

**GLAXOSMITHKLINE  
VACCINES INVESTOR EVENT  
Thursday, 26 September 2019  
Wavre, Belgium**

**Roger Connor (President GSK Vaccines):** Hello everyone. You are very welcome to Belgium. It is my privilege to be the Head of the GSK Vaccines business. I have been in this company just over 20 years. I have worked in Manufacturing and Supply for most of my career and I led our Global Manufacturing and Supply organisation for a number of years sitting on the Corporate Executive Team. It was just a year ago that Emma asked me to become the President of our Global Vaccines business and I have to say that I love my job, it is incredible the difference that we get to make to people's lives. We are the world's largest Vaccines company and we estimate that 40% of the world's children receive a GSK vaccine, which is something of which we are incredibly proud and we can't wait today to bring to live for you this business.

**Cautionary statement regarding forward-looking statements**

I want to start with the normal cautionary statement that we share before moving on to the agenda.

**Agenda**

We have two hours planned - two fun-filled hours I hope! I know you have had a busy morning having a look around this amazing facility. First, we are going to have some presentations. I hope to set the scene on the market, talk a little bit about why GSK is positioned well within that market and then Manu, who is Head of Research, will talk about our pipeline, our technology and our science.

Because we believe that manufacturing is such a critical part of this business, Russell Thirsk, who is Head of our Belgium operations and is a world-leading vaccines manufacturing expert, will talk a little bit about that. Then some of my team will come up and join us for the Q&A and we have an hour of Q&A, which I hope will be plenty of time. I shall be joined by Jay, CFO of the Vaccines business; Patrick, Head of the Commercial side of things and Thomas Breuer, who is my Chief Medical Officer.

**Attractive market dynamics**

I am going to dive in and get started. I talk about this being an attractive business to be in and two words really spring to mind for me when I think about vaccines and the marketplace: first of all growth and then durability. From a growth perspective, while it is pretty obvious, it is worth stating that we put vaccines into a lot of healthy people and the bigger the population in the world, the bigger the marketplace gets. The world's population

is predicted to increase by 25% between now and 2050. There are 130 million babies born every single year, so from a market perspective it is growing, which is an opportunity for us.

As far as durability, what has amazed me is that, when you find a vaccine, you will have a vaccine for a very long time. Unlike with Pharmaceuticals, you don't see the same patent cliff, you don't see the same generic competition. A vaccine is more like a Consumer Healthcare product: you keep investing in its lifecycle management and it can be around for a very long time to come.

However, the one thing that can really disrupt you and remove that vaccine would be a disruptive technology play: an innovation that raises the bar in the therapeutic area in which you are and changes that standard of treatment. That is exactly what happened with *Shingrix* which I shall come to talk about a little later on. Therefore, again, an expanding and durable market.

The term "barriers to entry" is used a lot in Vaccines: high capital intensity to start up. I do not believe we could be in a better place to bring to life the barriers to entry from a capital investment perspective than this facility at Wavre in Belgium. You can nearly see this place from space, it's that big in terms of its operation.

You cannot suddenly decide you are going to make vaccines and do it in your garage tomorrow. This takes massive investment, it takes focus, science and expertise, which we have here at GSK and we shall make sure that we exploit that as we push our strategy forward.

However, it is not just the capital to manufacture and develop vaccines that is a barrier. If you look at the clinical trial approach, I am used to Pharmaceuticals where we set a clinical trial, we set an endpoint and we are looking for the disease to get better through some sort of measurement.

In vaccines, we are typically putting our vaccines into healthy people, looking and waiting to see whether the disease does or does not arrive. That takes longer, it takes more time and it takes more money as far as investment.

Therefore, the net position here [for the global vaccines market] is that this is a very attractive business that between now and 2024 is predicted to grow by around 7% per annum, and we really believe that it has Pharma-like margins and Pharma-like cash conversion.

### **Market evolving: expanding disease areas and target groups across the life course**

However, it is a market that is evolving, it is not standing still. If you go back to 2000, and you think about vaccines, people would talk about kids' vaccination and to be honest, limited clinical differentiation between the competitors in that space.

Look at where we are now; we have high value vaccines that are being used to treat adolescents and older adults through innovation and look at where are going to go next though. That is the exciting bit! Through disruptive technology, more therapeutic vaccination. Having vaccines that aren't just there to prevent the disease but actually to treat it as well, and then on the slide we have tried to show that means that the population of people we are looking to treat with vaccines going forward has to change – not just babies, not just older adults, but through life. What we call life course immunisation.

What we want to show today is that in GSK we really think, we have set a strategy, we are optimised to absolutely make the most of this opportunity, both through our innovation and through our science.

### **GSK Vaccines: strong track record of performance**

Some of you may know GSK quite well, some of you may not know GSK Vaccines very well. I thought I would just double-click on our performance for a second, just to bring that to life for you. We are very proud of what we have achieved as a vaccines business. Between 2015 and 2018 our growth rate on an average basis is 12%, compound annual growth rate, our margin continuing to expand. We integrated Novartis very effectively. We have launched two key products in *Bexsero* and *Shingrix*, both of which I will touch on later on but, again, we are very pleased with the launch of those high value differentiated vaccines.

In the US it is really worth a specific mention from a performance perspective. Rewind to 2015; GSK vaccines in the US, there were four players, we were number four – 14% share. 2018; fast forward, we are now sitting at 24% share, and we are number two in that marketplace, and we are proud of this performance, but within GSK our importance is growing as well.

When you look at the first half results, if you just take the Pharma and Vaccines business, the Vaccines business is 27% of that total and we are growing. When the Consumer Healthcare JV within GSK does separate, and that will happen at some stage in the future, we are going to be playing a bigger role within GSK logically. Hopefully you get a sense that it is a very exciting time to be working in GSK, and we think it is a very cool place to work within GSK right now because of this opportunity.

### **Focus on delivering Vaccines priorities**

I wanted to just let you know what our priorities are. Completely aligned to what Emma has laid out at a group level; Innovation, Performance, Trust underpinned by an incredible culture.

From an Innovation perspective, it is really key and simple; accelerate our vaccines and the delivery of our disruptive new technology platforms.

From a Performance perspective; forwards – *Shingrix*, *Bexsero*, US, China, and we are going to stay completely focused on that. We are really pleased with how *Shingrix* has gone, *Bexsero* is continuing to grow that market. The US I have referenced in terms of our share growth and our opportunity. China is a big opportunity for GSK particularly with the *Shingrix* approval, and I will come on to it as well.

Trust is fundamental in this sector. Again, we see it as pretty simple. Our customers want their product when they need it. That means brilliant, reliable manufacturing and supply, and it is a real core competence of ours that we continue to invest in, and the key to this is you have to be relentless about your product quality, ensuring you always hit those highest quality standards.

Then on Global Health; making a contribution to society. We think there isn't a better example than vaccines in GSK of us making a significant contribution to the world, and we remain completely committed to our Global Health agenda.

### **GSK Vaccines pipeline**

If I double-click on Innovation and talk about our pipeline. Manu is going to come up and spend a little bit longer on this and go into more detail, and do it much more eloquently than I could ever do, but if you look at this, what I see in our pipeline is breadth. I see a transition into therapeutic vaccines, like I mentioned, also we are making the most of our platform technology.

Adjuvants and *Shingrix*; a key part of our *Shingrix* success – let's call it the thing that really makes the magic happen is our adjuvant. We call it Adjuvant System number 1 – AS01 you will hear us say. That is what has made *Shingrix* so successful from a clinical performance, and in our pipeline we are going to ensure that we maximise our adjuvant technology in future assets as well.

What am I most excited about in this pipeline? Life cycle management of vaccines is so key. *Shingrix* from a geographic expansion perspective will be key, also taking *Shingrix* into other indications. We are in the clinic currently looking at immuno-compromised patients.

Then, RSV – not just one vaccine but three vaccines, again, for a great unmet need. Then chronic obstructive pulmonary disease. I think it is very fitting that GSK is working on a vaccine in this space to fully complement our Respiratory competence and excellence as the world-leading Respiratory company.

I mentioned the need to continue to invest in technology and disruptive technology within Vaccines going forward. On this slide you will see reference to our Messenger RNA programme. This is a Self-Amplifying Messenger RNA platform, affectionately called SAM within GSK. Manu will go into in more detail, but the words to remember with SAM are pretty

simple in my mind: faster for development; more efficient in our manufacturing; and more effective as a vaccine.

### ***Shingrix*: a new standard of prevention in shingles**

That's the talk about and excitement from a pipeline perspective in GSK. From a commercialised product perspective, two products that we are working on at the moment – you may have heard of this one, *Shingrix*, and I am going to come to questions on capacity and supply, and ramp-up. I am sure there are a number of questions here that you would like answered. I am just going to go through this in terms of our current plans.

From a *Shingrix* perspective, we are delighted with the way the product has launched. Trust me, this is a devastating, horrible condition. Nearly everyone in this room will have been exposed to the herpes zoster virus, and as we get older – and I am approaching a big birthday this year, our immune systems start to decline and that virus can reactivate, and when it reactivates, shingles can appear.

One in three of us in this room will get shingles, so when we launched this product in the back end of 2017 we knew we were making a bold scientific, innovative move. The clinical efficacy of this vaccine is incredibly high, greater than 90%.

When we went to ACIP we had an amazing outcome, an unprecedented outcome. First of all, we got the preferential recommendation. Then, we got the recommendation for 50 years and above, and then we also got the recommendation that anybody who had been previously vaccinated with the previous vaccine should get vaccinated with *Shingrix*. This is big news.

