GSK Vaccines meet the management

Tuesday, 29 November 2016

Strategic overview

Luc Debruyne (President, GSK Vaccines): Hello everyone, good afternoon, welcome to this "meet the management" session for Vaccines. I hope you have been impressed, like every morning when I drive on this site, I am still impressed after three years how vast this is, this site, and you have only seen a part of it, because we have 9,000 people here in Belgium, it is one of the biggest sites in the world, where we do biologicals. I am sure you have seen, in your tour, the complexity of making vaccines, but I hope that you have also been impressed by the quality of the people you have met on the tour.

For those who don't know me, I am Luc Debruyne, I am 25 years working for GSK and I am a Belgian. I run, with my team, with the many people here, Vaccines, since the last three years, and I have recently joined the Corporate Executive Team. It is really a pleasure to have you here with members of my team, who will take you through some of the great aspects that Vaccines has as a business, the opportunity that is out there, the impact that Vaccines have on global health and in the world and how great it is to run it as a business, because that is what you are here for, to hear about that, how we run this business and how we grab this opportunity going forward in a sustainable way.

The agenda for today is I will give a general introduction, kind of flying over what is this opportunity, what is the impact of Vaccines, the value and so on, and what we said last year, when we first gathered you guys initially in London, in May last year, at the Capital Market's day and then later, in November, in New York, where we shared R&D as part of the bigger GSK, because obviously GSK Vaccines is one of those three pillars of this diversified business: Vaccines, Pharma and Consumer Healthcare.

Thomas Breuer, Chief Medical Officer, who is here with us today as well, will then share where we take these growth opportunities with our current portfolio on the market and the importance of lifecycle management, which is one of the specificities of the Vaccines business.

Innovation is the lifeblood of this company, GSK, but definitely as well for Vaccines and Emmanuel Hanon, our Head of R&D, who is here with us, will share the prospects that we have in different waves and updating of where we are versus what we said in November last year.

Then, John McGrath, who is sitting here with us, Head of GIO (Global Industrial Operations), will give some more insights of what you have seen during the tour, of the complexity and the expertise that we have, but also the confidence of why we have made those investments and what this can bring us for the future.

We will then finish with 45 minutes of Q&A. So I will stand here with my team, we also have other members of the team here, from Finance, from Commercial and from the key vaccine areas, so to comment on any question you might have, and then we will have, together, a coffee to say goodbye to each other.

Just be aware that everything is recorded, that is why I am stuck here, normally I would be walking around, but that is why I am here with the mic, we record everything, so if there are Q&As as well make sure that we speak to the microphone.

Cautionary statement regarding forward-looking statements

I am sure you know this cautionary statement, so I just want to draw your attention to this, but you are used to that, I am sure.

The value of vaccination

Let me start by talking about the value of vaccination. As I said, I have worked 25 years for this company. For more than 20 years I have been in Pharmaceuticals and I must say Vaccines is special, it is really special. Why? Because the impact that we have on global health. Think of the millions of people that are being vaccinated: it is massive and that opportunity is growing, it is not going away. It is growing because of the demographics of the world and we will respond, as you will see, to those demographics with the vaccines that we have and the vaccines that we have in development.

The beauty is that it is a business that allows us to be a responsible business, because, as you will hear later, there are only four major players in the world. We are very proud to be a leader, but at the same time we are very aware of the responsibility that brings, and you will hear more about that as we talk about it.

Also, if you see on the right hand side of the slide, at the bottom, there are still quite some areas where there are needs for vaccines, so those who think that we can prevent everything in the world that is absolutely not true, there is still unmet medical need and it is across all age groups.

My key message here is there is massive opportunity, growing opportunity, constantly, and it has an amazing impact on public health; the best intervention you can do, to have healthy economies and healthy citizens, is to vaccinate people. Nelson Mandela said

that if you are unlucky and you are born in a country where you are not being vaccinated that is where it starts to go wrong, so it is very important that we do this all the time.

Vaccines benefit all phases of life

Now, mostly when you discuss vaccines the first reflex is those who have children: “Vaccines, that is for the paediatrics, that is for children.” Well, that is true: new-born babies are being vaccinated against almost all the preventable diseases, although you will hear later there are still diseases that we try to tackle with the vaccines that we have in our pipeline. But as I talk about the opportunity, if you think about the demographics, we are going out of this paediatric segment, because if you look on the right hand side, if you know that by 2020 one billion people will be over 60, the elderly segment is really something we need to look after.

We know that today people get vaccinated against flu, we know that people get vaccinated, elderly people, with *Boostrix* against pertussis and you will, obviously, have read all the news about shingles, *Shingrix*, the protection against this disease, that is from my age onwards, about 50, that you can get vaccinated there. That is an elderly segment that is developing and you will hear later that we are confident that we can get in there and make sure that we grab that opportunity.

You also know that every year 130 million babies are born, that is a constant cohort that is out there, that is a demographic as well that needs constant vaccination.

Since the pandemic in 2009 the world has realised, the advising bodies, health authorities, that vaccinating pregnant women in their third trimester is a very good option to protecting both the mother and the child to be born. Why? Because there is still a high mortality in babies below six months, but you will, again, hear from the experts later why maternal immunisation, that is the word “maternal” immunisation, is a very important opportunity as well.

So we go from paediatric really across the whole lifespan of a person and even protecting the mother, the pregnant woman and her baby.

You are interested in health economics, I am sure; $1 invested returns $44, so it is clear that the best intervention after clean drinking water for healthy communities is vaccination.

Multiple drivers of the need for vaccines

Now, there are different reasons why you would vaccinate. It is clear that, as I just referred to Nelson Mandela, the left hand side, poverty: in those areas where people don't have all the healthcare measures that they should have, vaccination is the best intervention. That is where most of our doses go: 70% of our doses are provided to the developing world and for many years we have had a system of tiered pricing, so that we are a responsible business where we charge prices that are linked to the gross national income, determined by the World Bank. The bottom line is that the rich pay for the poor. The beauty of it is that it is a sustainable business and it is less under the pricing pressures that you know about in the pharmaceutical industry.

I want to make it clear for everyone: we are a business, we are not a charity. It is a volume-value business model. You will hear later from John how that works, where those massive volumes help to amortise the massive infrastructure investments that we need to do and make sure that we can do it for the world. There is no contradiction in having great business and doing great for the world, and that makes it very unique not just for what we do but also for the people who work here.

It creates massive opportunities for interactions with very important players in the world who determine what health policies should be decided. So we work with them very closely. It also allows us to make sure we can invest in products or in vaccines, like the malaria vaccine for over three decades.

Of those of you who think this is just philanthropy, it is not. If I take the example of the malaria vaccine, we use an adjuvant – and you will hear more from Manu and Thomas about what an adjuvant is – it helps the immune system. AS01 is the adjuvant that is being used in the malaria vaccine and that is also the adjuvant that you find in the shingles vaccine. So from an R&D perspective that is where we learn as well. So doing good business, innovating and doing well for the world absolutely can get married.

Vaccines is an attractive business, with barriers to entry

Now, why is Vaccines an attractive business from a shareholder's perspective? Well, I hope I have convinced you already with my first slide that the opportunity is out there, if you think about the demographics. This is a steadily growing market; if you look at this number from a reference 5% compound average growth going forward, it is an £18 billion business at this moment, so the growth opportunity is absolutely there.

The beauty is it can compete margin wise with Pharmaceuticals, so healthy margins, as I said, a good business to invest in, but it has an annuity, a long annuity, meaning a long

value, because there are no patent cliffs you fall off. We have 39 vaccines on the market and there are vaccines that are 20-30 years of age already, because obviously those children still need those vaccines. They are very valuable vaccines and, as you will hear later, it is not that easy to come with a new vaccine or a better vaccine.

Now, I said to you that there are only four players. To put that in numbers four players have 80% of the business. Why is that? Why do we only have four players? Well, I hope you have seen on the tour, I mean the building, I think you visited the IPV and Pertussis building. If I tell you that we did the ground-breaking in 2009 and that the first commercial vaccine will roll out of it in 2018 that gives you an idea of what the capital investment is that you need.

But not just the capital, also the expertise to be able to operate and validate and make sure that the regulators absolutely are convinced that what you make here or what you made, maybe just 5kms down the road, where a building has become obsolete, is still exactly the same vaccine. Why? Because there is an extra layer of quality you need to have with vaccines, you are injecting healthy people, healthy babies. So therefore no surprise that there are huge regulatory hurdles and that there are massive, complex quality controls. To give you an idea, 70% of everything that we do around a product production is based upon quality checks, to absolutely make sure that we deliver the vaccine safe to those who need it.

The expertise, I am sure you will be able to conclude yourself when you hear the experts talk about either the pipeline or the products that we have today or the manufacturing and the quality operations, it is huge expertise that is needed to do what we do. If you think about Pharmaceuticals, small molecules, that is a few atoms, if you think about Biologicals that is a bit more complex, but if you think about Vaccines that is really – John, you will give them a bit of a flavour of that, right?

The bottom line is that you cannot wake up as a CEO in the morning and say “Well, let’s be in Vaccines because it looks very attractive.” There is a huge capital investment, huge expertise and it takes quite a long time to get there.

Value and volume based business model

I have spoken to you about the fact that it is a value and volume business, so on this slide you can see the volume versus the value. That is why we have this tiered pricing in place, so basically based upon the ability to pay. But it also absorbs our costs and it provides lower costs of goods than in those markets where we make profit. I think it is a very simple equation and if you just think about Pharmaceuticals that I referred to: 30 years ago Pharma was only interested in 600 million people, basically the rich people, today the demographics

dictate that you need to respond to the world's needs. I think in Vaccines we have been there already for 20 years, serving the world of 6.5 billion people out there, with those large birth cohorts, and still running a sustainable business with competitive margins, but doing well for the world at the same time.

