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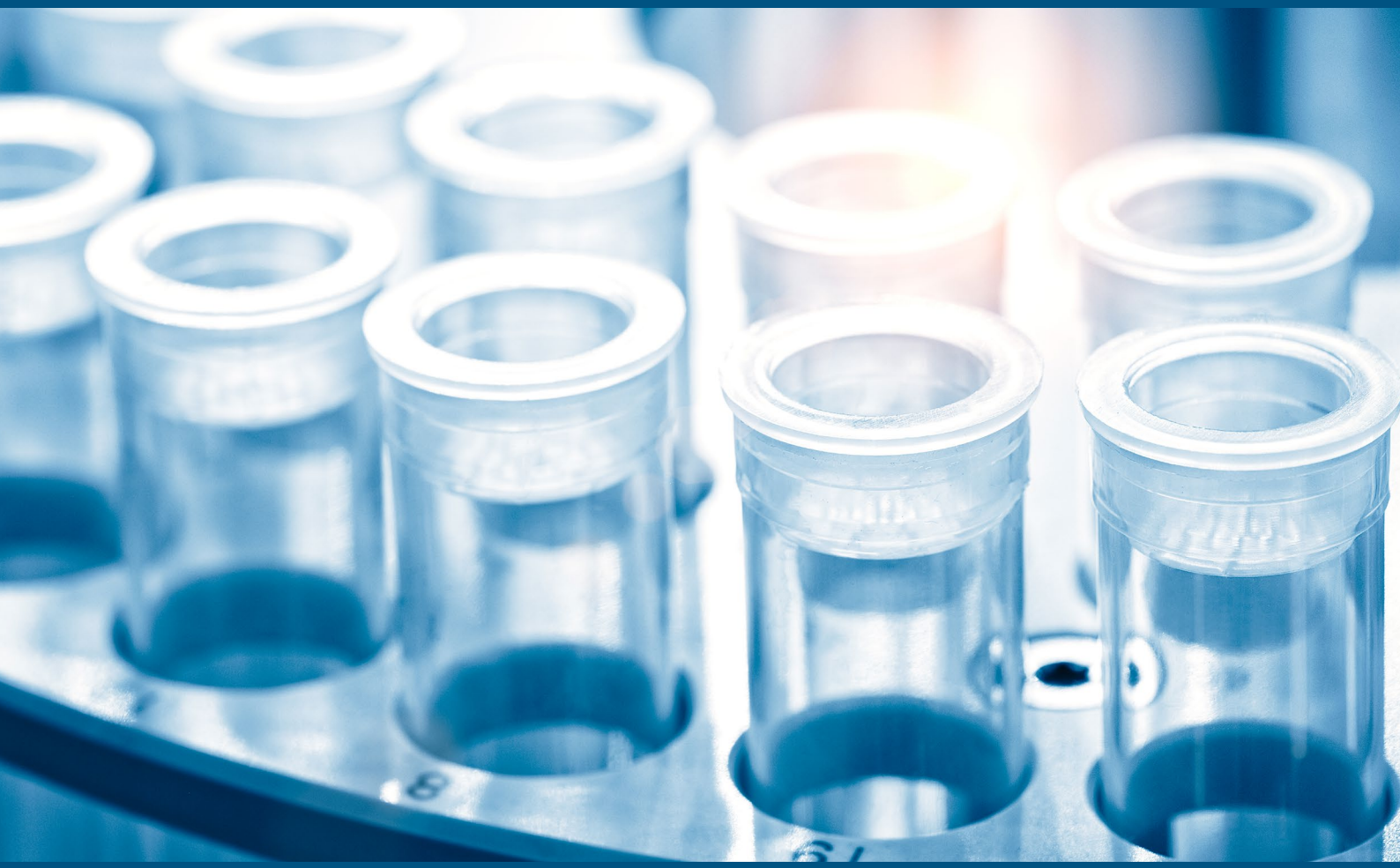

Building a Successful Vaccine Manufacturing Business in Lower and Middle Income Countries

Lessons from industry leaders and innovators

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This document has been produced as part of UNIDO's global project "Strengthening the local production of essential medicines in developing countries through advisory and capacity building support" with funding support from Germany's Federal Ministry for Economic Cooperation and Development (BMZ). Kris Howard, Pharmaceutical Manufacturing Expert, and Martin Nicholson, International Pharmaceutical Expert, have been the lead authors.

Federal Ministry
for Economic Cooperation
and Development

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Executive Summary

UNIDO has created a series of resources to support local vaccine manufacturing in developing countries/emerging markets. This document expands on the topic using industry experts' own words – both in this white paper and in the companion podcasts.

Over the past 50 years a number of trends, acting in concert, dramatically changed the industrial landscape and use of vaccination as a public health service. Vaccines became available for a wider range of diseases, and global policy called for wider use of vaccinations which ultimately lead to an increase in vaccine funding and supply infrastructure expansion. Both the public and private spheres saw vaccine manufacturers who could not compete on cost or quality fold or consolidate with others.

Three successful emerging markets vaccine manufacturers – Serum Institute, Bio-Manguinhos and Biovac – charted three different paths to success. While their paths are heavily influenced by their local and global policy environments, they share common factors. Planning timelines must be measured in decades, while execution strategies are subject to changing government policy and potentially inconsistent interest from or interaction with private vaccine firms. Furthermore, companies must have production technology, in-house expertise, product quality and prices that are competitive on the global scale for a company to succeed.

Vaccine manufacturing differs significantly from pharmaceutical manufacturing. Pharmaceutical products can be easily replicated and tested for purity, biologics can not. Maintaining the manufacturing process as close to identical between batches as possible ensures the final product has the same safety and efficacy profile as clinically tested batches. In industry parlance, "the process is the product".

Due to these highly specialised requirements, hiring experienced staff and obtaining manufacturing know-how are foundational steps for industry newcomers to consider. Most companies underestimate the cost, level of difficulty and time necessary to bring onboard enough skilled staff. Manufacturing know-how is typically obtained through a technology transfer from a larger company, where know-how is often provided in exchange for guaranteed market share in the local country. Negotiating a technology transfer can take years, completing one successfully can take close to a decade.

The other foundational area for a newcomer to consider is financial viability of a new facility. Organisations must determine which product to make, ensure there is a market for it, find a suitable technology transfer partner, put together a promising value proposition, coordinate with local regulatory authorities and carry out a full feasibility study. As well as learning from other successful companies in the industry, a new organisation requires its own team of experts to conduct feasibility studies and eventually plan and execute such a project.

This paper is based on interviews conducted prior to the COVID19 pandemic and therefore it is not a discussion topic covered in the document. However, COVID19 has underlined the importance of diversifying the vaccine supply base and manufacturing capacity in developing regions. As policy makers, entrepreneurs, investors and others develop and implement approaches to achieving these ends, it will be imperative that the complexities of the undertaking are considered and that lessons learned during the evolution of the vaccine sector are built upon. Hence, the insights from experts in the field of vaccine manufacturing captured in this document are even more prescient in light of the global pandemic.

1. Introduction

As part of its ongoing work to support the field of local vaccine manufacturing in developing countries, UNIDO has interviewed those who have played a pivotal role in the rise of successful vaccine manufacturing firms to share their story with the world. The goal is to highlight the common elements and factors that have created or driven successful and sustainable vaccine manufacturing enterprises for those interested in pursuing vaccine manufacturing for the first time.

The interviews have been recorded in their entirety and will be published as podcasts for people to listen and learn from. This document serves as a written companion to those full-length audio interviews. It aims to bring together the most salient themes discussed over approximatley eight hours of interviews in a cohesive and coherent manner along with additional input from its authors.

While the document is intended to be a useful resource in and of itself, it is also a map to related sections of the interviews. Readers, especially any stakeholder involved in the establishment of vaccine manufacturing in a new firm or country for the first time, are highly encouraged to listen to the full interviews to hear from these experts in their own words.

This work would not have been possible without the generous help of the following guests:

- Episode 1: Barry Garfinkle – Formerly of Merck and Co. Inc/MSD, USA
- Episode 2: Akira Homma – Bio-Manguinhos, Brazil
- Episode 3: Morena Makhoana and Patrick Tippoo – Biovac Institute, South Africa
- Episode 4: Gerd Zettlemeissl – Formerly of Chiron Behring and Intercell, Austria
- Episode 5: Rajeev Dhere – Serum Institute of India, India
- Episode 6: Ralf Clemens – Formerly of GSK, Novartis and Takeda

A more detailed biography of each guest is given during their podcast episode and is included in the podcast episode show notes in Appendix 1.

COVID-19 pandemic

This paper was prepared based on discussions that took place before the COVID-19 pandemic and therefore it is not a discussion topic that is covered in the document. However, the insights from experts in the field are particularly relevant in the light of the COVID19 pandemic and the renewed emphasis being placed on building vaccine manufacturing capacity in developing countries, as global supply constraints have hampered international efforts to roll-out COVID19 vaccination programmes around the world. The contents of this document can inform both short-term actions to help alleviate supply constraints being experienced in 2021 and longer-term initiatives to establish geographically more diverse manufacturing capacity for vaccines.

2. Looking Back: 50 Years of Change – The Evolution of the Vaccine Industry

The global vaccines industry of the 1960s and 1970s looked very different to the industry of today. A number of trends, all acting in concert, dramatically changed the landscape of industry and use of vaccination as a public health service.

More vaccines, better vaccines
One of the clearest changes over the past five decades is the increase in number and type of vaccines available. New methods of producing vaccines such as recombinant technology have led to vaccinations for a wider range of diseases, and increased the safety, purity and efficacy of older generations of vaccines.

Growth in immunisation program implementation
In the 1960s, most Western countries had standard vaccination programs, although widespread immunisation programs were uncommon through the non-Western world. In countries with immunisation programs, compliance was typically lower than today due to lack of availability and concern over the safety of vaccination in general.

From then, global policy increasingly called for wider use of vaccinations as well as to increase vaccine funding and supply infrastructure. In 1974 the World Health Organization (WHO) put forth its Expanded Programme on Immunisation (EPI), and in 1977 set a goal that every child in the world would be immunised against tetanus, diphtheria, pertussis (whooping cough), polio, measles and tuberculosis by 1990. In later decades, the EPI was expanded to cover vaccines against other diseases.

International efforts and pooled procurement mechanisms
The 90s saw greater international efforts to ensure more universal access to life saving vaccines. While the WHO and others had been recommending the minimum EPI vaccinations for over a decade, global funding organisations such as The Children's Vaccine Initiative and its successor GAVI, began raising the money necessary to buy the products for the world's most vulnerable populations. With funding available, supply naturally rose to meet increasing world demand.

