

Science and Technology Committee

Oral evidence: The Antimicrobial Potential of Bacteriophages, HC 886

Wednesday 15 March 2023

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Members present: Carol Monaghan; Aaron Bell; Dawn Butler; Tracey Crouch; Katherine Fletcher; Rebecca Long Bailey; Stephen Metcalfe; Graham Stringer.

In the absence of the Chair, Carol Monaghan took the Chair.

Questions 112 - 181

Witnesses

[I](#): Dr Jean-Paul Pirnay, Head of the Laboratory of Molecular and Cellular Technology, Queen Astrid Military Hospital, Brussels; and Dr Mzia Kutateladze, Director, George Eliava Institute of Bacteriophage, Microbiology and Virology.

[II](#): Professor John Iredell, Director, Centre for Infectious Diseases and Microbiology at The Westmead Institute for Medical Research; and Professor Robert Schooley, Professor of Division of Infectious Diseases at UC San Diego School of Medicine.

[III](#): Greg Merrill, Chief Operating Officer, Adaptive Phage Therapeutics; Dr Hans Petter Kleppen, Chief Science Officer at ACD Pharma; and Naomi Zak, Founder, BiomX.

Examination of witnesses

Witnesses: Dr Pirnay and Dr Kutateladze.

Q112 **Chair:** This is the second session in the Committee's inquiry into the antimicrobial potential of bacteriophages or, simply, phages. It is going to focus on their use in other countries and whether those countries have faced similar challenges as the UK, whether these challenges have been overcome and what lessons the UK can learn.

Of special note, we have witnesses coming in from around the world today from different time zones. We have witnesses from San Diego and Maryland in the US, from Belgium, Georgia, Sydney in Australia, and even Norway, this morning. Thank you all for joining us despite the time difference; it is very much appreciated.

In our first panel, we have Dr Jean-Paul Pirnay from Queen Astrid Military Hospital in Brussels. Good morning, Dr Jean-Paul.

Dr Pirnay: Good morning.

Q113 **Chair:** We have Dr Mzia Kutateladze, Director of the George Eliava Institute of Bacteriophage in Tbilisi. Welcome to both of you.

Dr Kutateladze: Thank you.

Q114 **Chair:** Dr Pirnay, when you are dealing with phages how quickly can they be obtained by clinicians? How much does it cost on average for a patient to be treated by phages?

Dr Pirnay: That is a complex question. They can be obtained immediately in certain cases but it can take much longer if we do not have any phages that are ready for use in our collection. That can take weeks. We provide them for free. It is all paid by the state. The users do not have to pay €1 or £1.

Q115 **Chair:** That is practically nothing. How much is it costing the state to support your facility?

Dr Pirnay: I once did a calculation of the cost price. It is about €50 per patient on average to produce phages in our system. That includes quality control.

Q116 **Chair:** That seems incredibly cost-effective. How have you managed to bring the price to that level?

Dr Pirnay: It is a very pragmatic approach. Phages are natural organisms, so there is not much development cost. You can find them in nature. To produce them is quite simple. They are propagated into bacteria, purified, which is not that difficult, and then pragmatic quality control.

Q117 **Chair:** Some of the evidence we have heard so far, Dr Pirnay, has talked about the cost of production because phages have to be produced to GMP



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or good manufacturing practice standards. What standards are you applying to phages used in Belgian hospitals?

Dr Pirnay: We do not have to produce them according to the GMP requirements. We need to produce them according to what is called a monograph. That is basically a recipe, a three-page document that describes how to produce a phage and to perform quality control.

This does not mean there are no quality requirements, but they are less stringent than GMP requirements. They are more pragmatic and adapted to phages, which are quite different from conventional drugs. Many of the GMP requirements are very difficult to apply to phages and are not necessary.

Q118 **Chair:** Has any pressure been put upon you to apply GMP standards to your phage production?

Dr Pirnay: Normally, we should produce them according to GMP. The EMA, for instance, at EU level, said that it is a drug, a medicinal product, according to its definition. We tried to do this and we partnered in studies sponsored by the European Commission, the Phagoburn Study, where we used GMP-produced phages. What we learned from that study is that it is very difficult to do so. It does not necessarily end up as a better product. It takes a long time, a lot of money and it is not a flexible approach.

As you might know, phages are very specific to which bacteria they infect. Sometimes, phages need to be trained, for instance, to be more efficient. If every time this means that it is another medicine product that needs to be produced according to GMP, this is technically impossible.

Q119 **Aaron Bell:** Dr Kutateladze, we understand that phage therapy is quite widely used in Georgia. How long and how widely has Georgia been using phages? How central are phages in the treatment of bacterial infections?

Dr Kutateladze: Thank you for the question. As you might know, the Eliava Institute is turning 100 years old this year. We will have a very nice celebration in July.

Phage therapy was a standard part of the healthcare system in the former Soviet Union. Even now, phages, as a pharmaceutical agent, are approved by the Ministry of Healthcare in Georgia. We have a phage production facility, which has a special licence. Until now, we did not have the GMP facility for phage production. Based on the Georgian Government's new regulation, from 2024 we must meet all the requirements for GMP production.

Phage therapy is quite traditional. It does not need to be explained in Georgia; everybody knows about it because it is very traditional. We have worked on phages for many years.

We treat patients on the same campus; we have our Phage Therapy Centre. Interestingly, phage therapy is not included in the Georgian



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Treatment Protocol of Pharmacopoeia for infectious diseases. One thing that was missed were the clinical trials according to international standards. As I mentioned, phages are now licensed. There is a pharmaceutical agent and the production facility has the standards and the licence to manufacture the products. Currently, it is producing six different products. Five out of six are mixtures and only one is a monophage. Simultaneously, we are working on individual phage preparations for individual patients.

Q120 Aaron Bell: Phages have been used for 100 years and they are traditional, but you mentioned that there is no evidence base from clinical trials. What evidence base is there from either the Soviet era or since the end of the Soviet era that phages are the most effective method in certain cases?

Dr Kutateladze: Absolutely, yes. We have no results on placebo-controlled or placebo-supported clinical trials. We have one of the largest libraries of publications on the clinical outcomes of phage therapy over the years. Absolutely, there are case-by-case studies, evidence-based studies. We also published special books, and we translated and compiled part of the library. This was with the help of the British Ministry of Defence, which provided financial support to publish one book.

Yes, we have a lot of information. We are even now trying to publish our case reports and description of cases in the high-impact journals.

Q121 Aaron Bell: Are those descriptive reports? Has anyone attempted to do a proper double blind clinical trial on the effectiveness of phages?

Dr Kutateladze: In Georgia?

Aaron Bell: Yes.

Dr Kutateladze: In Georgia, we had one on phages against bacterial infections in the urinary tract. It was only a safety study with help from our Swiss doctors and partners and according to their protocols. We did the trials in Georgia in the Institute of Urology. Once more, we proved the safety of phages.

Q122 Aaron Bell: We do not have an exact clinical trial. Regarding its effectiveness within your healthcare system and in the individual patients you treat, how is that monitored? What data, what statistics are you recording based on the experience of individual patients?

