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WHITE PAPER

Establishing Manufacturing Capabilities for Human Vaccines

Key cost drivers and factors to consider when planning the
establishment of a vaccine production facility



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Global UNIDO Project:
Strengthening the local production
of essential medicines in developing countries
through advisory and capacity building support

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Executive Summary

This white paper aims to give an introduction to the manufacturing of human vaccines, both providing information about the vaccine market and summarizing the necessary investment costs, project timelines and other factors to take into consideration.

The first key point is that project costs and timelines can be much greater than newcomers to the industry initially expect - tens to hundreds of millions of dollars and 5-10 years or more – as there are myriad extra costs and factors causing timeline extensions not mentioned in popular literature or sales presentations.

Secondly, there are a number of key factors that need to be aligned in order to deliver a successful project. These include finding a suitable market niche and purchaser, finding a suitable technology transfer partner, hiring skilled workers, consultants and specialized firms, and building GMP compliant facilities as well as coordinating all aspects of the project.

The main document summarizes these points, and is supported by three appendices. Appendix 1 gives examples of costs and timelines for both a real and a theoretical facility. Appendix 2 contains an expanded list of factors to consider. Appendix 3 contains a glossary of key terms.

By the end of this document the reader will have a good idea of key considerations and factors to be taken into account when considering the feasibility of establishing human vaccine manufacturing capabilities and what key next steps to take.

1. Introduction

This white paper aims to serve as a primer for entities that are new to human vaccine manufacturing and interested in developing production capacity for the first time in a new location. This primer does not cover developing a new vaccine from scratch, but rather building a facility to produce existing vaccines. **Bold** terms are further explained in the Glossary.

First, new producers must understand that the global vaccine market is unique. The vast majority of the global sales volume is purchased on a tender basis by large governmental and non-governmental organizations rather than on the private market by individuals. Next, this guide gives an overview of the different steps of vaccine production and the key aspects a new producer should understand.

Most importantly, this primer aims to give an accurate representation of the challenges within the sector so potential producers can accurately determine if vaccine manufacturing is right for them. Compared to other products and even pharmaceuticals, vaccine manufacturing faces relatively high costs, long timelines and significant barriers to entry.

Finally, this primer indicates some next steps potential producers should take as they hone their business cases and begin their concept level feasibility assessments.

The white paper forms part of a series of publications that have been produced in collaboration between UNIDO, WHO and AVMI. Currently, two other documents in this series can also be consulted. They are:

VMPA Study: Vaccine Manufacturing and Procurement in Africa (2017). This provides a comprehensive overview and assessment of the case for vaccine manufacturing on the African continent and covers four core areas: the vaccine market, vaccine procurement, issues related to the manufacturing capability itself and lastly financing considerations.

Commercialising vaccines: A methodology to identify potential market opportunities and conduct outline assessments (2017). This paper outlines a process for conducting an initial evaluation to determine the financial viability of setting up a new facility to supply vaccines to a particular market using real market data; in this instance South Africa was used as a country case study.

This white paper is intended to be a basic introduction to the complex world of vaccine manufacturing.

It serves as a primer, outlining key factors and considerations for those looking to establish their first vaccine manufacturing facility.

Summary messages, such as these, are provided at regular intervals throughout the paper.

2. Understanding the market

The vaccine market is distinct from any other market sector. Procurement generally happens on local, regional or national levels on a large scale. The required number of doses in a country is tied to the size of the birth cohort and number of doses per vaccine. As vaccines are recommended for an entire birth cohort, this sets the upper limit of demand for that country. However, a government or NGO vaccination program may not cover the entire cohort.

This fixed demand based on cohort size means a country or NGO might request 20 million doses every year over 5 years, with no interest in buying any more or less than the stated doses. In a case where production capacity is allocated for a tender that is delayed or awarded to another company, there is limited opportunity for a newcomer to sell excess stock through private sales channels as explained below.