Then follow-on approvals followed, so we had approval in Canada, approval in Europe, Australia, Japan, China, so a very exciting time for this vaccine.

### ***Shingrix*: US launch driving market expansion**

In terms of the US launch, this is a slide I put in front of my boss quite frequently just to show her the launch success in the US.

We really believe that when you look at this launch against the other portfolio of biopharm launches in the last ten years, it is a stand-out launch.

If you then look at where are we in terms of opportunity, I think we are just getting started. There are 115 million people who are 50 or over in the US. We have vaccinated with at least one dose of vaccine we estimate nine million people, so you get a sense of the opportunity that there is still to go.

### **Shingrix: global opportunity to expand the market as capacity increases over time**

But, Roger, what about the geographic rollout? What about your manufacturing plans? Can you keep up?

We have a phased geographical rollout plan for *Shingrix*, and it is completely supported by a very robust manufacturing expansion plan, which is on track. In fact, we are accelerating.

As we have said recently, in 2020 we expect to be supplying high-teens millions of doses, but it doesn't stop there. We have an extensive programme of capacity expansion – over 20 projects running around the supply chain.

After 2020 there will be steady progression in capacity, but you won't see that step change in terms of capacity – that tens of millions of doses, not before 2024 when our new facility will come online.

I mentioned China. The approval was a big day for us for this vaccine. There's a massive opportunity in China from a disease burden perspective as a significant. The challenge for China is that we are going to have to take a phased approach to that launch; it has to be phased.

Unlike the US, this did not have or does not have a market for a shingles vaccine currently, so we have to build that. We have to build with the market, we have to build disease awareness, and we will be investing in that to make sure that we continue and are ready to supply into that market going forwards with a phased launch for next year.

I mentioned the clinical expansion opportunity on *Shingrix* as well. We are in the clinic and we are looking at immuno-compromised below 50 as well, and that could be an exciting opportunity for us in the future. So I hope you get a sense of the opportunity around this vaccine, you get a sense that we're really only getting started, we're off to a great start, but this will be a growth driver for GSK for many years to come.

### **Bexsero: leading the market in Meningitis B**

I have to talk about *Bexsero*, and Meningitis B: Meningitis B is an infectious disease that doesn't have a very high occurrence rate, but when it does, its outcome is devastating. The regional variations are quite high in terms of its incidence rate, but in the main this is a disease that hits infants and teenagers.

*Bexsero* is the world's leading Meningitis B vaccine. We acquired this, it came in as part of the Novartis integration, we spent the first bit of time working on capacity security and making sure we could supply, that has been solved and now this is all about market growth for *Bexsero*.

It is a vaccine that we are, again, incredibly proud of, it's differentiated. It's differentiated in Europe first of all: we have a label and an indication for infants that no-one else has. That's key, because the disease burden of this particular area is ten times higher in infants than it is anywhere else.

Then in the US it's different again, because the ACIP recommendation is for adolescents in the US. Now, we're differentiated again here, most importantly by our dosing schedule, because when you have an outbreak in a college - which is what we've seen in the US recently - you want to be able to get as much coverage as you can, fast. We are the only vaccine that can be given after one month of the first dose, and that means we can get faster coverage, which again is important for differentiation, particularly in that market.

Another exciting point coming out about *Bexsero* soon: soon we're going to see published the real world data from the UK, where there has been a programme vaccinating infants and children. We'll see the real world impact data of a significant reduction of disease burden as a result of this vaccine - that for me emphasises just how important *Bexsero* is, going forward, in the future, and a Men B vaccine is as well. *Bexsero* will be a growth pillar for GSK vaccines, going forward.

### **Broad portfolio with quarterly sales fluctuations**

They're not our only vaccines, obviously: we have 40 in our portfolio. The graph on the left shows our split by categories: established vaccines are there, they stand out, 60% of our business. There are some vaccines in there that completely show that durability point that I mentioned at the start.

Then on the right hand side you look at our regional split: 50% of our business is in the US, 50% in international and Europe. The big opportunity on that chart is China, and what we can do in international as a result of that focus that I mentioned earlier.

You might look at that chart and say 'Roger, what's going on with the shape of it?'. Many of you may know this already, that the quarterly phasing in vaccines can be a bit funny. Q3 is typically our biggest quarter, for a couple of reasons: obviously, flu comes in at that time and then also, particularly in the US, you get some back to school vaccination initiatives as well that cause that spike.

Something else you'll hear us reference in our quarterly calls as well would be phasing, when we compare to previous quarters - it can be a bit lumpy in vaccines, because a lot of our customers from a government point of view can be stockpiling or running down stocks, so we get these timing differences as well, which we reference when we talk about our performance.

Again, we feel that we are geographically well-spread and we are diversified from a product perspective.

## **Established vaccines and flu: durable assets provide portfolio backbone**

If I go into established vaccines – I'm not going to go through all of our established vaccines. Maybe two that I would really focus in on is families. Our Hepatitis family, over £800 million of sales last year. In the US I'd specifically reference our Hepatitis A vaccine, where we've seen outbreaks recently, and this is where manufacturing flexibility can come in - you can react to that flexibility when you have outbreaks of that kind, and that's what we've done within Hep A.

In Hep B, *Engerix B*, amazing vaccine, it's 30 years old, it's been on the market for 30 years, and last year sold £300 million. We know that we had to step in because one of our competitors had some challenges, so I'm sure they will come back at some stage, but it shows you again the importance of that flexibility.

I don't think you can talk established vaccines without going into the diphtheria, tetanus and pertussis family, and if you drop into the paediatric section within that, that is a tough segment to be in right now, particularly in Europe. There are a lot of competitive pressures, and our *Infanrix Hexa* has to compete with other vaccines in that space. In the US, *Pediarix*, a very well-respected vaccine, and doing well. We know in the next two years we're going to face some pressure there, a hexavalent vaccine will come into the US in those next couple of years and I am sure that will have some impact on *Pediarix* in the future.

However, you can't forget in DTP the growth engine that is hidden in there a little bit, it is called *Boostrix*. This is our Tdap vaccine and in the US we are the only vaccine that has an indication in older adults. Again, it is part of that life course immunisation that I mentioned, which is a growth area and a growth opportunity for us given that differentiation. We call these vaccines the backbone of our business, with many still growing, profitable and generating cash for the business.

## **Trust: our supply reliability, safety and quality**

Let me move on to the Trust agenda and Russell will talk about this in more detail. I just want to say that this is a real area of focus, we believe it is a competitive advantage and we allocate capital strategically to our manufacturing space. In the last 10 years, we have invested £4 billion in our manufacturing capacity, we take it that seriously, and we shall continue to ensure that this is protected.

## **Value of vaccines for public health**

There are lots of numbers on this particular slide around our impact on public health for trust and on our impact for global health. Let me say a couple of things here. Two million doses leave GSK every day to go out into the world and make a difference to people. As I

said at the start, 40% of the world's children get a GSK vaccines; we make a unique contribution to society.

Then on global health, we work with very well-established, trusted partners together to make a difference to the world on specific vaccines like malaria and shigella. Again, this is a key part of our strategy.

### **GSK: the market leader in vaccines**

I am going to wrap up by saying I hope you get a sense of how excited we are about this business and the opportunity that there is within it. We are the world's largest vaccines company. We are very experienced and capable in this space as I hope many of you will have seen today. We have a broad portfolio of 40 vaccines, including, we believe, two very special vaccines - *Bexsero* and *Shingrix*.

We are geographically spread in over 160 countries with a focus in the US and a real opportunity to continue to grow in China.

We have a pipeline that is broad and that is moving into therapeutic treatment, making the most of our adjuvant technology. We really believe we are performing with growth, margin expansion and cash generation.

### **Innovation is key**

Before I hand over to Manu, I just want to show you one slide that summarises it all for me. Back in 2000, GSK had a turnover of less than £1 billion in its Vaccines business. Last year, we were almost at £6 billion. I have put on this slide all the launches, key assets and innovations that have delivered that profile. Now I shall hand over to Manu who will take us through the pipeline of vaccines and technologies that will ensure that line in the future keeps going in that trajectory. Thanks very much.

**Dr Emmanuel Hanon (Head of R&D):** Thanks a lot, Roger. Good afternoon everybody. It has been said several times that my name is Manu and I have been with GSK since 2001, and I have been leading Vaccines R&D since 2014. I hold a PhD PostDoc in the field of microbiology, immunology and vaccinology, and it is a great pleasure for me to be here with you and to present to you what is the research and development strategy at GSK Vaccines.

### **GSK history of vaccines leadership and innovation**

The science behind vaccinology was only introduced a few hundred years ago but a lot has been done, and this place has made several major scientific breakthroughs. Don't try to read everything on the slide; I shall cite a few of them selected from a long list.

In 1986 we made the first ever hepatitis B vaccine out of recombinant DNA technology. We more recently delivered a proven, highly effective meningitis B vaccine using the reverse vaccinology technology. We have also been working very hard to master the adjuvant field, taking the leadership in that field, making possible the delivery of vaccines like *Shingrix* with an efficacy level that was believed to be impossible to reach in a specific age segment. Therefore, I can tell you that this place knows how to innovate in the field of vaccinology and the field is moving very fast; these are exciting times.

Vaccines have been used up to now mainly to prevent diseases caused by infection, and we are convinced that we are taking a new direction where vaccines will be used with the intention to treat, as therapeutic vaccines, in addition to their prophylactic use. Why do we believe that? We believe that because life sciences are really exploding and it is now possible to predict your future health condition or an ongoing chronic condition, out of big data analysis, opening the door for a new intervention – prophylactic or therapeutic.