Dr Kutateladze: This is a combination of the different criteria, objective and subjective. It depends on what kinds of medical complication we are talking about. Of course, first and most important is the diminution or inhibition of the bacterial load of the bacterial agent causing the infection. In some cases, when we are dealing with chronic diseases such as cystic fibrosis where you cannot eradicate pathogens completely, we observe improvements in patients' quality of life. We had many examples of the



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good effect of phages in those patients. It is a combination of the different criteria.

Q123 Aaron Bell: Looking at whether they could be used more in the British healthcare system, it would be helpful to have some data and statistics rather than individual cases. It seems very difficult, not just from Georgia but around the world, to obtain the clinical trials and the data on how effective and how cost-effective we can expect them to be.

Dr Kutateladze: Absolutely. Again, there are two different scenarios in Georgia. We have ready-to-use phages for application; anybody can find them and buy them in pharmacies. Of course, the price of these phages is less than other phages.

The second approach is that, before phage application, there is testing. We test the pathogen, identify the pathogen and test which phage works against this specific pathogen. In cases where the commercially available phages work, it is easy to use them immediately. In cases where we do not have active phages, we go to our big library. We have one of the biggest libraries in the world of bacteriophages—laboratory bacteriophages.

Preparing the final product to be used for treatment by the patient will take about two months. In every case, we work on individual phages, to adapt and train the phage in order to increase the lytic activity.

Q124 Aaron Bell: Dr Pirnay, I have a similar question about the evidence base being built up in Belgium about the effectiveness and the manufacture of phages at scale. What evidence base have you built up since starting this in—was it 2018 that Belgium started using phages as active pharmaceutical ingredients?

Dr Pirnay: The first patient treated with phages at the Military Hospital was in 2008. Since 2018, there has been a dedicated framework for phage therapy. These phages have now been applied for some 130 patients. We offer support, of course, during treatment. We offer a number of tests such as phage antibiotic synergy, the emergence of resistance against phages and phage immune neutralisation.

By offering these services and acquiring data, we learn why phage therapy sometimes works and why, sometimes, it does not work. So, we are acquiring some knowledge with all these cases.

We also provide phages for clinical trials. In an ongoing trial in one of the largest hospitals in Belgium, the University Hospital in Leuven, personalised phage products are being compared to standard of care antibiotic treatment.

Q125 Aaron Bell: Is there a clinical trial that is double blind against the placebo, or is this just a clinical trial compared to the antibiotic approach?



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Dr Pirnay: No. From the cases treated, it was seen that it is very important to combine phages with antibiotics. Most of the time they work in synergy. The trial patient, eligible for phage therapy, will get the infecting bacterium tested against our phage collection. When the phage is active, this patient will get standard of care antibiotics plus phages. If we do not have any phages that are active, this patient will get standard of care antibiotics. Over time, we will be able to compare the group standard of care antibiotics against the group standard of care antibiotics plus phages.

Q126 **Aaron Bell:** Can we expect a scientific paper at some stage to track the results of that study?

Dr Pirnay: Yes. I am preparing a scientific paper that will give an overview of the first 100 consecutive patients for whom we have provided phages.

Aaron Bell: Thank you; that is very helpful.

Q127 **Rebecca Long Bailey:** Dr Kutateladze, what support does phage research and development in Georgia receive from the Government and other public bodies?

Dr Kutateladze: Thank you for the question. I represent a state institution. The Eliava Institute of Bacteriophage is a state institution at the Ministry of Science and Education. The institute is only supported by public money. The main funding resource to continue its scientific work is international grant support and some service contracts.

We treat patients at our spin-off company, the Eliava Phage Therapy Centre, a private company established by the foundation here on the same campus, the Eliava Foundation. In our case, compared with Jean-Paul's, which is very cheap, we have to support our scientific activities as well as our doctors and support personnel. In our case, we provide a complete two-week medical support to our international patients. We treat the Georgian population together with international patients; the geography is very wide. We offer a two-week round of treatment as a first round of treatment for our patients. The patients themselves pay the cost of treatment, so patients are paying it.

Q128 **Rebecca Long Bailey:** How much would that be on average compared to the £50 we have heard from Belgium?

Dr Kutateladze: It is much more. It is about €3,000, including medical consultation; it is a package. There are all kinds of instrumental investigations, sometimes a CT scan is needed or ultrasound or X-ray; everything is included—bacteriology, blood analysis, and all kinds of diagnostic services. There is then doctors' care, so consulting, and 10, 12 days of the phage application procedure itself.

After two weeks, they leave but we give them enough phages for the second round of treatment. It is a package of medical services.



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Dr Pirnay: I want to specify that €50 is only for the phage solution. That does not include treatment or consultations; it is just the phage solution. That is an average.

Q129 **Rebecca Long Bailey:** Dr Pirnay, I ask you the same question: what support does phage research and development in Belgium receive from the Government and other public bodies?

Dr Pirnay: We mainly work with funding that comes from research organisations and Belgian defence. We have several projects running. We finance the production of phages and quality control largely through that channel; it is largely research funding.

Q130 **Rebecca Long Bailey:** Dr Kutateladze, what has helped Georgia to commercialise phages? How does this help to fund further research and phage infrastructure?

Dr Kutateladze: As I mentioned, we are a state institution mainly creating intellectual property—phages and services that can be commercialised. We commercialise our products and services in the spin-off companies. The Phage Therapy Centre is one of the spin-off companies. We also have a diagnostic centre where patients receive diagnostic services. We have phage production, where we produce 60 products.

The idea is that part of the profit generated by the spin-off companies goes to the Eliava Foundation, which is a not-for-profit foundation. From time to time, the foundation announces the grant competition for the Eliava Institute scientists. It is a mechanism for the sustainable development of the institute. The institute, where the main scientific research goes on, is most crucial and important. We are returning the money generated by the spin-off companies, through treatment, production and selling our products back into the science.

Q131 **Rebecca Long Bailey:** How has private investment been attracted? What challenges does this pose? There has been much discussion about how interest in phages has been very limited, particularly from big pharma.

Dr Kutateladze: Unfortunately, Georgian products are not very attractive. From time to time, to be very open, they appear, but we do not have any successful marriage with any of the big pharma right now.

There are a couple of challenges: first, IP protection. It is very difficult to protect IP on phages. You can have patents on a combination of phages, trademarks or application. We are talking about a natural product and we have spent many years trying to find out how we can protect our IP; this is very difficult.

The second challenge, which Jean-Paul already mentioned, is the GMP facility for production. It is very laborious but possible to do. These are biological products, not a chemical formula that can be produced again



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and again. After time, when we have new bacterial strains with new mechanisms of antibiotic resistance, we can update our commercial product.

This is very challenging for the GMP standards. You have to update your procedure again and again. This is the main challenge that is true for the biological—it is vaccine development, so it should be more about biological products than pharmaceutical.

Q132 Chair: Dr Pirnay, how have you developed relationships in Belgium between the universities, the hospitals and the companies developing the phages?