Suppliers and consumers still needed to be connected. Pooled procurement mechanisms such as PAHO and UNICEF created a global market place where vaccines could be bought and sold more easily, greatly improving transparency among all players.

Consolidation of vaccine manufacturers
The 80s and 90s saw the consolidation of vaccine manufacturers both in the public and private sector. In South America alone, most countries had some level of publicly owned vaccine manufacturing capabilities in the past whereas today, only Cuba, Mexico and Brazil have state-owned production.

Private companies saw a similar consolidation, with many private vaccine firms active in the 80s shutting down their production or selling off their facilities and assets.

From boutique to blockbuster
Vaccine manufacturing used to be seen as a "boutique" industry or a side business by big biopharma companies such as Merck and Co/ MSD into the 1990s. Small molecule pharmaceuticals were the blockbuster moneymakers of the 1980s and 90s. However, by the early 2000s, some of these large Western biopharma firms started launching blockbuster vaccines (defined as global sales over $1B) using the latest advances in technology.
- Barry Garfinkle – Formerly of Merck and Co. Inc/MSD, USA, Episode 1 (paraphrased)

Shift towards higher-margin vaccines
By the early 2000s, some of the large Western biopharma firms started launching blockbuster vaccines (defined as global sales over $1B) using the latest advances in technology. This led to large Western manufacturers increasingly moving away from making the lower margin, higher volume EPI vaccines in order to focus on higher margin vaccines with the potential to become blockbusters (many of which also began to appear on EPIs around the world). The withdrawal of big pharma from the low-margin vaccines sector just as the global EPI Vaccine market expanded left a huge opportunity for vaccine manufacturers in developing countries. A void that companies like the Serum Institute of India were all too happy to fill.

Today, while products made by Western firms constitute the majority of the vaccines market by revenue, firms in developing countries and emerging markets produce a far greater number of doses of vaccine. However, many of these firms are now highly mature, and are taking the experience they gained over the years to develop new and increasingly more complex and valuable vaccines. Some of these novel products in development are designed to compete directly with the big Western blockbuster vaccines.

These changes caused a dramatic shift in the size of the global vaccine market, the organisations producing and buying vaccines, where vaccines are produced, and the barriers to entry for newcomers to the industry. For those looking to get into the modern vaccine industry now, how and where can they find their niche?

Podcast Sections:
Episode 1, Sections 1-6: Barry Garfinkle
Episode 2, Sections 1-2: Akira Homma
Episode 4, Sections 1-3: Gerd Zettlemeissl
Episode 5, Sections 1-2: Rajeev Dhere
Episode 6, Sections 1-2: Ralf Clemens

A. Three Pathways to Success

While there is no set formula for a newcomer to replicate another's success, learning from other emerging market vaccine firms is essential. Individual strategies must fit the available resources as well as the local and global markets and policy environments. Nevertheless, successful vaccine firms share many of the same characteristics. Below are the brief histories of three remarkable companies as detailed in the podcasts.

Serum Institute - India

Identifying and capitalising on an under-exploited niche
Serum Institute, a privately owned company, is the world's largest producer of vaccines by number of doses produced and sold. It began producing antigens for vaccines early in its history, decades later it is one of the foremost manufacturer of immunobiologics in the world.

Back in the mid-1960s, however, the only connection horse breeder Cyrus Poonawalla had to the vaccine and sera industry was the donation of retired horses to the Haffkine Institute in Mumbai. There, serum from donated horses was used to make vaccines such as Tetanus Toxoid. In 1967, Poonawalla decided to diversify his operation, setting up his own Tetanus Antitoxin and Tetanus Toxoid production in Pune.

Just a few years later in 1974 the WHO established its first Expanded Program on Immunisation (EPI). The EPI recommended routine vaccination against tetanus, diphtheria and pertussis – Serum decided to expand its production capabilities to include all three of those antigens. Serum Institute sought out help and negotiated a technology transfer from Biltohoven Institute in the Netherlands to get its production up and running. As the WHO added vaccines to its EPI, Serum Institute used it as a guide to which vaccines would see high demand in the near future.

In the 1980s a supply shortage of vaccines such as measles hit the global market. Serum spotted the opportunity to make its first viral vaccine, but recognised that it would need a technology transfer partner to capitalise on the opportunity. At the time, the Indian government applied restrictions on the availability of dollars – this combined with the high prices charged by Western vaccine firms for technology transfers led Serum to look elsewhere. With the engagement of the Institute of Immunology in Zagreb, Serum was able to launch their measles vaccine in 1989. In 1993, it gained pre-qualification (PQ) from the World Health Organization (WHO), enabling Serum to sell its product into global markets.

Although over 25 years had elapsed between beginning to produce anti-tetanus products and the WHO PQ of its measles vaccine, in the early 1990s it found itself at the center of a perfect storm of opportunity. Greater awareness and increased funding led to a global rise in vaccination rates at a time when the number of global vaccine manufacturers was contracting. Demand started to outstrip supply for many key vaccines – Serum began launching new vaccine products at an ever-increasing rate to fill the gaps opening in the market.

Pooled procurement agencies such as PAHO and UNICEF buy enormous quantities of vaccine products but have exacting standards and look to keep costs low. Many publicly owned vaccine manufacturers couldn't compete on price or quality, while many private western firms preferred to sell into higher margin markets such as North America and Europe. The scale, competitive prices and high quality standards of Serum Institute allowed it to dominate this high-volume niche without the need to search for its own customers.

From the beginning, Dr. Poonawalla built his company with a focus on technical excellence and flexibility. Serum Institute initially plowed its profits back into its infrastructure, becoming debt free early in its history – this gave them the freedom to think long term. It developed strong in-house technical knowledge over decades, with an early focus on increasing batch yields and process efficiency. This gave Serum Institute even greater flexibility in their operations and enabled its low cost approach. This abundance of capital and expertise enabled Serum to build world-class facilities which could be quickly repurposed to make any of their early products, consistently staying ahead of the demand curve predicted by WHO vaccine recommendations.

- Rajeev Dhere – Serum Institute of India, India, ***Episode 5, Sections 1-6***

Bio-Manguinhos - Brazil

State-sponsored self-sufficiency

Bio-Manguinhos currently makes 10 different vaccines, has completed nearly two dozen technology transfers and produces approximately one third of the vaccines needed to immunise the 3.5 million babies born each year in Brazil. This state-owned organisation was created in 1976 as part of the Oswaldo Cruz Foundation, part of the Brazilian Ministry of Health.

The Oswaldo Cruz Foundation's goal is improving public health in Brazil – Bio-Manguinhos was created to develop and manufacture the biological products to support this goal. In a country with such a large birth cohort and no private vaccine manufacturers, Brazil saw building a local publicly owned vaccine manufacturing industry as the best way to ensure the health of its people.

Beginning with a staff of just 16 people, its first project was to modernise the foundation's Yellow Fever vaccine production facility. In 1980, it began a pivotal set of technology transfers with the Biken Institute in Japan for the production of Measles and Polio. They then went on to do tech transfers with large vaccine firms such as GSK and Sanofi as well as other publically owned vaccine manufacturers in Brazil, Cuba and elsewhere. In all, they completed approximately two dozen technology transfers for vaccines and biologics.

The importance of this state-owned supplier was highlighted during the global shortages of Yellow Fever and Polio vaccines of past decades. While countries who are dependant on imported supplies of these vaccines were unable to provide these for their population – vaccine manufacturers are notorious for providing supply to their own country first in times of shortage – Bio-Manguinhos was able to keep Brazil supplied.

How was Bio-Manguinhos able to survive while many other publically owned vaccine manufacturers throughout Latin America and the world collapsed? Brazil has a significant advantage due to high product demand for its large domestic market, but the Brazilian government was also instrumental in securing the manufacturer's success. In 1985, a lack of anti-snake serum in the country led to the creation of the Self-Sufficiency Plan. Over the next decade the government would invest $100M into local publicly owned firms to modernise biological and vaccine production facilities and improve production standards. It also improved the level and enforcement of regulatory standards.

Public entities were forced to either improve their capabilities or be shut down. By 1995, only three organisations had survived – each one much stronger and self-sufficient. This allowed Bio-Manguinhos to compete on quality levels and price globally as well as domestically. Key products such as Yellow Fever could be exported, while ensuring their position supplying the local market. Bio-Manguinhos chose to focus on vaccine manufacturing without developing their own novel vaccines. Their strategy has been to negotiate win-win-win technology transfer deals with leading multinationals to produce Brazil's locally needed vaccines. Multinationals gain long-term access to the Brazilian market, the government gets a price cut and Brazil gains much needed expertise via its publicly owned entities.

Instead of spending its funds on development, Bio-Manguinhos was able to invest more on new facilities and incremental improvements and efficiencies to the products and processes transferred to them from their technology partners. However, even after 43 years, experience with over two dozen technology transfers and 10 active vaccine products in their portfolio, Bio-Manguinhos still only satisfies one third of all the vaccines needed for Brazil's EPI.

- Akira Homma – Bio-Manguinhos, Brazil, ***Episode 2, Sections 1,2,4,6-9***

Biovac – South Africa

Policy forces a change of direction for a public private partnership

Biovac was formed in 2003 as a public private partnership (PPP) between the South African Government and private investors. It was granted the previous state owned vaccines production facilities and took over the distribution and supply of vaccines purchased by the South African Government. The new organisation also had the mandate to develop and manufacture vaccines.

At the time of takeover, the legacy vaccine production facilities only had 24 employees left, and due to the aging technology no longer produced any products. Distribution and supply of imported vaccines provided an initial cash flow for the company while it put together the rest of its operation.

The first Biovac program was aimed at locally producing a widely-used pentavalent vaccine. This 5-in-1 vaccine protects against pertussis (whooping cough), tetanus, diphtheria, hepatitis B and haemophilus influenzae type B (known as Hib, a bacterium that causes meningitis, pneumonia and otitis). Biovac intended to develop its own Hib antigen, which was very hard to import as a

bulk product, while importing the other four antigens. Then, it would formulate and fill the final pentavalent product to sell it. From the beginning, it planned to be a fully integrated vaccine company, both a novel vaccine developer and a manufacturer.