Now, I know you, as investors or analysts, are interested to know exactly what we do every month or every quarter. I will have to disappoint you. Because the dynamics here in Vaccines are long lifecycles. But the beauty is guaranteed lifecycles, because of this longevity, you don't fall off a patent cliff. The dynamics that you see on the right hand side of this slide just give you a bit of a flavour of the quarterly volatility that is inherent to our business. Why? Because Lots of our business is linked into tenders, because it is about public health, ministries of health are very interested to look after their population, but therefore they do procurement through tenders, you win a tender you have it for two years and then maybe you lose the tender, because there are two competitors and then that creates volatility. Seasonality, if you think about flu, just think about croissants: you have to be in the bakery at seven o'clock in the morning, if you are only there at 10 o'clock you are too late, you won't sell them, that is why you see the great performance of GSK flu vaccines in the US this year: We were first to market, we have a QIV vaccine – you will hear more about that later – we have been very competitive, but flu is not predictable when it will hit the market, so seasonality plays its role. Governments, like the US with CDC, they stockpile and then sometimes they use part of that stockpile or not, again it creates volatility. As you know, we supply a lot to Gavi countries, which is basically a fund, a global alliance for vaccines, and depending on when they order big quantities to go to the developing world, again, that determines the volatility of the quarters.

My invite to all of you is to be make sure you take the long lens to judge where the business is going, but so far what we have said, what we have promised, at the Capital Market Day last year in May, we are over delivering on that. As a company, we need to have flexibility to deal with those parameters all the time and you will hear more from John about that.

GSK Vaccines is an ambitious global leader

Now, what I have said so far is basically linked to Vaccines, to any company, but, as I said, there are only really four players in the world. This is a picture of why we are a leader in Vaccines as GSK. We have the broadest portfolio, with 39 vaccines, in all those categories that I laid out, age categories. We are competitive in all those franchises.

We have high volumes, we produce 2 million – just think about that number – 2 million doses every single day. 2 million doses every single day. So we protect lots of people.

We have 15 programmes in development, but I will let Manu, Head of R&D, give you more flavour of that, but innovation is really the lifeblood of our company. The other key ingredient next to innovation is reliable, high quality supply; you create competitive advantage by reliable, high quality supply.

Of course, the commercial execution is critical as well, combined with reliable supply and innovation, but we have the confidence – and I hope you have seen in the results so far that we are really confident – to deliver and even over deliver on what we said so far.

The Novartis transaction complemented our strengths

In March 2015 we did the Novartis transaction, that was one of those CEOs probably who woke up and wanted to be in Vaccines and then realised that actually, after a few years, it was really lossmaking, and GSK saw the opportunity. Why? Because it allowed us to accelerate on our strategy that we had laid out. Why? Because the acquired portfolio gave us an amazing opportunity to add on to what we already had as vaccines, think about *Bexsero*, think about *Menveo*, the meningitis vaccines – Thomas will talk about that.

The innovation: an impressive pipeline of products they were developing, but impressive also the scientists that came on board in GSK.

The supply chain was one of our main reasons as well. Why? Because we are convinced that we need to own the antigens, the bulk that we produce. John will be able to explain what that exactly is, but two of our critical components of our vaccines, our paediatric vaccines, diphtheria and tetanus, were sourced from Novartis, so we now own those in our network.

As I said, the people. We were really impressed about the people we were able to bring on board, in Quality, in R&D, in Manufacturing.

As you will hear later, the US is a major focus for us. With *Menveo*, *Bexsero*, we got an accelerator to our US strategy and, of course, we have announced, last year and we will have the official opening next month, in December, of our R&D facility in Rockville. So we are on the ground to grab that opportunity, being close to FDA, NIH, ACIP, to the regulators in the US, to work with the institutions, to accelerate on that strategy.

The bottom line of this transaction is this: I have gone, in my 30 years in Pharma, through some mergers and acquisitions, but this is unique. Why? It is not just taking the assets and realising the synergies, obviously the synergy realisation is very important, but

this is really an accelerator to the strategy that we have laid out. It is complementarity that is the key word here.

All of this has given us the foundations to make sure that we can deliver on the long-term growth that we have projected.

GSK is well positioned in US, Europe and International

This is just a map to give you that confidence that GSK is well-positioned across the world, in all geographies. If you look at the absolute values it is actually one third, one third, one third. But it is clear that the opportunity is out there in the US, so our strategy is absolutely to continue that great leadership that you see in the orange, in Europe and in International and Emerging Markets. As I just laid out, with the Novartis acquisition the acceleration of our US strategy and, of course, *Shingrix* that we filed in the US first is an amazing opportunity again to accelerate our growth there.

Strong growth for GSK in US, Europe and International

The foundations to deliver growth worldwide are there and if you cut it a bit different, here, you can see that year-to-date our growth is balanced across that geography. So, again, it is one third, one third, one third. You see the year-to-date performance here and as Simon Dingemans has said at the Q3 results update, we are on the higher end of what we said of the mid-to-high single digits, so we are at the high end of that for this year.

Strong growth across most franchises

Now, that was geography. This is across the franchises, from a portfolio perspective. You see that seven out of these eight are growing and, if you look in the middle, the meningitis, which is the one we acquired: That is a very profitable and growing franchise with meningitis. You will hear later from Thomas, we have the full alphabet of dealing with meningitis A, B, C, W, Y.

You need to know there are portfolio advantages, I explained that we are dealing with healthcare authorities, with high health councils in the countries and then to be able to talk to a partner who has 39 vaccines in its portfolio is obviously a great advantage.

On track to deliver vaccines sales growth targets*

I hope I have been able to give you a bit of a flavour that we are really on track to deliver the Vaccines' long-term sales growth targets that we have given out and it is pretty easy to understand where the growth is coming from until 2020: It is one third from our Marketed portfolio and Thomas will give a view on that, on what that means and what we are doing to make sure that we deliver on that; One third is coming from the Meningitis portfolio

and, again, Thomas will lay out what we are doing there to maximise that opportunity; Then one third of the growth will come from our *Shingrix* candidate vaccine and I can share with you today it was announced, this is pretty unique, we have filed *Shingrix* first in the US on 21st October; we filed in Canada and today it was announced we have filed in Europe as well. So that sequence we have pulled off 18 months earlier than what we had initially forecasted, and this should allow us to deliver on what we have laid out here.

I hope that is clear here that this gives us the opportunity not only to deliver on what we said but to continuously be a very important growth driver and growth contributor to the overall GSK company with Pharma, Vaccines and Consumer Healthcare.

Just think about the synergies that we have as a company, to use all that power to be successful with those vaccines in the markets. Think about the back office, think about the government interactions we have, think about the Consumer skills that we can use for products like *Shingrix*, so an important growth contributor.

On track to deliver improved margin expectations*

We also stick to what we said on the margin delivery. As I said, it is competitive with Pharma and, again, we are on track to deliver there. If you think about the Novartis acquisition, basically we have turned a loss-making business into a profitable business and we have improved our margins already substantially this year. But I need to manage the expectation here. Why? I just explained: quarterly volatility is something that is out there, but we stay and stick to what we gave as a guidance last year.

Innovative R&D programmes aim to deliver sustainable growth to 2020 and beyond

Emmanuel will give an overview on these waves of investment, as the lifeblood of our company, of Vaccines, is innovation and will give also the confidence that beyond 2020 we are making the right investments to sustainably grow and grab the opportunities that are out there. He will share with you some innovative R&D programmes that we have, that should give you the confidence that this is really continuously making sure we are leading the industry in Vaccines.

Positioned to be global leader for a very long time

My final slide is just to conclude on our strategic focus. We also use “FDA”, not as the controlling body, but as “Focus, Discipline and Alignment”, to execute flawlessly on the strategic pillars that we have laid out. These are reliable, high quality supply, delivery on key milestones in our R&D portfolio and make sure that we are focused on the US, to continuously grab that opportunity whilst we continue to sustain our growth and our strong position in the rest of the world. I hope I have been able to give you a bit of a flavour that this

is really a good business to be in, that it is an amazing business from a public health perspective, but that it is a good business because it brings long-term value to shareholders and it is worthwhile investing and it is really long term you can do this.

I will now hand over to my Leadership Team to give you a bit more flavour from their expertise areas in the different domains and then, afterwards, we can get into a Q&A, so, Thomas, Chief Medical Officer of GSK Vaccines, over to you.

Portfolio strength and growth drivers

Presented by

Thomas Breuer

Chief Medical Officer, GSK Vaccines

Thomas Breuer: Good afternoon everyone – Thomas Breuer, Chief Medical Officer of GSK Vaccines. I have been with the company for 16 years in the space of R&D. Before I joined GSK I worked for the German Public Health Institute, the Robert Koch Institute in Berlin, and the CDC, the Centre for Disease Control, in the US.

Luc has given an overview about our business aspects and GSK's contribution to global health. I will concentrate on our current Marketed portfolio, as well as our candidate vaccine against shingles. I will be followed by Emmanuel Hanon, who will cover our pipeline.

GSK's strong vaccines portfolio

Here you see GSK's strong Vaccine portfolio, which is the broadest in the industry. It covers a large number of vaccines and vaccine combinations across all ages, as Luc has already alluded to.

GSK's strong vaccines portfolio - maternal

Again, I would like to also highlight that over the last few years a new segment of vaccine recipients has emerged, maternal immunisation for key vaccines is recommended by the WHO and implemented in many countries, in the US and in Europe. This approach not only covers the mother as well as the unborn child and even the new-born during the first months of life, by the passive transfer of antibodies through the placenta into the baby. You will hear more about this really exciting approach in the pipeline presentation as well.

Vaccine product lifecycle is a lifelong endeavour

There are many similarities between the Pharmaceutical industry, the Pharma industry, and the Vaccine industry. However, there are noticeable differences. The Vaccine product lifecycle is a lifelong endeavour, there are no patent cliffs, no generics and each vaccine is a unique entity. Any company that wishes to develop a new vaccine has to go through the same entire development lifecycle. Therefore we, at GSK Vaccines, put a lot of emphasis on the lifecycle of our products and constantly update our vaccines.

Allow me to give you a few real examples on the next slide.

Flu vaccines: from trivalent to quadrivalent

First, I use the flu vaccines as an example. Please concentrate for the moment on the left side of the slide. Until a few years ago a standard flu vaccine contained antigens against three strains, two A strains and one B strain. The selection changes every year and it is driven by a WHO recommendation which applies to all vaccine manufacturers.