There are many new technologies to simply make vaccines better, and there are novel partnerships ahead of us because there are a lot of new players with new technologies going after new things. So I am really convinced that there is a universal opportunity in vaccinology and not only in the classical field of the paediatric segment, as we used to do, but actually across all ages with prophylactic intervention as well as therapeutic intervention. My objective today is to take you on this exciting journey.

### **Vaccines innovation trends**

What is our strategy at GSK? At GSK, we are taking the best science, with the most impactful technologies, and combining it with a special mindset or culture. It is really the three together that we are trying to get, because that is the moment where you have the magic of innovation. That is what we are really looking for. We are definitely pushing ahead with ground-breaking vaccines, whether it is through lifecycle management as was mentioned – with *Shingrix* and meningitis, by introducing new products, or by entering into new fields like therapeutic or anti-microbial resistance.

We do that by investing strategically in technology platforms that allow us to go faster in research and development, to get better vaccines, or to get manufacturing more efficient. All of that is combined with that special mindset – a mindset where we put the right talents in the great position where, basically, we are taking smart risk, where priority is the most important aspect – our prioritisation and focus in the management of the pipeline. I can tell you that this is really my daily priority.

### **Our vaccines R&D approach**

The most obvious deliverable of a vaccine research and development organisation is obviously a pipeline of new products – be they commercial assets or global health assets,

but there is an incremental value in doing vaccines research and development. It is what we call the strategic lifecycle management. We can invest into that field with the aid of improving the presentation of a product, moving from a multi-vial presentation to a single pre-filled syringe. We can invest to expand the use of a vaccine for a new population or against a new disease, or we can actually invest to conquer new geographies. The approval of *Shingrix* in China, I can tell you, will be like launching a new product.

### **Classification of pipeline assets in clinical testing**

I think it is really important for you to know that when delivering a new product in vaccine research and development, the probability of success lies at around 30%, which is three times higher than what you usually say for the pharmaceutical industry.

### **GSK Vaccines pipeline**

When speaking about lifecycle management it is even higher and this is why our pipeline is actually a balanced combination of these two areas – the lifecycle management, shown in orange, and the new product development shown in green and in blue.

For lifecycle management, I will not describe everything but I will focus on the two mainstream investments. The first one is definitely *Shingrix*. It is approved in Europe, the US, Japan and Australia and was recently approved in China. Basically, we want an incremental opportunity and we believe there is an incremental opportunity as we have already generated Phase III efficacy data in immune-compromised individuals. So it is really about using *Shingrix* in people aged 18 and above, who suffer from a chronic condition or who are actually treated in a way that their immune system is weaker and they are prone to reactivate the virus. So that is an incremental opportunity and it is one of our top priorities.

The second mainstream investment that we are doing is on the meningitis franchise. We are leading the market – we are the market leader on the meningitis B vaccine, with 70% market share. Our ambition is to become the leader in the meningitis franchise and we want to do that by delivering the highly convenient pentavalent meningitis vaccine combining ACWY and B valances. We have invested heavily and we have reached the end of the Phase II stage and now we are looking forward to align with the FDA for the next Phase III development plan that will roll out soon.

On the new products, I will not cover global health assets that have been briefly mentioned by Roger but I really want to focus on the blue commercial assets, which really express the ambition that we have, going after major medical needs and entering new fields like therapeutic and anti-microbial resistance, or investing in new technologies. You will understand why this is strategically important to invest in new technologies.

## **RSV vaccine opportunity: high unmet need**

Let me start with the respiratory syncytial virus. This virus is still causing a big burden of disease. In children, this disease causes acute bronchiolitis, which can lead to respiratory distress and hospitalisation. Please note that, actually, the rate of hospitalisation due to that virus is sometimes 10 times higher than that caused by influenza. In older adults, that infection also causes pneumonia leading to hospitalisation and, unfortunately also, death. Simply in the US, there are 16,000 people who die every year from that infection. Therefore, in response to that big medical need, GSK wants to be bold.

### **Three RSV vaccine candidates**

We have actually designed three vaccines that are really fit for purpose and tailored for each individual need that needs to be addressed to cover the whole medical burden. We have a maternal vaccine which aims to achieve protection during the first six months of life of children, which covers half of the burden.

We have a paediatric vaccine that will expand that protection up to two years, and we have an older adjuvant vaccine that will be used for individuals aged 60 years and beyond.

Designing and developing a vaccine against RSV has been really tricky. There has actually been 50 years of research and development that to date has not been successful, but the science behind RSV has really exploded over the last five years, and we know now precisely which antigen needs to be included into the material vaccine. It is the fusion protein of the virus. The protein needs to be in a very specific conformation – the pre-fusion – and it has to be locked, so you can imagine there is really a great deal of science to achieve that in the vaccine, but that is exactly what we have been able to do here at GSK, and that is fundamentally different from all the other fields of efficacy trials that have been reported.

For the paediatric vaccine, again, following this tailored approach we use an adenovirus platform technology that out of our research has been the only one able to teach the immune system of the baby to actually provide protection for years. Then we have an older adult vaccine that capitalises on the pre-fusion antigen and we combine it with the AS01 adjuvant, exactly the same as the one for *Shingrix*, and it is really important for two reasons; first of all, because that adjuvant really addresses the very specific immunological status of older adults. It has been beautifully shown with *Shingrix*, but it also impacts quantitatively and qualitatively the immune response including the persistence of the immune response, and so that allows us to entertain the ambition to deliver a seasonal RSV older vaccine, a vaccine that will cover several seasons and that could be used whenever you want during the year.

That is what I wanted to say about RSV.

## **COPD: therapeutic vaccine candidate designed to reduce exacerbations**

Let me take you into a new dimension, a new category of vaccine; a vaccine that targets the chronic obstructive pulmonary disease. It is a condition of the respiratory tract that occurs in recurrent inflammation leading to progressive loss of lung function. The burden is huge. 300 million people on the planet have the disease. Simply in the US we are talking about 16 million people. That will be the third leading cause of death on the planet by 2030, and GSK is the only company that is moving ahead with a COPD vaccine to complement the existing drug treatment.

How did we design that vaccine? On the pie chart on the slide you can see that we, and others, have confirmed two bacteria; haemophilus influenzae, and moraxella catarrhalis, two bacteria associated with these exacerbations and it is close to 50%. So what did we do? We basically extracted from these bacteria the functional antigen and combined with them with the AS01 adjuvant, again, the same adjuvant as for *Shingrix*. The vaccine is safe. It is highly immunogenic, it induces very high functional antibodies against these bacteria, and we are just in the middle of a Phase 2b proof of concept trial, for which we should see the results by the end of 2020.

## **Scientific expertise opens new fields in vaccines R&D**

We have an ambition to move into therapeutic vaccines, and why is it so important for us? It is important for us because it is really a new set of opportunities before us. We have technologies that definitely allow us to entertain that ambition, and developing a therapeutic vaccine is different from a prophylactic vaccine, it actually in some instances can be much faster. So there is a notion of acceleration in the R&D timelines, and to be consistent with that, we are investing in a chronic Hepatitis B vaccine aiming at curing that chronic infection. There is no need to describe the medical burden and the number of deaths every year, and we just started for the first time in humans recently. This vaccine capitalises on our technology platform including the AS01 adjuvant.

In the same direction, we also want to address another global burden of disease associated with the development of antimicrobial resistance. This is as worrying as global warming, and specific bacteria really acquire that capacity to resist against antibiotics. Clostridium difficile is one of them. We isolated the toxin and we detoxified this toxin using genetic methodology, combined it with the AS01 adjuvant and we also recently started a Phase 1.

You can understand that the strategy of innovation at GSK is really, really focused in investing in technology platforms. If there is really one thing that differentiates GSK vaccines from other companies, it is really a portfolio of technologies of options that we have to design

the vaccines of the future, and we know that this is really making the difference. We know that this is actually increasing our chance to be successful going after the new field.

### **Advances in platform technologies are the foundation for breakthrough vaccines innovation**

We have the reverse vaccinology – I mentioned *Bexsero*, the adding a viral vector that we use for the paediatric RSV and the hepatitis B vaccine, the bio-conjugation technology behind several discovery assets that I cannot speak today about, but I really want to focus on two technologies that are really, really important – firstly the adjuvant system, definitely the most advanced technology that we have.

We have been spending decades to understand the molecular mechanism behind their mode of action. These adjuvants have been approved by the most stringent regulatory authorities. The factories are in place and millions of people have already benefitted from these Adjuvants.

The other technology that I want to mention is the SAM platform – the self-amplifying messenger RNA platform. There is a lot of buzz around the messenger RNA platform. This one is the next generation. It is the one that has the self-amplification property, and I am going to explain to you why actually it makes a difference.

### **Adjuvant systems – a technology evolution**

The adjuvant is a substance that you mix with the antigen, the active ingredient in the vaccine, and that really impacts quantitatively and qualitatively the immune response.

We have been working really, really hard to create this adjuvant system that really combines different biological molecules - and they are not all the same - to create this adjuvant system that have very specific, well-defined properties.

