which have led to the rise of MDR bacteria. It is also important to avoid destroying "useful" bacteria when using an antimicrobial treatment.

Finally, the question of whether or not to **use genetically modified phages** remains to be discussed. Phages can be genetically modified, to improve their purity and/or stability for example. But we need to have a good understanding of the mechanisms at work in the phage-bacteria combination so as not to alter their useful characteristics, especially their ability to replicate.

• *An organised production framework*

Since the effective range of phages is quite limited, we will need to develop a **wide variety of products** in order to treat each strain of target bacteria.

Phages or phage cocktails that target the most common strains can be produced industrially.[23] But we also need to be able to produce other phages according to the specific needs of the patient. We could therefore set up a **dual system**, with pharmaceutical products marketed by the laboratories on the one hand and academically produced phage preparations on the other. This is the model that was proposed in 2010 by the infectiologist Olivier Patey and supported by the Hospices Civils de Lyon.[24] The aim is to establish a **phage reference centre** to develop phage formulations and produce academic phages that comply with GMP, within the FRIPHARM in-house pharmacy.[25]

• *An appropriate legal framework*

Given the specific and highly individualised nature of phage-based treatments, and because the conditions of standardised tests are very different from those in real life, it is difficult for phages to move from randomised clinical trials to being marketed as a medicinal product.[26] There are several avenues to consider: **either create a specific legal status**, such as that for pro-biotics, or keep them in the pharmaceutical system but **adapt the guidelines** to qualify their effects and measure their benefits and risks.

Also, as the use of phages is today only used for compassionate purposes and under the exclusive responsibility of the prescribing physician. Phages are therefore **not legally secure from a medical-legal point of view**. Today, it is clear that phages do not pose a threat to human health, the only risk being that they are inactive. Nevertheless, securing the conditions of prescription could encourage their use. In this sense, the 2019 ANSM CSST called for a "**national guidance and approval platform for the use of phages**" to be put in place.

■ Conclusion and recommendations

Phages remain relatively unknown and underdeveloped. **Phage therapy, once forgotten or overlooked, is now being taken more seriously.** It would be unreasonable to assume that phages are the perfect solution for cases where the use of antibiotics is not effective. Nevertheless, their effectiveness for certain indications, such as chronic prosthetic joint infections, and against certain types of bacteria (pseudomonas and staphylococci) has been well documented and their non-invasive nature is a genuine advantage.

Phages are part of a highly personalised medical approach, adapted to the specific needs of each case. Ignoring their potential would be a serious strategic mistake. The best approach would be to **increase the use of phages in the near future** by establishing a clear and well-defined legal and financial framework for the academic, medical and industrial teams working to re-launch phage therapy both in France and across Europe.

The Office's websites:

http://www.assemblee-nationale.fr/commissions/opecst-index.asp
http://www.senat.fr/opecst

Persons consulted

Dr. Christelle Ratignier-Carbonneil, Dr. Alban Dhanani, Dr. Nathalie Morgensztejn and Mrs. Carole Le Saulnier from the French National Agency for Medicines and Health Products Safety (Agence nationale de sécurité du médicament et des produits de santé - ANSM)

Prof. Céline Pulcini and Dr. Christine Godin-Benhaim from the French Directorate-General for Health (Direction générale de la Santé - DGS)

Dr. Alain Dublanchet, honorary hospital doctor and former head of the Microbiology Laboratory at the Villeneuve-Saint-Georges Hospital (94)

Prof. Tristan Ferry from the Department of Infectious and Tropical Diseases and Prof. Frédéric Laurent, Head of the Bacteriology Department at the Hôpital de La Croix Rousse Lyon (HCL)

Dr Laurent Debarbieux from the Microbiology Department at the Institut Pasteur

Dr. Nicolas Dufour from the Medical and Surgical Intensive Care Unit at the René Dubos Hospital in Pontoise

Dr. David Lebeaux from the Microbiology Department at the Hôpital Européen Georges Pompidou, French Society of Infectious Pathology (Société de pathologie infectieuse de langue française - SPILF)

Dr. Jean-Paul Pirnay, Dr. Daniel De Vos and D.r Maia Merabishvili from the Hôpital Reine Astrid in Brussels

Dr. Grégory Resh, PhD. Project Director - Head of bacteriophage research - University of Lausanne

Mrs. Charlotte Brives, anthropologist of science and health and research fellow at the CNRS