Flu vaccines: from trivalent to quadrivalent (2)

But then the world faced a problem, new B strains emerged and sometimes co-circulated in the same season. On average every second year there was a wrong B strain in the vaccine, something we call mismatch: a mismatch between the circulating strain and the B strain in the vaccine.

Flu vaccines: from trivalent to quadrivalent (3)

In 2012 GSK was the first company which solved the issue by introducing a four-valent flu vaccine, as part of our lifecycle activities.

Over the last few years we have progressively switched from a trivalent vaccine to a four-valent vaccine and this step, as you can see on the bottom of the slide, really has given us a competitive advantage, the market rewarded the innovative step resulting in a price increase in a highly commoditised market segment, which led to a revenue increase of 46%, as illustrated here.

Rotarix: continuous label & technical improvements since initial licensure (2004)

The next example is *Rotarix*, our vaccine against rotavirus infections. The rotavirus causes severe gastroenteritis and is a major contributor to infant morbidity and mortality around the world. Since the initial licence of *Rotarix* in 2004, GSK has continuously worked on label updates and technical developments, as illustrated on this slide, leading to a compound annual growth rate of 15% for this specific vaccine.

On the next two slides I will give you two real examples on the impact of *Rotarix* on infant mortality and morbidity.

Rotarix: impact on the number of diarrhoea-related deaths in Mexico[1]

Here you see published data from Mexico on diarrhoea-related deaths. I want to emphasise that these are surveillance data on diarrhoeal deaths not just deaths due to rotavirus infections. On the y-axis you see the number of diarrhoeal deaths, on the x-axis you see a timeline starting in 2002. As you will notice, during the winter months you see a peak in diarrhoea-related deaths. A pattern which unfortunately repeats every year.

In 2007 the Mexican Government introduced *Rotarix* as a Universal Mass Vaccination programme countrywide. As you can see the annual rate in diarrhoeal deaths disappeared and the number of diarrhoeal disease and deaths plummeted in Mexico.

Overall, the introduction of *Rotarix* in Mexico reduced diarrhoea-related deaths by 45% to 55% versus the baseline.

Rotarix: introduction of Universal Mass Vaccination in infants in UK (2013)

Here you see data from a developed country, namely the UK, which introduced *Rotarix* as a Universal Mass Vaccination programme in 2013. On the y-axis you see the number of rotavirus laboratory confirmed cases, the x-axis is an annual timeline in weeks.

If I can draw your attention to the black dotted line, which symbolises the number of rotavirus reports, you will notice an annual peak of rotavirus disease in England during the winter months. The black dotted line symbolises the average number of cases per a year over a 10 year period. With the introduction of *Rotarix* in 2013 you see a rapid decline of rotavirus disease in infants in the UK. Please concentrate on the red line on the bottom of the illustration, which symbolises the number of reports in 2016: the annual peak has essentially disappeared.

Infanrix (DTPa) franchise: expanded combinations and indications

(from 3-in-1 to 6-in-1)

The last example of lifecycle management comes from our paediatric portfolio. In 1994 we introduced a trivalent combination vaccine called *Infanrix*, which contained antigens against diphtheria, tetanus and pertussis. Over the years we introduced additional antigens, which resulted in the launch of a six-valent paediatric vaccine, adding antigens against polio, hepatitis B and haemophilus influenzae.

Infanrix (DTPa) franchise: expanded combinations and indications

(adding vaccines aimed for boosting)

Over time it became apparent that, although the vaccines have a very high efficacy, lifelong protection for certain antigens can only be achieved by providing booster shots at regular time intervals. As part of our lifecycle activities we developed a booster product line which, today, is one of our major growth drivers in our Marketed portfolio.

To link it, again, back to the business, the 10 year CAGR for *Infanrix* and *Boostrix* franchise is around 9%.

GSK Vaccines sales growth ambition by 2020

Okay, let's now change gears, the growth ambition of GSK Vaccines until 2020 can be summarised on this slide. One third of the growth will come from our existing portfolio, and I have covered that to some extent, one third from our Meningitis portfolio, which we acquired from Novartis, and one third will come from our shingles candidate vaccine, which is currently under regulatory review.

Please let me elaborate on the last two boxes.

Meningococcal meningitis

Meningococcal disease: uncommon, however progresses rapidly with unpredictable outcome

Meningococcal disease is uncommon, however progresses rapidly with an unpredictable outcome.

Meningococcal disease incidence peaks in infants and in adolescents. Early signs and symptoms often resemble those of common viral illnesses; however, the disease comes with a significant morbidity and mortality.

Despite appropriate medical treatment a case fatality is between 5% and 10% and up to 20% of survivors of invasive meningococcal disease suffer from sequelae – like limb amputations, seizures and hearing loss.

I would also like to mention that serogroups causing frequent disease are named with letters A, B, C, W, Y, and the frequency varies by region and over time, making combination vaccines a necessity.

Broad meningitis vaccines portfolio*, including candidate pentavalent

Here you see GSK's broad meningitis vaccine portfolio. *Menveo*, on the left, is our four-valent combination vaccine, approved in 64 countries including the US and Europe. *Bexsero*, in the blue box, is our flagship meningitis B vaccine, it is approved in 38 countries and it is the only MenB vaccine currently licensed in and outside the US. Again, for both vaccines major lifecycle activities to further improve the profile of the vaccines are ongoing.

Lastly, I would like to mention our five-valent candidate vaccine, which attempts to combine five serogroups in one vaccine and the candidate is currently in phase II.

UK infant effectiveness data major milestone for Bexsero

Here you see first real-life effectiveness data for *Bexsero*. A little more than 12 months ago the UK Government introduced *Bexsero* as a universal mass vaccination programme for infants in the UK. Initial data were just published showing a great impact. The vaccine showed real-life effectiveness against Men B in the order of 83%.

The UK halved already their cases of Men B in infants after vaccinating an initial cohort of 600,000 infants. The programme continues and updates will be published on a regular basis.

Excellent execution of Bexsero's launch

Strong performance globally

Again linking it back to the business, *Bexsero* is showing a strong performance globally. So far we have sold more than 10 million doses and we will continue to invest to expand capacity to capture market growth over time.

GSK shingles candidate vaccine

In regulatory approval process

Let me finish by presenting to you our shingles candidate vaccine and here you see the two landmark articles which were published in *The New England Journal of Medicine* last year and this year.

Epidemiology of shingles/herpes zoster (HZ) in the US

Let me start to describe the epidemiology of shingles using US data as an example. In the US around one million cases occur on an annual basis. The estimated lifetime risk is around 32% and people living over the age of 85 have a risk of one in two.

The most important risk factors are increasing age and immunosuppression. A feared complication is postherpetic neuralgia, a pain syndrome which can develop after shingles disease occurs.

Shingrix candidate vaccine developed to differentiate

The *Shingrix* candidate vaccine for GSK was developed to differentiate and to provide a real alternative to the existing vaccine on the market. GSK's ambition at the outset was five-fold; develop a sub-unit vaccine, so a vaccine which doesn't contain the live virus, develop a highly efficacious vaccine in 50+, including older subgroups; show sustained efficacy over time; and develop a vaccine for use in immuno-compromised individuals; And last but not least, provide a refrigerator stable product.

On the next three slides I will show you key data from our Phase III programme and you will see that we fulfilled our ambition.

Two dose vaccine: strong efficacy across different age groups

ZOE-50 / pooled ZOE-50 / ZOE-70 results

Here you see strong efficacy from our two dose candidate vaccine across different age groups. In the blue box you will see efficacy against herpes zoster in people 50 years and older of 97.2%. In the box below you see efficacy results in people 70 years and older of 91.3%. The box on the bottom shows efficacy against the feared complication of zoster, postherpetic neuralgia. The efficacy was 88.8% in people 70 years and older.

High and sustained efficacy over 4 years

Pooled ZOE-50 and ZOE-70 results

On this slide you see high and sustained efficacy over a time period of four years. Each row shows you efficacy per year post-vaccination. Even after four years we showed efficacy close to 90% which is absolutely remarkable in the age group of 70 and above.

Safety and reactogenicity profile

ZOE-50/70 results

Here you see the summary of the safety and reactogenicity profile of our candidate vaccine.

In terms of safety there was no imbalance between vaccine recipients and people who received placebo in terms of serious adverse events, potentially immune mediated diseases and deaths.

In terms of reactogenicity, the vaccine showed that local and systemic reactions were common. However, the majority of reactions were of mild or moderate intensity and of short duration.

Of note is the last column. The second dose compliance was very high – 95%. It shows that in spite of experienced reactions, the vast majority of participants came back for the second shot.

Key milestones on track

Filing completed in US, Canada and Europe

Here you see the key milestones of the candidate vaccine which are on track. They have already filed in the US, Canada and in Europe and will file in Japan in 2017 and to speak in the spirit of life cycle, we are also expecting more important data from our ongoing clinical trials throughout 2017.

Additional data will become available for co-administration, revaccination of people previously vaccinated with Zostavax and efficacy data in immuno-compromised populations.

Shingrix candidate vaccine: the opportunity...

Here is my last slide. GSK believes that we will capture major opportunities with our shingles candidate vaccine. We have to remember that globally only a very small proportion of the older adult population has received a shingles vaccine.

We are confident that we can redefine and expand the market with a new standard of prevention with the highly efficacious vaccine with the potential of revaccination, by increasing immunisation rates over time and through geographic expansion and through extension of new cohorts.

Thank you very much and I am handing over to Emmanuel Hanon, our Head of R&D.

Research & Development

Presented by

Emmanuel (Manu) Hanon

Head of R&D, GSK Vaccines

Okay, so good afternoon everybody. My name is Emmanuel Hanon, but as you can see, you can also say Manu. I am the Head of R&D at GSK Vaccines. I have been with the company since 2001. I hold a PhD and a Postdoc in the field of microbiology, vaccinology and virology and I am a doctor in veterinary medicine as a background.

It is really a great pleasure for me to stand in front of you to tell you more about the R&D organisation as well as a few selected assets. It is also a great pleasure for me to be part of a company that has contributed so much to the innovation in the field of vaccinology. Just two examples: in the seventies with the world's first live attenuated rubella vaccine, in the eighties with the world's first recombinant DNA Hepatitis B vaccine; and in 2015 with again the world's first malaria vaccine using adjuvant.