### **GSK leadership in adjuvant systems**

The AS04 adjuvant that delivered the *Fendrix* and *Cervarix* vaccine, impacting the antibody response of the immune system, including the persistence; the AS03 adjuvant for our influenza vaccine, specifically the *Pandemrix* vaccine, enabling antigen sparing; and the AS01 adjuvant – potentially, or I can tell you, the most complex that we designed. I can tell you, I remember 18 years ago being a young scientist trying to understand and read out the very first clinical trial where we were testing a formulation like AS01, counting what we call the antigen-specific T cells on the screen, and I can tell you, we were blown away by the numbers that we were seeing, and it took a long time, but, actually, this translated in two amazing products, *Shingrix*, malaria, and we also got amazing results for our tuberculosis vaccine, the infectious disease that has killed the most on the planet.

## **GSK Vaccines pipeline**

This adjuvant is exceptional. It's basically a major technological advantage that we are leveraging across the pipeline. Whether it is to go after a very special population that are immuno-compromised – again, I told you that we already have efficacy of *Shingrix* in this population, with an efficacy level is close to 90%.

We also use the adjuvant to go after major remaining medical needs, to enter the therapeutic universe, as well as the antimicrobial resistance.

## **SAM Technology (self-amplifying mRNA)**

The last part of my presentation is really on the one that excites me the most, basically. It is really the SAM platform technology, and let me tell you why it is so exciting.

Up to now vaccines have been made by using the pathogen, the microbe inactivated or killed, or trying to get a fragment of it, or identifying a sub-unit of it, or toxin.

Each time it is a very complex, slow, expensive and unique methodology of production. Each time you need a different factory to make this vaccine. That's the big difference here, because the only thing you know you need is the genetic code of the antigen that you put into the messenger RNA molecule that is packaged in a lipid nanoparticle, and once injected in the patient, this self-amplifies, produces the antigen, and the body learns to react against the antigen.

## **SAM Platform – a technology revolution**

That is the vaccination process, and that's really a revolution for three reasons. First of all is that that process of making the vaccine candidate using that technology takes only a few months at the maximum, while the conventional methodology takes years, so using the technology is going to dramatically increase the productivity of a research and development organisation.

The second advantage comes from the self-amplification properties. You don't need to inject a lot because there is a lot of amplification later on, and that means, basically, that you don't need to put a lot in the vaccine dose, and so the manufacturing footprint for this vaccine might be much smaller than what we used to see up to now.

The third property, again, coming from the self-amplification, is really linked to the fact that as it self-amplifies in the body, it triggers the same molecular mechanism as the adjuvant, and we call that technology self-adjuvanted. It actually provides a very strong immune response against the antigen, and again that's really consistent with our ambition to move into new fields like therapeutic and anti-microbial resistance. We just started Phase 1 using a model antigen in rabies, and we are really looking forward to seeing the results.

## **Vaccines R&D priorities**

Let me wrap up and summarise the key major data points that we have ahead of us. My objective was really to review with you our intent to advance innovative mid-stage assets, invest in strategic lifecycle management, go into new fields like therapeutic microbial resistance, invest in new technologies to actually increase our chance to deliver in this field, but also, establish strategic partnerships: we recently disclosed two of them – VBI and Innovax, we can speak about it later on if you want to cover that in the Q&A.

Over the last quarter we started three new clinical trials, actually over the last 12 months we started five new clinical trials, and behind that innovative vaccine, and I didn't say it when I presented RSV but it's really important for you to understand that for the RSV franchise we got fast-tracked designation by FDA. The major set of data for the three programmes will be available by the end of next year, and that will really be conditioning the next lead stage phase development in that specific field. The COPD vaccine would also readout at that moment.

Thank very much, I'm going to leave the floor to Russell, who will speak more in detail about the manufacturing.

**Russell Thirsk (Head of Belgium Operations):** Thank you, Manu. Great to see you all again, and I hope you enjoyed the tour round our manufacturing facilities here in Wavre. Unfortunately we only got to show you a small part of what we do here in Belgium – if we were to show you the whole thing we'd have to have you here for a week at least, but I hope you got a feel of the passion that we have around vaccine manufacturing and the efforts that we put in to ensure the very highest level of quality within our vaccine production.

I'm incredibly proud to lead the operation here in Belgium, which is really leading the industry in vaccine manufacturing capability and supply.

## **Vaccines differ from small molecule drugs**

I want to start this section off by talking a little bit about what are the key differences between a vaccine and a traditional pharma product. In the pharma business there are two technologies that have a reputation of being difficult to master: steriles and biologics, and that's what we do in vaccines, because we like a challenge more than anything.

A vaccine consists of multiple biological components, sometimes up to ten, each of which have to be individually manufactured. This, as you can imagine, significantly complexifies the manufacturing process, but perhaps even more importantly, it complexifies the analytical testing that needs to take place in order to show that those vaccines are truly safe and efficacious.

Vaccine products are amongst the most regulated products in the world, and that's hardly surprising, given that they go into babies and healthy people. They are products that have to be distributed through a cold chain, which adds significant complexities to our distribution process. So it's a sophisticated, it's a complex business, vaccine manufacturing, but it's not complicated if you know how to do it, and we do know how to do it, here at GSK.

### **Vaccines manufacturing journey**

You heard Roger speak earlier about barriers to entry, and this really is manufacturing multi-component, biological products to the very highest quality standards, in enormous volumes, it's a capability which has taken us decades to master here at GSK, but we have mastered it.

In addition, the barrier to entry that we have to be aware of is the infrastructure: here in Belgium we have 13 different factories, which we are using to make individual components of our vaccines. Each one of those factories costs hundreds of millions to build, start up and licence. That process can take anywhere from five to seven years, it's a huge investment that it takes to build a really strong vaccine manufacturing infrastructure, but when you have the capability, when you have the infrastructure, you can start making vaccines.

It's a process which starts off with sourcing thousands of raw materials, all of which have to be tested to the very highest quality standards. We then produce our biological products through a series of technologies from bacterial expression to cell culture, all the types of technology you typically see in biological pharmaceutical production.

We combine those different biological components together into a vaccine product and then we fill them in sterile containers and package them for the markets to which they are destined. That manufacturing process can take anything from perhaps nine to 30 weeks, depending on the vaccine that we are talking about but that is really only the start of the journey. Once we have made the vaccine, we need to release it to the market which involves testing and it requires a lot of actions with regulatory authorities. That release process can take anywhere from four to seven months for each batch of vaccine product, so you can see why the lead time for vaccine production is so very long.

### **Example: *Shingrix* production process**

Let us look in a little more detail at the manufacturing process for our flagship vaccine *Shingrix*. You have heard a lot today about the unprecedented demand and we are incredibly proud of how we have been able to ramp up the supply chain over the last 18 months. We have a really exciting programme to continue that expansion in the months and years ahead.

The manufacturing process for *Shingrix* starts with the manufacturing of the gE antigen and you saw the start of that manufacturing process today, which is the cell culture base manufacturing process. We grow up cells, they express an antigen, we purify it, that is our antigen product.

In parallel to that, we make the adjuvant, the famous AS01 which Manu has spoken about. AS01 is made from two separate biological components - MPL and QS21 - which are formulated together in a complex formulation process to produce our proprietary adjuvant product. Both of these separate components are filled into sterile containers and packaged for the market in which they are destined to be distributed, so that is the *Shingrix* manufacturing process: three biological components combined together to produce two sterile containers that go into one vaccine shot.

### **Sites and batches - stringent quality testing**

However, as I said before, that is only the start, that is making it but then we have to test and release the product as well. There are two things that need to happen in order to release a vaccine product to the market. First, the manufacturing facility in which you manufacture it needs to be licensed, not just once but in every single country in which that vaccine is sold. We have a real expertise in GSK in managing that regulatory process. Here in Belgium, I host 20 to 25 regulatory inspections every single year. Rarely a day goes by when we are not being inspected by some regulator here at GSK that is holding us to the very high standards of vaccine manufacturing that are expected. In fact, we just said goodbye the other day to the Belgian authorities who were here to approve a new manufacturing facility, and in the coming week we shall be welcoming the US authorities who are coming to approve another new manufacturing facility that we have on the site. Therefore, we need to have licensed factories in which to make our vaccines and we need to test.

How on earth does it take four to seven months to test a vaccine? It can be that complicated surely? Unfortunately, it is because not only do we need to test that product here in GSK where we have a whole battery of tests, hundreds of tests that are performed on every single vaccine batch, but that testing is repeated by regulators sometimes by every country in which a product is distributed. That adds significant lead time to our supply and it impacts our ability to act quickly when we have sudden changes in demand.

### **GSK vaccines manufacturing capability**

To conclude on this section on manufacturing and supply, the vaccines business is sophisticated, it is complex but it is not complicated when you know how to do it and we do! They are products that have long lead times. There is complex repetitive testing that needs to take place but, despite that, here at GSK we have been able to increase the supply of our

*Shingrix* vaccine and we are now supplying more *Shingrix* vaccine than ever into the market, and that growth will continue over the months to come.

Finally, we have a world-class capability here at GSK manufacturing, built up over decades, a global supply capability which is really second to none within the industry. That is not something about which we are complacent: we continue to invest in it all the time with people and technology, and we continue that with the mission of becoming and remaining the world's most reliable vaccines manufacturer. On that note, I shall hand you back to Roger.

**Roger Connor:** Russell, thank you. Before we move into Q&A, I just want to wrap up with one final slide.

**GSK Vaccines are positioned for success, growth & differentiation for a very long time.**

I hope you have heard us all come across with just how passionate we are about this business and how attractive this business actually is. Why I say that is going back to what I said previously as far as the durability of our products and the growth of the overall market. There are barriers to entry which we have brought to life, which means that there are a small number of players really competitively within this space. We truly believe in our strategy and, from an innovation perspective, we shall never be complacent. We have to continue to invest and continue to innovate both vaccines and the disruptive technologies that Manu talked through.

