screening strains containing multiple antibiotic-resistant genes).

So long as major challenges in biotechnology and biomedicine remain (e.g. emerging diseases, established diseases, antibiotic resistance, and environmental pollution and need for renewable energy) microbial resources will be of interest to mankind providing sustainable and environmentally friendly solutions. Microorganisms continue to offer the versatility of their products providing a stimulus for interaction between different disciplines, major support from governments and agencies, as well as an understanding and supportive public and philanthropic organisations [20,21].

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From discovery to commercialisation of vaccines

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Having spent the first 25 years of my [IG] working life involved in research on vaccine development and delivery and then a decade in industry, working for and with, companies that actually made vaccines, I am reminded of the observation, attributed to Charles Dickens:

> ***When I was 14, I thought my Father was the stupidest person on earth. When I was 21, I was amazed at how much he had learnt in the past 7 years.***

Exposure to the harsh realities of product development challenged my academic preconceptions, gave me a greater insight into the nature and complexity of the development process and a greater respect for the skills of those involved.

The public health community often laments the fact that vaccines produced by the research-based industry take so long to develop and initially cost tens, sometimes hundreds of dollars per course. They tend to assume that the high price of modern vaccines

leads to huge profits for industry without understanding the underlying economics.

Researchers in pursuit of funding and biotech companies seeking support from investors often claim that their candidate or production process has properties which guarantee that the final product will be inherently safe and inexpensive. While appealing to granting agencies, these claims are out of touch with the realities of modern product development: which, irrespective of the process employed, is data-based, time-consuming and capital expensive and requires patient investment, exceptional technical skills, good management and a tolerance for risk.

Vaccines differ from drugs in that they are usually prescribed for individuals (often infants or children) who are healthy and at relatively low risk of developing severe complications of the particular infection. Consequently, the public and their guardians, the national regulatory agencies, place a premium on the safety of the product.

As vaccines are often produced in living cells and are defined by their biological activity, their regulation is inherently more complex than the regulation of drugs, which can be characterised at a chemical and, sometimes, molecular level.

Ensuring that a vaccine, which has been shown to be safe and effective in clinical studies, can be produced consistently in bulk, is largely a design issue that must be built into the production process. Since quality cannot be guaranteed solely by inspection or testing samples of the final product, every step of the manufacturing process must be defined and controlled to maximise the probability that the finished product meets all its specifications.

To avoid human error, wherever possible, the process is automated and computer-controlled.

Since World War II, most of the advances that have led to the development of new vaccines have originated in academic laboratories and research institutes, with a disproportionate number originating from groups funded by the US National Institutes of Health (NIH). With a simple vaccine, the cost of the basic research may be as little as US$10–20 million, although in the case of difficult agents like HCV and HIV, we will have to move the decimal point a couple of places!

The technology and relevant Intellectual Property (IP) are usually transferred to industry when a manufacturing process has been established at bench scale and proof of efficacy has been demonstrated in an animal model. A typical licensing arrangement will require the industrial partner to pay a significant upfront fee, with additional and escalating sums as the candidate achieves commercially significant milestones as well as a royalty on future sales. The industrial partner is expected to bear the cost of maintaining and if necessary defending the IP.

In addition to the original technology, the manufacturer may need to make similar arrangements to access some of the processes needed to manufacture the vaccine and/or to access a suitable adjuvant or delivery system. Each of these commitments becomes a component of the final development cost.

Once product development is brought in-house, the manufacturer assumes the commercial and technical risk and begins preclinical development. An attempt is made to scale up the production process; for example, by moving from shake flasks, to pilot scale bioreactors then to large-scale production bioreactors, each of which has its own set of technical challenges, which need to be defined and resolved.

For example, some techniques like dialysis, which work well at the small scale, are found to be inappropriate at the large scale and need to be substituted with modern filtration techniques. When this occurs, critical decisions need to be made on membrane material, pore size, flow path, choice of equipment, and, since large investments are involved, need to be justified with adequate quantities of data.

Typically, preclinical development takes several years and costs US$50–100 million – or more. Standard Operating Procedures (SOPs) are written, which define each step in exquisite detail and assays are established for in-process control, lot release and characterisation of the final product. The technical and managerial skills involved in each step in the process are considerable and in limited supply.

As the production process becomes more carefully defined, it becomes possible to determine the size and configuration of the facility that will be required to house the manufacturing plant. Because the facility needs to be designed, constructed, equipped and validated in time for the launch of the product and the process typically takes several years and is very expensive, the decision to invest in a new plant is a very significant one for the company and may involve significant risk. Sanofi has recently announced plans to commence construction of a manufacturing plant for production of their candidate Quadrivalent live attenuated dengue vaccine at a cost of more than US$1 billion, several years before the results of phase 3 studies on the product are known.

Strict regulatory oversight impacts on every step of the production cycle. From sourcing raw materials from external suppliers to the testing of final lots, regulatory agencies require that every step be described and characterised, including the nature and performance of each piece of equipment used and even how it is cleaned. These requirements create great rigidity and are designed to minimise the chance of human error.

Once each step in the process has been defined, parts that may vary and affect product quality are challenged by conditions which could be met under a worst case scenario and these challenges must be repeated sufficiently frequently to ensure that the results are both consistent and meaningful. Some areas such as sterilising filtration, inactivation and toxoiding receive special attention, as failure has such a large impact on product safety.