Dr Pirnay: In Belgium, historically there has always been a critical mass of phage research at all levels. In 1921, a paper on phage therapy was published in Belgium. Many techniques used today—for instance, the Appelmans technique, or the Double-Layer Agar technique—were developed in Belgium in the 1920s; so, we have some history. This has meant at different levels—including the authorities and, for instance, the organisation running quality control for medicines—we had people who knew about phages. That made it easier to develop this dedicated pathway.

We also created a society, the Belgian Society for Viruses of Microbes, a group of stakeholders from industry, academia, hospitals and regulators. The advantage is that Belgium is small and at different levels we had people who knew about phage therapy.

Q133 Chair: Being small gives you the agility, but how successful have you been in attracting private investment?

Dr Pirnay: The very personalised phage therapy approach makes it difficult for companies. To give an idea, for the first 100 patients we used combinations of 26 different phages. As Mzia said, before every production we adapt the phages to the newly merged bacterial pathogens. In 13 cases, we trained phages specifically for the patient. That is a context that makes it very difficult for companies that like to develop a product for use with thousands of patients all over the world.

In addition, as somebody mentioned, there is this GMP issue. In Belgium, GMP is not required. If a company wants to sell its products not only in Belgium but in Europe, for instance, most countries require GMP. For a company to produce a large number of phages according to GMP and regularly to update these products, it is quite a nightmare.

Q134 Chair: That is very interesting. If Belgium has looked at these issues, are you still a distance away from manufacturing phages at scale?

Dr Pirnay: In our approach, we do not want to produce phages at large scale. We know we will regularly need to update these products. We will need to find new phages regularly. So, there is no real need for huge amounts. Of course, we would welcome the industry to produce some



“super phages” or even cocktails that could be used as first-line. That would take some of the weight off our shoulders. We receive one request per day on average. Then we could go back to our research and development tasks. In cases where these more generic phages or phage cocktails do not work, we could help to try to train phages or find new phages and develop them. These phages could then go to industry, for instance. There is room for collaboration between academic settings or hospitals and industry.

Q135 Stephen Metcalfe: The purpose of this inquiry is to make some recommendations to Government. What should the UK learn from your experiences in Belgium and Georgia? What should we be recommending to increase the use and commercialisation of phages?

Dr Kutateladze: I am very happy that so many countries are interested in phage development and application—20 or 30 years ago, we were alone and it was very difficult to convince people that we could treat bacterial infection with viruses.

This is a very good question. Of course, there are a lot of possibilities but there are challenges as well. It is easy to isolate a phage from the environment but then there are the challenges of how to prepare it as a final product and how to use it. It is a combination of several things. First of all, there are the good phages: professionals who know how to work on phages, and how to select and train them are a really very important part. You can take phages from the environment but it is never as a final therapeutic product. In addition, experienced people. From my understanding, as already mentioned, it should be a biological product, not a pharmaceutical product. It should be subject to different regulations than pharmaceutical products.

Again, it is possible to have a GMP product with mixtures of different phages, but after time it would need some updating and new formulations would need to be developed.

It is not so easy to answer in two minutes, but I would be happy to provide any more information if needed.

Q136 Stephen Metcalfe: Thank you. Finally, Dr Jean-Paul?

Dr Pirnay: My advice would be to try to build a pragmatic framework for phage therapy. It is also very important not to reinvent phage therapy. Phage therapy has been around for one century and it is still there. It has mainly been developed at the Eliava Institute. Two researchers from the Eliava Institute formed a cornerstone of our laboratory. What we do is based on the experience of the Eliava Institute. As Mzia said, it is very important to be able to see what is a good therapeutic phage and not just something that makes plaques into a lawn of bacteria—to be able to train the phages to become better.

My advice would be to look at what the Eliava Institute is doing; we are basically doing the same. Try to develop a pragmatic framework.



Chair: I thank Dr Pirnay and Dr Kutateladze for joining us this morning.

Dr Kutateladze: Thank you very much for the invitation.

Dr Pirnay: Thank you very much.

Examination of witnesses

Witnesses: Professor Iredell and Professor Schooley.

Q137 **Chair:** We are waiting for our next two witnesses who are joining us online. We are trying to get Professor Schooley, but I will welcome Professor Jonathan Iredell, who is an infectious diseases physician, and splits his time between Westmead Hospital in New South Wales and the University of Sydney.

Professor Iredell, I believe it is roughly 9 o'clock in the evening where you are, so we really appreciate your joining us. Can you tell us a bit about how phages are used in Australian hospitals?

Professor Iredell: They are used to a very limited extent, I have to say. We have treated a little more than 25 cases in Australia, and they are limited to one, and now only recently a second, site that is managing this therapy. In some cases, it is driven by enthusiasts, which is a bit of a story around the world at the moment. There are small groups that are driving most of the therapeutic applications.

Chair: Thank you very much. We had some questions for Professor Schooley. We are going to change our order, so I am going to go first of all to my colleague Graham Stringer to ask you some questions.

Q138 **Graham Stringer:** Professor Iredell, what do you see as the future of phage treatment in Australia, or the rest of the world, for that matter? Is it going to grow and develop?

Professor Iredell: At the moment, most people would see the use of phage therapy as an application in extremis. Notwithstanding the experience in Eliava, which you just heard about, the most common request for phages is when ordinary therapies have failed—typically, an antibiotic treatment has failed.

It is important to point out that there is a strong argument for their role as adjunct therapies and, in limited circumstances, replacements for antibiotics. That is where the regulatory requirements may differ and where the commercial opportunities may differ. Certainly, at the moment, most of the demand is in rescue cases, I think you could best describe them.

Q139 **Graham Stringer:** You do not really see a huge increase in their use; it is when antibiotics or other treatments have failed.

Professor Iredell: I think that is when they are being used at the moment. They almost certainly will have value, as I said, as adjunct



therapy to enhance the value of antibiotics. There is some good evidence that they add firepower to antibiotic therapy, and they work, clearly, in situations where antibiotics are not very good because antibiotics do not work the right way.

The classic example is infections of prosthetic devices, which are very common, of course. Once we are familiar enough and they are available enough, I expect they will be used alongside antibiotics. There will be a significant increase in the use and availability of these products. At the moment, there are several structural barriers that make it hard.

Q140 Chair: Graham, I will interrupt you to say we have now been joined by Professor Robert Schooley, who is the co-director for Centre for Innovative Phage Applications and Therapeutics at the University of California San Diego School of Medicine. Welcome, Professor Schooley. I believe it is 3 am where you are, so we are really appreciative of your joining us this morning.

Professor Schooley: I apologise for being late. What has happened is that we have added daylight savings time since the invitation was made, so an hour changed. I was anticipating an hour later than this, so I apologise for being late.

Chair: You are very definitely early at 3 am, so thank you very much, Professor Schooley. I will go back to Graham Stringer. Apologies, Graham.

Graham Stringer: I have slightly lost where I was.

Chair: We are all lost now.

Q141 Graham Stringer: I will come back to Professor Iredell, if I might, when I have collected my thoughts.

I will go to Professor Schooley. How quickly are phages assessed by US clinicians, and how much does a typical treatment for a patient cost?