R&D organisation

Let me tell you about the R&D organisation. There has been ongoing major evolution over the last two years. We have redesigned that organisation to host not only one but three R&D centres and this is actually really important. When it is about innovation, smaller is better and it is much better to have three small R&D centres than one big, uniform entity.

We have one R&D centre located in Rixensart here in Belgium, another one located in Siena in Italy, the historic R&D centre from the two legacy organisations and one brand new R&D centre located in Rockville close to Washington DC in the US. The choice to create that centre was highly strategic and totally aligned with our ambition to grow in the US, to attract more talent in the US and to be much closer to key stakeholders in vaccine development such as the FDA and NIH.

We have now three R&D entities that basically are interacting with each other. It is one scientific community, a lot of diverse people but these people actually work in these R&D centres incubating ideas and then interacting to exchange these ideas. I can tell you that already now that has translated into an amazing boost in our ability to find new vaccine solutions.

Vaccines R&D timelines (illustrative)

Now about the process of discovering new vaccines let me tell you a few characteristics of it. First of all, discovering and developing a new vaccine is a long process. Whether it's the discovery as well as the development part it can take 20 years to make a new vaccine.

It is capital intensive because of the duration of the innovation process, because of the most of the time big investment you have to do for the Phase III or because you have to do sometimes investment at risk for the manufacturing facility. What does this mean?? It means that for newcomers entering into that vaccinology field, it is very, very challenging. It is only when you have a commercial portfolio, and GSK has 39 commercial assets, that you can really actually invest also that revenue into what we do.

That is important because there is no real patent cliff in the field of vaccines, so as Thomas just explained, we invest close to one third of the R&D budget in lifecycle management as the return on investment of that is extremely attractive.

Innovative R&D programmes aim to deliver sustainable growth to 2020 and beyond

Now about the R&D pipeline and a few selected assets I want to present to you, what I am going to do is I am going to speak about what happens after the first wave, the first wave being lifecycle management, the meningitis portfolio as well as the launch of *Shingrix*.

It is clear that what I am going to present to you is not the totality of what we do in R&D - it is not possible to do that in 20 minutes! But it is certainly the expression of our strategy to focus in the coming five years on RSV, on Group B Strep and on new concept vaccines and in this case I want to present to you potentially a great asset, the COPD vaccine.

Respiratory Syncytial Virus (RSV)

Let me start with RSV, respiratory syncytial virus.

RSV-associated hospitalisation burden significantly impacts infants and the elderly

This virus is actually responsible for quite a substantial disease burden, whether it is in very young children or in the elderly. In very young children, that infection, it is a respiratory infection that is called often bronchiolitis, it actually causes respiratory distress that requires urgent medical attention. In the elderly, that infection can cause severe pneumonia that can also lead to hospitalisation as shown on this histogram that classifies by age the RSV-associated hospitalisation rate.

We believe at GSK that several discoveries as well as several findings from the competition in terms of development guide us on what should be done to develop a highly effective RSV vaccine, whether it is for children or for the elderly.

Novel RSV candidate vaccine approaches

Let me tell you what we know. We know first that to design a vaccine against RSV you absolutely need to include the RSV fusion protein, the RSV F. But it is not sufficient. That protein, and that is the second thing we know, can exist in two different conformations, two different shapes; the one that is called pre-F, pre-fusion and the one that is called post-fusion. The post-fusion is the one you will spontaneously get if you try to produce that protein to make a vaccine and you will only get the pre-F discrete conformation if you really want it, if you artificially lock the protein in that conformation.

Novel RSV candidate vaccine approaches

That is what we have done in GSK in collaboration with NIH and it is important. I actually believe it is even critical. Because only the pre-F conformation – the one as shown on this histogram – that is recognised by the serum of individuals that recently recovered efficiently from an RSV infection, so in their serum they have antibodies, neutralising antibodies that are highly efficient to eliminate the virus from their body. You can see that there is a big difference between pre-F and post-F.

For your note, competition – Novavax, MedImmune – that respectively failed either in Phase III or in proof of concept, as recently disclosed, have been working on the post-F conformation protein.

Novel RSV candidate vaccine for the elderly

For the elderly vaccine that we plan to develop, we are going to capitalise on the pre-F protein combined with the AS01 adjuvant, the adjuvant that we have been leveraging for the *Shingrix* vaccine that we know is extremely effective in the elderly to boost the immunisation process. It is an adjuvant that we know extremely well, we have been working 20 years on it and it is an adjuvant we can produce at industrial scales already now.

Novel RSV candidate vaccine for the elderly (2)

After completing the Phase I, Phase II, the classical we plan to enter late stage development for that asset by 2020.

Period of most severe RSV cases for young infants occurs from birth to 12 months

For the protection of children, I need to tell you a little bit more about the hospitalisation burden. This histogram illustrates it well. You can see that close to 50% of the hospitalisation burden happens during the first two months of life of these babies and then the rest of the 50% comes during the next 18 months of life.

That is really important because it influenced the strategy we have designed to address that major medical need and our strategy is double. The strategy is first developing what we call a maternal RSV vaccine where the objective will be to immunise the future mother that will raise its protection level and then transfer this protective immune response to the future baby.

In parallel and as a complementary approach, not at all in competition, we will also develop an RSV paediatric vaccine where the objective is really to prime an immunological memory in these live children to protect them for the first year of life, so I am going to describe to you what we are doing for these two vaccines.

Maternal immunisation strategy to help prevent diseases that afflict very young infants

For the maternal immunisation vaccine, the phenomenon of the transfer of immunity from the mother to the baby is a well-known phenomenon documented for many different diseases.

On the present slide you can see that applied to influenza, so in many countries of the world future mothers are immunised against influenza because it is demonstrated you can increase the protection of the future baby against the same potential influenza threat. As shown on this graph it was 50% of efficacy, so whether it is pertussis vaccine or influenza vaccine, these vaccines are recommended by health authorities and this intervention is considered to be safe and effective.

Novel RSV candidate vaccine approaches

That is exactly what we want to do by developing an RSV maternal vaccine, capitalising on the RSV F protein, so that specific conformation that induced the right type of antibodies. We don’t need an adjuvant for young adults and we are just finishing the Phase I/Phase II dose-ranging clinical trial in the right population to put ourselves in a position to start the Phase III by 2019.

A different novel approach for paediatric

Now for the RSV paediatric vaccine. The challenge is you need to be able to induce an immunological memory, a protection for many, many months, even years and you need to be able to induce the right profile of immune response, not only antibodies but actually what we call T cells, and specifically CD8 T cells, cytotoxic T cells.

For that you need a very specific technology platform that we have acquired in 2013 by the acquisition of the Okairos company. That is really a highly potent platform that allows us to induce this profile of immunity and so this recombinant adenovirus that is defective and hepatogenic is able to induce the right profile of immunity.

We also know that that approach in the very stringent preclinical challenge model, a calf model actually, that we have developed we have systematically observed a very, very high level of protection.

Again, we are in Phase I/Phase II and we plan to be in a position to start the Phase III by 2020.

Group B Streptococcus (GBS)

As I already told you it is possible to protect the new-born through maternal immunisation. I spoke with you about influenza, pertussis, potentially the RSV vaccine. Actually there is another bacteria for which we could raise protection against through maternal immunisation. It is called Group B Streptococcus.

Maternal immunisation for GBS

That bacteria is the leading cause of pneumonia, meningitis and sepsis in neonates and the current, let's say prophylactic approach using antibiotics for the colonised mother is conferring some benefit but it is not sufficient and there is no vaccine.

On the histogram on this slide you can see on the X axis the level of antibody in the mother and the higher this level is, the lower the chance you see the baby with disease in black on the histogram. Actually above a certain threshold, there is no baby that develops any GBS disease, so we believe that with these observations there is a very good rationale also to develop a maternal immunisation vaccine against Group B Strep, so what have we done already?

GBS maternal immunisation expanded programme

We have already developed a trivalent vaccine containing the polysaccharide conjugated against three serotypes. This vaccine has been already used in 700 pregnant women, it is immunogenic, the immunity is transferred to the future baby and we are in the

process now to upgrade that vaccine from trivalent to pentavalent in order to cover more than 95% of prevalent serotypes.

We also are developing an internationally validated and standardised assay. That is really important because that will be the basis of the discussion we must have with regulators including the FDA, to agree on the correlate of protection which is needed for the Phase III and especially a threshold above which we want to see the immune response to be above.

With all that we expect to be in Phase I and start the pentavalent vaccine development by 2020.

A new vaccine concept for COPD

Okay, so let me then present a last vaccine candidate that we have in the pipeline and it is about a vaccine against chronic obstructive pulmonary disease. More and more GSK Vaccines is willing to investigate the possibility to use vaccines not only for prophylactic purposes but also to really influence the evolution of disease, some kind of a disease-modifying vaccine.

This disease is characterised by what we call inflammatory exacerbations that each time they happen it worsens the condition of these patients. There is a big medical need, there is more than 300 million people diagnosed for that condition and we all know that actually there is an under-diagnosed situation.

By 2030 that condition will be the third leading cause of death on the planet, so the medical need is there and we should continue to try to address it and we want to address it using a vaccine approach.

Role of microbes in acute exacerbations of COPD

Recent studies that we have done internally have confirmed what was already described in a lot of academic research, that we have several infectious agents, including bacteria that are associated with these inflammatory exacerbations. Two bacteria actually account for 50% of these exacerbations; *haemophilus influenzae* and *Moraxella catarrhalis.* After many years of research and antigen discovery applying what we call the reverse vaccinology technology platform, we have been able to identify several antigenic candidates from these two bacteria; *haemophilus influenzae* and *Moraxella catarrhalis*.

Testing hypothesis for a COPD vaccine

These antigens, PE, PD PilA and UspA2 have different biological functions and being able to neutralise the biological function is hopefully going to impact the ability of these bacteria to cause these inflammatory exacerbations.