Once the product has been made, it is subject to rigorous safety testing for sterility, pyrogenicity and abnormal toxicity and carefully defined according to physical, chemical and performance characteristics and stability studies are undertaken to define the shelf life of the product under likely storage conditions.

Finally, once this has been achieved, the manufacturer must produce a number of batches of vaccines to demonstrate that the process is reliable and the product can be produced as specified consistently. Ensuring the consistency and quality of a vaccine is dependant not only on a defined production process, but on highly trained staff using validated procedures and equipment, in a carefully designed and controlled environment.

When the vaccine has been developed and the manufacturing process is under control, the product needs to be evaluated in a sufficient number of subjects to both demonstrate efficacy and determine the absence of serious side effects. Currently this involves testing in at least 50,000 subjects and may cost in excess of US$200 million. Regulatory authorities frequently impose an additional requirement on companies to monitor the performance of their products post-licensure (phase 4) to ensure that rare or delayed side effects are detected. The level of documentation required by regulatory authorities before a product is approved, reflects the magnitude of the effort and can fill a small van.

While these strict requirements have not prevented the research-based industry from continuing to develop and license new vaccines, they have had a profound effect on the shape of the industry, the time taken to develop a new vaccine (now 20 years or more) and the costs (typically in excess of US$1 billion) which inevitably has an impact on the price of the final vaccine.

Biographies

Ian Gust is a medical virologist with advanced training in pathology and infectious diseases, who has led large public and private sector research organisations and been an advisor to government, industry and international organisations. He completed a combined science/medicine degree at the University of Melbourne (1964) and undertook postgraduate training at the London School of Hygiene and Tropical Medicine and the Regional Virus Laboratory, Glasgow (1967–1969). He was appointed medical virologist at Fairfield Hospital for Communicable Diseases, Melbourne, and built the virus laboratory into the strongest diagnostic and public health virology laboratory in the Southern Hemisphere. To accommodate for the increasing research interests of the group, he established an independent research Institute, the Burnet Institute (1986) and became its founding director.

This period led to the publication of four books, more than 300 papers, the generation of several patents, membership of numerous influential national and international committees, consultancies for WHO, UNICEF, the World Bank and the South Pacific Commission, Professorial appointments at Melbourne and Monash Universities and a number of major awards.

In 1990 he became the R&D director at CSL Ltd, then a small government-owned entity with some production capabilities, which was earmarked for corporatisation and possibly privatisation. He transformed CSL from an insular division with a wide range of interests, into a focused, internationally competitive group. CSL's global R&D Division now has a budget of $330 million per annum and the company has been voted one of the 10 best performing in the world.

His retirement from CSL coincided with an explosive growth in interest in and funding for, international public health and increased interest in the Australian biotechnology sector. Over this period he has been able to assist public and private sector organisations, either as a board member or scientific advisor. These include: Biota Holdings P/L, Promics P/L, Opal Therapeutics P/L, Virax P/L, Chemgenix, Genocea P/L, The International AIDS Vaccine Initiative (New York), The Paediatric Vaccine Initiative (Seoul), the Australian International Health Institute (Melbourne), International Vaccine Institute (Seoul) and Chair of the Bio 21 cluster.

Rodney Carbis started his career in vaccines at CSL where he worked in influenza vaccine development and also spent some time in quality control of viral vaccines. He implemented many changes to the influenza vaccine manufacturing process, which included process validation and submission of documentation to the National Regulatory Authority (TGA) to approve the changes. After CSL he joined Sartorius Australia in the position of technical manager, where he assisted vaccine and pharmaceutical companies in Australia and Asia to develop downstream processes and optimise filtration systems. He also provided critical support in the validation of numerous filtration systems with key customers.

He joined the International Vaccine Institute (IVI) in Seoul Korea in June 2003 and is currently head of vaccine development. He investigated the suitability of the Vietnamese oral cholera vaccine for technology transfer and discovered that it did not comply with the WHO requirements. The vaccine manufacturing process was modified and the final formulation changed following developmental work supervised by Rodney and performed at IVI and with the Vietnamese manufacturer. New assays to control the quality of the cholera vaccine were developed at IVI and these assays along with the necessary reagents were transferred to the Vietnamese manufacturer. The new vaccine technology and formulation and quality control assays were transferred to Shantha Biotechnics in India and the vaccine was licensed in February 2009.

A second vaccine development and technology transfer project headed by Rodney is the typhoid vaccine, based on conjugation of Vi capsular polysaccharide (produced by *Salmonella typhi)* chemically conjugated to Diphtheria Toxoid (DT). In this project the process development team has increased the yield of Vi during fermentation, developed a new Vi purification method and optimised the conjugation process. The resultant product complies with WHO recommendations for Vi and the conjugation optimisation has resulted in 80% recoveries of Vi, translating to a vaccine that will be affordable to the poorest communities in the world located in typhoid endemic areas. The technology transfer for the production and testing of this vaccine has been completed and clinical trials are now being planned. Licensure of this vaccine should occur in either 2010 or early 2011.

The process development laboratory has a strong focus on bringing products to market designed for use in poor communities in developing countries. The laboratory places a high level of importance on developing processes that are compatible with large-scale manufacture under GMP conditions.