Global

Most procurement on a global level is conducted through **UNICEF**, purchasing on behalf of donor organizations such as **GAVI**. GAVI and similar organizations fund vaccine purchases on behalf of the poorest countries. Countries graduate out of this support as they become richer. UNICEF prices are available online, and are generally accepted as reflecting a price point that is either close to the cost of goods (**COG**) or COG plus a small margin for most products. Selling to UNICEF requires WHO Prequalification, which is typically a high barrier for a newcomer. Prequalification is an assessment by WHO of the product to ensure that it is safe, appropriate and meets stringent quality standards. Manufacturers wishing to enter this large market need to meet the prequalification criteria. Additionally, their country's National Regulatory Authority needs to have reached a specific level of maturity/accreditation.

Regional

Regional alliances are made up of several countries, the largest of which is the Pan American Health Organization (**PAHO**) covering the Americas and Caribbean. PAHO prices, depicted as a **Weighted Average Price**, are also freely available online. Generally higher than UNICEF prices, PAHO prices are a good guide to vaccine prices in medium-income countries across the world. Selling to PAHO also requires WHO Prequalification.

National

Countries that are not part of an alliance must negotiate individually to set purchasing prices and volumes for any national vaccination programs they may have. While individual countries' vaccine prices may be hard to verify with publicly available information, the PAHO prices are a good estimate for medium-income countries, with wealthier or poorer countries paying proportionally more or less. Regulation to enter a country's market depends heavily on the individual country.

Private

Vaccines bought privately, in both the developed and developing world, have the highest margins. Vaccines bought on the private market are either paid for directly by the patient or through a private health insurance program. As such, competition is fierce; multinationals with good quality and safety track records and strong brands are often the most successful here. A newcomer wielding low brand awareness and an unknown track record may find it difficult to succeed in this arena.

Market circumstances subject to change

Many deals to localize some portion of vaccine production come from the agreement of a government to buy a sizeable amount of vaccines at a relatively high price, exclusively from a local producer and their **technology transfer** partner.

As it takes several years to get a facility ready to start production, by the time the local facility is up and running the government may have decided to terminate the exclusivity of the purchasing program or change the price it will buy at due to a host of reasons including a change of power, budget cuts or the arrival of cheaper competition on the open market.

The vaccine market is not a free and open market and in fact is very different from typical pharmaceutical markets¹.

This has significant bearing on the viability of vaccine production and therefore needs to be taken into account during the initial phase of a project's feasibility analysis.