Professor Schooley: I will start with the second question first. Right now, patients are not charged for phage therapy. We are in a pre-FDA approval phase, and we do not charge patients for treatments that have not yet been approved.

The phages are being primarily made in academic laboratories with funds that academics have found from other sources and just do it as a compassionate effort to help people who need the phages, so currently there is no cost.

The time from identifying a need for a phage to having a phage at the bedside depends very much on the organism that the patient has. Some organisms are ones for which phages are already made and are basically sitting in vials ready to go. In that situation, you can have a phage ready in two to four days.



As things get up to speed, they could be made available in hospital pharmacies just like a drug could—they could be stored there. If you do not have a phage for that organism and have to go out and search for one, it can take weeks to months. That is a barrier for rapid access to phages or having larger phage libraries that are characterised and ready to go for use when a patient comes in with a novel organism.

Q142 Graham Stringer: That is very interesting. Can you tell us a little bit about how you go about establishing funding streams for building a phage infrastructure?

Professor Schooley: That is one of our barriers, as I am sure it is for Professor Iredell. We have had some philanthropy from people who are concerned about AMR. Our chancellor at the university provided some seed funds to establish our phage centre.

Some clinical trials are being run by the National Institutes of Health—I am the chair of one of the studies. In clinical trials, the funds come from either the US Government or from commercial sponsors. For clinical use, we are pretty much stuck with trying to scramble to find funds from wherever we can, and right now it is primarily philanthropy.

Q143 Graham Stringer: In terms of the assessment, how do you monitor? Do you do double-blind trials using placebos?

Professor Schooley: That is where we need to be. Some of the studies are now doing that. We are doing one now in people with cystic fibrosis, trying to look at how effectively phage clears *Pseudomonas* from their sputum. In this study, patients are randomised to receive one of three different dose levels of phages or a placebo, and we measure the amount of *Pseudomonas* in their sputum. These are patients who are clinically stable and do not need to be treated right now, so we can look at the phages by themselves.

In patients who need to be acutely treated, we would randomise them to receive the best antibiotics and phages we can find—often, the antibiotics are not going to be effective because of the resistance of the organisms to the antibiotics—and we would see if, in a blinded way, those who also receive the phages had a better outcome. You are absolutely right: the way to approach the evaluation is just like antibiotics—randomised control trials.

Q144 Graham Stringer: How do you see the future of the use of phages? Will it be a large increase in its use, or is it always going to be an adjunct to other treatments?

Professor Schooley: We should think about phages as being living antibiotics, not as anything different from that. If I had a new antibiotic that I was studying, we would not expect it to replace all the other antibiotics; we would be trying to learn how to use it with antibiotics we have.



That is basically a way you do phage therapy. They are going to extend the effectiveness of antibiotics by broadening the spectrum of bacteria that we can kill and by increasing the ability to kill bacteria that are hiding in biofilms and sitting on implanted devices like prosthetic knees and joints and pacemakers where antibiotics alone are generally unable to clear the infection without removing the foreign body and replacing it.

I see them as an additional tool for us to use, and we will be using them increasingly in many different niches of medicine, but I do not see them as five years from now replacing all antibiotics.

Q145 Graham Stringer: Thank you. Professor Iredell, I have remembered what my final question to you was going to be. It was the question I just asked about assessment and double-blind tests using placebos. How are you assessing, and are you doing double-blind tests?

Professor Iredell: At the moment, I absolutely agree with Professor Schooley, and I think that all clinicians would: the only way to assess this is as objectively as possible, and that obviously needs a randomised comparator group.

This just requires funding, and we are certainly, like everyone in the world, seeking funding to do those kinds of comparative studies. We have set up in advance of those studies being developed and rolled out a more pragmatic collection of data to try to better inform the regulators, which is a standardised protocol that we use.

The short answer to your question is that we have only one randomised trial just opening in Australia at the moment, which is a study in staphylococcal infection, which is, in fact, common to the US and sponsored by a US company. We are trying to develop other randomised trials of that type for a variety of important indications.

Q146 Katherine Fletcher: Thank you so much, gentlemen, for zooming in from around the world.

Professor Iredell, there are lots of opportunities in Phage Australia for researchers, clinicians and SMEs. Could you explain to us a little more about what it is and how it is benefiting the industry?

Professor Iredell: To some extent, it was a purposeful gathering of what we would describe as like-minded scientists and doctors. We recognised that there was a need that was likely to be increasingly met by ad hoc applications of research-produced phages, so we gathered as a group trying to present the kind of face that Government would seek.

If you were dealing with a new experimental question like the arrival of covid in your country threatening your entire health system and new therapies and vaccines that you had to roll out quickly, you would designate a group of experts that you would turn to for advice. That was essentially what we tried to assemble. Of course, that was bedevilled by the fact that all those people were already busy dealing with covid.



Nevertheless, that was the kind of group that assembled. It is the senior clinicians and the senior scientists from around the major universities and major hospitals.

We partnered with industry partners inasmuch as we needed to learn from what they would require to make this sustainable, because you will recognise, of course, that you do not want to lean this entirely on the public purse, and that, if you bring a drug in, clearly this is the business of industry more than it is of Government. Our group met, with the primary agendas being to standardise possible key things such as data collection and agree on approaches to develop early conversations with our national regulators.

We have been talking to our regulators for some time now about what they think is important, the data that they need that we should be providing for them to understand how to proceed with this, and to make sure that therapies that were being introduced were being overseen very carefully by the people we have assembled as the available experts in the country. That is essentially the purpose.

Q147 Katherine Fletcher: To summarise, the benefits are the facilitation of three-way communication between Government, academic research and practical application within industry. Understood. Thank you so much.

If it is okay, I would like to move on a bit in understanding how you are trying to develop the evidence base that allows for the confidence. Professor Schooley, what progress are you making in manufacturing at scale? You talked about the timescales earlier. Are they always going to be for specific and individual instances, or is there a ramping up that allows them to be much more mass market?

Professor Schooley: It depends very much on the organism you are looking at. Some bacteria have a collection of phages that are quite broad in their activity, and you could develop a cocktail of three or four phages that would hit 85% of *Staphylococcus aureus*. Most antibiotics have a spectrum like that as well, so you could envisage a situation where you would have a commercial-sized production of a phage cocktail that would be directed at *Staph aureus* and make it at scale.

Some organisms, though, are limiting because the phages that exist in nature generally kill only a small percentage of the bacteria you might encounter of that species in patients, and to have a similarly covering cocktail you would have to have 200 or 300 phages, which is both practically impossible and theoretically impossible because of interactions among the phages.

In those situations, we will either have to do phage engineering to alter the phages to have a broader spectrum of activity or have to come up with personalised cocktails in which individual phages could essentially be pre-prepared—pulled from a shelf and made into a personalised cocktail. Right now, we are captives of the biology of the interaction between



phages and bacteria, but, with time, phage engineering will help us with some of that.

Q148 **Katherine Fletcher:** How are we doing with the evidence base? Is it so early that nothing has gone from start to finish?