From a performance perspective, key products, key markets, four words: *Bexsero*, *Shingrix*, US and China are our focus.

From a trust point of view, we cannot lose the trust of our customer base. We have to ensure that we continue to protect the competitive advantage that Russell brought to life. We are relentlessly focused on the quality of our products and we truly believe that, when you package all of that up into GSK Vaccines and you execute brilliantly, that is where we deliver continued growth, we continue to expand strong margins and we generate cash for many years to come in this business. With that, I would like to thank you again for joining us today and we can move to Q&A. Thanks very much.

I would like to invite up my team as well. We will just introduce ourselves, and then we are going to have some microphones that go round the room as well. Shall we just run down and say who we are.

**Thomas Breuer:** Chief Medical Officer of the company and Lead Physician.

**Russell Thirsk:** Head of Manufacturing Operations in Belgium.

**Jay Green:** I am the CFO.

**Patrick Desbiens:** The Head of Global Commercial. Perhaps it is worth mentioning that I have been in the role for six months. Prior to this, I was running the US vaccines business and this is not a New Jersey accent.

**Dr Emmanuel Hanon:** Head of Research and Development

**Roger Connor:** I should have mentioned mine is not a Belgium accent. First question; nice to see you.

### Question & Answer Session

**Graham Perry (Bank of America Merrill Lynch):** I have a couple on *Shingrix* and then one on RSV. Starting off with *Shingrix*, can you just help us understand where the bottleneck in manufacturing expansion is. We saw today that you are a recombinant production, and presumably that does not take too much time to actually scale up. Is it actually sitting in the adjuvant where the bottleneck is or is it just the amount of time, paperwork for regulatory inspection? Just help us understand that.

Secondly, why can't you go for external manufacturing? Presumably, they are a third party contractor so you could do a lot of that and, third, the lyophilisation seems to have quite a lot more manual visual inspection. That looked like a bottleneck when we were looking at it today, but why couldn't that be a liquid vaccine, for example?

Then a question on RSV; it has been very hard to develop a vaccine in this area – many failures previously. Why do you think you have hit it this time, and could you compare your product with the antibody based approach – for example Synagis (palivizumab) that Medimmune and Sanofi are working on?

**Roger Connor:** Why don't we start with RSV with Manu, and then Russell, you can take the bottleneck, why not external, and then talk through what has been seen in terms of labour usage as well.

**Emmanuel Hanon:** First of all on the strategy that we are pursuing on RSV, I want to insist again on the fact that it is really a portfolio of vaccines that we are developing; maternal and paediatric as well as the older adult. Specifically for paediatric, and let's say to protect the new-born, the strategies with this notion of going on the maternal vaccine, and it is important to mention that that vaccine will obviously confer protection to the baby for the first six months of life – a polyclonal type of protection – but it also actually will confer some protection to the mother. That is really important as the mother plays in the role in the transmission of the virus to the baby.

I also think it is important to mention we have a lot of experience in maternal vaccination. We have already two vaccines that are being used, millions of doses every year. Health authorities have a lot of experience with maternal vaccination, and we really are speaking about protecting the child. We need to protect it at day zero because it actually can already develop the disease at that point.

Concretely now about the scientific reasons we think this time is the right time is that most of the vaccines tested up to now were actually testing post F version of the F protein and we know now it has been beautifully demonstrated by NIH that actually you absolutely need to have the pre-fusion confirmation to boost what we call the protective immune response.

**Russell Thirsk:** With the *Shingrix* bottleneck, it is clearly moving, and it moves as we ramp up the manufacturing operation. When we launched, our bottleneck was in lyophilisation. We have been able to clear that. We have brought on a new lyophilisation site at the end of last year. We will bring on a third site early next year, so that part of the process is now de-bottlenecked. We then moved to a bottleneck within the adjuvant production which we have now resolved, and we have that part de-bottlenecked. We are now working on the antigen production; two parts going on there – a new facility, but also process performance and yield. The wonderful thing about biological manufacturing is you can really do great things with process performance and yield as you better understand the manufacturing platform. So the bottleneck is moving. We have projects working on each part of the manufacturing process to de-bottleneck it, including leveraging third party operations, especially for the secondary operations.

Your point on visual inspection is a good one. We have recently licensed automated visual inspection for *Shingrix* globally. When we launched, we had some difficulties with getting that validated for the lyophilised presentation. Technology is advancing in that space and it is quite a difficult technology to master. That is done now and licensed so we do have fully automated visual inspection process now licensed for *Shingrix* across the globe. We do inspect small quantities of each batch by hand just to make sure that the automated technology is working well.

**James Gordon (JP Morgan):** A couple of questions please; I am just following up on one of the answers to one of the previous questions to see if I have understood correctly. For *Shingrix*, is it the case that from 20 to 24 million doses the constraint is just making more of the antigen and that is just about high yield of the antigen where you are currently making it and, if so, how phased will that be, please?

Second question on *Shingrix*; can you give us any hints about how the profitability compares to the rest of Vaccines and how that might evolve, say over the next five years?

One other question is you were talking about how great Vaccines is, and it does look like a great business; what are the synergies between Vaccines and Pharma? It does not seem like you are very integrated with Pharma and in light of the Consumer spin-off as well, could it ever make sense for Vaccines to be a different company?

**Roger Connor:** Perhaps I will start with that last point in terms of the company shape. Then in terms of *Shingrix*, perhaps Russell could just give a perspective as well.

In terms of profitability of the vaccine, we wouldn't typically issue that or give guidance on it in terms of specific vaccine profitability.

Just going back to your question on the Vaccines business, we are actually quite integrated with the Pharma space. Although we have research and development and manufacturing integrated in this business from and LOC (local operating company) commercial operation, we keep that as one group. Commercially, we use that engine to commercialise vaccines, going forward. We believe that the real proximity and benefit is together and so the connection is strong.

The other synergy that I would reference, that is very strong although not organisationally linked, is on the R&D space – the scientific links and understanding of the immune system going into Pharma R&D are key. Certainly, with GSK's oncology focus on immune-oncology, we are making sure that, scientifically, we are strong. There are absolutely no plans to do anything with GSK Vaccines group, separating from GSK: we see it as a key part of that combined Pharma and Vaccines organisation.

**Russell Thirsk:** On the adjuvant manufacturing, yield is certainly an important part of that capacity expansion but we also have other avenues to expand capacity for the antigen, including run rate, which is something we are working hard to increase. We are also leveraging other manufacturing infrastructure that is already built and licensed here in GSK. As we gain more experience with the technology, we can use our existing manufacturing infrastructure to further build out and expand that manufacturing capability.

As Roger said, we have 20 different programmes running to drive the expansion of this product, which touches every single part of the manufacturing process. We are really pleased with the progress that we are making in that regard. In fact, we are a little ahead of our plans, so we are excited.

**Roger Connor:** We have accelerated that to the high teens for next year, that we talked about – that doesn't need to stay flat. There will be progression, and steady

progression, in that capacity but it will not just suddenly jump in terms of numbers until we get that next facility online. That is not before 2024, as we said.

**Michael Leacock (MainFirst):** I have two questions, if I may. Firstly, it seems that C.diff is so difficult to produce as a vaccine – others have tried and failed and it goes forward and backwards. Can you enlighten us as to why that is the case?

Secondly, we have not heard anything about AI or big data and I just wondered how that impacts your business?

**Roger Connor:** Manu, why don't you take C.diff and give an R&D perspective on big data, because that is one area where we have a big play. We are doing stuff in manufacturing and on understanding our process but perhaps we will bring that to life within the R&D space.

**Emmanuel Hanon:** There are different methodologies to make C.diff vaccine. As I have said, you actually need to isolate the toxin of the bacteria and one methodology is to inactivate the toxin with a chemical treatment. This is actually the complex aspect of it and that is not the methodology that we have selected at GSK. The way we inactivate the toxin is, as I said, by changing the genetic code of the toxin to inactivate it, so we don't actually have the same problem in terms of production.

**Roger Connor:** And then big data, Manu, in terms of data and technology and how you are using that within R&D?

**Emmanuel Hanon:** This is definitely something that we are using across research and development, whether it is about using big data in terms of understanding the process of a production of a specific antigen, or whether it is using big data to get access to patients having a specific genetic profile or having a specific micro-biome situation. These technologies are actually used across the development organisation.

For example, I spoke about the RSV prefusion: we would not have been able to make that antigen without actually having a very complex system which allows us to understand what is the structure of the protein and whether it was in the right conformation and kept across the whole production. For that, you actually need big data and artificial intelligence.

**Roger Connor:** On *Shingrix*, the easiest link into that topic as well - one thing that we are doing in using data analysis, multivariate analysis, is looking to understand, of all of the multiple inputs that go into an antigen manufacturing process, which ones truly impact the yield and therefore can ramp it up? We are using it very practically in our key priority areas at the moment as well.

**Marc Booty (Pictet):** You could argue that your successful integration with Novartis has shown that new entrants have a real problem doing it themselves and that, when you integrated it, you made the returns. My question is, going forward with these new technologies – and the self-amplifying RNA is one – will those barriers to entry still be there, or does that change in manufacturing process allow other people to enter what is presently an oligopoly?

**Roger Connor:** First of all, we completely understand the importance of disrupting technology. The adjuvant, we think, is an example of that and we will continue investing, as we mentioned.