3. Steps of Vaccine Manufacturing Production

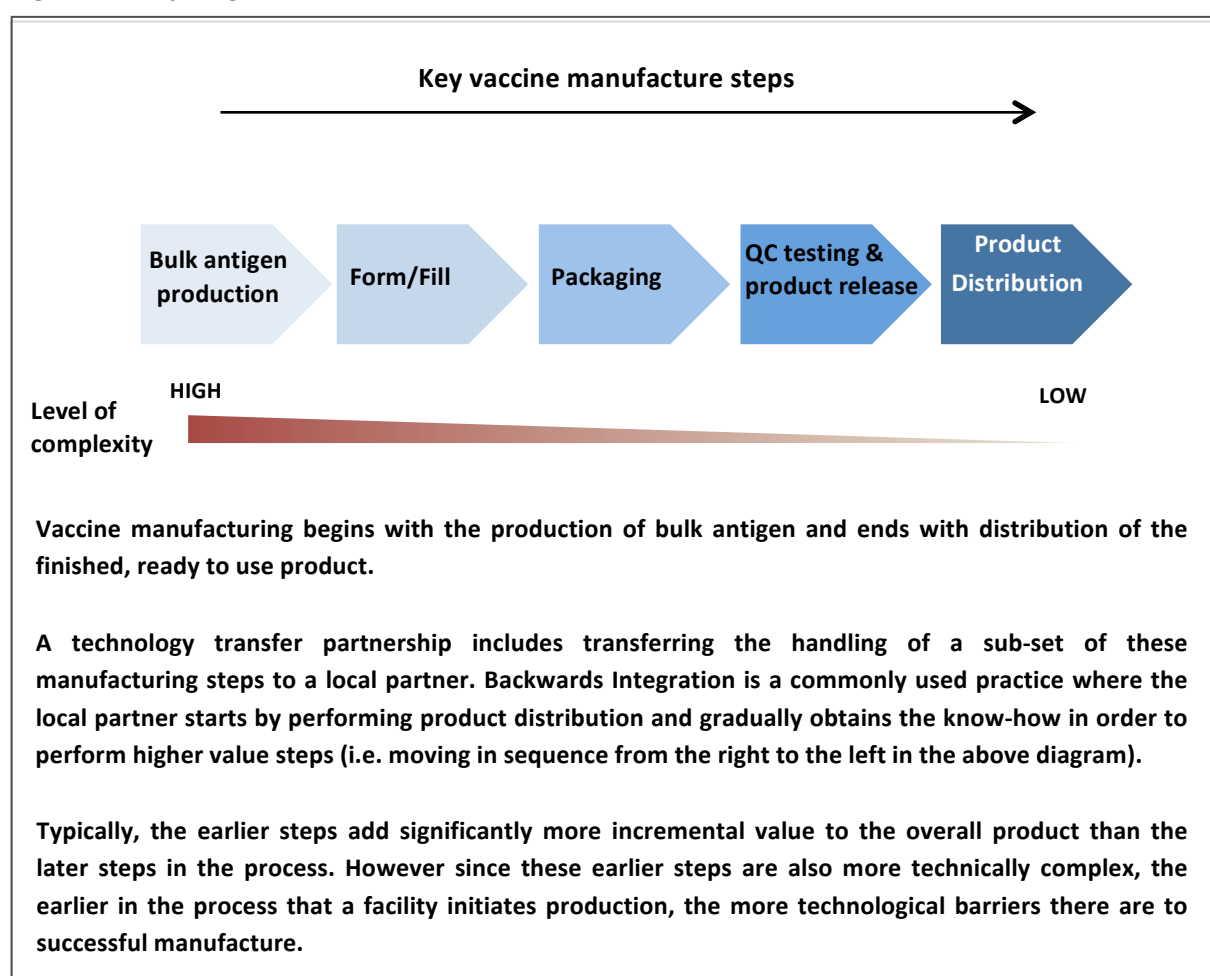
Each stage of the vaccine manufacturing process requires significant investment and know-how, with packaging and distribution needing the least, and bulk antigen production the most. In general, the manufacturing process for vaccines is much more complex than it is for pharmaceuticals and necessitates the use of highly specialized facilities and equipment. Unlike pharmaceutical production, which requires a series of relatively well-understood chemical reactions and physical manipulations, vaccine production involves complicated biological synthesis steps that are often not fully understood. Instead, vaccine production often relies on the ability to demonstrate that a certain production process, which has yielded a product shown to be efficacious through clinical trials, can be repeatedly followed and controlled. Furthermore, while there are sterile

¹ For more information, please see chapter 2, Vaccine Market Dynamics, in "VMPA Study: Vaccine Manufacturing and Procurement in Africa", 2017.

pharmaceutical products, many of the sterilization methods used in the manufacturing process, for example, sterilization of the final product in a vial or ampoule via autoclave, are not possible for vaccines. Finding companies willing to share their know-how with a newcomer can be an added challenge as most will be competitors.

With a **technology transfer**, a current producer teaches one or more of the steps to a local producer, or sells the local producer partially completed vaccine for them to finish. Many technology transfers are structured via **backwards integration** - that is, the current producer sells a partially completed product to the local producer who then handles the end of the production process (usually starting with distribution or packaging). As they gain experience, the local producer can move back along the value chain in a stepwise and controlled manner to the more difficult processes.

Figure 1: Key Stages in the Manufacture of Vaccines



Bulk Antigen Production

The first step in the process is to produce bulk antigen, the substance that induces the immune response in the body. There are several types of **antigen**, with distinct attributes and characteristics. Due to differences between vaccines, they cannot all be produced with the same method or with the same equipment. Due to safety regulations, some cannot be produced in the same facility.

Bulk antigen production is the most cost-intensive step in the chain of processes, and the most difficult, especially where mammalian tissue culture is used as the production medium. Table 1 depicts how the choice of an expression system – the initial method for production of the antigen – can affect everything from product cost and facility size to the ease of gaining regulatory approval.