Professor Schooley: Engineered phages have been given to patients already. There are phages that are made, essentially, synthetically from scratch, and others in which natural phages have had their warheads tweaked so they are better able to destroy biofilms or more potent in killing bacteria. We, working with Graham Hatfull, treated the first patient with a genetically engineered phage in the UK. This was a patient who had a non-tuberculous mycobacterial infection and cystic fibrosis. The phage we had was one that preferred to insert itself into the DNA of her bacterium as opposed to kill it. The phage was, as we call them, temperate. The phage was engineered. The gene that allowed the phage to integrate into the patient's bacterium without killing it was removed, and we then had a killing phage, and that phage was used to treat the patient.

Both conceptually and practically, engineered phages are in patients. There are several companies that are starting with much more tailored, or engineered, phages, one based in the US and another based in Denmark, and there are others around the world that have been in phase 1 trial. Increasingly, there are going to be pathways to make phages at large scale for specific indications.

Q149 **Tracey Crouch:** Professor Iredell, for the record, will you tell us a little bit about the STAMP protocol and perhaps how it is helping Australia move beyond the compassionate use of phages?

Professor Iredell: It is really designed in recognition of the fact that we expect an increasing demand for ad hoc use of phages that can be imported under a GMP exemption when they are brought in from overseas, much like, I think, is the case in the UK.

The group that has been gathered together felt that it would be appropriate to establish a standardised monitoring protocol, which is essentially what that is. That means that although every patient who is now being treated in Australia is using different phages each time, and may even have different routes of therapy, most of them, or at least all of them so far, have had intravenous routes, and all of their therapy has been monitored in the same way. In this way, we are assembling a database about the way phages behave in humans. What it lacks is a control arm because it is actually a process study, a monitoring protocol, and that is what we have been able to standardise.

Our primary objectives are to understand systematically whether adverse events are being experienced, which of course is everybody's first question when we consider a new therapy, notwithstanding the years of safety data that we already have, and to understand the natural



behaviour—that is: how much should we be giving, how often should we be giving it, and when do we see evidence that we have given enough?

These data are being systematically collected. We are presenting them to the regulator so that the regulator can understand the safety signals, essentially, as we are harvesting them, and we can continue this conversation around the country, including with Government, about how best to go forward and what kind of evidence we need to develop a fit-for-purpose regulatory framework.

Q150 Tracey Crouch: Do you think that phages will be manufactured at scale in Australia, and, if so, what do you think the key enablers will be for that to be achieved?

Professor Iredell: I would certainly echo Professor Schooley's comments, but I would add that for some of the organisms in which there is significant diversity that does create that problem there is also an understanding in every country of the natural epidemiology. No doubt, you could turn to Public Health England, and it could tell you what the most common types of E. Coli or Klebsiella or any other bug that you care to name are that are encountered in the UK, and could, if so inclined or so funded, define the likely calls on bacteriophages that would be generated if phages were called to treat those things.

Clearly, you are less interested in those things for which you already have an antibiotic solution, but for severely resistant bacteria there is a relatively limited, or more limited, diversity that is entirely predictable and knowable and is known, I think, for a country.

Phage Australia has integrated into our system a study of the epidemiology of Australian bacteria so that we can predict for next year what the likely calls for phages are going to be, and therefore if we were set up to produce at scale we could generate the most likely entrance into a GMP-type pathway.

Q151 Tracey Crouch: That is really interesting. I was going to ask you both, given your experience, what you think are the key things that need to be in place for the UK to make phages a mainstream clinical option and a viable commercial proposition. Professor Iredell, I will start with you just to build on your previous answer. Is it about data, or is it about protocols? What do you think it should be?

Professor Iredell: It is Professor Schooley's point about some of the low-hanging fruit. We know that some organisms are relatively easier to target. Your assembled clinicians could soon tell you what the likely requests are going to be. When we surveyed all the Australian clinicians to ask them that question, we got the answers we would predict.

Professor Schooley mentioned prosthetic device infections like pacemakers and artificial hips and knees, which was an obvious one; bugs that you really cannot treat like the genetically engineered solution he also just mentioned; and then things that are very resistant. There is



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a limited subset of indications that are the low-hanging fruit, and you would start with those. You would assemble the group that you would normally turn to for expert advice on how to approach this question and to assess the evidence that is available.

If you decided, as many of us would think the evidence is clear, that there is a public benefit to be had here—that is to say, if you had phage therapy available in certain circumstances, there is a clear benefit to the public purse and to taxpayers, health consumers—you could envisage a scenario in which the state was calling on phage therapy frequently enough that the economies of scale started to emerge, at which point industry would find this less risky to invest in.

When we asked industry from Australia—we did a bit of an international survey—they highlighted three major barriers. The first one is that no one is clear yet about the best-use cases. Professor Schooley and I could probably suggest to you what they are, and many people would intuit them, but they need to be defined and clinical trials need to be done to prove benefit in those circumstances.

Secondly, they were universally expressing concern about intellectual property, which I think you heard from the previous panel. There are ways to manage that risk, one of them being chemical and genetic engineering of phages to fall under conventional patent law, but there are other ways to manage IP.

The third thing was the regulatory framework. It is really imperative to ensure that the conversations with the regulators are early enough that you can design a fit-for-purpose framework. In our country, when we had to do faecal microbial transplantation, that needed to be re-regulated, and it took about three years. We have been going for about a year or a year and a half in Australia, so we reckon we have about two years' worth of conversations to go.

Professor Schooley: Professor Iredell has outlined the key barriers. We are very fortunate with respect to the regulators; the Food and Drug Administration is very interested in phage therapy and is probably one of the greater facilitators of making it possible to get phages to patients in the context of these individual experiences and in the context of clinical trials.

The people who are regulating phages within the FDA are the same ones who do faecal transplants. When I first called the FDA for the first patient whom we wanted to treat, who was basically dying in front of us, she said, "Thank God. I have been waiting for a patient like this. During the day, I have to do faecal transplants. This is scientifically interesting." From that point on, the FDA has been on board. They see phages as being safe. It just wants to know how to use them.

If you have a proactive regulatory framework that is guided by frequent interactions that include the Government, people who know about how to



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use phages clinically within the constraints of our knowledge today, and industry, those sorts of dialogues will facilitate things.

GMP is a barrier, but it is not an insurmountable barrier. It is actually fairly straightforward. It is like a recipe that needs to be followed. It is important to have well-characterised phages going to patients so that we know what we are giving, but that is, again, something that can be achieved with a relatively modest investment to get started and then generalise once they are in place.

In sparking phage access, it is important to have a contribution from Government in helping to support the clinical trials because industry has been reticent to study antimicrobials in general and phages in particular for some of the reasons that Professor Iredell said. This is a signal to them that Government see this as something that down the road will not be impossible to commercialise because of their niche.

Q152 **Tracey Crouch:** A bit more courage is what you are saying.

Professor Schooley: It takes more courage. Right now, suppose you are a middle manager at a company that has been around for a couple of hundred years. You try to do something bold. You go to your boss and say, "Here is something that has failed for 100 years. I am going to stake my career on this." A lot of people do not have the courage to do that.