We plan, we actually have done, the combination in the formulation of these antigens with the AS01 adjuvant, we have generated Phase I/Phase II data that the vaccine first is safe in the target population, secondly it is highly immunogenic and thirdly it induced functional antibodies that inhibit the biological properties of these bacterial proteins.

We are just at the moment where we will start what we call a proof of concept by the end of 2017 and hope to get the results by 2019 which will position ourselves into the possibility of starting a Phase III by 2020.

Let me conclude and open to the future. I described to you whether it is on paediatric, adolescent, elderly franchise, maternal immunisation or new concept vaccines, except the Group B Strep vaccine, all the assets I presented to you might be able to start Phase III by 2020.

Unique expertise in platform technologies

Supports current and future pipeline

As I told you in the introduction, I cannot present to you all the other things we are doing. However, I can give you some kind of a taste in the conclusion and you have seen that one of the strategies we are deploying in R&D to make new vaccines possible is by leveraging technologies platforms. You saw I think a good example today with the adjuvant platform, speaking about *Shingrix*, RSV elderly or COPD vaccine.

The adjuvant platform might be used in the future for other candidate vaccines, for example a supraseasonal influenza vaccine, a *clostridium difficile* vaccine, all that is possible and the adjuvant platform is not the only platform we have.

Unique expertise in platform technologies

Supports current and future pipeline

We actually have a platform that allows us to do some kind of a new type of glycoconjugate. You know conjugate vaccines like *Synflorix* at GSK or Prevnar in the competition are highly successful vaccines, highly effective vaccines in protecting against bacterial infection. That methodology of doing conjugates can be very complex if you try to apply it for specific bacteria, these bacteria today that are the big threat in terms of antibiotic resistance.

With that new platform, and I don't have the time to explain to you how we do that, we might be able to design vaccines now against these new emerging threat, antibiotic resistance.

You also saw the adenovirus vector platform, so the chimp adeno that we used for the RSV paediatric. We also used the same platform for Ebola vaccine and again the same platform, because of the very specific nature of the immune response we can induce with this approach, could be used for chronic viral infection - Hepatitis C, Hepatitis B, HPV or HSV.

Finally, last but not least, we also have a very, very promising descriptive technology platform called the SAM platform, the self-amplifying messenger RNA platform. You basically code your antigen into a messenger RNA that is your vaccine and it is a platform that might allow us to completely redesign the way we make vaccines, do that much faster, much cheaper, much better. It is very early on, but it is something in which we are going to invest substantially.

Thanks very much and I leave the floor to John McGrath who is going to speak about the manufacturing of vaccines.

Thanks very much.

Vaccines Global Manufacturing Network

Presented by

John McGrath

Head of Global Industrial Operations, GSK Vaccines

Good afternoon. The microphone is set for someone who is a lot taller than me, so if you can't hear me, just let me know! It doesn't seem to be moving too well.

My name is John McGrath, I'm responsible for Industrial Operations which essentially means we design the plants, we build the plants, we run the plants.

I have been working on making biologics for about 30 years now in the US, Switzerland, the UK and Ireland and now in Belgium, so I have been with the company for about three years. Prior to that I worked for various companies: Lonza, Genzyme, other companies around the world.

We are going to start with a quiz and the way the quiz works is if someone doesn't answer me, I just sit here to see if I can outwait you, so if we want to get out of here it's best if someone actually takes a stab at the quiz, okay?

How long does it take to manufacture a single dose of vaccine? [*Two slides*]

How long does it take to manufacture a single dose of vaccine? Three to eight, six to 12, six to 18 or ten to 26 months?

It's D – ten to 26 months, so what I am hoping to demonstrate in this short presentation is that vaccines manufacturing is complex. To me it's not complicated. A slight difference, a slight play on words, I am not sure I would get through Webster's Dictionary with it but when I talk about complex, it means it's not simple. In our hands it follows a rhythm and I will show you how that rhythm works. Complicated to me means it's difficult; you really don't want to get off the couch to do it, right, but we know how to make vaccines.

What percentage of the world's children receive at least one GSK vaccine? [*Two slides*]

What percentage of the world's children receive at least one GSK vaccine, A, B, C or D? Come on guys, work with me. The room is getting warmer.

It's C, so if you keep going for D you won't always be right. It's not always the big number! 40% - that goes to the level of responsibility we take in the business and we take it very, very seriously.

What percentage of the world's countries receive our vaccines? [*Two slides*]

The last question – honest. What percentage of the world's countries receive our vaccines, 50%, 70%, 80% or 90%?

90%, so when I talk about our network I am going to show you – D it was this time! Two out of three. Two out of three ain't bad, right?

Our strong manufacturing network is a competitive advantage: our people, buildings & processes

When I talk about our global network you will see we have quite a large global network because we have quite a large global reach. Vaccine manufacturing to me is all about people, plants and processes. There are very few companies out there that can get all three right.

Vaccines is a business where experience counts. I've made monoclonal antibodies, I've made enzymes; vaccines are more complex, so when I say experience counts, we have been making vaccines here in Belgium for over 70 years. We have been making vaccines in Germany for over 100 years, we have been making vaccines in Italy for over 100 years.

We have we believe, and we have a proven track record of navigating a complex regulatory environment and I have a slide later to show you how complex it is to get inspected, to get approved and just to get product released. It is unlike any other biologics I have ever worked with.

We have extensive capacity. On average we ship about two million doses a day every day. We could easily go up to a billion doses. We can respond to variability in the market in the short-term, depending upon how big that variability is but there have been numerous occasions where we have stepped in because the competition has had one issue or another. It is not unusual even for us to occasionally have an issue.

The most important thing to me is we have great expertise in balancing supply and demand. We spend a considerable amount of my time – my time, my colleagues' time here from Finance, Jay, Luis from Commercial on sales and operation planning. Every month, every week, it goes every week from the plant to every month at the global level and back and forth and you will see why. If you have a 24-month horizon before you can increase your supply you need to predict very, very well.

Vaccines differ from medicines in many aspects, from composition to development and administration

Why are vaccines so complex? If I look at typical pharmaceutical compounds, if you think of paracetamol. If you went out last night and you had too many glasses of wine, paracetamol is one of your best friends. It is relatively straightforward. If I think of monoclonal antibodies, it is now starting to get a lot more complex; you are using fermentation technology, chromatography technology, a lot of analytical technology to get that one compound you need out of the stew of other compounds.

If I take something like *Synflorix* it is a ten-valent antigen. It is almost identical from a manufacturing point of view to making ten monoclonal antibodies, formulating them together and putting them in a syringe so that they react well together as opposed to interfering with one another.

One of the other big complications with vaccines is it has to be cold. If we ship from here to Singapore, we have to keep it at 2-4^{o}C. It sounds simple, right; you just pack in more ice. If we are shipping here from winter and it freezes and it's a liquid vaccine, it's no longer of any use to anyone so we have to keep it in a very tight range whether we ship by air, whether we ship by sea, whether we ship from here or Singapore, whether we are shipping to Europe or to Africa.

And the one thing we never forget, and we talk a lot about quality is unlike classical pharmaceuticals, we inject healthy people. We are preventing disease, not trying to cure it.

A complex manufacturing journey

A very big slide, lots of details. I am just going to go in the boxes around the top first and the bottom.

Typically it takes us about two weeks to clear raw materials. We have a supply chain that orders raw materials one to two years ahead of time, but it typically takes about two weeks in incoming testing. To make the antigens themselves, it is two to four weeks which is relatively straightforward. By the time we get into coupling, filling, formulation and quality control, here is where you start the complexity and having to know exactly what you are doing.

We test; 70% of the time in that ten to 24 months is testing and quality assurance time. It's not hands-on vaccine manufacture; it's testing, it's liaising with regulatory authorities, it's having us test, having them repeat the testing and getting the vaccine ready for shipment. That's why you see lot release and shipping is six to 18 weeks and I have a

slide later that tells you exactly how after we have released it, it still takes time to land in a particular country.

Our global manufacturing network

Here is our global manufacturing network. It's complex but not complicated. There are a lot of plants. The plants in general specialise. We make Hepatitis B in Belgium for the world. We make *Synflorix* in Singapore for the world, so it is a complex process where we have centres of expertise worldwide that focus on making that component of that vaccine.

The ones in blue are major sites, the ones in grey are either for local distribution or we also have our 'flu sites in Dresden and Ste Foy which we have greyed out but the big blue ones, these are worldwide supply for all countries.

Shelf life management is critical

What does it mean from a supply perspective?

The other thing to understand about vaccines is you typically get 12 to 36 months' shelf life. In terms of knowing how to do supply and demand planning, you typically get 12 to 36 months.

The clock starts when you formulate the vaccine, so by the time you formulate it, we release it, the countries release it, you have already lost about a third of your shelf life and no-one wants to buy a vaccine that only has a few months' shelf life left on it, so you have to be very precise because once you formulate it, the country it is going to is generally locked in because we formulate it, we send samples to the country that it will eventually go to for release testing. We do, our competitors have the same hurdles to cross, so then we have to be very precise on knowing the demand and knowing how quickly we can supply that market.

For a vaccine available in 2019:

When would manufacturing be initiated?

You walked around plants today. The vaccines we start making today, late 2016 will arrive in markets sometime in Q1 2019, so we are making today what we believe, strongly believe will be required in 2019. Whether it's us, whether it's our competitors, whether it's a new start-up, that's the confidence and the forward ability you need to have to look two years out and say "Is this correct?"

Manufacturing sites for vaccines are first approved and then regularly inspected by regulatory authorities

Regulatory authorities. We inject healthy people. There is a huge amount of regulatory oversight on vaccines and there should be because we inject healthy people.

WHO will pre-qualify vaccine manufacturers which means they say 'It is okay to buy from these vaccine manufacturers because they know what they're doing'.

If we are going to the US we have to get FDA approval. If we are in Europe we need EMA approval, pretty soon EMA and British approval. We need Japanese approval if we are going to Japan, Brazilian approval if we are going to Brazil, so for us to reduce the complications and make it less complex, we have one quality standard worldwide.

Anything we make can go to the US, it can go to Singapore, it can go to Nigeria so rather than trying to deal with different substances for different places, we have one quality standard so whether you are a kid in Africa or a kid in Belgium, you are getting the same quality vaccine.