Table 1: Comparison of the four main expression systems for bulk antigen production

	Low		High	
Speed	Mammalian	BEVS/insect cell	Yeast	Bacteria
Cost	Bacteria	Yeast	BEVS/insect cell	Mammalian
Typical yield	Mammalian	BEVS/insect cell	Bacteria	Yeast
Post-translational modification	Bacteria	Yeast	BEVS/insect cell	Mammalian
Regulatory approval	BEVS/insect cell	Yeast	Bacteria	Mammalian

The expression systems used to produce antigen use bacterial cells, yeast cells, mammalian cells, or insect cells combined with a baculovirus expression system (BEVS).

A number of factors are important to consider when choosing an appropriate expression system, including speed of production, cost, yield, ease of introducing post translation modifications (some antigens require further biochemical modification after their initial synthesis in the chosen expression system, in order to stimulate the required immune response), and regulatory approval.

The table indicates, for each of the factors shown, a relative ranking between the different systems. It can be seen that no single expression system can be considered as an overall ‘best option’ since each one has certain advantages and disadvantages. In addition, not all expression systems can be used to produce all antigens so the options available also depend on the particular vaccine to be manufactured.

Next, the antigen is harvested and isolated from the materials used to grow it. The antigen is isolated via purification processes usually involving centrifugation, chromatography and/or filtration resulting in purified antigen; the exact process will vary between vaccines.

Vaccines can be monovalent (containing a single antigen, protecting against a single strain or microorganism) or multivalent/polyvalent (containing two or more antigens, protecting against two or more strains or microorganisms). Producing multiple types of antigen can require much higher initial costs and larger facilities than producing a single type. Different production methods also require different infrastructure which can have very significant impact on the associated infrastructure costs.

Formulation/Fill (Form/Fill)

The purified antigen (or drug substance) then undergoes formulation: it may be combined with **adjuvants** to enhance immune responses in the body, stabilizers to ensure the product remains potent until it is administered and, in the case of multi-dose vials, preservatives to ensure sterility over the entire course of administration to multiple patients.

This finally formulated bulk vaccine (or drug product) is then filled into vials, plastic tubes, ampoules or syringes. Some vaccines which are not stable as liquids at room temperatures are **lyophilized** (freeze-dried) at this stage, adding an extra layer of cost/complexity. Lyophilized product also requires the vaccine to be distributed with the appropriate diluent so it can be reconstituted later, prior to administration.

Finally, each vial must be visually inspected to ensure its physical integrity and that the vaccine is free of noticeable foreign particles and there are no issues with the product's appearance. Each of these form/fill processes must be carried out under strict temperature and sterility controls in specially designed **clean rooms**.

Because the formulation and fill process is broadly similar for most vaccines, multiple types of vaccine can often be formulated and filled in the same facility. However, there are still restrictions regarding which vaccines can share form/fill facilities for safety reasons. This is further explored in both Appendices 1 and 2.

Packaging, Cold Chain and Distribution

The filled and inspected vials must then be packaged, undergo final quality control release testing (the last step of the quality control process, since QC tests occur throughout the above processes as well) and be distributed to doctors and hospitals before finally being administered to patients. The quality control tests include analysing a sample of the finished product to ensure it has the required potency, purity, concentration of key ingredients and sterility. The range and types of tests as well as their level of complexity will vary between vaccines.

Temperature must be strictly controlled and monitored from manufacturing all the way through to administration to the patient, a concept referred to as a **cold chain**. Most liquid vaccines must be kept refrigerated (typically between 2 - 8°C) for each step. Lyophilized vaccines are typically stored frozen at -20°C or lower making for a more expensive **cold chain**.

Product Registration and Clinical Trials

The product registration requirements vary worldwide and thus should be investigated on a product-by-product basis for a given regulatory agency. A critical feature is that unlike drugs, where a copy of an existing drug can be approved without clinical trials (generic drugs), in most cases vaccines require the fully fledged phase I, II and III clinical trials process to demonstrate safety, immunogenicity and efficacy. This is the case even when the vaccine is a copy of an existing product.