I see vaccines manufacturing in particular transforming over time with that disruptive technology. The challenge will be that that will take some time and it will not be tomorrow: we can imagine that in about 10 years' time, you could see those disruptive technologies coming into the market.

I have a great deal of experience in converting API manufacturing to continuous and there are parallels here as well. I can see that this will happen over time for new products and I can see that it will make sense economically to change to that new process as and when you have a new innovation or a new vaccine coming through. The idea of retro-filling all your old products to the new technology – I just think that the economics and the capital would not make sense. I think that, for that current portfolio, you will not see that same level of change, but there is no doubt that in the future, disruptive technology will transform the way that we make.

The barrier, however, can then move elsewhere. It doesn't change the R&D complexity and the size of the R&D investment that you have to make in this industry as well, because as we described, those are very long trials and expensive trials as well. Thank you.

**Geoffrey Porges (Leerink):** A few questions, Manu. On the MenABCWY, a great product concept. Could you give us a sense of what the scale of pivotal trials might be required there? Will you be able to get it approved on the basis of immunogenicity, or are you going to have to do some sort of a very large efficacy study? It is hard to imagine.

Secondly, could you also address what's required to bring a measles vaccine to the market in the US, and then related to that, what you have achieved with QS-21 with varicella is remarkable in *Shingrix*. Is there the possibility to somehow transform other low-viral vaccines where there has been a lot of negative resistance – measles outbreaks, etc.? Can

you not bring a *Shingrix* approach to other viral vaccines and transform the product in the market.

**Emmanuel Hanon:** I think the first question was on ABCWY, so first of all, meningitis vaccines from GSK and the competition have been approved based on immunological data, not efficacy trials.

As Roger said, we have been doing post-marketing effectiveness assessment that actually runs really positively, so the strategy on pentavalent ABCWY will be the same. It will be based on immunological non-inferiority, but as I said, we are moving forward to align with the FDA on what is exactly going to be the development plan, so that was one question.

Going to the last question around could we expand the use of the adjuvant to replace some live virus vaccine with, let's say, sub-unit adjuvant? That's what we did, replacing Zostavax, in a way, with *Shingrix*.

I don't think you can expand that like it is going to be easy to do that for every single virus. It's each time a different situation, but, clearly, these are things that we investigate and the self-amplification messenger RNA technology could also, actually, be an approach for that.

Then the third question was about MMR, so on that specific asset, yes, there is a need, so we have completed the Phase 3, and so we are basically programming now the next step, which would be submission of that asset to the regulators.

**Thomas Breuer:** Maybe on measles, because I think it is a good example with the shingles vaccine, we did a leap in terms of efficacy, so it really made sense to come with an alternative for a live viral vaccine. A measles vaccine has very high efficacy, so the finances also would never add up, so using this technology wisely where we can make innovative leaps.

**Peter Welford (Jeffries & Company):** I have three broad questions. Firstly, just on the mRNA technology again. I get the fact that you are using the rabies as a model, but I guess longer term do you see this as having obviously therapeutic uses? I guess I am thinking oncology, etc., or also, I guess, flu - potentially beating others? I don't know how quick this could be?

Are you looking as well at individualised, potentially, vaccines, and is that even viable with this technology?

I guess, related to that, have you already been investing in manufacturing to keep up with the science if this works? Presumably, this is a different sort of manufacturing to what you normally do.

**Roger Connor:** Yes.

**Peter Welford:** Just then on RSV, are you confident that an F-antigen is going to get you a broad enough – particularly, T-cell response, etc. I think other people with just one antigen have failed to get a sufficiently broad response. Are you confident you will get that?

Then, thirdly, just one for Jay, just on maintenance CAPEX. Can you give us an idea as to what the rough maintenance CAPEX is for the Vaccines division of Glaxo? I guess, just thinking about it, it is obvious that there is cash flow conversion that you have talked about, but beyond that £4 billion that you have spent, what does it cost, roughly, to keep this going?

**Roger Connor:** Why don't we start with the capital Jay?

**Jay Green:** As Roger said, we have spent £4 billion over the last ten years. Obviously, we don't give specific forecasts, and it does vary year-by-year, but we see that as a rough approximation of how you go forward. That would include the maintenance element of it, so when we build up and do capital allocation for capex we start with what is the requirement to make sure that we maintain quality, supply, capacity, and then we put projects on top of that.

**Roger Connor:** Thank you. Why don't you go into RSV next, Manu?

**Emmanuel Hanon:** Designing a vaccine, it is not always putting everything from the virus that would make it work.

If you look at *Shingrix*, which is a herpes virus that has, actually, ten different viral glycoproteins at the surface, we only put one. You need to put the right antigen, and this is when I say the science has been exploding in the field over the last five years, it is very, very, very clear that it is against the RSVf that you need to actually induce that immune response.

Most of what we call the neutralising antibodies, those that protect us actually are targeting this RSVf protein, so this is why we are optimistic on the approach that we have selected.

The other question related to the SAM platform, basically, your question summarised the potential of the platform. That platform has, indeed, the potential to make vaccines in a completely different way – accelerator on the timelines, but also get a more potent vaccine, and it is true that that allows us to entertain the ambition to go into challenging fields like therapeutic or antimicrobial resistance, but, indeed, the technology is compatible with the notion of personalisation.

As for adjuvant, I had the chance to really see the evolution of the technology in the company. You need to go sequential. It is dangerous to go too wide at the very beginning. You need to understand how the technology works, and even if it appears to be special to have a model antigen to test this, exactly what made us discover AS01 is to make an experiment to really understand the potential, using a model antigen. That's what we want to do with the SAM platform.

**Thomas Breuer:** Maybe another aspect that this is hot technology is clear because several other companies use similar technologies – I just mentioned two, CureVac and Moderna. I think what you really have to take back from here, that GSK is one of the big four companies and we have the technology in house, so if that works, which still has to be proven, we have a clear advantage because we have all the other elements how to develop, licence and commercialise vaccines in house, and have the technology here and don't have to buy it somewhere else.

**Keyur Parekh (Goldman Sachs):** I have four questions, please, separate ones. I think *Shingrix* has been a phenomenal success story for you guys and congratulations on that, but preceding *Shingrix* we also had *Cervarix* and *Synflorix*, so just help us understand as an organisation what have been your learnings from those two not so great successes, and as you look at developing the next generation of vaccines, how is it influencing the way you're thinking about it? That's question number one.

Question number two, and apologies if I missed this earlier, but Roger you said there were about 20 programmes ongoing currently to try and maximise what you can do with *Shingrix* in the near term before you get kind of the step change – can you help us understand what the boundaries of confidence or what the confidence is on those 20 programmes are; so if everything works phenomenally well, does that high teens go to 25 million doses, 30 million doses, what is that? What if things don't work, does it stay at 20, 21? Just help us understand what the width of that interval is.

Thirdly, as you think about launching *Shingrix* in China, what is the risk that you upset a lot of the other regular customers that you have, who also want *Shingrix*? You talk about using *Shingrix* as a commercial opportunity for rebuilding China, but what's the risk on the other side?

The last question being, as you think about cash conversion and you think about profitability, in the near term, why shouldn't this be a business that is materially higher than your pharma business, especially as you're thinking about capex being flat, R&D being reasonably flat, so all the upside from *Shingrix*, why shouldn't that translate into meaningfully better margins?

**Roger Connor:** Thank you. Maybe I'll just give people warning as to which one. Jay, maybe if you start with the margin question and the opportunity. Thomas, would you take the *Synflorix* and *Cervarix* piece? In terms of China, Patrick, may we have a discussion there around that reputational risk, which is no doubt raised in terms of what we do as well. Then the last one on programmes, Russell, maybe have a quick chat as well – is that okay? Good, let's start with Jay, then.

**Jay Green:** There's a bit of a margin piece and a cash conversion piece. So, as you know, 2015 we talked about by 2020 we'd be 30 plus, and then last year, as a result of our success in the US, which was obviously driven somewhat by *Shingrix*, I'll say, we then upgraded that till mid-30s. We actually think that that remains quite a reasonable number for this business, going forward. This year we've obviously been quite strong in the early part of the year, but we did also talk about for the first half, if you normalise for some one-offs we're still about mid-30s – Q3 will always be bigger and Q4 is normally one of our lower.

One of the pieces that you talked about a bit was with capex flat and R&D flat, actually I think what we've talked about is, we're going to increase the investment in R&D over time. In addition we are investing behind increasing the capacity for *Shingrix*, and we want to make sure that our launches and our pipeline are very successful and therefore we need the flexibility in the P&L, and therefore mid-30s we think is quite a good, strong delivery of margin, which is, as we've said, pharma-like against a broad pharma portfolio.

Then when we think about it from a cash perspective, yes, we've talked a lot about barriers to entry - as Russell said, once you have that base, that actually is quite a cash-generative business. In that respect, we do look at and generate cash, again, similar to a pharma-like cash conversion. The additional opportunity we have that GSK has talked about broadly is in the management and perhaps further optimisation of working capital.

**Roger Connor:** Thanks, Jay. Thomas, do you want to take the next point?

**Thomas Breuer:** Yes, so I hope these are the most challenging questions of the afternoon – what have we learned? First of all, we can't get it right all the time. I still know that *Cervarix* is the best cervical cancer vaccine, and when you see recent data which came out of Scotland, it essentially wipes out HPV and therefore cervical cancer in women. However, from a commercial point of view we have clearly lost out versus Merck, so what have we learned?