We also have frequent inspections. On a site like Belgium, we get audited just about every week by somebody, so vaccines is a really fantastic business if you like someone looking over your shoulder every time you are doing something. I would advise you to come here if you like that.

Each vaccines batch undergoes repeated, rigorous quality testing

Why is it so complicated? We said 70% of our time is spent on QC and paperwork, not actually hands-on vaccine manufacturing. We have our own internal quality standards that we have to hit, we have a lot of QC testing. *Synflorix*, one dose of *Synflorix* will have had 500 quality control tests by the time it gets to someone to be vaccinated.

We will do our internal manufacturing release and then it will go to a reference lab in a country, so typically if we are shipping somewhere in Europe it will be tested again either in Belgium or in Germany. Now this is unlike monoclonal antibodies. Monoclonal antibodies or all the other classes of biologics, the manufacturer tests them, the manufacturer releases them, it's done. Here we have to get through one more reference laboratory which means once we are ready to ship, we still have between six and 18 weeks before we will ship because we are waiting for that piece of paper from an independent laboratory.

If we are then going further and we are going to the US or Brazil it may be tested again if we sublot, so it adds to a lot of the timeline.

We are investing in capacity expansion

Hopefully you were impressed by what you saw today when you did the tour. If you weren't please tell Andrew Witty you were, because otherwise he is going to want to know why I'm spending so much money. It is serious amounts of investment. Vaccines don't have a patent cliff. We don't build a building thinking that "You know, we are going to be good for eight or ten years and then we are going to lose patents, so don't worry about it". We are building for 20 to 30 years, so that means when we build today, we need to make sure we know where the regulatory standards are going for construction and the manufacturing building in the next ten, 15, 20 years.

What we will also do with this is we have new buildings for Pa, IPV and Hepatitis A. We have had some supply constraints in the last couple of years as we have taken some of these buildings off-line to do major renovations on them to make them last for several more years at current compliance levels. These buildings will be replaced by brand new buildings.

Experience counts; we know how to navigate the regulatory requirements. We do have capacity, we can respond in the short term, but sometimes it does take some addition time. If I look at *Bexsero*, which a lot of people ask me about, it takes eight months from when we formulate *Bexsero* to when we get through all the various tests and to allow us to release it in external labs. We can respond, but we need some time to respond. We do have a lot of time and expertise in balancing supply and demand, otherwise we would not be building everything you see around you, and you see similar situations in Singapore, in Germany and Italy.

That is it. Thank you.

Luc Debruyne: Thank you very much. I hope this has given you a bit of a tour of what it takes to produce a vaccine, but more importantly to discover and develop it and then, ultimately, bring it to the people who need it and that it makes a business worthwhile investing in.

I want to open for questions. We have microphones because we are recording and we will provide transcripts afterwards, so if you could just speak to the mic and I would ask you to come one question at a time, because that makes it easier because then I can also see who, of my colleagues, can answer those questions. Thank you.

Question and Answer Session

Jo Walton (Credit Suisse): Comparing the slides that you have given us today with the slides from your last R&D day, there does seem to be a bit of a delay in terms of the proof of concept, in particular for the COPD vaccine. I wonder if somebody could tell us a little bit about the history of that and why the proof of concept was going to be in 2017 and is now in 2019?

Perhaps aligned to that, just a broader one – maybe it is a second question, but I wonder if you could address whether you feel or how you have moved on so that you aren't going to be second in the field with some of these new vaccines? For example, Zostavax came before *Shingrix*, Gardasil came before *Cervarix*. Perhaps you could tell us a bit about how your new facilities here mean that if you have ideas at the same time you will get to the market sooner?

Luc Debruyne: Thank you very much. I will ask Manu to comment on the COPD piece, but I will first give some of my perspectives. First, the last question that you asked: it is a good observation that we are second, but I hope that you have also noticed that we have, as one of the critical parts of our strategy, is to focus on the US. Historically we were not that focussed on developing antigens specifically for the US; we now have a strategy which is a global filing, and *Shingrix* is an example, because you can say it is second, that's right, but there is no second to the efficacy that we have shown in our results. We filed globally, but first in the US, then Canada, then Europe and then in Japan in April 2017. That is different from what we did in the past. We are focussed there and we are looking specifically at developing antigens for the US to be competitive in that market, whilst we continue to sustain what we do in the rest of the world.

From a timing perspective, let me just give my perspective and then I will ask Manu or Thomas to comment on that, but as I said, what I have learnt, so I am sure you met in London or in New York Moncef Slaoui, Chairman of Vaccines, who will retire from the company early next year, the first thing he has taught me is to go thorough in Vaccines. You have heard all the reasons: we are injecting healthy people, so time, because of the long lifecycles, should not be the driver to go fast. If you think about what Manu has said of RSV, you could say "Let's compete on time with Novavax"; we compete on the science. I would say that is the reason why we take the time.

Does that mean that we betray what we said last year? No, we will keep on updating you, that is why you are here to show where we are with our advances, but the positive news

that I gave as well is that on Shingles we advanced at 18 months of what we initially said a few years ago. Manu, do you want to comment on the COPD?

Manu Hanon: Specifically on COPD, I want to reassure you there is no delay at all. There is a slight confusion, so in November 2015, when it was presented, Moncef Slaoui spoke about the proof of principle that is a trial that is ongoing and for which, indeed, we will get the result in the course of 2017, but what we call the formal proof of concept, which really measures the level of efficacy that we actually use to design the Phase III; that is the timing that I just gave you, which is start at end of 2017 for the read-out in 2019, but that project is not delayed at all.

Thomas Breuer: The last comment on Zostavax versus *Shingrix*. The Zostavax technology is essentially nothing but a highly-concentrated varicella vaccine. We have this technology because we have a varicella vaccine, but we consciously decided to take a different path, so this is not really comparable in terms of timeline and, I think the efficacy data which I have presented to you today speak their own language.

Luc Debruyne: Thank you. Next question.

Marietta Miemietz (Primavenues): You touched a couple of times on the lack of a patent cliff and I just wanted to follow-up on that. We have always understood that generics for vaccines are a moot issue when you look at things like flu vaccines where you have different strains every year. I am wondering, as some vaccines like Menactra come off-patent, how difficult would it be for you, for example, irrespective of your business strategy, to copy that? Would the investment for that be prohibitive? Would you be able to use the biosimilars pathway? Could we simply end up in a situation like we have with the insulin companies now copying one another's insulins?

Then I have a very short and simple question just on the economics of vaccines for multi-drug resistant bacteria. In Eastern Europe, they use phages quite a bit in those cases; I am just wondering what sort of economics you need from a vaccine to be able to compete there? Would you invest in a vaccine no matter what? Would you say that, unless it has really super-high efficacy, or there is a really significant target market, you wouldn't go for it? Thank you.

Luc Debruyne: The first one I will refer to Thomas probably but, just to make sure we understand each other, on Menactra going off-patent, we do have an ACWY vaccine ourselves, which is *Menveo*, which competes with Menactra, so there is no point in copying the vaccine. There is no patent cliff.

Marietta Miemietz: It is not about business strategy, it is about the feasibility.

Luc Debruyne: We do have a vaccine that competes with that and I don't know if you want to add anything to that?

Thomas Breuer: Just to clarify that vaccine development is product specific, but also building specific, so whoever wants to develop any kind of vaccine which is already in the market has to start from scratch; they have to develop the antigen composition, they have to go to Phase I, II, III, they have to build a building like the one you saw today. It is not like in the Pharma business where the compound is known and the licensure pathway to get a similar product onto market is much shorter. Everyone who wants to develop a vaccine has to go to the entire development cycle and licensure and approval of the building. That is what we mean, that there is no cliff on our vaccines.

On antibiotic resistance, I hand over to Manu.

Manu Hanon: Thanks very much. Thanks a lot for that question, it gives me the possibility to explain something really important. There is a big problem in terms of number of vaccine companies investing into R&D for antibiotics. I will give you one number: between 1990 and 2010 there has been a drop between 18 to four companies working on new antibiotics. This is because there was a lack of incentive. The business model does not work.

If you think, when you launch a new antibiotic, you expect to use it at the smaller possible volume only for the very specific patients that need it, and public health authorities will never like to see a big price because, in case antibiotic resistance grows, then there is an explosion of cost for the payers.

If you apply the same model, or the same business model for vaccines, the equation is completely different because a vaccine is not used to treat patients, it is used to prevent infection. You vaccinate everybody to prevent the infection of the few. This vaccination of everybody is driven by recommendation made by authorities. The lack of incentive, in summary, that exists for the development of new antibiotics is not the same as for the vaccine field. If you add to that the absence of patent cliff and the fact that, with the evolution of technology platforms, we think it is feasible to do these kinds of vaccines, there is definitely a new business opportunity there.

Steve McGarry (HSBC): Firstly, you said about the operating margins being comparable to existing or to traditional pharmaceuticals, let's level the playing field – what are your pre-R&D operating margins, cash operating margins in Vaccines?

Secondly, given the importance of your vaccine manufacturing, what are your backup plans for manufacturing and is it feasible to back up manufacturing for some of the vaccines that you produce?

Luc Debruyne: I will ask John to talk about the manufacturing or the back-up or the lack of back-up manufacturing. Jay, can you think about answering the next question. John, go first.

John McGrath: From a manufacturing point of view, we split the world into bulk and fill finish. In our bulk antigen facilities, the IPV the Pa facility that you saw today, they are very big, they are very expensive to build and operate. We tend to single-source those globally and hold stock as a buffer. When we fill, we fill, depending on the vaccine, but we generally have two sites to fill, like Belgium and France, or France and Germany, so we always have a second site that is licensed to fill for major markets, for major vaccines anywhere in the world. We use a combination of stock, time and capacity.

Jay Green: Good afternoon, I am the Head of Finance. On the question around the margins, good question. As we said, Pharma-like operating margins and what we are trying to achieve, of course, is 30% plus by 2020 and that makes it comparable. When you think about it on a pre-R&D we disclose R&D spend in the annual report. If you look at that you can then back out and get back to that pre-level, which is quite comparable.