The time required to conduct these studies, as well as their cost, can be a major barrier for new entrants to this field.

Currently roughly 30-40 countries manufacture vaccines. Countries with experience in vaccine manufacturing are more likely (but not guaranteed) to have regulations in line with globally recognized standards, such as those recommended by the US, EU or WHO.

Regulators from countries new to vaccine manufacturing are less likely to be familiar with the regulations specific to registering a transferred vaccine (essentially a new product) and new vaccine production sites. Sometimes, this can result in either an overly permissive environment or one where producers are held too strictly to the letter of a regulation instead of being able to scientifically demonstrate they effectively meet its intent.

Vaccine manufacture involves the production of purified antigen which is then filled along with other ingredients into sterile containers under clean room conditions.

The vaccine is then packed, tested and distributed to doctors and hospitals all under strict temperature control and monitoring.

A technology transfer occurs when an incumbent vaccine producer teaches a local firm how to perform a portion of the manufacturing steps required to make a vaccine.

The effort required to register this locally produced vaccine in its target markets will vary from product to product and country to country but may require additional clinical trials in some cases.

This additional scope of work may add a significant amount of cost and time to a project.

4. Facility Design Considerations

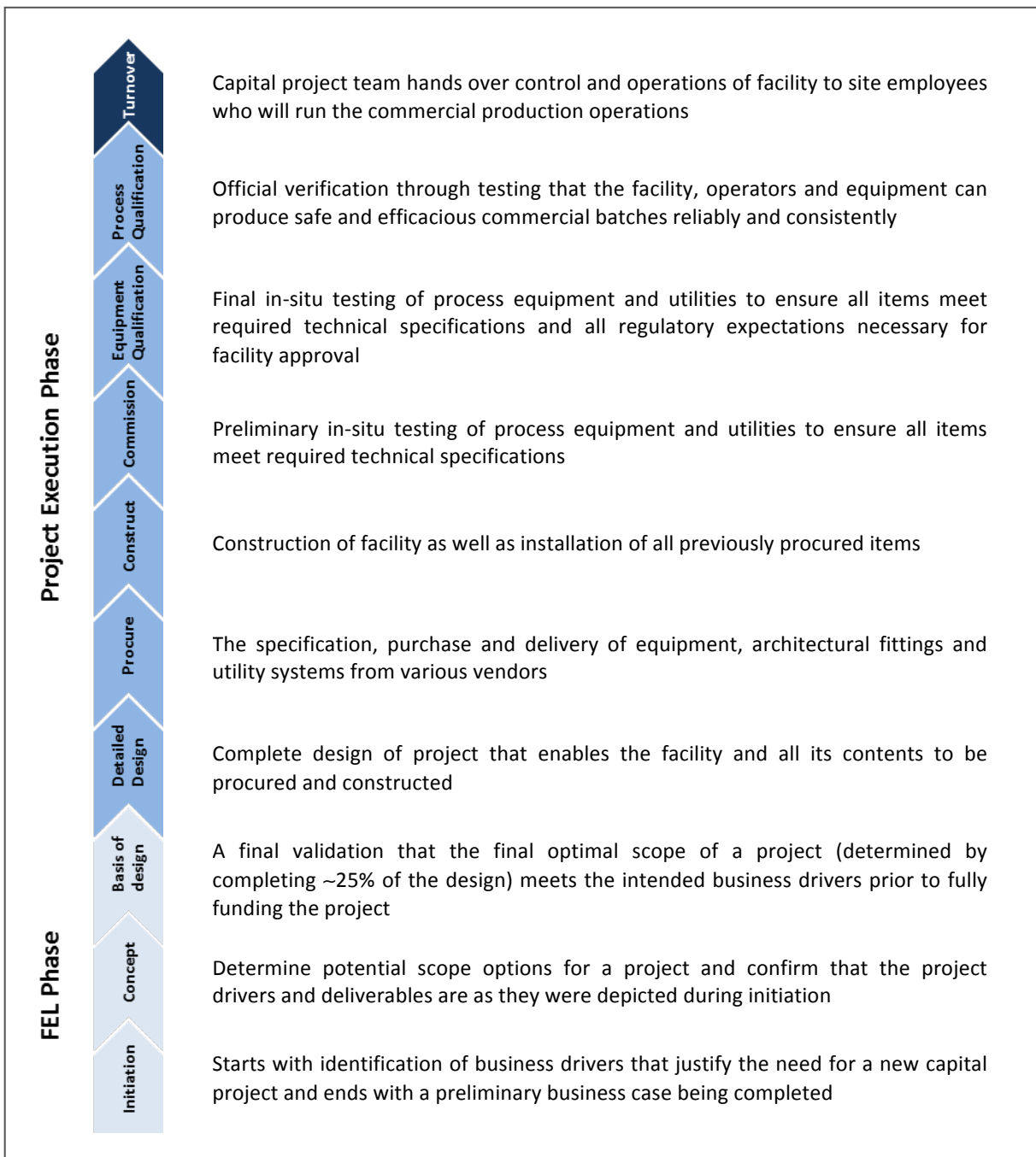
When considering the commercial viability of vaccine manufacture, key considerations include:

1. Facility type and scope
2. Production demand forecast

The first has significant bearing on the time it will take to reach commercial output and therefore the number of years that investment is required before moving into a positive cash flow situation. The second has a major impact on the ongoing cost of manufacture once the facility is fully operational. It alone can impact the ability to repay initial investment costs relating to facility design and construction since the initial level of profitability is a key determinant of the rate at which upfront facility design and construction costs can be repaid.

One of the most common mistakes is for companies to rush ahead and begin building a facility without fully completing the earlier planning steps or **Front End Loading (FEL)**. In order to conduct a successful FEL, both of the points above need to be explored and integrated together to determine a project’s financial feasibility. According to industry benchmarking, conducting a rigorous FEL phase has been shown to decrease project costs, irrespective of project size, by an average of up to 20%². As the **FEL** phase progresses and the market demand and project scope become better defined, it is crucial to continuously verify that the business case remains financially viable. A large percentage of projects often do not make it through the full **FEL** phase due to lack of financial viability.

Figure 2: New Facility Capital Project: Stage-by-Stage Breakdown



² http://www.pwc.com.au/industry/energy-utilities-mining/assets/miningcapitalprojects_nov08.pdf

Due to the number of variables, it is not possible to give an accurate cost for each type of facility. The type of vaccine produced, facility location, construction methodology, type of equipment, regulatory requirements and production volume can all have significant effects on the final cost.

This document examines the feasibility of commercial-scale facilities. Lab-sized facilities follow a similar process but on a totally different scale which will not be covered here.

The planning and building process shown below covers the work necessary to design, build and receive regulatory approval for a facility. However, new products being made in this facility may require additional testing in order for the products themselves to gain regulatory approval. Please refer to the section on product registration and clinical trials for more details.

Scenario Analysis Summary

Scenario analyses examining four types of facility in detail can be found in Appendix 1; a summary is provided here. Using a matrix approach, the four examples fit into four quadrants according to production volume and whether the facility is fully integrated or form/fill only.

Table 2: Scenario Analysis: Using four examples to create a bounded design space that can be used to estimate cost, timeline and scope for a range of small vaccine facilities

Facility\Volume	Low (10m dose/year)	High (30m dose/year)
Fully integrated	<p>COST: ~\$30-65 Million TIME: 3.5 to 7 years</p> <p>Facility Details:</p> <ul style="list-style-type: none"> ● Modular facility ● Capable of making 10 Million doses per year ● 1-3 valent product ● Average antigen fermentation efficiency ● Single dose vials ● Bulk production using mostly single use technology (SUT) ● Form/fill with reusable stainless steel equipment ● Manual visual inspection and packaging ● Based on a theoretical facility 	<p>COST: ~\$105 to 225 Million TIME: 7-10 years</p> <p>Facility Details:</p> <ul style="list-style-type: none"> ● Stick built facility ● Capable of making 30 Million doses per year ● 4 valent product ● Bulk production using mostly Stainless steel ● Form/fill with reusable stainless steel equipment ● Based on real tech transfer using publically available information
Form-fill only	<p>COST: ~\$14-29 Million TIME: 2.5 to 5 years</p> <p>Facility Details:</p> <ul style="list-style-type: none"> ● Based on facility above, without bulk production ● Staff and facility size has been reduced ● Bulk antigen to be imported from technology transfer partner 	<p>COST: ~\$46 to 98 Million TIME: 5-7 years</p> <p>Facility Details:</p> <ul style="list-style-type: none"> ● Estimated cost if above facility did not have bulk production ● Bulk antigen to be imported from technology transfer partner