Mr. Guy-Charles Fanneau de la Horie, Managing Director of Pherecydes Pharma

Mr. Olivier Boisteau, President, and Mrs. Françoise Aubrit, Head of Development - Clean Cells

Mr. Xavier Duportet, President of Eligo Biosciences

Mr. and Mrs. Chatain from the company Vétophage

Mr. Christophe Novou Dit Picot, President of the association "Phages sans frontières"

Mr. Henri Communal from the Association des victimes de l'interdiction des bactériophagiques étrangers et de leurs proches (AVIBEP)

Mrs. Paola De Carli from the Association Vaincre la Mucoviscidose

Références

[1] Reference data on antibiotic resistance in France can be found on the Santé Publique France website: https://www.santepubliquefrance.fr/maladies-et-traumatismes/infections-associees-aux-soins-et-resistance-aux-antibiotiques/resistance-aux-antibiotiques
as well as on the National Observatory of the Epidemiology of Bacterial Resistance to Antibiotics (Observatoire National de l'Épidémiologie de la Résistance Bactérienne aux Antibiotiques – ONERBA) website: http://onerba.org

[2] Two World Health Organization (WHO) reports published in early 2020 highlighted the poor prospects for developing new antibiotic drugs: https://www.who.int/fr/news/item/17-01-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections

[3] Nicolas Dufour and Laurent Debarbieux "La phagothérapie, une arme crédible face à l'antibiorésistance" *(Phage therapy, a credible weapon against antibiotic resistance)* Med Sci (Paris). 33(4): 410 to 416.
http://www.ipubli.inserm.fr/bitstream/handle/10608/9179/MS_2017_04_410.html?sequence=16&isAllowed=y

[4] Alain Dublanchet and Emiliano Fruciano "Brève histoire de la phagothérapie" Médecine et Maladies Infectieuses *("A brief history of phage therapy" Medicine and Infectious Diseases)* Volume 38, Issue 8, August 2008, Pages 415 to 420.
https://www.sciencedirect.com/science/article/pii/S0399077X0800173X?via%3Dihub

[5] Dr Alain Dublanchet "La Phagothérapie, des virus pour combattre les infections" *(Phage therapy, using viruses to fight infections)* Éditions Favre SA, April 2017

[6] According to Mya Breitbart, there are approximately 10 million phages per millilitre of surface seawater:
https://pubmed.ncbi.nlm.nih.gov/22457982/

[7] Today, there are about 5,000 to 6,000 known varieties of phages, but there may be more than ten times that number, according to the International Committee on Taxonomy of Viruses (ICTV). https://talk.ictvonline.org/

[8] Source: Proceedings of the National Academy of Sciences of the United States of America:
https://www.pnas.org/content/116/50/25097

[9] In its Bulletin 198 No. 3 of March 2014, the Academy of Medicine published a document listing alternatives to antibiotics for treating multidrug-resistant bacteria (MDR bacteria), including antibacterial peptides (or bacteriocins), antisense oligonucleotides, immunomodulating therapies, faecal transplantation and phage therapy.
https://www.academie-medecine.fr/wp-content/uploads/2013/03/2014.3.pdf

[10] The concept of the microbiome was developed in 2001 by Joshua Lederberg, an American microbiologist and 1958 Nobel Prize winner in medicine. It refers to the ecological community of commensal, symbiotic, and pathogenic microorganisms within a given body space or other environment.

[11] Bacterial biofilms are communities of bacteria cells embedded in a polymeric matrix which attach to and subsequently grow on surfaces of abiotic materials. The biofilm protects the bacteria and enables them to survive in hostile environmental conditions. Biofilm bacteria display antimicrobial tolerance and immune response evasions and are much more resistant to antibiotics and disinfectants when compared to planktonic bacteria cells

See Yannick D.N. Tremblay, Skander Hathroubi, and Mario Jacques "Les biofilms bactériens: leur importance en santé animale et en santé publique" *(Bacterial biofilms and their importance in animal and human health)* – Canadian Journal of Veterinary Research 2014 Apr; 78(2): 110 - 116
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3962273/

[12] For prosthetic joint infections (PJI): see Tristan Ferry et al, "Medical innovations to maintain the function in patients with chronic PJI for whom explanation is not desir-able: a pathophysiology-, multidisciplinary-, and experience-based approach." SICOT-J, EDP Open, 2020, 6, p. 26 https://hal.archives-ouvertes.fr/hal-02904019/document

[13] The compassionate use of a medicinal product is provided for in both European (Regulation No. 726/2004) and national texts (Articles L. 5121-12 et seq. of the French Public Health Code). This allows access to non-licensed medicines (without an MA). Compassionate use is the responsibility of the prescribing physician.

