INJECT SOME THOUGHT

Vaccines are forecasted to be the fastest-growing sector in the pharmaceutical market. But if this market is to take off as predicted, will companies be able to stay on top of R&D, secure financial support and have the infrastructure to capitalise on it? Nic Paton talks to Rino Rappuoli, Novartis, and Jaap Goudsmit, Crucell.

Even a decade ago, if there was forecast that the global vaccine market was poised to enter a golden age of R&D-led opportunity, there would probably have been embarrassed silence around the table. But that is precisely the situation that big pharma finds itself in today: poised on the brink of a range of hugely exciting and potentially lucrative opportunities, with breakthroughs in vaccine technology and development opening up new frontiers in the fight against diseases such as cancer, malaria, HIV and tuberculosis that have outsmarted scientists for generations.

Contributor profiles

Dr Rino Rappuoli is head of vaccines research for Novartis Vaccines & Diagnostics. Previously, he was chief scientific officer and vice-president, Vaccines Research, at Chiron Corporation. He is a foreign associate of the US National Academy of Sciences and the European Molecular Biology Organisation. In 2005, he was awarded the Gold Medal by the Italian President for contributions to public healthcare.

Dr Jaap Goudsmit is Crucell's chief scientific officer and is responsible for all R&D activities. He joined Crucell in 2001 as senior vice president vaccine research. Prior to Crucell, he held positions at the Academic Medical Center at the University of Amsterdam and was chairman of its Research Institute for Infectious Diseases and Institute for Science Education.

In October 2008, pharmaceutical market researcher VisionGain published a report examining how the global vaccine market was likely to develop over the next 15 years, and concluded that the future was bright.

'The period 2008-2023 will see a vaccine "boost",' the report stated. 'During this period, vaccines will be one of the fastest-growing segments of the pharmaceutical market. Vaccine revenues will increase in size by several hundred percent.'

While this is excellent news for big pharma, with opportunities come with challenges. For example, what will be the best business model to maximise growth and not get left behind, and how do companies ensure they stay on the R&D curve without being overly exposed to risk?

'I have been in the vaccines field for 30 years and it has never been as buoyant as it is now,' says Dr Rino Rappuoli, global head of vaccines research at Novartis Vaccines & Diagnostics. 'Even just three or four years ago it was not as attractive.'

So, what has changed? The main reason for the stasis in the market was that, technologically, it had hit something of a brick wall.

'All the vaccines that could be developed with the technology available had already been developed,' says Rappuoli.

But waves of technological advances, particularly around recombinant DNA and the development of conjugate vaccines, or vaccines that can confer the immunological attributes of a carrier protein to an attached antigen to create a new immogen, have brought vaccines back into fashion with a vengeance.

Genomics and economics

Since the 1990s, another breakthrough has been genomics, particularly the availability of the whole genome of bacterial parasites or viruses, and the mapping of the human genome. This has led to the development of genome-based approaches to vaccine development, such as reverse vaccinology, a technique pioneered by Novartis that has allowed pharmaceutical companies to study vaccine development in silico or without the need of cultivating a pathogen.

Reverse vaccinology has been used for the development of vaccines against serogroup B meningococcus, while there is also potential for its applications in the development of viral vaccines.

'These developments have entirely changed what is possible and have opened up how we can manipulate the immune system to conquer many diseases, however, there are still some diseases, such as HIV and cancer, that we have not yet overcome,' says Rappuoli. 'The knowledge for all this is coming, but it is not there yet.'

Meanwhile, there has been a growing awareness that everyone is part of a global health community, according to Dr Jaap Goudsmit, chief scientific officer at Crucell.

'People have become much more aware how issues such as travel and climate change make the world more susceptible to disease,' he explains. 'You only have to look at outbreaks such as SARS and avian flu. There is a greater awareness of the global nature of disease risk.'

Industry has focused more on developing high-margin/ low-price vaccines, often combination vaccines, that can then be delivered within emerging markets such as India, China, Africa and South Asia, and particularly to children. Goudsmit cites the example of Crucell's Quinvaxem liquid vaccine, codeveloped with Novartis, which combines antigens for protection against diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* type b, one of the leading causes of bacterial meningitis in children. Because it is one of the first internationally available fully-liquid vaccines that contains all five antigens, it offers major advantages in terms of convenience of use. On top of this, there is the issue of more pathogens, such as tuberculosis and flu, becoming more resistant to drugs.

'People are becoming aware that we have to move away from just treatment to more preventative measures such as vaccination,' says Goudsmit. 'You not only need an antibody response, but also a T-cell response. Both immunological responses must be created.'