Disaster struck when a decision by the Ministry of Health completely changed the market outlook. The MoH decided to change the recommendations for their EPI from the type of pentavalent being developed by Biovac to one with a more advanced pertussis antigen. This change in policy immediately wiped out Biovac's domestic demand for their product. It also made it extremely difficult to conduct clinical trials on its product in South Africa as children were only to be given the newly mandated pentavalent product type.

Biovac pivoted to a strategy that sought out large multinationals to do technology transfers of leading products. The tech transfer route came with many of the benefits of developing products in-house but allowed it to take place faster and with less risk. With no local biotech industry to provide support or local venture capital industry to finance high-risk projects such as new products, technology transfers offered a financially viable way to go forward.

The technology transfers allowed Biovac to learn more about the industry as well as build a proven track record as a manufacturer. As of today, Biovac has signed agreements with Sanofi for the filling of Hexaxim and Pfizer for the formulation and filling of Prevenar. The decision to stop pentavalent production was a wise one – the global price for a dose plummeted from a high of $3.65 in 2004 to between $0.69 and $1.15 today.

Nevertheless, the early development work on a Hib vaccine was not a complete loss. In the following years, Biovac was able to license their Hib technology to 3 organisations. It was also able to use its experience and technology from the Hib development to work on the development of other products with other partners such as PATH and the Gates Foundation. While a Biovac pentavalent product was never completed, the expertise gained enabled a number of follow-on successes.

- Morena Makhoana and Patrick Tippoo – Biovac, South Africa, ***Episode 3, Sections 1-12***

B. Key Takeaways

Three organisations... three very different pathways to success. However, all three success stories share many similarities. Newcomers to the industry should take note of these key takeaways before moving forward with their vaccine operations.

1. Long-term timelines

In the vaccines industry, investment strategies unfold in terms of decades, not in years or quarters like some other industries. A successful manufacturer typically hits its stride after a decade or two in production. Vaccines are difficult to make and develop. Establishing the skills to do one or both well takes a long time.

- Serum Institute took 22 years to launch its first three human vaccines, none of which were developed in-house. It took four years from launching its measles vaccine to get WHO PQ approval for it. Over the next 25 years, it would launch over a dozen more prequalified vaccine products as well as other non-vaccine products, many of which were developed in-house.
- Full technology transfer projects can take close to or more than a decade. Dr. Homma (Bio-Manguinhos) offers an example of a technology transfer negotiation taking 3 years.
- Even after 43 years in business, Biomanguinhos still only satisfies 1/3 of all the vaccine doses in Brazil's EPI.

2. Complex policy landscape

Vaccines is an industry steered by policy as much as by innovation. Shifting EPI program recommendations, changing funding guidelines by NGOs and national governments, evolving regulatory requirements as well as the competitive landscape between public and private vaccine manufacturers and innovative vaccine developers makes for a complex landscape for a new comer to navigate through.

Private multinational firms are not typically dependant on one main market, but beholden to various requirements from multiple countries. Fully state owned firms may be able to compel all government stakeholders in their home market to align, which may cause them to be uncompetitive in the open market. Semi-state owned or private firms which are mostly dependant on one main market can run into problems when policies in that market are incongruent with one another.

Understanding this complicated landscape is the key to success in this industry – changes in policy can derail long-term plans but also create niches to exploit.

- Biovac was forced to completely change their strategy following the South African MOH's decision to shift to a new pentavalent vaccine.
- Brazil's Self-Reliance program provided and drove investment in local manufacturing capabilities but also forced some entities to close down.
- The introduction of WHO's EPI, growth in funding for low income countries, and incumbent vaccine manufacturers either closing down or focusing on rich markets created an enormous opportunity. Serum Institue were able to harness this early opportunity to become highly successful

3. Global competition

The vaccine industry is unforgiving for both public and private firms alike if their strategic direction and execution are sub-optimal. Additionally, vaccine developers and manufacturers must be ready to compete at the local, regional and global level. Local governments can be a source of support and early sales to a budding manufacturer, but no government is willing to purchase lower quality product at higher prices from a local entity for very long.Modern facilities, in-house expertise, product quality and price must be competitive on a global scale for a company to succeed.

- The number of public owned firms making vaccines has reduced over the past few decades in places like South America, Brazil and South Africa due to the loss of competitiveness in their product range, price and quality.
- Serum's opportunity was amplified because a number of public and private firms were going out of business or had their vaccines units sold off or shut down. In an ironic turn of events, Serum's continued financial success and security allowed it to buy its first technology transfer partner, Bilthoven Institute, in 2012.
- Having a source of baseline income (distribution and supply) independent of new vaccine development or manufacture of tech transferred products helped Biovac survive during shifts in the policy and market landscape.

3. Looking Forward: Foundational Steps

Newcomers to the industry can learn from successful established vaccine firms, but must be ready to forge their own path. The landscape of today's vaccine industry looks very different to that of 50 years ago, and any new developer or manufacturer will need to respond to the challenges and opportunities in their commercial and policy environment.

Nevertheless, several key concerns are applicable throughout the globe and across the decades. All organisations considering entering the industry must consider whether development or manufacture will be their focus, how they will obtain the technical know-how and experienced staff to run a facility, the regulatory and clinical considerations and finally how to finance the operation.

A. Choosing a Role: Development or Manufacture

To understand the type of know-how and staff experience a new operation will need, it is important to understand what type of company it will be. Most newcomers will pick either development or manufacture to focus on. Each area faces very different challenges.

Vaccine development

Much of the innovation in the vaccine world today comes from small clusters of biotech companies gathered around talent hubs such as Singapore, Boston, USA or Cambridge and Oxford, UK. These clusters are ecosystems where talent from top universities and funding from venture capital firms with a specific focus on biotech combine to take calculated risks to discover vaccine innovations.

In most cases, when a small vaccine development company is successful in finding a new technology or product candidate, the company is sold or the technology is licensed to a large multinational company who will then commercialise it. This is because in most cases, the innovative development firm doesn't have enough of the following:

- Clinical and regulatory capabilities necessary to get the product registered and approved quickly.
- Commercial horsepower to market, promote and sell the product effectively after approval.
- Manufacturing know-how to set up their own production facility or find an appropriate contract manufacturing organisation.
- Money to hire in experts or consultants to plug any gaps in the above.

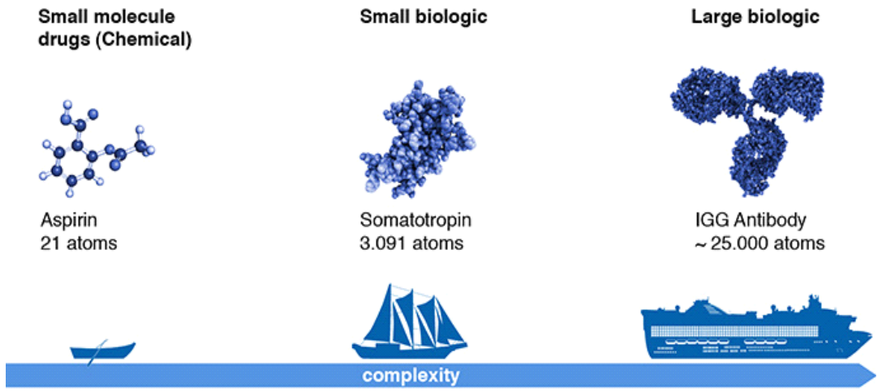
A growing trend today is for companies, even established vaccine manufacturers, to use a contract manufacturing organisation to produce a product during the clinical trial or early commercial launch phase. This is because manufacturing facilities are very expensive and the technology needed to make vaccines differs from product to product, so an existing faciilty may not be capable of making a new vaccine. With this strategy, if a new product fails during the clinical phase or sales don't grow as expected, the company is not left with an underutilised expensive capital asset.

Podcast Sections:
Episode 4, Sections 8-9: Gerd Zettlemeissl
Episode 6, Sections 13: Ralf Clemens

Vaccine manufacture

Manufacturing vaccines differs in significant ways from manufacturing small molecule pharmaceuticals. Vaccines and biologics are larger by a few orders of magnitude and are much more complex that pharmaceutical active ingredients. Furthermore, they cannot be replicated in the way that pharmaceuticals can.

Figure 1: Relative complexity of small molecule pharmaceuticals and vaccines/biologics*



To get an idea of the relative size and complexity between molecules such as aspirin (a small molecule pharmaceutical compund or 'chemical drug') versus biologics, which themselves can be small or large biologics, consider a simple rowing boat with a schooner and a cruise liner.

***Source: https://www.azbio.org/small-molecules-large-biologics-and-the-biosimilar-debate**

Small molecule pharmaceutical	Vaccine / Biologic
Relatively simple structures	Intricate, complex structure
Can be easily modelled	Cannot be easily modelled or defined
Synthesised through chemical reactions	Produced in living cells via synthesis pathways
Chemical reactions required to make the product well understood	Production pathways rarely completely understood
Purity of final product can be predicted with high accuracy and tested analytically	Purity and efficacy cannot be completely determined using analytical lab tests
Identically produced pharmaceuticals in different facilities can be assumed to act identically	Only real way to determine their comparability or similarity to other vaccines is to run trials in humans to ensure they are equally safe and efficacious

A high-school student can fully characterise the synthesis and potential impurities when making generic aspirin on a sheet of paper. Many even make aspirin as part of their chemisty lab class. This is simply not possible for biologics or vaccines. In fact, there is no such thing as a generic vaccine. That is to say, there is no way to make "identical" vaccines to ones made by a competitor (or even in a different facility owned by the same company). Vaccines are produced in living cells via synthesis pathways which are rarely completely understood and their purity or efficacy can't be completely determined using analytical lab tests. The best outcome that can be expected is to make a "similar" vaccine product which has a comparable safety and efficacy profile to the originator vaccine as determined by clinical testing in humans.

Same vaccines, different vaccines

The same vaccine can be made by the same company, with the same process and equipment but at two different sites and can turn out to be noticeably different. It is then up to the company to prove if the product from the new site has a sufficiently similar safety and efficacy profile to the product that originally underwent clinical trials and regulatory approval.

In the late 1980s, different strains of the mumps vaccine were in use – the older Jeryl Lynn strain and the newer Urabe strain. It took years of data and testing to prove that the Jeryl Lynn strain was safer and more effective than the Urabe strain, eventually resulting in the use of the Urabe strain being halted.

This is the reason why many regulatory agencies will require products that have been tech transferred, either within a company or to a new company, to undergo some level of human testing to ensure the transferred product is similar enough to the originator product.

- Barry Garfinkle – Formerly of Merck and Co. Inc/MSD, USA, Episode 1 (paraphrased)

The process is the product

Given that vaccines are injected into healthy individuals, in many cases infants, how can a company ensure the millions of doses produced each year are not harmful to those who take them?