Right now, we are at a stage where we have technology that we did not have even three years ago that makes it a new day for being able to evaluate well-characterised phages in a rigorous way. If I were in industry, I would have more faith in the natural engineering of phages to kill drug-resistant bacteria than my chemists. Those chemists have been at this for about 75 years and are running out of ideas. The phages have been working on this for hundreds of millions of years and have lots of ideas. We just need to learn how to bring them to the bedside.

Q153 **Katherine Fletcher:** Gentlemen, I am listening and I am excited, and I am almost awed by the potentially positive scale of what phages could do to things like drug-resistant bacteria. If your phages are so effective that they effectively take out a class of drug-resistant bacteria or an environmental class of E. Coli or something, is there any risk that what replaces it is worse?

Professor Schooley, you talked about how natural phages have relatively low efficacy rates because obviously it is nature in balance. I am trying to test whether there are any potentially deleterious effects of having a wonderful phage in either a human or a broader natural system. I will start with Professor Schooley, but I would be interested in both of your views.

Professor Schooley: Phages and bacteria have been at this dance for hundreds of millions of years. So far, with probably quadrillions of experiments in nature, a phage has not emerged that has been able to take out a whole class of bacteria and make them more pathogenic. I do



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not think we will be able to do it readily as mere humans. Having said that, we need to watch this very carefully.

When the bacterium that a particular phage kills is no longer available, that phage is no longer produced and it recedes into the background of phage world. They need to be continuously fed to continue to exist. With the narrow spectrum they have, we do not have phages that have enough of a selective advantage to be able to take out enough bacteria to have us come in with a superbug that will lead to more deleterious consequences down the road.

We have a selection of bacteria that are resistant to more antibiotics, but generally they are not more pathogenic. They are not more likely to cause disease. I see the same sort of relationship happening with phages.

The difference is that with antibiotics we have a finite number of antibiotics that are available to us, whereas with phages we basically have an infinite number to go to to deal with resistance that may develop in the clinic.

We are going to need to follow that in the clinic. We have already seen situations where phages select for resistant organisms, but we also have situations where we have gone back and taken that same resistant organism in a patient and gone back at that organism with a new set of phages. That was what we did with our first patient. That is something that is going to make this quite manageable.

Q154 Katherine Fletcher: That is brilliant. It is important. I wanted to get it on the record. Professor Iredell, would you add anything to that? There is nothing to worry about in terms of what could come behind the organism that is wiped out by the phages.

Professor Schooley: Your first comment about the natural dance is a really good analogy. It is worth remembering that at any point one third of you in the room listening to us at the moment would be colonised with golden staph, but if we checked you again in a month or so it would probably be a different third.

There is a natural waxing and waning of these relationships between bacteria colonising, and a lot of this is mediated by these controls. These viruses are the natural controls in nature on unchecked bacterial overgrowth. All we need to do is learn how to harness that. It is certainly true that you can drive adaptive mutation in bacteria with phages just like with anything if you put them under enough lethal pressure, but most of what we see is emergence of previously susceptible things, and we just need to get the balance right to win that local battle.

Katherine Fletcher: Thank you very much, gentlemen. I appreciate it.

Chair: That concludes our second panel. May I give huge thanks to Professor Iredell and Professor Schooley? I have been on this Committee for eight years, and I do not think we have had such a wide range of time

zones covered in one panel before, so we really appreciate your joining us.

Examination of witnesses

Witnesses: Greg Merrill, Dr Kleppen and Naomi Zak.

Q155 **Chair:** We will now welcome our third panel. Dr Hans Petter Kleppen is the chief science director at ACD Pharma, which is a Norwegian research and development company developing pharmaceutical and health products. Dr Kleppen has headed the R&D work on phages at ACD Pharma. Thank you for joining us. You join us from Norway, but you are here in person, unusually, for this session, so welcome.

Greg Merrill is the founder and CEO of Adaptive Phage Therapeutics, which is a clinical-stage company founded to provide effective therapeutic response to the global rise of multidrug-resistant pathogenic bacteria. Thank you for joining us.

Naomi Zak is the president and chief operating officer at BiomX, which is developing both natural and engineered phage cocktails, and she is joining us from Israel, so thank you for that. Again, we have a range of time zones represented here this morning, so thank you. Greg Merrill, you are in the middle of the night, so we appreciate your joining us here this morning.

Greg Merrill, how far are you from manufacturing phage therapies for non-emergency uses, and how have clinical trials played a part in that?

Greg Merrill: We are manufacturing GMP materials currently for clinical trials, but the GMP process here is iterative in that the early and middle-stage clinical trials require one range of standards for GMP manufacturing because the regulators understand that the final commercial scale processes are not locked down, so they allow for an iterative process of GMP.

We have GMP facilities just outside the Washington DC area, where we are manufacturing and supporting phase 1 and phase 2 clinical trials. I estimate that we are three to five years from commercial allowance for our investigational phage therapy right now.

Q156 **Chair:** We have heard a lot of evidence that GMP is putting off private investment in the development of phages. How well have you found that you are able to link up with private companies, and how have you managed to secure private investment?

Greg Merrill: Advancing phage therapy to market ultimately requires hundreds of millions of dollars, and both Government and private investment is necessary. Clearly, we as a society need antibiotics. They are necessary not only when we have infections but to support modern surgery and chemotherapy, where the immune system is suppressed. Antibiotics are critical, but, as has been mentioned, antibiotics have generally been a failed business model for pharma companies, and that is



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because bacteria are constantly evolving resistance and the antibiotic products become obsolete.

The pharma companies have been divesting themselves of antibiotics. It has not been an attractive market for the investment community. We have attracted private investors because our phage bank approach holds promise. We have the first antimicrobial that is able to adapt to emerging bacterial resistance. We are constantly adding phages to a phage bank. We are disrupting the infectious disease industry, and at least a few private investors are seizing that opportunity.

Q157 Chair: How well have you been supported in terms of links with universities, hospitals and Government agencies?

Greg Merrill: The US Government have an ongoing significant role. For my company, Adaptive Phage Therapeutics, the early work was done at our National Institutes of Health, and then that work was taken up by the US military when the US was engaged in the Iraq war. The soldiers were coming back with infections that were not responding to antibiotics, so they started to leverage the early research from NIH, National Institutes of Health, to develop a phage bank to be able to address those antibiotic-resistant infections.

My company acquired the rights from the US Government for that phage therapy programme, and subsequently the US Department of Defense provided us with contract funding to support our clinical trials with the intent of continuing to fund the trials through regulatory allowance and then to buy the phage products to support our war fighters. The Government have been very active there.

In addition, our National Institutes of Health is also supporting our efforts with pre-clinical animal studies and providing small business innovation research grants that support our GMP manufacturing scale-up activities.

The US Government have also now invested in equity in the company. From many different aspects, the US Government have been supporting phage therapy. The US Government had identified phage therapy as strategically critical for national security, and that is why they decided to invest in the company. Hospitals and universities are critical collaborators for us in conducting our clinical trials.

Q158 Chair: One of the messages we are hearing is that it is quite difficult to build up the evidence because it is individual cases that are being treated. Are you finding that you are starting to build up an evidence base in terms of the work that you have been doing with the military?