We still believe that an adjuvanted vaccine, where you want to have really long-term protection over an entire life of women, is important. What you also see when you see what the Gates Foundation, for example, is interested in, is they still believe - and we are confident this is actually true - that an adjuvanted one-dose vaccine is a real option, and this

is currently tested with Gates money in several countries, so the *Cervarix* game is not yet over from that point of view.

I would also like to highlight that China is the new market for HPV vaccine, the 4-valent and the 9-valent for Merck is licenced there, *Cervarix* is there. We are just starting, and one difference for the time being at least, and for several years to come, is that *Cervarix* is the only vaccine licenced in young women, which is the age group which can most benefit from cervical cancer vaccine. However, since it's currently a predominantly private market vaccine, most women who currently receive the vaccine are women who can afford it – they don't necessarily need it any more, but they can afford it.

So from a disease awareness point of view in the months and years to come we will really focus to make sure that young women get the existing vaccine. You have heard a few weeks ago that we announced a collaboration with the Chinese company Inovax, which has a battery of antigens and we have the adjuvant. The commitment is to develop a next generation HPV vaccine with antigens from Inovax and our adjuvants and, in the years to come, we shall run a big Phase 3 trial to get it licensed all across the world under the GSK leadership.

On *Synflorix*, if you know the incidence and the pathology, there are many serotypes, so the question is always when you invest in the next generation pneumococcal vaccine, are you playing the number game - 13, 15, 20, 23, 30 - or are you looking out for an innovative way to get out of the number game. We have already tried it once and we failed to find another approach and, rather than playing the number game, we are looking out for new technologies and that is the approach that we want to take.

**Patrick Desbiens:** Perhaps that builds on *Shingrix*, so clearly these learnings apply to *Shingrix* and, hopefully, you will give us some feedback on how we have launched *Shingrix* so far. We are just getting started and there are more marketing campaigns and more marketing processes to deploy but we are definitely taking all the learnings here to make sure we are very deliberate, that we focus on differentiation for this vaccine and really take a stepwise approach to our go to market model, as we know we have something really special. I would say that the marketing piece of it is very important.

To your question regarding reputational risk as we are focusing on China, the reality of this marketplace, as you know, from a vaccines standpoint is that the US is the single largest market with about 50% of the world's vaccines sales. The second largest market is China, which was heavily dominated by local companies but since 2017 we have seen a real development of the private market. The private market in 2017 went from £1.5 billion to now about £3 billion in a couple of years, so we see a really strong appetite in China to bring in innovation, hence our accelerated filing for *Shingrix* in China, and this represents a high value opportunity for *Shingrix* for the years to come. Therefore, we have to make sure that

for the life-cycle management of this brand we generate value for the years to come, focusing on the US and we have to succeed in terms of launching this product in China. Yes, the other markets are important but these two, in our view, are the must-win markets.

Does that mean we are not going to launch elsewhere? Of course, we shall be launching elsewhere across the world in more traditional markets but these will be staggered over the course of the next few years as we have more volume coming on board. However, to be clear, the US and China will be our two most important opportunities as we try to maintain value of this vaccine for as long as we can through the life course of this asset.

**Roger Connor:** Russell, do you want to take the one about the probability of success on projects?

**Russell Thirsk:** The probability of success on the projects is pretty high. However, the important point to understand is that we are not just scaling one manufacturing step here; we are scaling many different manufacturing steps. As I said, we have three biological components, two sterile containers for each vaccine dose that we produce, and even getting to high teens means producing 40 million sterile containers, which is not a small amount of sterile containers that we have to ramp up.

We are very confident with the initiatives that we have in place: this is technology that we understand; this is technology that we master. Therefore, we are confident in our success but we are not going to see the step change. We are not going to see going from high teens to fifties without additional bulk manufacturing capability in place.

**Keyur Parekh:** Sorry, can I just follow up? Do you mind reminding us what your pre-capex cash flow was last year?

**Jay Green:** We don't give specific cash flows by division.

**Keyur Parekh:** When you talk about cash conversion being equal to Pharma, margins equal to Pharma, how do we make any sense of those numbers?

**Jay Green:** In your models, we have given you the sort of margin range and obviously estimates as to what we think we shall do with working capital and capex and a bit of information on that. That is the best you can come up with in terms of how do you convert. For me, we talked about Pharma-like cash conversion, where, although I am not going to give a specific number, the majority of the profit gets converted into cash in any given year.

**Roger Connor:** Next question please? We have moved from three, to four, to five per person!

**Elizabeth Walton (Crédit Suisse):** I have a quick question referring back to your 2016 slides. We notice that you no longer include your GBS - group B strep - asset. I wonder whether there is any update there and any lessons you have learned from that that you could share?

**Emmanuel Hanon:** Managing a portfolio means that you constantly need to evaluate the profile of the product you are pushing in development and, if the data are not supportive of moving ahead, you must stop the project. Specifically, for GBS at one point we realised that the project in development was not convincing enough and it has been put back into discovery.

**Roger Connor:** The one thing that I would add is that we are being completely focused on the prioritisation within the pipeline as Manu mentioned. Therefore, wherever we see a failure, it is important that you fail fast and where you don't see a return or a significant enough impact, you make a call fast. That is something in Vaccines on which we are completely focused. We don't want to be distracted, we want to make sure that our capital is allocated to the priority R&D assets.

**Graham Parry (Bank of America Merrill Lynch):** This is a follow-up from before on *Shingrix*, the capacity and the bottlenecks. It seems to me what you are saying is that the production of the antigen, which is the rate limiting step, and that is something which presumably just recombinant protein production technology you could outsource if that is the only bottleneck and that is what you have worked through now, so what is it that you don't want to outsource? From something like that, is there anything proprietary in your antigen production which means you don't want to outsource, so why wouldn't you just go to a company that can give you that capacity tomorrow?

**Russell Thirsk:** There is not anything that we wouldn't look to outsource. We are clearly looking at all opportunities to expand the production of *Shingrix*. Of course, when we look at third party options, we compare what it would take to do internally compared to what it would take to transfer it and then license it at a third party. So far, we think we have expansion opportunities internally within our existing manufacturing infrastructure that would provide quicker capacity expansion than going to third parties for cell culture, for example, but if we reach the point where we need to do that, we will certainly go down that road, absolutely.

The priority we have is to expand the capacity of this vaccine as quickly as possible. It is a great asset for the company and we have complete focus in making that expansion happen.

**Thomas Breuer:** Having worked in regulatory for a long time, this is simply the fastest way to get there. If we engaged with external companies they have to build the manufacturing, we have to transfer technology, and from a regulatory point of view, we would end up beyond the timeframe we have currently given you.

**Graham Parry:** Just to follow up on the question previously on RSV and the comparison of that versus the palivizumab approach by Sanofi and Medimmune, so they have a five-month monoclonal antibody which just covers the kids for the first season. Could you just compare and contrast why you think a vaccine might be better than that?

**Emmanuel Hanon:** Actually I already briefly covered it. I am going to repeat myself so, first of all, the maternal vaccine will actually achieve this passive transfer of antibodies to the baby. The antibodies are polyclonal, and it is not a single specificity, it is important, and the second point is that that vaccine being actually given to the mother also confers some protection to the mother. So it is a different approach, and we believe that actually also leveraging a channel of vaccination that is used already for different vaccines like the pertussis booster and the influenza vaccine is another advantage as health authorities are used to using it for millions of women every year.

**Patrick Desbiens:** If I can just translate that commercially. If you look at the US, just the US cohort, there are four million pregnancies per year, so with four million pregnancies a year we could potentially get the maternal vaccine, plus four million babies could get early immunisations, so we think commercially it is a very good proposition. Then from market behaviours, there is already a large number of mothers that could immunise. If you look in the US at a Tdap booster, it is about 50% of the mothers already get a Tdap shot, so the practice is well embedded.

**Emmanuel Hanon:** Let me add one additional thing. I said it, covering the first five or six months is only 50% of the burden in children, so you still need to cover the up to two years group. You cannot achieve that actually with the competitor technology as it is passive immunisation, it fades away. With the adenovirus technology that we have been selecting for that approach, this is active immunisation that confers the protection to the baby for several years. That is really the objective, and actually GSK is the only company, to my knowledge, that is testing this approach in sero naïve children, children that have not been exposed to RSV. It is a really important step as there is a lot of historical testing RSV vaccine in children, and we are very hopeful that we will be moving positively on that programme.

**Geoffrey Porges (Leerink):** A follow-up question on your strategy, Roger. You highlighted the good features of the vaccine business, and you conveniently glossed

over some of the bad features around commodity pricing and intense competition. As you plan out the future, and we see manufacturers of commodity vaccines coming in from China, India, perhaps other places, is it ever possible that you would think about getting out of some of the commodity vaccines where prices have eroded and, conversely, would GSK be willing to have, for example, a thousand dollar vaccine that would have genuinely pharmaceutical like margins? The benefit is pretty remarkable, and yet, we don't.

**Roger Connor:** I think it is a great portfolio question, and we do in the strategy look at what is the right portfolio going forward. At the moment we look at breadth in our portfolio being good, but I think we have to continue to look at it. As we become more and more therapeutically focused in those higher value areas, do we want to deploy capital resources to the lower margin spaces? We didn't talk flu, for example, but that is commoditised, and the pricing is heading in one direction. We have a very strong flu business with a strong history of delivery, and then you look at, I mentioned, DTP vaccines again driving pricing in Europe; very, very tough. So my answer is we will constantly look at it, and it has to come down to where do we best allocate our capital investments and manufacturing choices and looking ahead to what needs to be replaced is a key thing, and ensuring that we use that to trigger portfolio discussion is important.