Since it is impossible to use clinical testing to check the safety and efficacy of each batch, it is of utmost importance that the production process is as identical as possible between batches. The industry standard is to ensure quality of the product by carefully selecting and then closely monitoring and controlling a wide array of production process parameters during manufacturing. Provided that the process stays within its allowed limits and the final product passes a set of rigorous analytical tests, the produced vaccine can be expected to be safe and effective.

In industry parlance, this is referred to as "the process being the product" – but controlling the process to within such tight parameters is challenging.

- Vaccine manufacturing requires highly sophisticated production and analytical equipment, the majority of which is highly specialised and will need to be sourced from the US or Europe. This equipment and clean room environment will need to be constantly maintained and kept free of biological and non-biological contamination.
- It is not uncommon to have a malfunctioning piece of equipment on a weekly or even daily basis in most facilities. Just one is enough to shut down the whole production process. Manufacturers outside of the US and Europe or away from established hubs often cannot rely on timely attention from equipment vendors and must have skilled staff on site to resolve issues quickly and avoid losing expensive product batches.
- Manufacturers need specific scientific and biotechnical engineering expertise to be able to understand the production process and interpret any deviations encountered along the way. A deviation is any departure from the extremely long list of process parameters discussed above. It is not uncommon in a world class vaccine manufacturer in the US or Europe to have a dozen or more deviations in a batch that is ultimately released.
- Staff must understand the fine line between acceptable deviations and deviations that can affect product quality. Being on the wrong side of that line means throwing away a perfectly good batch (very expensive) or sending out product with questionable safety and/or efficacy (very dangerous).

This is the core of why vaccine manufacturing is so difficult, why technology transfers take so long, and why it is so different from pharmaceutical manufacturing.

Podcast Sections:
Episode 1, Sections 11-13: Barry Garfinkle
Episode 6, Sections 7-12: Ralf Clemens

Why not both?
What keeps organisations from doing both? The two areas require totally different skill-sets, both which are highly expensive and time-intensive to develop. Additionally, both vaccine development and manufacture feature lengthy, uncertain timelines and large, uncertain costs. Ensuring that product development and production facility readiness timelines align perfectly without running out of capital is a colossal undertaking. In nearly all cases, these ventures are taken on by larger companies with more experience, deeper pockets and a portfolio of other products to offset any delays or cost overruns.

While developing novel products is one aspect of vaccine development, another valuable aspect is to improve efficiencies and attributes of products received via technology transfer. Bio-Manguinhos chooses to focus their development work on the production efficiencies and follow on developments of products received from technology transfers. Serum Institute has been developing its own products with increasing success over the years, but in the early days, its research and development was focused mostly on production efficiencies. Biovac began with the aim of both developing and manufacturing its own products. However, the eventual cancellation

of their pentavalent product program caused it to decouple these efforts – today its products for production come from tech transfers, while it continues to develop novel products to be licensed out to other companies.

Developing and manufacturing a Japanese Encephalitis vaccine
Austrian firm Intercell (now Valneva) developed a Japanese Encephalitis vaccine, and becoming a rare exception, also chose to launch it comercially. In part due to good Phase III results, Valneva decided to take the calculated risk of seeking approval for the product on their own and carry out manufacturing by themselves.

It closed the gaps in its capabilities by hiring in a number of experienced people as well as purchasing an existing manufacturing facility in Scotland. The whole commercial launch process took 5-6 years from the time the decision to go it alone was made until the product and facility were ready to start making commercial product. Had Valneva chosen to build a new manufacturing facility, the process would probably have taken another two years. Even in highly fortunate circumstances – circumstances unlikely to be present for a new firm starting out in a developing country – the process takes many years.
- Gerd Zettlemeissl – Formerly of Chiron Behring and Intercell, Austria, Episode 4 (paraphrased)

As vaccine development is mostly confined to a few key hubs of biotechnology, the majority of newcomers entering the industry in developing countries will be looking to manufacture. For this reason, the bulk of the information in this document is geared towards the manufacturing side of the vaccine industry.

Podcast Sections:
Episode 3, Section 12: Morena Makhoana and Patrick Tippoo
Episode 5, Section 10: Rajeev Dhere
Episode 2, Section 8: Akira Homma

B. Hiring Experienced Staff

It is impossible to run a successful manufacturing plant without the right expertise.

According to the podcasts guests, finding and bringing onboard enough of the right people is of utmost priority, on par or even above securing financing. Unfortunately, most companies underestimate the cost, level of difficulty and time necessary to achieve this task. What factors make hiring the right staff so difficult?

Number of skilled staff required
A full-fledged manufacturing facility requires a much wider group of expertise than a few executive level experts lured from an established international manufacturer. As shown in the first white paper, the bulk of the facility's workforce will be comprised of skilled employees ranging from PhDs and engineers to production floor operators.

Why are skilled production operators so important?
People new to the industry tend to underestimate the importance of the general production operator in the facility. A skilled operator can be the difference between a safe and efficacious batch and a ruined one.

In vaccine manufacturing, the biggest source of contamination comes from people themselves. Biological material and organisms that are sloughed off the skin on a continual basis, an errant cough, or an incidental touch of a shoe followed by an interaction with the product or equipment can lead to product contamination. Much of this can only be detected after the product has been made, and some things may even slip through these final quality checks.

Furthermore, there are typically a number of operator-executed process steps that have no direct monitoring by a computer. Therefore, operators must be fully knowledgeable of what is expected and must be self-aware and honest enough about their actions to identify and report potential issues.

Expertise and specialised knowledge
The vaccine industry is about know-how, both explicit and tacit. Explicit knowledge can be codified or written down, stored in documents or databases, and is relatively straightforward to transfer from one person to another via training. Transferring tacit knowledge, intuitive knowledge and know-how rooted in context, experience, practice and values, is much more difficult. Vaccine manufacturing is not just following a fixed recipe (explicit knowledge) but involves a large amount of experiential-based tacit knowledge which only comes from doing things repeatedly, preferably in the presence of a more experienced mentor. For example, the average person still can't replicate a dish from a top restaurant even if they were given the recipe due to their relative lack of tacit knoweledge. Making vaccines is much the same, albeit, with much more dire consequences of failure.

Specific scientific and biotechnical engineering expertise is required to be able to understand the production process and interpret any deviations encountered along the way, and to pass on this understanding to other personnel. In a country with a sizeable pharmaceutical sector but where local regulatory standards are not up to international standards, recruiting from the pool of local pharmaceutical experts may not be viable. Even if suitable people with pharmaceutical experience are recruited, they will need to be trained to relinquish the pharmaceutical way of thinking and indoctrinated into the "treating the process as the product" mindset in order for them to be fully effective in the vaccine industry.

Location and relocation
Unlike many other resources you will need to set up and run a facility such as capital and equipment, people are not very fungible and they often don't relocate easily. This means either building a facility near to a large pool of available talent, or recruiting talent from another location's pool.

Available talent tends to cluster around biotech manufacturing hotspots and universities with rigorous biotechnical research programs. Attracting top talent within these clusters is costly and highly competitive – even in a biotech hub like Ireland, the cost and time to recruit and onboard people is higher and longer than most companies expect. Meanwhile, new vaccine operations that are far from such hubs will still need to spend enough time and/or money to recruit their experienced personnel from such competitive hotspots.

Salaries and other costs
Even if the vaccine facility is based in a low-cost country, bringing on experienced skilled employees (whether expats or emigrants returning home after working in the West) is a high-cost affair.

Costs for such roles can include US or European level salaries for 2-5 year contracts, paying for employees' children to attend private international schools, and maintaining employees' home country healthcare insurance so they can return home for treatment. On top of this, a local employee is often employed for the duration of the contract to be mentored by the expert – when the expat returns home, the mentee would be ready to take over the role. All this results in a much higher personnel cost than expected if cost projections assume all employee salaries will be lower than in the West.

Podcast Sections:
Episode 1, Section 18: Barry Garfinkle
Episode 3, Sections 16-17: Morena Makhoana and Patrick Tippoo
Episode 4, Section 4: Gerd Zettlemeissl
Episode 5, Sections 8, 13: Rajeev Dhere
Episode 6, Sections 14: Ralf Clemens

Four ways of building human capital

Enticing expensive staff from biotech hubs is often necessary to get started, but successful vaccine manufacturers take steps to secure a long-term dependable supply of skilled staff.

A strong national educational and university system in the manufacturing country is a good foundation, but not enough – untrained graduates coming out of school with no experience need years to be trained to the point of leading operations in a facility.

University of Siena - Italy
The University of Siena's Institute for Global Health provides Masters degrees focusing on immunisation, infectious disease and clinical development. The courses are 12-18 months long, taught by top specialists from the world of vaccinology and includes an internship. Stipends are even available for qualifying international students. They also offer executive courses on a number of topics relevant to the vaccines industry. The Gates Foundation also has plans to create a similiar, albeit shorter, course focused on vaccine manufacturing.

- Ralf Clemens – Formerly of GSK, Novartis and Takeda, Episode 6 (paraphrased)

IDA Ireland - Ireland
IDA Ireland is a semi-governmental agency dedicated to attracting and retaining foreign direct investment to Ireland. They have gone as far as to connect biotech companies to the network of local University and Technical College resources focused on the biotech industry. This allows these organisations to coordinate and develop specialised course curriculum for their students as well as troubleshoot and enhance production processes.

- Barry Garfinkle – Formerly of Merck and Co. Inc/MSD, USA, Episode 1 (paraphrased)

Serum Institute - India
Serum Institute took a very long term approach to attracting, training and retaining skilled personnel and building its human capital. The company is headquartered in Pune, sometimes known as the Oxford of the East for its high number of universities, which has approximately 100,000 university students enrolled across the city.

The company has been able to capitalise on this environment by offering six month unpaid internships for promising individuals looking to learn about the vaccine industry. Upon completion of the internship, Serum Institute has its pick of the most promising interns to hire on as full-time employees. Serum Institute offers a competitive salary and nurtures a rewarding corporate culture where employees are empowered to make important decisions at all levels of the organisation. This paired with Pune being an attractive city for people to live in, has enabled them to retain key staff over the long-term.

- Rajeev Dhere – Serum Institute of India, India, Episode 5 (paraphrased)

Biovac - South Africa
Biovac has built up its staff over the past 15 years with a focus on limiting expat hires and nurturing homegrown expertise. It recruits new graduates from technical schools and universities as well as experienced personnel, especially people for their Quality department, from traditional pharmaceutical firms in South Africa. It is important to note here that South Africa has quite a strong traditional pharmaceutical industry with many facilities that are owned by big multinational firms.