Greg Merrill: Yes. As Professor Schooley articulated with his initial case, which was supported by the US military's phage programme—the exact programme that we acquired and are advancing now at Adaptive Phage Therapeutics—over 50 cases have been on an emergency or compassionate-use basis, which is obviously important from a humane perspective, but is not placebo controlled and the type of rigorous



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scientific study that is necessary for regulatory approval. Our major focus is to conduct the randomised, double-blind, placebo-controlled clinical studies that provide the statistical proof that phage therapy is both safe and effective. That is what we are currently involved with. That is why we have invested in our GMP facilities and are now advancing our clinical trials at multiple sites across the United States to have those scientifically rigorous studies done.

Q159 **Chair:** What is the timeframe for that?

Greg Merrill: The studies are now ongoing. Our regulatory groups at the FDA have acknowledged the excellent safety profile of phages and have encouraged us to collapse the phase 1 pure safety trials into looking for efficacy. They are asking us to accelerate development and focus on efficacy as well as safety in these initial trials. The trials that we are conducting now are considered phase 1 and phase 2, or even phase 2b, which would only require one additional study to get to licensure.

Q160 **Chair:** And the timeframe?

Greg Merrill: We are completing the initial trials within the next 24 months and anticipate another year or two to be able to apply for licensure.

Q161 **Chair:** So, certainly within the next four to five years is your goal on this.

Greg Merrill: That is correct; four to five years.

Q162 **Chair:** You have talked a lot about regulations. Are there regulatory barriers that still need to be overcome for your products to be marketed in the US, and is there going to need to be further regulatory reform in order to do that?

Greg Merrill: The big breakthrough from a regulatory perspective when we started the company five years ago was that the Center for Biologics Evaluation and Research at the FDA had experience in regulating a product that changes consistently over time, and that was our annual flu shot. That same group recognised that to combat bacteria that are constantly evolving we need to have some adaptive approach, so it leveraged its regulatory experience in the flu vaccine to allow us to constantly add phage to our product over time, and even in the middle of the trials.

It is allowing us to do that now for our existing clinical trials, and we would require that it continues to take that position as we advance through the clinical road map to regulatory approval. We hope we can demonstrate safety and efficacy in those early trials to support that regulatory approach moving forward. Other than that, it is the more standard need for showing the continuing safety and efficacy through the progressive clinical trials.

Q163 **Dawn Butler:** Naomi, one of your products has moved to phase 2 clinical trials. How does that differ from other products in other companies that



have moved to clinical trials?

Naomi Zak: We have spoken a lot about chronic *Pseudomonas* infections in cystic fibrosis patients, the association of those infections with higher instances of morbidity, and the fact that their chronic presence means that they cannot be treated by antibiotics. Our trial is in two parts.

The first small part was somewhat of a dose-finding trial on a small number of patients. It is double blind and placebo controlled. The primary outcome was meant to be safety, but even from this first part of our study we were already able to announce top-line results showing evidence of efficacy of the difference in the amount of production in bacterial burden among the patients who had been treated with the phage as opposed to the patients who had been treated with the placebo, and that is on top of standard care.

This first study is not statistical because the numbers are very small, but we have permission and we are immediately going into the second part, the 2a part with a larger number of participants and a higher dose level, and there we hope to reach a statistically significant result. At the same time, we are already beginning to plan a larger study that will follow that.

Q164 **Dawn Butler:** Have you had something else that has enabled you to make faster progress?

Naomi Zak: We have had some Government assistance in Israel through what is called the Israel Innovation Authority. We have had assistance from the Cystic Fibrosis Foundation. We also have private investors. All that has enabled us to bring in-house a lot of capabilities that have allowed us to be very agile. We are able to do GMP manufacturing to scale, which will allow us to carry out these clinical studies on materials that we have manufactured.

We have also been able to set up a very sophisticated computational group that allows us to design cocktails that have a very wide capability of targeting the infectious agents and to allow the possibility of potentially having off-the-shelf products for some bacteria, maybe not for all. Off-the-shelf products are more attractive to pharma and to investors. They would like to see the possibility of off-the-shelf products. They would like to see that GMP is not a problem. We are able to manufacture for clinical trial scales. We would be able to scale up further for commercial manufacture, and we would probably get some Government assistance in that.

To see that the GMP is not a problem and to see that the regulation is not a problem is very reassuring to investors—then, of course, to begin to see data from properly controlled blinded studies. The individual compassionate-use cases for drugs are very important. Certainly, it has convinced us all of the safety of phages but has not produced the kind of data that really reassures investors.

Q165 **Dawn Butler:** Thank you. Could you provide that in writing to the



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Committee, please, because some of it was a bit glitchy, and it is important evidence?

Greg, you said that antibiotics are a failed business model. Why do you think that pharmaceutical companies would continue to invest in a failed business model?

Greg Merrill: Unfortunately, I do not think they are generally continuing to invest in antibiotics. Antibiotics have been failing because bacteria evolve resistance. On top of that, there is the practice of antibiotic stewardship that is required, and that is where hospitals will hold the new antibiotics in reserve to protect the lifespan of those new antibiotics and just use them only after the older antibiotics have failed. That makes sense from a science standpoint, but, as you can imagine, if you are a pharmaceutical company that has invested hundreds of millions or billions in advancing that new antibiotic, you do not want that product sitting on the shelf; you want it to be sold.

For those reasons, many of the large pharmaceutical companies have divested themselves of their antibiotic portfolios, and many of the start-up companies, even if they have achieved regulatory approval for their new antibiotics, have unfortunately soon after that had to go bankrupt because of the depressed market from antibiotic stewardship. That is why I feel that the investment in advancing new antibiotics, and even phage, requires both public and private capital to move these programmes forward.

Q166 **Stephen Metcalfe:** If I may, I shall direct my questions to you, Dr Kleppen. Can you tell us a little bit about the work that your organisation is doing particularly around phages? I understand that you are building a bacteriophage factory. Can you explain what that is and how you are getting on with it?

Dr Kleppen: We have been working with phage for 13 years now, starting from scratch in collaboration with the Norwegian University of Life Sciences, where we have labs; I have a lab group there. We are taking it step by step. We work in the field of aquaculture and veterinary medicine.

The background for this, and the reason we got private funding for it, is that, back in the 1990s, we had extremely high use of antibiotics in aquaculture. That was solved by vaccines. We see that vaccine development is slow and that vaccines are not perfect, and we know that we cannot go back to the antibiotic use we had before in aquaculture. That would mean a shut door for Norwegian salmon farming, which is a billion-pound industry. It is similar here in the UK; it is a big and important industry.

When we started working with phage, we wanted to solve all the bacterial problems in the industry. We ended up having to select one target bacterium, *Yersinia ruckeri*, for which we originally started off aiming for a medicinal product. With guidance from the Norwegian Medicines Agency



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and the European Medicines Agency back in 2012 and 2013 and, finally, the requirement for GMP production, we ended up taking one step back and redefining the treatment strategy for the use of phage.