The rest of the elements in P&L we don't talk about specifically, but you can probably imagine from what you have seen that cost of sales and vaccines, a bit higher, SG&A generally lower because of our tender business in particular geographies – that will vary depending on the product, for example, like *Shingrix*. That is hopefully an answer to your question.

Alistair Campbell (Berenberg): Thanks, can I ask another question where we compare and contrast again with Pharma versus Vaccines, more a kind of risk profile in R&D? I guess in Pharma if we felt you suddenly had a new target you were going to look after, the chances of you getting a drug against that target might be 5 to 10% in terms of getting something to market. If you get a new antigen programme coming through in Vaccines, what is your thinking there and chances or probability of getting something out at the end of the day? Is it higher? I am guessing it must be.

Luc Debruyne: It is a lower risk profile, but Manu, can you give some flavour to that? Once you pass a certain step.

Manu Hanon: Yes. Usually what we see and what we have been observing over many years – we need to look forward, but once you pass what we call proof of concept, the demonstration that your vaccine candidate has a relevant biological effect, we estimate that we have 70% of assets will be successful later on in Phase III licensure.

What begins to be more challenging in the field of vaccines is before proof of concept the identification of new target or actually leveraging the right technology platform to be able to make this target. That is why we have been investing deeply in a portfolio of technology platforms, as we have seen will enhance our ability to come with new candidates.

William Hamlyn (Manulife Asset Management): Just to follow-up on the cash and margins question, could you perhaps just give an idea of how much you are going to be spending on capex; what a normalised working capital to sales would be for this business? What I am trying to get to is, if you are going to grow mid to high single-digit sales growth, how much operating cash will get eaten up by the cost of growing and how much would go back to the whole co?

Luc Debruyne: I will not share the details of how much capital, but what I can share is that over the last 10 years we have invested close to 4 billion and, as you have listened through the presentation of John, over the next 10 years that is what we will be investing as well. Why? Because we want to replace obsolete buildings; that is a huge cost to us, as already explained, and we need to continue to invest to be competitive on reliably supplying and therefore we also invest in process robustness and in our people, as you heard about the expertise. It is a constant feature of our business to continue to invest in those.

William Hamlyn: Pounds, dollars or euros?

Luc Debruyne: Euros[1].

Richard Parkes (Deutsche Bank): Firstly one on *Shingrix*. You pointed to data that 95% of patients came back for the second vaccination. I am just wondering what data do you have from the real world about two-dose vaccinations, what proportion of patients generally come back? Do you have data on efficacy of that vaccine when it is only given as a single shot? That is the first question.

[1] The majority of the £4 billion spent on Capex in the last 10 years has been spent in Europe.

Second, just a simple one for John on manufacturing. You talked about having the flexibility to respond to short term restrictions in supply, but I didn't quite get how you managed to build that into your planning? If you can just highlight how you build that flexibility in when you have such long lead times.

Luc Debruyne: Thomas, do you want to take the first question, because we have indeed experience with 39 vaccines.

Thomas Breuer: For the shingles vaccine in particular, obviously the vaccine is not licensed so we don't have real life data, but 95% is extremely high when you look at our other clinical trials. We strongly believe that education around the high efficacy more than outbalances the reactogenicity profile we have seen.

In terms of one dose versus two doses, we will clearly market this as a two-dose vaccine because in our Phase I, II, III trials we have run what we call immunogenicity trials and you really see a higher immune response after the second dose. We strongly believe that it is a two-dose vaccine. We have some anecdotal data around the one dose; obviously there is significant efficacy, but the vaccine is and will be marketed as a two-dose vaccine.

John McGrath: On the flexibility what we tried to do was we tried to keep bulk stocks and then we tried to delay the labelling as late into the process as possible. Once a label goes on a pre-filled syringe or a vial it has a language on it so the flexibility to go from one market to another diminishes dramatically. We try to fill and package as rapidly as we can and that is where we try to shrink the time within dealing with the regulatory agencies that we have to deal with, and then we try to hold bulk so that we can respond.

Luc Debruyne: That is, again, what you refer to as the "core commercial cycle" that we use, which is this communication between the demand side to commercial, finance and the planning for the whole supply chain, which is an expertise as well, to be able to respond – as you know, all those different timelines.

Sonal Sagar (Columbia Threadneedle): Hi. I just wanted to follow up from the capex question. When you make a new or decide to do a new expansion capex project, do you look at things like ROCE, what your targets are, what year you want to achieve that by, etc.?

My second question is on the supply chain: you talked about supply challenges being quite unique for Vaccines, what percentage is external and how many suppliers do you have on average?

Luc Debruyne: I don't know if I understand your second question with what suppliers we have on average; do you mean those who supply us for raw materials and so on?

Sonal Sagar: Yes, exactly.

Luc Debruyne: John, can you comment on that? I don't know if it is really relevant because if you think about 39 vaccines and all the materials we have, we talk about quite some suppliers, but obviously, John, do you want to give some flavour to that?

Sonal Sagar: My question was how that compares to your competitors? Do you think that could be streamlined or do you think it is in a good place today?

John McGrath: If I look at raw materials could it be streamlined? Yes. Are we streamlining it? Yes. If I look at external supply, so we have people contract manufacture for us. All our bulk antigens we do ourselves. All of them. We do contract out some fill and some packaging, but again, it is usually a second source as opposed to a primary source and we do contract out some things like diluents so putting water in a vial. The number is not that high and, best as I can figure, it compares with our competitors.

Luc Debruyne: We definitely have strategic partnerships with our key suppliers because we work together.

John McGrath: Our key suppliers, we work very closely with them. Our problem, if you like to see it as a problem, is we have 39 vaccines and a 40/50-year history, so we have a lot of cleaning up to do in our SAP system.

Luc Debruyne: On the capex question, it is clear that we calculate our ROIs each time we do a capital investment project. The fact that it has a long term value is again, when we have compared this, it is competitive with investment in Pharma or in Consumer Healthcare. We absolutely do actively look into that.

Kerry Holford (Exane BNP Paribas): Two questions, please. Firstly, on efficiencies: you mentioned that it takes on average between 10 to 26 months to manufacture a single dose; does that vary? Which vaccines are at either end of the scale? Are you seeing that you are becoming more efficient with some of your newer vaccines? What can you do to reduce that and what is your future target?

Then on flu vaccines we have, as you have said, seeing as we have moved towards quadrivalent vaccines, what is the future there? Have you reached the maximum capacity

with what you can do there with R&D on quadrivalents? Could we go to pentavalents? What is next, or is it more about operations now and being first to market?

Luc Debruyne: Thank you very much for those questions. On QIV, on the flu piece, Manu alluded already a bit that we have an ambition to go to supraseasonal flu, so if you want more information on that I will refer back to Manu, which is basically making sure that we don't have to re-vaccinate all the time.

We continuously work to increase our capacity, because we have been very successful in the US and now with QIV in Europe as well and in the rest of the world. We are increasing our approach to QIV from an efficacy perspective, and a protection perspective, it is clear that now health authorities more and more are convinced that this is the way to go.

Think about also this maternal immunisation. We have also achieved the six-month indication in the US to be even more competitive in that segment, of flu as well.

Do you want to say something on the supraseasonal? Please; then I will come back to the other question.

Manu Hanon: On flu, basically, there is no real scientific rationale to go above four strains in the classical seasonal vaccine, as these are the four families of virus that can potentially cause the annual seasonal epidemic.

Indeed, in the longer term, one of the ambitions that we have at GSK, we want to be disruptive. We really want to move away from the incremental improvement of influenza vaccine, we want to do something that is very different – a vaccine that you would not have to give every season and a vaccine that would cover protection against several strains. At the extreme, a vaccine that might also be used to prevent pandemic. In that context, it is very early on and these are discovery programmes, but there is again a good set of scientific evidence that allows us to believe that it is a strategy that is worthwhile to be considered, especially capitalising not only then on a very specific type of antigen, conformation again will be critical there, as well as the use of the adjuvant that we have.

Besides that, we have also been continuing to do what we call life-cycle management for the pandemic vaccine and making sure that this vaccine, in case a pandemic will start, the licence could be reactivated across the age to offer potential protection for people.

Luc Debruyne: On your first question on the lead times, it is clear that there are different lead times according to different vaccines, because indeed, we do have historic vaccines, but basically the process in those days, we talk 30/40 years ago, were less well-described and therefore less robust. We continuously invest to make those processes more robust so that we more reliably can manufacture it. To be clear, there are enough, and I

hope that you had that from the presentation from John, quality tests – we never release a vaccine that doesn't respond to the quality tests that are required by the regulators.

That is one piece, process robustness. If you ask the question about the newer vaccines, we do way more design, quality by design, from the early development process to involve manufacturing to absolutely make sure that process is robust and can product reliable and therefore can reduce. The fact that we invest, the capex question, in new buildings, again make sure we can introduce new technologies, less human interference, which again can reduce the lead times and obviously constantly investing in the quality of our people and the expertise to make sure that we can handle things better, faster and therefore reduce those lead times. That is a very important programme and we track it very carefully, but as this is competitive edge I will not share how good we are at it, but count on us; we're good!

Marc Booty (Pictet Asset Management): Could you talk about how important, if at all, pandemic planning is for the Vaccines business, and the structure of the business? Is it done as a retention/a contract? What do you do about maintaining capacity, or is it just a seasonal, every so often kind of blip and you make a shed load of money?

Luc Debruyne: Thank you very much for that question, because it is quite a hot topic. If your question is just restricted to pandemic flu, it is not, I am sure, because Ebola and Zika are the wake-up calls. Let's be very clear, it was a wake-up call to the world that the world is not ready to deal with these kind of things.

However, as we said at the start, we are a responsible business, so we do get that phone call that says "Do you have a vaccine?" In the case of pandemic flu, we are used to making flu vaccines and we could rapidly invest and increase production, but I will come back to one element there. Ebola: Manu spoke about the Okairos technology that we bought in 2013 and there was an Ebola vaccine candidate on the shelf. We worked together with many partners in the world to accelerate a development of 10 years to push it into 10 months; luckily it was not needed in the end. With Zika we are working as well with the NIH on a platform, but the key message is we don't have factories waiting for Ebola or Zika to happen.