It then helps these industry newcomers to learn about the vaccines industry through external training programs outside of South Africa and by leveraging the skills and experience of their more experienced technology transfer partners. Biovac still hires some expats from other countries, but has been able to keep the expat hires to a limited number of key people.

- Morena Makhoana – Biovac, South Africa, Episode 3 (paraphrased)

C. Technical Know-how

New companies in the vaccine industry need to learn how to manufacture the products they will sell. The production process for different vaccines can be very different. As we have seen, even companies that develop their own products may lack specific technical know-how for large-scale production.

Gaining the know-how to manufacture each new vaccine product often requires a company new to the industry to find a more experienced company willing to perform a technology transfer. The motivation for the more established company to perform such a transfer to a potential future competitor is profit, public health, or a combination of both.[1]

Tech transfer – finding the right partner and building the right team
Not all products, processes or transfer teams are the same – the right technology transfer partner can go a long way to keeping mistakes and lost batches to a minimum. Look for a partner who is willing to offer lots of training and support to your team and who has a robust and straightforward production process. A good partner can be a vital source of training, mentoring and experience for your staff, learn as much as you can from them.

- Gerd Zettlemeissl – Formerly of Chiron Behring and Intercell, Austria, Episode 4, (paraphrased)

Tech transfer – finding the right partner and building the right team (continued)
The donor organisation should devote a team of employees who support the the receiving company with the technology transfer year round. Someone flying in for a week periodically will not be enough. Reverse integration is the best way to perform a technology transfer, and if the donor organisation doesn't plan to transfer the master seed to the receiving site, its a sign they don't trust that partner. Don't be surprised if the upfront discussions just to lay out the framework for what the technology transfer will entail takes nearly a year.

- Ralf Clemens – Formerly of GSK, Novartis and Takeda, Episode 6 (paraphrased)

For-profit technology transfers

Most high profile technology transfers include a for profit organisation transferring technological know-how to a local manufacturer, in order to make money via royalties or the supply of semi-finished goods. Typically, these types of technology transfers are provided by large multinationals, such as Pfizer, Sanofi, Merck, GSK and similar. But as we have seen, smaller firms such as Intercell and Biovac have also performed technology tranfers. In both cases, big and small companies see technology transfers as a strategic means to increase revenue by capitalising on their valuable manufacturing know-how.

1 See UNIDO's White Paper "Establishing Manufacturing Capabilities for Human Vaccines", available at UNIDO's website, for a more detailed analysis of dynamics and drivers

Over the past 10-15 years a number of technology transfers similar to the ones taking place at Biovac have been initiated by multinationals into middle income countries such as Brazil, Argentina, Russia and Turkey. Local firms are likely to be granted lengthy tender awards from their national government, ensuring a stable source of long-term income and a relatively secure foothold in the local vaccine market for the originating partner.

Large, middle-income countries are the most attractive prospects for this type of transfer due to their relatively high birth cohorts and the fact that they are no longer eligible to buy vaccines at UNICEF prices. Middle-income countries are also likely to have at least one local entity technologically advanced enough to receive such a transfer.

In the future, the geographies where these transfers take place will shift towards the next wave of emerging middle income countries that are self-procuring their vaccines and have relatively mature manufacturing know-how ready to receive technology transfers. It is also expected that mature developing country manufacturers such as Serum Institute, will start filling the role of the large multinationals by initiating their own technology transfers teaching newer firms to make their products.

Key drivers of for-profit technology transfers

Technology transfers are often used as a means for global vaccine manufacturers to capture local market share ahead of their competitors – locally produced products often receive preferential treatment over imported ones.

For novel vaccines which only have two or three multinational competitors, the race is on for the companies to win a small number of key markets which incentivise local production. In these cases, the technology transfer receiving partner is almost always restricted to sales of the new product within their own country, or in some cases the immediate region.

A smaller firm that has developed a product with more competition experiences different pressures. As they are probably more interested in growing their market share rather than domination of a few key markets, they may take a more open approach to whom they transfer their product to.

An additional driver can be to increase production capacity. Technology transfers allow a company to delay or eliminate the need to invest in new production capacity for specific products. Production is essentially outsourced to its local partners, yet the company still wins market share. This can be the case for large multinationals who are looking to relieve pressure on a certain portion of their manufacturing value chain or a smaller firm which is unable or unwilling to build new capacity at that time.

Podcast Sections:

Episode 2, Sections 7, 9, 12: Akira Homma
Episode 3, Sections 13-14: Morena Makhoana and Patrick Tippoo
Episode 4, Section 10: Gerd Zettlemeissl
Episode 5, Section 15: Rajeev Dhere
Episode 6, Sections 3-6: Ralf Clemens

Public health driven technology transfers

Some technology transfers take place with the primary objective of promoting public health, rather than seeking profits. The multinational company or non-profit develops the product that may be relevant to both the developed and developing world, then licences them out to various manufacturers who will supply them to global markets. Unlike with the for-profit technology transfers above, the originator may receive limited or no profits and royalties.

Examples of public health driven technology transfers

- Hilleman Laboratories, a joint venture non-profit between Merck and Co Inc and the Wellcome Trust, is working to create vaccine products which are better suited for the developing world than those currently on the market. For example, a heat stable Rotavirus vaccine which can be more easily administered in hot countries – existing Rotavirus vaccine must be continuously refrigerated to be effective.

- Hilleman Laboratories has also developed a new lower cost cholera vaccine which will increase the access to this product in the world's poorest regions which are hardest hit by cholera.

- In the early 90s, China was facing a public health issue from the extremely high prevalence of Hep B in its population. Merck transferred the technology necessary to make its recombinant Hep B vaccine to Chinese manufacturers. There were no profits or royalties paid to Merck as part of this deal.

- Barry Garfinkle – Formerly of Merck and Co. Inc/MSD, USA, Episode 1 (paraphrased)

There are also a number of organisations focused on developing vaccines to fight the devastating diseases that primarily affect developing countries, with no expectation of making a profit. Rather than driving innovation through pure competition, these organisations often complement each other's efforts or collaborate directly.

The Coalition for Epidemic Preparedness Innovations (CEPI) – its mission is "to stimulate, finance and coordinate vaccine development against diseases with epidemic potential in cases where market incentives fail". CEPI has so far targeted MERS, Nipah and Lassa which often hit developing countries the hardest.

The Bill and Melinda Gates Foundation is working to eradicate Polio, in part by funding the development of low cost vaccines for it. They are also funding work on the development of a Universal Flu vaccine as well as a vaccine for Tuberculosis.

The International Vaccines Institute develops and delivers vaccines against infectious diseases with limited commercial potential yet high public health importance in an effort to enable the world's most vulnerable people to full and productive lives. They are currently working on vaccines for products such as Cholera, Typhoid, Dengue and MERS.

Multinationals are also developing their own vaccines for diseases that are mostly prevalent in developing countries. The GSK Vaccines Institute for Global Health is developing products for Typhus and Shigella, among others. Merck produced an Ebola vaccine after the 2014-2016 West Africa outbreak and was able to quickly respond to the recent outbreak in 2018 in the Democratic Republic of the Congo. However, products which are being developed for diseases in the developing world may be decades away from being transferred to new manufacturers in the developing world.

Which manufacturers are best suited to receive technology transfers of vaccines from non-profit development organisations in the short term?

- New manufacturers are typically not best suited for any product that requires a quick response to an epidemic or dangerous breakout. By definition, a new firm will be relatively inexperienced with regards to the skills and know-how to manufacture vaccines.

- The need for these products is unpredictable and requires relatively small volumes. However, production facility for these products must be kept active and ready to respond. Carrying these high overheads can be financially burdensome for small firms.

- It is most likely that highly experienced and long established multinational vaccine manufacturers will be chosen to make products developed by CEPI in the near term. Effective epidemic preparedness relies on a reliable supply of safe and efficacious product to be ready whenever disaster hits.

- Gerd Zettlemeissl – Formerly of Chiron Behring and Intercell, Austria, Episode 4 (paraphrased)

- Any companies that are chosen to manufacture vaccines for outbreak response would need to commit a portion of their capacity to making this product at short notice. Furthermore, they would need to ensure the facility is kept "warm" meaning the explict and tacit knowledge needed to make the product isn't lost or forgotten due to long periods of not making the product.

- Some of these products could be of great interest to those in developing countries because many utilise more flexible and technologically advanced production platforms than older products.

- Ralf Clemens – Formerly of GSK, Novartis and Takeda, Episode 6 (paraphrased)

Podcast Sections:
Episode 1, Sections 7-10, 14: Barry Garfinkle
Episode 4, Sections 5-7, 10: Gerd Zettlemeissl
Episode 6, Sections 15-17, 19: Ralf Clemens

D. Regulatory and Clinical Plan

The maturity and functionality of local regulatory authorities, while completely outside of the influence of any manufacturer, can significantly affect the future of any project and should be an important consideration when planning a project in a given country. They will be the final authority on whether a new facility will gain approval to manufacture a product, but should also be a partner in guiding a newcomer over the regulatory hurdles necessary to achieve that.

Products for export will most likely need to achieve WHO prequalification status – one of the prerequisites for this process is for the local regulatory body to be highly functional in the eyes of WHO. Your local regulator is also the one who must grant your initial license to manufacture, so problems or delays with them can lead to a halt in your entire project.

A highly functional regulatory authority has good scientific knowledge and grounding in vaccinology. They should be able to offer support and guidance on the operation of a facility and registration of a product. In the case of the Measbio vaccine registration, described below, the regulatory authority's experience allowed for an alternative way to show the vaccine's safety for concomitant use. Otherwise, a concomitant administration study would have been necessary to verify there was no interference between the immune responses from multiple vaccines given to a patient at the same time.

Registration of Measbio in South Africa

Even the registration of a new product in the local market which is being imported as a fully finished product from can raise some concerns. When Measbio was being registered in South Africa, the regulator was reluctant to allow this new product to be injected during the same immunisation session as other products in the EPI – there was a lack of data showing concomitant use between these specific vaccines was safe. This would have caused the entire EPI schedule to change, adding two additional trips to the doctor to receive a Measbio injection on its own.

Biovac were able to make its case to the regulator using decades of safety data for Measbio. The regulator's experience allowed it to understand the related data and rationale and eventually allowed concomitant use of Measbio with the other vaccines in the EPI. This level of scientific based decision making and flexibility may not be possible with less mature agencies.