On the pricing side, it is the same as this industry. I think innovation and differentiation drives price, and people will pay for the differentiation and innovation that you provide. When you look at the mathematics and the health economics of vaccines, it is still a very strong case, and if you have a mathematical model that shows that return on savings and healthcare provision, I would fully support that level of pricing if it is appropriate.

**Patrick Desbiens:** Hopefully you have seen in some of Manu's assets that he has presented, RSV portfolio and COPD portfolio as *Shingrix* like in terms of potential value, so clearly our direction of travel is in *Shingrix* type of potential assets, which would be high impact, but also high value for the organisation.

**Will Hamlyn (Manulife Investment):** I am still trying to reconcile the comment on Pharma-like cash flow conversion, with the fact that we have heard that there is a 12-month production process with lots and lots of hoops to go through, combined with the fact that you have been growing in mid-teens over the last few years. There must be considerable working capital drag on cash conversion. Is there any colour, or numbers, of what that is, and just what the puts and takes are versus Pharma cash conversion?

**Jay Green:** There is no doubt, because of the lead times – we obviously don't talk about specifics when we disclose our results but when you are talking about the

lead times that Russell was sharing in terms of the products, relatively speaking, if you talk about days of inventory, we carry more inventory than a pharma business would.

We already have a great deal of that in place actually and it therefore really comes down to, as we continue to look at efficiency in manufacturing and lead times in particular, is there the opportunity potentially to get at that. That is when I talked about the opportunity that we have as part of the overall GSK to look at working capital. That is one of the key areas.

**Roger Connor:** I was just going to add there, from a cash conversion perspective, we have invested significantly in our capital infrastructure, in terms of building facilities like this. There is a phase, as well, where you continue to exploit that infrastructure that is in place as well. Next question.

**Elizabeth Walton (Crédit Suisse):** If we could just touch a little on pricing in China, obviously you have just launched *Shingrix*. I am wondering whether there are any of the other paediatric vaccines, or could you give us any commentary on the price point for those paediatric vaccines in China versus other countries in the world.

**Roger Connor:** Perhaps I will make a comment and then hand it to Patrick as well. Just on *Shingrix*, we have not launched just yet but that starts next year: we have a 2020 phased launch, as we mentioned.

Our portfolio in China doesn't include paediatric vaccines at the moment. *Cervarix* and a hepatitis vaccine, *Engerix*, is there as well. I would say that strategically what we are looking at is whether there are other vaccines in our portfolio that should follow up and go into China, going forward, and expand that portfolio. Obviously, the pricing environment would be key. My thoughts on paediatric vaccination in China is that is a very intense, locally manufacturing dominated space and we would see the private market probably being the most logical place for us to play, going forward.

**Patrick Desbiens:** I think we will be looking at this asset by asset. This is obviously a very long-term opportunity for us in China.

In terms of your specific question on pricing, if we look at the newer vaccines that were launched in China, I will not comment on *Shingrix*, but they are fairly close to US level prices. I can leave it at that.

**Jane Bleeg (Alliance Bernstein):** Just following up on that question on China, given your narrow portfolio there, what do you mean by 'long-term opportunity'? When might you be able to re-enter with your broader portfolio?

Then, after you have discussed, with faster innovation and faster time to market, for those key pipeline assets that you have discussed with us today in RSV and COPD, how should we be thinking about the length of the Phase 3 clinical trial journey? When could that materialise into a commercial opportunity?

**Roger Connor:** Perhaps on the last point, on timeline, the new reference, the key data read-out, is coming next year. Typically, in vaccines, from that read-out, through Phase III and the regulatory approval, we would not expect to see launch until five years and beyond for those products, just to help you with the timeline.

From a China perspective, the portfolio choices, again we will be very disciplined in looking at where we will create the biggest return for our investment on our choices of what else goes into China. You can imagine we are looking across the portfolio but, again, looking at our established portfolio and looking at our meningitis portfolio, what would be the priorities and how would we work that?

We have to continue to build our capability on the ground in China, that is what I say, from an infrastructural perspective, ensuring that we have the right regulatory, medical and commercial activities there. We are building that now, to ensure that we are ready to expand and using *Shingrix* would be a key part of that as we continue to build.

**Patrick Desbiens:** If the outlook in China remains the same, what we have seen is a real change in terms of valuing innovation in China. That is the agenda and so, if that remains the same for the next several years, looking at the portfolio we have, you may have seen the COPD opportunity in terms of vaccine. There are 16 million Americans living with COPD, but there are 100 million people in China living with COPD. That is what we mean by longer-term, and we have to be choiceful, but if the environment continues in China, that could be a significant long-term opportunity as a market place.

**Roger Connor:** Thomas mentioned our Innovax partnership as well. Having a presence with a sophisticated player in China is important, again sending a signal in terms of our investment in that market and building capability. That is a very important part of our overall strategy.

**Marc Booty (Pictet):** Just going back to the *Shingrix* capacity, you referenced in the past that you won't have an uplift of tens of millions of doses until Marburg comes online. You said you won't get to the 50s with the incremental ones. My first question is, is Marburg bigger than Wavre? Will it get you to the 50s? Finally, will that Marburg be phased or will it come on in one go in 2024?

**Roger Connor:** I will not get into specifics, as you can understand. I think it is important to understand that when Marburg comes on it is a significant volume. I won't

say how much, but that's really going to be needed to cause that step-change that we referenced, but from the high teens through to that point, that's where we are going to continue to exploit the projects that Russell has mentioned, that continues to give that steady growth, but I am not going to give a specific number.

**Keyur Parekh (Goldman Sachs):** Manu, you have highlighted COPD and RSV. Is there a reason you chose those two over the pan-stereotype meningitis vaccine, given that might be quicker, you should have proof-of-concept data in-house already, so why did you choose those two over the ABCWY there?

Then, secondly, your C Diff programme, how does it differentiate versus some of the other potential competition? I think Valneva has a Phase 3 ready asset there, so just why you are going down that road, as opposed to licensing that?

**Emmanuel Hanon:** Maybe I can start on the C Diff?

**Roger Connor:** Yes, please.

**Emmanuel Hanon:** One of the major differentiations is that we basically combine the genetically detoxify toxin with AS01, AS01 being, again, the adjuvant that not only improves the immune response in terms of amplitude, in terms of quality, but also in terms of persistence, so that is going to be – our ambition, basically, is to do what we did with *Shingrix*, even if we come years after the competition. If you come with the best in class you can really position the vaccine very, very effectively.

Maybe I wasn't clear, but, actually, we didn't choose between RSV, COPD and the pentavalent vaccine. We do the three together.

**Roger Connor:** I think what we are presenting today, is that it? Honestly, we just have too many cool things to show you, I think! We had to make a choice.

Again, we could talk for minutes on this. We are completely committed to meningitis. We think ABCWY is a really important programme. We have two great vaccines in *Bexsero* and *Menveo* with a proven history, so we are at an important point.

We will read out our data early next year. We are talking now with the regulator about that journey to Phase 3. We see that as a really important asset. We just wanted to talk about something that's maybe – in terms of excitement we ran out of time, but don't interpret that as something that's not a priority for us. Thank you.

**Graham Perry (Bank of America Merrill Lynch):** Just following on C Diff. I think one of the reasons why C Diff has been quite hard to reach as well is that the infection

is at the gut endothelium, and you can get very high levels of immunity systemically, but actually getting to the actual infection itself is quite difficult. I think whenever we have spoken to clinicians on any other projects that have been in development they have always been really sceptical about the ability to get that, so how do you overcome that part of the problem with a systemic vaccine?

**Emmanuel Hanon:** I think, basically, scientifically that needs still to be unravelled out of clinical trials.

First of all, there is another company that is a little bit more advanced in terms of a C Diff vaccine with a non-adjuvanted approach. I am pretty sure we will learn a lot from that specific readout of the clinical trial.

I want to remind you also that there is a monoclonal antibody that is used to treat chronic C Diff infection that is given in a systemic way, and not in a local way, so I don't think anybody can state today that, actually, inducing antibodies in the blood is going to be useless in protecting against a gut infection.

**Emily Heaven (Newton Investment):** Thank you. Just one of the flu business, actually, and just what you are doing in terms of a cell-based vaccine?

**Roger Connor:** We have made a conscious decision not.

**Emily Heaven:** Why?

**Roger Connor:** First of all, we think that egg-based is very well established, and I think it is going to be around for a long time to come. A high level of safety, and also from security supply perspective, very strong and proven through pandemic as well.

When I look at the economics I think the economics are challenging. We talked earlier about the commoditisation, the pressure on pricing, profitability and we have just made a call that, actually, in terms of where would we allocate investment and cash to get a return, we don't think the conversion to a cell-based would be a priority in terms of capital allocation for us.

**Thomas Breuer:** It is just a new technology. There is no innovation. The current flu vaccines suffer from mediocre efficacy, especially in the older patients, so that is the leap, but using a different technology to reach the same result financially doesn't add up.

**Roger Connor:** Thank you. We have two minutes – maybe time for one more?

If that is it, it is perfect timing. Maybe just on behalf of my team and on behalf of the folks who hosted today, we just want to say a massive thank you for taking the time to travel and to see us and visit us.

We really look forward to seeing you the next time and talking, I am sure, on other occasions about our results, and as we execute the strategy that we brought to life today, but thank you so much for joining us. Thank you.

*[Applause]*

*[Ends]*