[14] The 2019 report of the French National Agency for the Safety of Medicines and Health Products (ANSM) Temporary Specialised Scientific Committee (CSST) reported that 45 requests for the use of phages have been received at the ANSM since 2015, resulting in only 15 phage administrations for 12 patients, mainly for joint prosthesis infections. https://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Phagotherapie-Publication-du-compte-rendu-du-CSST-Phagotherapie-retour-d-experience-et-perspectives-Point-d-Information

[15] The laboratory at the Faculty of Biology and Medicine in Lausanne has compiled a library of 140 phages, which, according to researcher Gregory Resch, who was interviewed on 26 November 2020, covers a broad spectrum of bacterial strains. Only 5% of bacterial strains have no known phage. The Hôpital Militaire Reine Astrid in Brussels has developed an extensive phage database through close cooperation with the Eliava Institute in Tbilisi, which has a collection of over 1,000 phages dating back to the 1930s. But in France, the Institut Pasteur's phage library disappeared when it was closed down in the 1980s.

[16] According to Professor Céline Pulcini during an interview on 20th November 2020, the "Clinical Science" database lists only about 50 clinical trials worldwide related to phage therapy. Pherecydes Pharma has estimated that it would need to secure between €8 and €15 million to fund its new clinical trial. To provide more accurate data, more patients need to be included in the clinical trial, which makes the trial more expensive.

[17] A randomised controlled trial (RCT) is a method used to test the effects of a new drug or treatment by removing external factors. RCTs are designed to provide sound evidence of the efficacy of the drug or technology being tested.

[18] Phagoburn was a randomised, double-blind, phase II/III clinical trial conducted between 2015 and 2017 to measure the effectiveness of Pherecydes Pharma's phage cocktail on patients with burns infected with *Pseudomonas aeruginosa*. 27 patients were included in the trial. The bacteriophage solution's instability over time made it impossible to complete the clinical trial.

[19] Pharmaceutical compounding is the creation of a particular pharmaceutical product to fit the unique need of a patient.

[20] Phagoburn, Phagos and Phagopied.

[21] In 2018, the ANSM supported a team from the Institut Pasteur and the Assistance Publique Hôpitaux de Paris to develop a pharmacometric model for administering phages to treat lung infections. At the end of 2018, the French government launched a €40 million priority research programme to tackle antibiotic resistance. This programme has been established to fund projects that focus on the use of treatments other than antibiotics, including phages. The Fondation des Hospices civils de Lyon submitted a project to the French National Research Agency (Agence nationale de la recherche – ANR) to set up its own phage compounding pharmacy and was awarded funding at the beginning of 2021. In addition, towards the end of 2019, an interdisciplinary team of researchers from the Institut Pasteur and the Georgia Institute of Technology was awarded $2.5 million from the US National Institutes of Health (NIH) to study phage therapy.

[22] For example, the Centre for Innovative Phage Applications and Therapeutics (IPATH) at the University of San Diego has received support from US federal agencies. https://medschool.ucsd.edu/som/medicine/divisions/idgph/research/center-innovative-phage-applications-and-therapeutics/Pages/default.aspx

[23] The potential for the industrial production of phages has already been considered for treating acne or urinary tract infections.

[24] Project supported by Professor Tristan Ferry and Professor Frédéric Laurent: https://www.crioac-lyon.fr/phageinlyon-fondation-hcl/

[25] This project would be additional to, and not in competition with, that of the industrialists, insofar as an in-house pharmacy can only produce medicines that do not exist on the market on an ad hoc basis. When a market-approved (MA) medicinal product is produced by a manufacturer, the in-house pharmacy purchases this product.

[26] Charlotte Brives and Jessica Pourraz "Phage therapy as a potential solution in the fight against AMR: obstacles and possible futures" Palgrave Communications 6 n°1 – 2020.
https://www.academia.edu/43116362/Phage_therapy_as_a_potential_solution_in_the_fight_against_AMR_obstacles_and_possible_futures