- Morena Makhoana – Biovac, South Africa, Episode 3 (paraphrased)

Clinical Trials

New vaccines require clinical testing to prove:

- **Safety:** Whereas pharmaceuticals target sick people, vaccines target healthy people; safety is of paramount importance during development. Determining the adequate level of safety for a vaccine involves a complex risk-benefit calculation; the more detrimental the disease, the higher the acceptable risk.
- **Immunogenicity:** The vaccine must be shown to be immunogenic, causing an antibody or T-cell response when injected.
- **Effective:** It is not sufficient to show that the vaccine causes antibodies and t-cells to be created, the trial must show that these antibodies/t-cells prevent disease or infection.

Even technology transfers of existing products to a new facility can often trigger the local regulatory authority to request further clinical testing in humans to prove equivalency of the new product or efficacy in the local population. Additional clinical data is unlikely to be needed when only the packaging stage is transferred to a new facility locally. However, if formulation, filling or finishing is localised, certain regulators may require additional studies ranging from stability studies to small in-human trials. Once bulk antigen production is transferred to a new facility, clinical studies are almost always going to be necessary.

Proving efficacy and safety

Most licensures will require a field efficacy trial to prove efficacy of a vaccine. This involves vaccinating half of the study population with the vaccine candidate, and half with a placebo or control vaccine. The study population is then monitored for incidence of the disease to get a measure of efficacy, and for adverse events to measure safety. The number injected with the vaccine candidate is known as the safety database. The manufacturer will need to discuss with the local regulatory authority what size of safety database is sufficient to show efficacy and safety of the vaccine.

Field efficacy trials require a high enough incidence of the disease circulating in the study population to measure results. When disease incidence is too low to perform a field efficacy trial, other options of showing efficacy must be negotiated with the local regulatory authority.

Proving consistency and equivalency

Manufacturers must show they are able to manufacture a vaccine consistently in order to receive licensure using lot-to-lot consistency trials. Three consecutive lots, manufactured at the manufacturer's scale facility using their final process, are compared head-to-head in a clinical trial. This shows that the vaccine response is consistent across the three lots.

For technology transfers, it is standard to include a fourth lot from the technology transfer donor. The three lots are compared to the donor lot in a non-inferiority trial, to show that the locally produced lots do not perform worse than the original vaccine.

The local regulatory authority will determine if clinical testing is required and the criteria for acceptance. Manufacturers must involve regulatory authorities to get their advice and buy-in early in their process, far before the clinical phase.

Podcast Sections:
Episode 3, Section 8: Morena Makhoana and Patrick Tippoo
Episode 4, Section 12: Gerd Zettlemeissl
Episode 6, Sections 7-12; 20: Ralf Clemens

E. Financial Viability and Funding

The third important resource, after experienced staff and manufacturing know-how, is money. Can a vaccine manufacturing facility be financially viable for a newcomer to build within a certain market? How will the new endeavor stay afloat long enough to gain the experience needed to make vaccines and amass a portfolio of different products? The next step is to put together a feasibility study to evaluate the viability of the manufacturing plan. This feasibility study will serve as the main justification for a government, donor, lender or investor to provide support or capital for this project.

Gathering information and resources

The first thing anyone interested in entering this industry for the first time should do is to get on a plane and visit a number of existing vaccine manufacturers to learn the intricacies of the industry. Furthermore, organisations such as the Developing Country Vaccine Manufacturing Network (DCVMN) and the African Vaccine Manufacturing Initiative (AVMI) are devoted to the promotion of the manufacturing of high quality vaccines in developing countries and Africa, respectively, and thus can serve as a means to gain further direct insight from experienced manufacturers and key stakeholders in the industry.

- Morena Makhoana – Biovac, South Africa, Episode 3 (paraphrased)

The previous documents in this vaccine industry series are essential reading for any newcomer. The reader should now be familiar with:

1. The functioning of the markets in developing countries such as those in Africa - **VMPA Study: Vaccine Manufacturing and Procurement in Africa***
2. The basic functioning of a vaccine manufacturing plant as well as the cost and duration to build and run it - **Establishing Manufacturing Capabilities for Human Vaccines***
3. How to conduct a high level feasibility study for establishing vaccine manufacturing in a new country - **Commercialising vaccines: A methodology to identify potential market opportunities and conduct outline assessments***

* These are all available on UNIDO's website, see https://www.unido.org/our-focus-advancing-economic-competitiveness-investing-technology-and-innovation-competitiveness-business-environment-and-upgrading-pharmaceutical-production/project-publications-pharmaceutical-sector

This document, the fourth in the series, and accompanying podcasts, aims to give first hand experience and knowledge of what is required to actually set up and run a vaccine manufacturing facility in a developing country.

No amount of resource gathering can take the place of assembling a team of experts in order to assist in conducting the feasibility study as well as eventually plan and execute the project. The core functionality of this team should include the following key expertise as a minimum:

- Vaccines Market and Commercial Expertise
- Vaccines Facility and Manufacturing Expertise
- Vaccines Development and Registration Expertise

This list is not exhaustive, however these three key areas can be used to highlight further considerations one should take when evaluating the feasibility a project.

> Podcast Sections:
> **Episode 2, Section 10: Akira Homma**
> **Episode 3, Sections 20-21: Morena Makhoana and Patrick Tippoo**

Market and Commercial Considerations

The first consideration is to determine which product to make and to ensure there is a market for it. Most vaccines are purchased by governments or donor procurement systems such as GAVI and UNICEF. Thus, direct dialog with these organisations as early in a project as possible is vital. As in any business dealing, these organisations must feel the value proposition offered by the new product and/or facility is worth their investment.

One or two organisations can represent a majority of the target market for a product and a strong indication that they won't buy can instantly kill a budding project. Some in the industry refer to these pledges to purchase from a certain supplier as a "guaranteed buy back". The company will also need to survive financially during the time before the facility is making commercial product, which can take 3-5 years.

As mentioned in the previous White Papers, the size of your market will also define what type of localised production is feasible. As a general industry rule of thumb, a packaging facility needs at least 5M doses to per year to be finacially viable. A formulation and filling facility needs at least 10M. The number of doses for a bulk antigen facility varies depending on the technology used and number of antigens in a product and needs to be determined on a case by case basis.

Price and other forms of value
It can be very difficult for a new comer to break into the global UNICEF EPI market without a very significant unique technical differentiator for your product. This market is very cost sensitive and unless you can compete on price, it will be hard to enter successfully.
- Rajeev Dhere – Serum Institute of India, India, Episode 5 (paraphrased)

A local vaccine manufacturer may be able to present an attractive value proposition to its own government or region. Value to a local or regional economy can be based on more than just a low purchasing price of a vaccine and includes things such as security of supply, job creation, lower forex expenditure and technological capacity building. Understanding what is important to these entities is key to being able to building a case for your value proposition in these terms.
- Morena Makhoana – Biovac, South Africa, Episode 3 (paraphrased)

Even a public owned entity must present a good value proposition in order to maintain strong commitment from its government. History has shown that public vaccine manufacturers can be closed down if they fail to meet their public health commitments at a reasonable price and quality. No government will continually subsidize an ailing vaccine manufacturer when they can opt for a better price to quality value proposition on the open global market. Changes in government budget surpluses or leadership which happen every few years in most countries can turn a once committed government into one that is looking to stop your funding or switch its source of supply.
- Akira Homma – Bio-Manguinhos, Brazil, Episode 2 (paraphrased)

> Podcast Sections:
> **Episode 2, Section 11: Akira Homma**
> **Episode 3, Section 22: Morena Makhoana and Patrick Tippoo**
> **Episode 5, Section 14: Rajeev Dhere**
> **Episode 6, Sections 18: Ralf Clemens**

Facility and Manufacturing Concerns

Many people are under the illusion that manufacturing in developing countries equals low cost products. Newcomers to the industry frequently underestimate their facility and manufacturing costs by an order of magnitude due to faulty assumptions. Many of the costs of a facility in a developing country will be on par with those of a more developed country, however, there are some areas where significant cost savings can be made over the long term.

Cost-increasing factors

- As stated above, a country with relatively low wages does not automatically equal a cheap workforce. Highly skilled workers, especially experienced expats, are much more expensive than the average worker. Furthermore, wages will eventually rise as development increases in a country, wiping out any early advantages in this area.
- Low cost manufacturing requires large scale in most cases. The most cost effective manufacturers are making tens of millions of doses of a single product each year. Economies of scale have a big impact on final cost. Newcomers are unlikely to have either the know-how, experience or buyers to operate at this scale.
- Many of the required raw materials, components and equipment may be imported from the US or Europe and have a relatively fixed price for all but the biggest players in the industry. Whereas some reliable locally made pharma equipment is available in Brazil, China and India, this is generally not yet the case for critical vaccine equipment. Furthermore, some countries have been to known to place very large tariffs on imported capital equipment.

Equipment sourcing

All of our critical equipment came from the US or Europe

- Rajeev Dhere – Serum Institute of India, India, Episode 5 (paraphrased)

Nearly 90% of our equipment was imported, mostly from the US and Europe.

- Akira Homma – Bio-Manguinhos, Brazil, Episode 2 (paraphrased)

Biovac chose to import most of its equipment from the US and Europe not only because it was the best, but in order to win over potential partners and the regulators.

- Morena Makhoana – Biovac, South Africa, Episode 3, (paraphrased)

Cost-reducing factors

- Using local materials and construction services for some of the non-critical areas of the site (office space, warehouse, site civil works and possibly the shell of the manufacturing facility to which you install all your equipment and clean rooms) will be cheaper compared to what it would cost in more developed countries.
- Shipping product around the world from a single manufacturing site can be a very large component of the final product cost. This is especially true for products that need to be refrigerated or even frozen. Sizeable cost savings can be made by manufacturing vaccine products as close as possible as to where they will be consumed.
- Taxes can also constitute a high cost burden for many products, having the most impact for high value products. Tax relief or low tax rate jurisdictions can help bring down costs.

Podcast Sections:

Episode 1, Sections 14, 18: Barry Garfinkle
Episode 2, Sections 3, 15: Akira Homma
Episode 3, Sections 15, 18: Morena Makhoana and Patrick Tippoo
Episode 4, Section 11: Gerd Zettlemeissl
Episode 5, Section 11: Rajeev Dhere

Fitting the strategy to the situation

Even with technical know-how, experienced staff and financial viability in place, the vaccine industry is as competitive as any other private enterprise. Strategically navigating the challenges and opportunities that present themselves will make or break a new business.