Therapeutic potential

A lot of the R&D focus is on developing therapeutic vaccines against cancer tumours, AIDS, hepatitis B, tuberculosis, malaria and even against the bacteria that cause gastric ulcers.

'It may be possible to develop vaccines against infectious diseases for which it is not possible to vaccinate against at the moment, such as streptococcus, chlamydia or even malaria,' says Rappuoli. 'But there are also vaccines that can be developed just by mining the available technologies. One of the big dreams for many pharmaceutical companies is to be able to develop therapeutic vaccines. They are not ready yet, but these will come possibly within the next 15 years.'

Such vaccines will require a different business model and, crucially, new ways of working and collaboration from big pharma.

'Up to now, in developing therapeutic vaccines, people have been using the old model of looking for preventative

vaccines where you immunise people and then expect them to be clear of the disease,' says Rappuoli. 'But that is not going to work for these types of vaccines. In order to succeed you will need to combine vaccination with conventional therapy.'

The challenge for companies that specialise in vaccines will be whether they can feasibly partner with experts, perhaps rivals, in the therapeutic arena. Even if they are big enough to work on both sides, there may still be challenges such as simply ensuring everyone is working in a more joined-up, holistic manner.

'It is a dream to think that, by vaccination only, we will be able to cure cancer,' says Rappuoli. 'But if we combine antibody therapy and chemotherapy against cancer with a vaccination, then you may have the possibility of doing something really good. So pharma will need to be able to inhabit internally the expertise in, say, developing the anticancer drugs as well as the vaccines. We need to be able to have collaboration across divisions and across different competencies.'

THE VISIONGAIN REPORT: KEY FINDINGS

- The main growth driver for vaccines will be their cost-effectiveness in combating disease. This in turn will encourage greater use of vaccines by governments and private healthcare providers.
- Vaccination will be more commonly used against high-profile (and potentially profitable) diseases such as cancer.
- Many healthcare providers see preventative medicine, including therapeutic vaccines as a way to increase the quality of life and reduce future healthcare expenditure.
- Advances in biotechnology have led to a boom in vaccines R&D, with more than 1,000 vaccines in the R&D phase worldwide.

> Public health programmes have a role in creating incentives for effective vaccinology R&D and delivery, particularly when it comes to preventative medicine.

Goudsmit agrees with Rappuoli that the future is likely to be more collaborative. He cites his company's close ties with Novartis, particularly with Quinvaxem, as well as Crucell's partnership with Sanofi Pasteur on creating a rabies monoclonal antibody cocktail vaccine. 'If there is a benefit in partnering, we are never shy to say so,' he adds.

The role of governments is another consideration for pharmaceutical firms. Clearly there are major public health issues concerning therapeutic vaccines as well as significant costs issues, especially for countries such as the UK that have state-funded healthcare systems. Yet, governments through their public health programmes do, and increasingly will, have a role in creating incentives for effective vaccinology R&D and delivery, particularly when it comes to preventative medicine.

'Vaccines will start to be increasingly targeted not only at infants but at adolescents, adults and the elderly,' says Rappuoli. 'More often, they will become a part of preserving the health of the elderly, for example, preventing or delaying cancer.'

Another issue is likely to be the role of private charitable and philanthropic organisations such as the Bill & Melinda Gates Foundation. 'Among its many areas of work, they have a focus on putting in place reliable logistics and cold chains to help get vaccines to where they are most needed in poorer and developing nations,' suggests Goudsmit.

Cure for cancer?

While helping to tackle tuberculosis, HIV, malaria and rabies through vaccination are all key challenges for the future, the main vaccination frontier is likely to be cancer, in particular, taking on viral cancers, agree Goudsmit and Rappuoli. For example, the link between hepatitis B and human papillomavirus (HPV) and cervical, liver and pancreatic cancers, opens up huge opportunities and challenges when it comes to vaccination.

'Being able to protect against cancer by vaccination will be a paradigm shift,' Goudsmit. 'The vaccines against HPV, for example, are showing very promising results. Preventing cancer through anti-viral vaccinations is potentially an enormous area.'

While the future for pharma in terms of vaccines is looking positive, the bigger gain will be that to humanity as a whole if diseases such as cancer can finally overcome through vaccination, according to Rappuoli.

'Vaccines could become the best insurance policy that people could have for their future,' he says. 'If you can vaccinate someone now and in doing so prevent a possible cancer occurring 30 or 40 years later, that is a beautiful proposition.' WPF