Through initial trials in 2013 and 2014, we saw the mechanism of action of the phage and that the way it saves fish is by removing bacteria from the water, so it prevents the spread of the disease from carriers to naive fish. Through that mechanism—we call it a water-conditioning product—we use phage to modulate the microflora of the water, which is a way of defining it that we have not been successful with here in the UK but, in Norway, because of a lack of clear regulatory guidance for how to proceed with a medicinal track for phage, it has been accepted.

Q167 **Katherine Fletcher:** Did you say yersinia, as in yersinia pestis?

Dr Kleppen: Yes.

Q168 **Katherine Fletcher:** Yersinia pestis is the bubonic plague, so you are treating fish plague with this stuff. I apologise for interrupting.

Dr Kleppen: This is yersinia ruckeri, which is a very distant cousin.

Katherine Fletcher: Yes, I just thought I would try to bring a bit of colour to it. Sorry, Stephen.

Q169 **Stephen Metcalfe:** It is all right. Thank you for that.

So, you are scaling this up and now it is going to be a commercial, agricultural product, effectively.

Dr Kleppen: Yes. We launched the product in 2018. Last year was the first year when we had significant sales, and we are currently producing it. There is no GMP but there are very stringent quality controls because that is necessary, basically, to know what we are doing.

Q170 **Stephen Metcalfe:** Quite. So, you are manufacturing one product at the moment.

Dr Kleppen: Yes.

Q171 **Stephen Metcalfe:** Are you looking at investing in others?

Dr Kleppen: Yes.

Q172 **Stephen Metcalfe:** Hence the requirement for a factory, as it were.

Dr Kleppen: Yes. We are working on a portfolio of new products in aquaculture and veterinary medicine. With the next one, we are most likely not going to be able to claim an effect on water; it is going to have an effect on the fish, hence the need for large-scale production and GMP.

Q173 **Stephen Metcalfe:** You mentioned GMP, and I think you said in your first answer that your product is manufactured not to GMP but to a set of stringent standards set by the Norwegian Government. Is that right?



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Dr Kleppen: It is not set by the Norwegian Government because phage and biocontrol are not regulated in Norway. This would fall within the animal welfare legislation that in Norway is governed by the food authorities. It is basically a food quality standard.

Q174 **Stephen Metcalfe:** Why did you not decide to go down the GMP route? Would that help you expand your markets and export the products more widely?

Dr Kleppen: Yes, it definitely would, but a GMP production facility is a very big investment. We have had very good support from Norwegian Government funding bodies. We received a record grant from Innovation Norway of about £4 million, but that is a very small part of that investment. As Greg said earlier, hundreds of millions of dollars would go into that kind of facility.

Q175 **Stephen Metcalfe:** Presumably you hope to expand the business to the point where that would make economic sense.

Dr Kleppen: Yes. We are in a very lucky position because we have an owner who is a phage enthusiast and has been financing probably more than 95% of my expenses over the last 13 years. It is kind of a unique story. It is also why the factory is located where it is in Norway.

Q176 **Stephen Metcalfe:** Excellent. You have obviously had a very engaged owner who provides a lot of the finance, and you have some money from the Government. Have any other public sources of income been made available to you?

Dr Kleppen: No. We have the Norwegian Research Council and Innovation Norway. The research council is primarily about early, basic research, and Innovation Norway is more for when it is at a higher technology-readiness level. We have grants, as the other analysts here earlier described—scientists will find funding wherever they can—but the majority of the funding has been private.

Q177 **Stephen Metcalfe:** Do you have one particular owner, or a range of owners?

Dr Kleppen: There is one owner.

Q178 **Stephen Metcalfe:** And that owner has been with you for a long time: you said that they have paid your wages for the last 13 years.

Dr Kleppen: Yes.

Q179 **Stephen Metcalfe:** But you do not have any other private investors. What do you think is the appetite in Norway for private investment in this technology?

Dr Kleppen: It is difficult in Norway, and worldwide, because of the specificity of the phage: no big blockbuster products will come out of this. We are not going to see one phage project making \$100 million; it will be



a range of different products in combination that make a business profitable. That is a very hard sell to private investors.

Q180 **Stephen Metcalfe:** Indeed.

I have one final question for all three of you. I mentioned earlier—you may have heard—that, obviously, the purpose of an inquiry such as this is to gather evidence and make recommendations to the Government. What do you think those recommendations should be? What would encourage you to come to the UK and continue to develop your businesses here? Do you think there is something in particular that is missing in the UK landscape?

Dr Kleppen: Phage therapy is about getting enough of the right phage at the right density to the target area you are treating—be it water or an organ in a patient. It needs to be regulated in a way that makes it medically viable. It needs to be the right quality, safe and efficacious, but, as was said here earlier, it is possible to ensure safety and the right quality without the full GMP and GCP.

For us to succeed here, it would be necessary for either some sort of financial instrument to reduce the risk, to invite private investors, or to lower the bar of market access. I would prefer the latter. As Jean-Paul said in the first session, it is possible to get the right quality, safety and efficacy without the full GMP production and GCP trials.

Greg Merrill: I was going to say basically the same things. There are two aspects. First is collaboration on the regulatory pathway to allow this. We have an adaptive phage approach where we are constantly finding new phage and we are adding that to our product. In the US, it has been a true collaboration with our regulatory authorities to design how we are going to support that regulatory approach. That is one thing.

The second is co-investment with us and our other investors to establish manufacturing facilities in the UK and to support clinical trials. Those two things would make it attractive for us to be in the UK.

Naomi Zak: I echo everybody's words about the regulatory framework and the need for it to be clearer and aware that regulation of the product might be different in cases of individual use, as opposed to the early stages of a clinical trial and compared to later stages and commercial. That should be taken into consideration.

The regulatory authorities need to be open for discussion. Again, to echo Greg, watching what has happened in the US over the last five years, I know that they have been very open to discussion from the very early stages, and they have also evolved with the field as more information, data and support have come from various studies. That has been very encouraging.

Certainly, anything that would make the hospital system in the UK more accessible for clinical trials would be greatly welcomed, because while we



started our clinical trials in the US and Israel, we are, for example, now looking to expand into Europe. We have already made contact with some countries and are proceeding in a good way, but certainly anything that would make the UK hospital system more accessible would be very beneficial.

Stephen Metcalfe: Thank you all very much.

Q181 **Chair:** Dr Kleppen, you have sat through all three panels this morning, and I wonder whether there are any key messages you have heard that you think are important to highlight. Have you had any surprises this morning?

Dr Kleppen: No, not many surprises. It is important to remember that phages are fundamentally different from other antimicrobials. To compare an effective dose of phage and an effective dose of gentamicin, for example, there are 8 billion gentamicin molecules per phage, so it is fundamentally different. They are alive, and they are very specific. Those fundamentals need to be remembered.

It is important that regulators help SMEs and others working with phage therapy to make them medically viable. They need to be safe, efficacious and of the right quality. But they also need to be financially viable. It is very easy to make regulations too strict and make the products non-financially viable, and then nothing will happen—nothing will be developed.

Chair: Thank you. That is a really important message, and we appreciate you joining us. I thank all three witnesses—Dr Kleppen, Greg Merrill and Naomi Zak—for joining us internationally this morning. It is very much appreciated.