Successful vaccine manufacturers share foundational features, but the local market and country idiosyncracies and regulatory burdens will make each local environment unique. A winning strategy fits the situation while being amenable to stakeholders and investors.

Our guests indicated it is best not to bite off more than you can chew. Don't try to do everything in the value chain, focus on the areas where you have the relevant skills, competitive advantage and funds to get started. Then invest the time to get started, make it profitable and gain a deep level of knowledge about that area before expanding further.

Two perspectives on achieving financial sustainability

Biovac is not driven to maximise net profit after tax. In many years it has shown a negative profit and not issued a single dividend – the focus is on managing cash flow and expenses to remain solvent. As the shareholders are all aligned on the goal of delivering long term value in the form of high quality vaccine products made in Africa, long term strategy has not been sacrificed for short term gains.

- Morena Makhoana – Biovac, South Africa, Episode 3 (paraphrased)

After years of abiding by a philosophy of maintaining low levels of debt and ploughing profits back into its facility, Serum was able to begin to build its profits by building a portfolio of complementary income streams. It created a portfolio of products where new products were coming online to replace older products just as their profitability and demand quantities began to decline. This created an evergreen approach to ensure steadily increasing profits and consistently high facility utilisation, fuelling its ability to create the next generation of products.

- Rajeev Dhere – Serum Institute of India, India, Episode 5 (paraphrased)

Podcast Sections:

Episode 3, Sections 19-20: Morena Makhoana and Patrick Tippoo
Episode 5, Sections 7, 10: Rajeev Dhere

4. Conclusion

The vaccine industry today is almost unrecognisable from that of 50 years ago. As the sector and organisations within it have matured, the early opportunities supplying emerging markets have shifted and morphed into something quite different. Nevertheless, to chart a course going forward, it is essential to understand the vaccine landscape of the past and how it has changed over time.

There is simply no substitute for experience, and building deep experience for any new vaccine manufacturer will take decades, not months or years. The first step is to learn as much as possible from those who have successfully navigated, and continue to navigate, the industry and its continually changing landscape. The detailed stories of three of the most successful developing country vaccine manufacturers – Serum Institute, Bio-Manguinhos and Biovac – serve here as an inspiration and example to others.

The previous three white papers in this series gave an overview of the unique characteristics of the vaccine industry, then began to map the initial steps of conducting a feasibility study. This document, thanks to the time and expertise of the podcast guests, is able to expand on critical aspects of acquiring and managing key resources such as technology, talent and capital. It is highly recommended that those who are interested in starting or growing a vaccine manufacturing firm listen to these podcasts in full.

Appendix: Show Notes

Episode 1: Barry Garfinkle – Formerly of Merck and Co. Inc/MSD, USA

Section	Timestamp	Topic
1	0:55	Barry's view of the changes in the vaccines industry over the past few decades
2	3:15	The evolution of immunisation programs and debunking of common myths relating to vaccine safety
3	7:45	Transformation of the global vaccine industry through the 80s and 90s
4	13:05	Discussion of differences in vaccination policy between countries and how that has changed over time
5	16:10	Vaccines and biologics becoming blockbusters for the first time
6	21:10	The rise of the developing country manufacturers
7	25:20	Merck's role in starting Hilleman Labs and their goal of bringing new technology to developing countries
8	28:15	Example of a tech transfer deal between Merck and China for Hepatitis B in the early 90s
9	33:40	How the early tech transfers compare to some that are being done today
10	35:20	The importance of ensuring a vaccine originator's IP will be protected and methods of assuring that
11	39:40	Why there is no such thing as a generic vaccine and why vaccines are so difficult to transfer from one manufacturing facility to another compared to pharmaceuticals
12	50:25	Barry's thoughts on reverse integration and why technology transfers usually take so long (even for transfers within a company)
13	55:45	Differences between pharmaceutical and vaccine products and their manufacturing
14	1:05:10	Barry's advice to a company considering entering the vaccine manufacturing industry
15	1:13:05	Therapeutic areas Barry's work is now focused on: Malaria, Antibiotic Resistance and Muscular Dystrophy
16	1:18:05	Barry's opinion on the future of the biotech and vaccines industry
17	1:22:35	Types of work Barry is looking to do in the future
18	1:24:25	Why low wages in a country don't necessarily equal a low cost manufacturing bases and more things to consider with respect to the production cost of vaccines
19	1:33:05	Parting thoughts on the absolute need to ensure IP security and quality of the vaccines produced anywhere

Bio

Barry has held three different VP roles at Merck: VP biological sciences and strategy, VP Vaccine Technology and Engineering, VP vaccine quality operations. He has extensive experience in the development and manufacture of vaccines and biologics with a focus on facility design, validation, startup and operation (technical operations, regulatory affairs and quality) Currently Principal at Barry Garfinkle and Associates consulting, LLC.

Useful links

Merck & Co. Inc (officially known as MSD outside of the US and Canada) – www.merck.com

Hilleman Laboratories - www.hillemanlabs.org

Arrevus - https://arrevus.com/

UNIDO Vaccines Publications:

https://www.unido.org/resources-publications-advancing-economic-competitiveness-investment-technology-and-sme-development/project-publications-pharmaceutical-sector

Episode 2: Akira Homma – Bio-Manguinhos, Brazil

Section	Timestamp	Topic
1	2:05	Origins of Bio-Manguinhos and evolution of publicly owned vaccine production in Latin America
2	15:20	Impact of globalised trade in vaccines on publicly owned vaccine manufacturers in Latin America and win/win tech transfer deals between governments and multinationals
3	27:00	What is considered commercial production scale and the benefits of operating at this level
4	35:00	Brazil's self-sufficiency program and the effect of improving quality standards and requirements
5	50:00	The financing model Bio-Manguinhos is using for their new production facility
6	52:55	Brazil's current vaccine manufacturing capacity in terms of fulfilling local needs of the Brazilian vaccination program
7	55:00	Bio-Manguinhos' use of reverse integration and the benefits gained from it
8	58:15	Bio-Manguinho's mix of technology transfers and in house research to improve efficiencies and follow on developments to fuel their growth
9	1:01:15	Overview of a typical reverse integration project and interactions with the partner
10	1:08:15	Origins of Developing Country Vaccine Manufacturers Network
11	1:15:00	Advice for a new entrant into the vaccines industry and the need for strong sustained support from government
12	1:21:30	Bio-Manguinhos' outlook on providing technology transfers or partnerships with other developing country vaccine manufacturers
13	1:23:15	How Bio-Manguinhos built their human capacity and talent
14	1:25:45	Advice on finding your niche as a new entrant to the industry
15	1:31:00	Where Bio-Manguinhos sources their equipment
16	1:32:15	Closing thoughts

Bio

In 1976, Akira was designated Director of Bio-Manguinhos Institute and remained in this position until 1989 when he was assigned President of Fiocruz. In 1990, was assigned Coordinator of the National Self-Sufficiency Program on Immunobiological of the Ministry of Health. In the period of 1991-1997 he served as the Regional Advisor for Vaccines for the Americas for PAHO. He returned to Fiocruz and was assigned Vice-President of Technology of Fiocruz. In 2001 he became again Director of Bio-Manguinhos Institute where remained until 2009. Today, he is Senior Scientific Adviser of Bio-Manguinhos Institute. In the past he was instrumental in the creation of DCVMN, has been on the executive board of GAVI and during his two tenures as the Director of Bio-manguinhos, he presided over the majority of their tech transfers.

Links

Bio-Manguinhos/Fio Cruz – www.bio.fiocruz.br

Developing Country Vaccine Manufacturers Network – www.DCVMN.org

Contact information: www.dcvmn.org/-Contact-

UNIDO Vaccines Publications:

https://www.unido.org/resources-publications-advancing-economic-competitiveness-investment-technology-and-sme-development/project-publications-pharmaceutical-sector

Episode 3: Morena Makhoana and Patrick Tippoo – Biovac, South Africa

Section	Timestamp	Topic
1	1:15	Story of the initial formation of Biovac
2	3:50	State of the South African vaccines industry when Biovac was formed in 2003
3	5:45	Starting up Biovac in 2003
4	8:00	Biovac's early product development work
5	9:35	Biovac's journey to re-establish vaccine manufacturing in South Africa (use of backwards integration with Sanofi and Pfizer and product development work with PATH)
6	13:50	Importance of government policy coherence for a local manufacturer
7	17:45	Example of how government policy incoherence created challenges for the Pertussis vaccine
8	19:50	Story of Measbio and the need for regulatory flexibility
9	24:25	Benefits of using a backwards integration approach
10	29:40	Importance of building a track record in R&D and product development
11	33:45	Example of how product development failures can lead to success
12	45:15	Biovac's strategic decision to pursue both tech transfers and develop their own products
13	51:20	What attracted Pfizer and Sanofi to localize production in South Africa
14	55:25	Are American and European multinationals still looking to do vaccine production tech transfers and what opportunities there may be for others in the industry
15	59:15	Where Biovac sourced its equipment and facility designers
16	1:02:00	Finding qualified personnel and staff training
17	1:07:35	Challenge of getting technical support in countries without an extensive industry
18	1:09:40	Thoughts on cost and duration to build vaccine manufacturing facilities
19	1:13:35	Biovac's perspective concerning the financial viability of a manufacturing facility
20	1:16:55	What advice would you give to a new entrant to the vaccine manufacturing industry
21	1:20:35	Overview of the African Vaccine Manufacturing Initiative (AVMI) and the importance of increasing the manufacturing of vaccines in Africa
22	1:24:10	Importance of Securing a market for your product
23	1:30:15	The future of Biovac: Exports, expanding the product portfolio and product development partnerships

Bio

Morena joined Biovac in 2004 and holds the role of Chief Executive Officer. He is a member of the Board and the Biovac Executive team. Prior to his CEO role at Biovac he held the role of Deputy CEO and prior to that of Medical Affairs Director for Biovac and Litha Healthcare Group.

He serves on a number of committees within the vaccine industry and serves as a board member of other healthcare and non-healthcare companies.

Patrick Tippoo has more than 30 years experience in the vaccine manufacturing industry. His responsibilities at Biovac have included product development, strategic alliance partnering, international relations, projects and business development. Currently as Head of Science and Innovation he is focused on growing Biovac's product development capability and scientific & technical capacity as a centre of excellence for vaccine development and manufacture in Africa. He is a founding member of the African Vaccine Manufacturing Initiative (AVMI) and has also served as a member of the Executive Committee and the Grant Advisory Committee of the Developing Country Vaccine Manufacturers' Network (DCVMN) since 2014.