We are not sure that the conclusion should be that pandemic made us lots of money. Why? Because it is a huge disruption to everything you do. You need to delay research projects because you cannot say "No" to the world.

The key message that was launched at the World Economic Forum by our CEO, Andrew Witty, in January this year was we need to be prepared all the time. GSK is now working in this Coalition for Epidemic Preparedness and Innovation, CEPI, which is basically a coalition of industry and regulators and WHO, Bill and Melinda Gates Foundation, the Indian and the Norwegian Government, to create sustainable funding, call it an "insurance policy", that makes sustainable funding for the industry, because the opportunity cost cannot all be sitting with the industry. We are, at GSK at least, dedicated to having an organisation that is fully dedicated to constantly working with scientists on validating the platforms that Manu has explained, testing antigens – there is a list of pathogens that is held by the WHO, it is up to scientists, not to us as a company, to determine which pathogens we should work on first. We will commit at no cost, just at breakeven, that we constantly work with a dedicated organisation to make sure that when the next Zika happens, we can accelerate production of something we have validated and we have worked upon.

If we can do that with our partners, other industries, great, in a network, but let's not wait until the whole world agrees because we absolutely need this. I don't know, Thomas, if you want to comment, or Manu – if you just look at the rhythm of how fast these happen, there is a next Zika probably on the doorstep in two or three years' time, but it will be called different, so the world needs to be ready.

Marc Booty: I understand the public service side and getting things ready, but are you trying to defray some of these costs by signing contracts with certain countries in advance so that you have put aside supply or they have first call?

Luc Debruyne: We don't have, and we are not intending to do that for Ebola, Zika because we first have to have the vaccine, so it is basically a research question first that we need to respond to.

In the case of the pandemic flu then we have existing contracts that we are still fulfilling because those date back from the 2009 experience. There is also a WHO coalition again of the industry that deals with pandemic flu.

Steve McGarry (HSBC): Two questions: firstly, if you look at the pricing environment, especially the US, for traditional pharmaceuticals, it has been difficult, to say the least, and probably going to get more difficult going forwards. Could you explain why vaccines might be different, or if it is going to be different in the government market, the supranational market and the private payer market?

Secondly, you are going to have a CEO change in the company early next year, can you give anybody comfort around the table here that there is going to be continuity of thought in the vaccines business?

Luc Debruyne: Let me take the last question first. Let me share that we are very excited as a team with our new CEO that has been announced, Emma Walmsley. She was fully part of five years/six years of creating the strategy that we are following and that, I think you can clearly agree with me over the last quarters, is clearly delivering sequentially. Vaccines is a key part and growth driver of this company with Consumer, Pharma and Vaccines. I am actually very excited because, if you think about a product like shingles, to be able to tap into that expertise of Emma Walmsley and her Consumer organisation, that is an amazing strength we can apply. Continuity I can guarantee you and she is already getting very close, but we need to give her the space and time to make up her mind where she wants to work, but she is already very close to Vaccines, because she is as excited about it as me.

The pricing environment: as much as I said that the demographics of the world start determining where Pharmaceuticals is going as well, I said that Vaccines was already there for 20 years because we were supplying to the whole world; the same thing is true for pricing.

The fact that we have tiered pricing, which basically is pricing linked to the affordability or how much people can afford to pay for based upon this gross national income, is something we have already applied for a long time. There are many variables: it is the commitment of a government, the coverage that they will do, the length of contract that they will do, that are today already determining the price.

If you know that less than 3% of a healthcare budget is spent on prevention, it is not the first place where they will go and look for money. My message here is that, with all the pricing discussion that is going on in pharmaceuticals, where you have clearly heard the expression of where we think GSK is with its pricing, in Vaccines this is not a threat that we see coming.

Roger Franklin (Liberum): Just a question on manufacturing and barriers to entry, just going back to that. I guess we have seen in the monoclonal antibody space, a trend towards modular production, even some small players getting quite competitive on CoGS at lower volumes, I am just wondering is there any similar trend in terms of new technologies in production in Vaccines that could lead to that happening here? Not in the context of competition for your existing products, but in terms of competition from newer

entrants in terms of them going after new targets, or, indeed, any benefit for your own business from those types of technologies?

Luc Debruyne: Your question has two answers that can come from Thomas and from John, because the technologies, of course, we are looking for technology constantly, but the complexity that you need to be aware of is, imagine that you bring in a new technology for a vaccine that is already existing, you will have to be able to show that what you produce with that new technology consistently is as safe and as efficacious as the vaccine that is already on the market. Just look around, when companies want to bring a similar vaccine on the market what it takes to get there. It is a huge complexity that is not comparable just showing what you make is the same; you need to be able to show that it is as efficacious and as safe and if you were a health minister, and you have been using a vaccine for 20 years safely, because pharmacovigilance is very well applied to it, and then you need to replace it with something that is the same but it is just produced in a different way, you will have to pass many hurdles to do that.

Having said that, what Manu has alluded to, where we think is the future, is new technology platforms that we will master, but that will still take – the timelines will take long and we hope we can apply them to new vaccines where there is still unmet medical need. John; you are the expert!

John McGrath: Almost an expert at getting the microphone on too! If you take the newer technologies out there, like modular technology disposables, do we use it? Absolutely. Does it make stuff cheaper? Absolutely, to a point. Modular technology disposables is fantastic for switching to lower capex; you do increase your opex. There is still a trade-off between when you build a stainless-steel facility and when you build a modular facility. Modular facility disposables might be slightly faster, but we scan it, we are looking at it, we have already got it implemented in existing vaccine processes in order to simplify those and make them faster. We also look at things like blow fill seal technology, which is not new – it is relatively old, but for vaccines it is quite new, versus prefilled syringes or something.

It can lower the capex cost to entry, but you still need all the other expertise to go with it and if you want to get into serious volumes it is not going to dramatically impact your operating costs.

Jo Walton (Credit Suisse): You have said there are only four major players and there is really only two major players in the paediatric vaccines – yourself and Sanofi, or Merck Sanofi in Europe. My kids are now 20 and I remember that they were stuck with a

gazillion different vaccines when they were small, but if we were to look at the cost of a paediatric suite of vaccines, say 20 years ago, or maybe 10 years ago, and now, have you managed in, let's say, the developing world market? Choose a country, because there are tenders and things that distort it, but how has price developed? Have you been able to get real price rises or are we getting more and more antigens for the same money from a paediatric point of view, so you just have to be bigger and better to retain profitability? That is my first question.

My second one was looking at your regional split, you are biggest in Europe – that is where you have the highest market share. This is a market which is about to have a change because your primary competitor, Sanofi Merck, the JV is breaking up and they are going to be two single competitors. Do you expect that to make it a more competitive market going forwards, or do you think it will be irrelevant to you?

Luc Debruyne: The last question, it is quite irrelevant in the sense that we are not against having an extra supplier, because they have their supply problems, we have and we are talking about public health here. How that will play out, for the moment I would say it is distracting for them and not for us, so that gives us a pathway and it is very unclear where it will really go, so I cannot really comment on that.

On the pricing piece, I don't know, Luis, if you want to give some flavour on that? If we are talking public health it is coverage that is a driver, to make sure that more people are vaccinated, but, as I said at the start, the lifeblood of our company is innovation. If you just think about *Bexsero*, the meningitis B vaccine – if you see the amazing results in the UK and then think about what an amazing opportunity is still out there to vaccinate many infants, or adolescents against meningitis B and then the combination with ACWY, so the alphabet: ABCWY – that is an amazing opportunity where payers are prepared to pay. It saves so much cost afterwards of hospitalisations or dealing with everything that is linked to that.

If you think about the shingles vaccine, today in the US Zostavax is generating $800 million a year; they only cover 30% of the population that is eligible and, I can tell you, all the 50 plus here in my team are already lining up to be vaccinated. Why would you still take the risk of having shingles if you can have a vaccine with that efficacy with just two shots?

My message is here we invest in innovation and therefore we work towards – if you think of the example that Manu gave for flu, flu TIV, trivalent, the three components, is indeed a commodity they almost don't pay for it anymore; the prices are very low. If you look at QIV, which is an innovation, that is a reasonable price. Is it expensive? Absolutely not – just go for your own flu shot, it is cheaper than a bottle of water. That is why the volume

value equation that I laid out earlier is very important to amortise and to have the cost of goods low.

Marietta Miemietz (Primavenues): Thank you. I was just wondering if you could share some high-level thoughts on infant immunisation schedule, because there is already some concern that it is almost too many jabs that babies are getting in a very short period of time. I was just wondering in terms of adding more vaccines to that, do you think it depends a lot on the tolerability of the vaccines or do you think there is scope to maybe push some of the vaccines that the kids are getting slightly later into life? Is this really where we need to move more towards, maternal immunisation, to de-bulk in terms of the vaccines the kids get?

Luc Debruyne: I will ask the doctor - I am not the doctor, Thomas, to answer. I will give you my lay answer to that, which I use when I talk to friends about vaccination: a baby who plays on the playground on the floor, or on the ground in your house is vaccinating itself a thousand times a day. That is how I explain the impact, but the doctor will be able to do that better.

Thomas Breuer: Built on this, one myth which is out there with concerned parents, and obviously you are concerned about your children, is the amount of antigens you expose your child to doing one vaccine, specifically with the new combination vaccines. What Luc just said is true - if you inhale air, if you eat, you really ingest or digest millions of bacteria every day and from that point of view, having six or 10 antigens in one vaccine is not a problem from an antigen load point of view.

Yes, maternal immunisation is one solution, then oral vaccines, like the rotavirus vaccine, is another solution and then also staggering vaccines across different ages. Some vaccines are only given in the second year of life; MMR vaccines – some of the meningitis vaccines are given later on in life, so there is still room for manoeuvre.

We keep a close eye on it and if we manage to put more antigens in our vaccine we will come up with higher combination vaccines as well.

Luc Debruyne: It is basically reducing the number of injections that is the most important thing and that is why we have been investing so long on the combination vaccines. It is not the number of antigens.

Thanks to my team for your presentations. Thank you very much.

[*Meeting concluded*]