Links

African Vaccine Manufacturing Initiative – www.AVMI-Africa.org

Developing Country Vaccine Manufacturers Network – www.DCVMN.org

UNIDO Vaccines Publications:

https://www.unido.org/resources-publications-advancing-economic-competitiveness-investment-technology-and-sme-development/project-publications-pharmaceutical-sector

Episode 4: Gerd Zettlemeissl – Formerly of Chiron Behring and Intercell, Austria

Section	Timestamp	Topic
1	0:15	A perspective of how the industry has changed over the last 30-35 years
2	4:40	Drivers for the rise of the Indian manufacturers over the last 3 to 4 decades
3	7:20	Interactions between western and developing country manufacturers in the past, present and future
4	14:10	The importance of having the right human resources in place to develop the ability to manufacture vaccines and how some companies have built this local expertise in the past
5	21:00	An introduction to the Coalition for Epidemic Preparedness Innovations (CEPI)
6	24:25	The potential for Ebola vaccine manufacturing in Africa
7	26:35	What is the incentive for large western multinationals to develop vaccines for developing countries and how they are doing it
8	33:15	The role of small innovative biotech firms in developing new vaccines and the options available to them to bring those new products to market
9	36:30	Example of how Valneva created their own manufacturing capacity in order to bring their product to market by themselves
10	41:35	How do new entrants to the vaccine industry who haven't developed their own product get the appropriate know-how?
11	44:30	Some considerations when planning a technology transfer
12	47:10	Thoughts on what things governments should do in order to nurture the development of a vaccine manufacturing industry in their country
13	52:30	Various boards and projects Gerd is working on now
14	59:00	Closing remarks

Bio

Gerd is the former CEO of the Austrian-based biotechnology company Valneva SE (formerly Intercell AG), and is an accomplished vaccine expert and biopharmaceutical business executive. Dr. Zettlmeissl has more than 25 years of scientific and leadership experience in the biopharmaceutical industry. He currently serves as representative of the Board of Directors of several non-profit organizations and biotech companies.

Until early 2015 he was chairman of GlycoVaxyn (Switzerland), an innovative vaccine company acquired by GlaxoSmithKline. While at Intercell AG from 2001 to 2011, he built the company from a private start up venture to a publicly listed international organisation with more than 400 employees. As CEO, he secured regulatory approval for and led the launch of an improved Japanese Encephalitis vaccine, and oversaw efforts to build and advance a broad based development portfolio of vaccines.

Prior to joining Intercell, Dr. Zettlmeissl held senior management roles at Chiron Corp and Behringwerke AG. In 2010, he was named Vaccine Biotech CEO of the Year at the World Vaccine Congress.

Links

Coalition for Epidemic Preparedness Innovations (CEPI) – www.cepi.net
Hilleman Laboratories - www.hillemanlabs.org
GSK Vaccines Institute for Global Health - https://www.gsk.it/chi-siamo/gsk-vaccines-institute-for-global-health/ (text in Italian)
Valneva - http://www.valneva.com/en/
Aeras - http://www.aeras.org/
Themis - https://www.themisbio.com/
ASIT Biotech - https://www.asitbiotech.com/
Medigene AG - https://www.medigene.com/home/
Biological E - http://www.biologicale.com/
Curevac - https://www.curevac.com/
Developing Country Vaccine Manufacturers Network – www.DCVMN.org

UNIDO Vaccines Publications:

https://www.unido.org/resources-publications-advancing-economic-competitiveness-investment-technology-and-sme-development/project-publications-pharmaceutical-sector

Episode 5: Rajeev Dhere – Serum Institute of India, India

Section	Timestamp	Topic
1	1:05	An overview of SII's origins; from horse breeder to world's largest producer of vaccines by doses
2	10:05	SII's unique approach to the business of vaccines which enabled them to be financially viable while selling very affordable vaccines
3	12:50	A visionary's risk based approach to building the right amount of production capacity and infrastructure
4	16:44	The importance of increasing process efficiency and production yields
5	17:35	The growth of the measles vaccine market - an example of how SII's philosophy of infrastructure utilisation and planning coupled with the ability to spot a trend fueled their growth
6	21:05	The rationale behind SII's conscious decision to focus on markets outside of countries such as the US and Europe
7	25:15	Using a portfolio of various products and the development of next generation products to ensure financial viability of the company
8	27:35	SII's approach to attracting, developing and retaining the right personnel
9	33:35	Any regrets on not doing a technology transfer with an established large multinational BioPharma firm?
10	36:15	Advice to a new entrant to the vaccine manufacturing industry: use of reverse integration, ensure you have a market and decide if you want to be a developer or a manufacture (doing both is very difficult)
11	39:45	Thoughts on purchasing and maintaining equipment
12	42:50	The types of problems government can fix through policy and the need to recognise it doesn't make sense for every country to make vaccines
13	46:05	Finding personnel for a new vaccine manufacturer in a location without an existing industry
14	48:00	Thoughts on how a new industry entrant can find a market niche
15	52:40	SII's growing role as a technology transfer partner and the role of other multinationals here
16	55:45	SII's future endeavors: new acquisitions, products and markets
17	1:02:50	Types of technologies or collaborations SII is looking for now

Bio

Rajeev is an Executive Director and Board Member at Serum Institute, has 41 years of Industrial experience. After starting his career in vet vaccines, he moved to Serum Institute in 1987. One of his first projects was the development and scale-up of production of the Measles, Mumps and Rubella group of vaccines. This vaccine grew to become Serum's mainstay product, making them the largest producer of Measles containing vaccines in the world (Avg. 500 million doses/year). Since then, he has headed the teams working on Influenza, Rotavirus, Rabies vaccines that have been licensed. He currently heads the R&D groups for Meningococcal, Pneumococcal and Dengue vaccines. Apart from vaccines, he heads teams working on Monoclonal Antibodies for Rabies (licensed) and Dengue. He also wears the hat of being the technical ombudsman for the company producing more than a billion doses of vaccine annually.

Links

Serum Institute of India : http://www.seruminstitute.com/

UNIDO Vaccines Publications:

https://www.unido.org/resources-publications-advancing-economic-competitiveness-investment-technology-and-sme-development/project-publications-pharmaceutical-sector

Episode 6: Ralf Clemens – Formerly of GSK, Novartis and Takeda

Section	Timestamp	Topic
1	0:55	Ralf's background and how he came into the vaccines industry
2	5:15	Ralf's perspective on how the industry has changed over the course of his career
3	9:30	Story of how GSK was able to focus on both the rich world and developing country needs with the development and launch of Rotavirus and DTPa and DTPw combination vaccines.
4	13:20	How GSK worked closely with PAHO to develop DTPw combination that would be affordable yet still made business sense for GSK's
5	15:45	GSK's use of technology transfers as another way to build capacity and deliver much needed vaccines to low and middle income countries
6	17:15	Ralf's imperatives for a successful tech transfer: continuous support and training from company sending the technology, building of trust, use of reverse integration and win-win business proposal.
7*	22:30	How to prove your product is safe, immunogenic and protective.
8*	35:35	How to show a product will work in a local population who wasn't covered by the original clinical trials
9*	37:30	After a technology transfer, how to prove the product made in the new facility works as well as the original product and how well that product works when administered along with the other products already in the local vaccination schedule
10*	43:15	Which phases in a reverse integration technology transfer will trigger clinical trials?
11*	45:25	Why is a well functioning local regulator required to receive WHO Pre-Qualification and why isn't it all being done remotely from Geneva?
12*	53:10	Why does WHO Pre-Qualification take so long?
13	56:25	Takeda's use of contract manufacturing organizations to launch new products to defray capital investment on a product early in its lifecycle.
14	1:00:00	University of Sienna's Institute for Global Health training course for those entering the vaccines industry as well as the Gates Foundation's plan to launch a similar course for the manufacturing of vaccines.
15	1:04:45	Ralf's involvement with the work the Gates Foundation is doing to eradicate Polio as well as development of vaccines for Tuberculosis, Respiratory Syncytial Virus and Universal Flu.
16	1:07:25	Ralf's position on IVI's board of trustees and his work with CEPI's development of MERS, Lassa and Nipa vaccines and a platform to protect against an outbreak of an unknown disease.

Section	Timestamp	Topic
17	1:09:15	Who will be the most likely companies to produce products being developed through CEPI's work
18	1:12:30	Advice to those companies looking to get started or grow in the vaccines industry: well trained employees across all disciplines, need to survive financially for the first 3-5 years until your product is commercially launched, secure your market early and use demand volumes as an indicator of what type of production will be viable locally (packaging, form/fill, bulk antigen).
19	1:16:15	GHIT's funding for development of pre-clinical and clinical work for solutions to neglected diseases
20	1:18:00	A recap of what Ralf feels is most important for industry newcomers: hire well trained people, engage regulators early and ensure you have both the capabilities to manufacture the product as well as carry out the clinical trials for the products.

* Includes 'Crash course in Clinical Trials and Product Registration Requirements' – sections 7-12

Bio

Ralf Clemens, MD PhD, is a long-time leader in vaccine industry and academia. He is currently serving as Advisor to the Bill & Melinda Gates Foundation and is Member/ Chair of various scientific and management boards including IVI, GHIT, CEPI), AREF as well as Curevac AG, Germany, and Valneva SE, France. Prior to this he was Head Global Vaccines Development at GSK, Novartis and Takeda Vaccines. At GSK Vaccines he was additionally in charge of developing country business strategies and technology transfers to developing country manufacturers. During his almost 30 years in vaccine industry he developed and brought to licensure over 25 different vaccines. Ralf graduated in medicine from the University of Mainz, Germany, and he holds an executive degree in Management from the Wharton Business School. Ralf has more than 180 publications and given more than 250 scientific presentations mainly on vaccines, immunization and pharmaceutical development.

Links

Coalition for Epidemic Preparedness Innovations (CEPI): www.cepi.net
University of Siena's Institute for Global Health: https://ifgh.org/
Bill and Melinda Gates Foundation: https://www.gatesfoundation.org/
International Vaccines Institute (IVI): https://www.ivi.int/
Global Health Innovation Technology Fund (GHIT): https://www.ghitfund.org/en

UNIDO Vaccines Publications:

https://www.unido.org/resources-publications-advancing-economic-competitiveness-investment-technology-and-sme-development/project-publications-pharmaceutical-sector

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