The costs in the matrix are given as **order of magnitude** estimates, that is, ranging from -30% to +50% of the estimated value. These costs depict the baseline cost to design, build and start up the facility but exclude other key costs which are further explained in the Appendix 1.

The project durations depicted represent the time from start of Basis of Design to the start of commercial production on a product with minimal local registration requirements and assumes clear and efficient decision-making, a well executed FEL phase, sufficient staffing and no significant delays.

More detailed cost and timeline breakdowns for these examples can be found in Appendix 1. These are provided as a guide only; there are dozens of variables involved, and this is no substitute for making a case-by-case calculation.

Low Volume vs High Volume

Production volume is determined by the capacity and utilization of the facility. A small-scale commercial facility, run at low to moderate utilization, can produce around 10m doses/year - enough for one product for a region, or two or three products for a country. It also leaves open the possibility of increasing production in the future. It is not typically financially viable for a single commercial facility to produce lower volumes than this as the underutilization of facilities and equipment is usually too inefficient in recouping the initial investment.

The upper range of a commercial facility for which most newcomers opt would produce around 30m doses/year. This higher capacity compared to the low volume facility would be due to higher utilization of the facility and/or larger capacity equipment. With a technology transfer, it may not be possible to go straight into high volume production since established producers can be wary of partnering with local producers without existing track records or whose large production scale would cannibalize their own sales.

The cost of a facility does not scale linearly with production capacity, even if all other facility costing variables remain constant. The filling equipment used in a 10m dose/year facility can be run twice as often to double production volume without doubling the required initial investment. Using multi dose vials also increases production volume for a given piece of filling equipment. Producing a polyvalent vaccine versus a monovalent one can severely change the output of your bulk antigen production on a dose per year basis. The estimated required production volume of a facility can be assessed from the birth cohort of the target country. Be aware that many vaccines require multiple doses to be administered to a patient in order to provide the required immunity.

Fully Integrated vs Formulation/Fill

While producing the bulk antigen (i.e. fully integrated facility) offers the greatest returns, a form/fill only facility can be built for roughly 35-45% of the initial investment of a fully integrated facility.

Advantages to the form/fill only or form/fill first approach typically include relatively fewer regulatory requirements, shorter project durations and the chance to build a track record with

partners and suppliers. It also offers flexibility - one form/fill facility can typically process more types of vaccine than one bulk facility (see Appendix 2 for further explanation).

The main disadvantage to form/fill is being dependent on a supplier for the bulk antigen. This can be up to 90% of the cost of the vaccine, and up to 60-70% is not unusual. Pricing of bulk antigen is opaque and can be freely set by bulk suppliers who may be keen to encourage or discourage its purchase.

Project Duration

The matrix above gives a sense of the cost and duration to complete a project via a **backwards integration** technology transfer strategy. Many companies opt for a **backwards integration** approach in order to enable them to get a viable product on the market as soon as possible. It also allows the work to be spread out over a few extra years so as to not overwhelm the local production partner (see Appendix 2 for more information on this). Thus the time to complete a **backwards integrated** project for a given facility scope can vary depending on how large a gap is planned between the different phases of the technology transfer. See Appendix 1 for more information on how the different time frames above were estimated. The time to complete a facility is also directly linked to the construction methodology chosen for the project. Projects starting “from scratch”, where full preclinical and clinical development are required, generally extend from 7 to more than 10 years.

Construction Methodology

Note that the chosen construction methodology can greatly impact on the final cost of the facility as well as the time to complete it. Two important considerations for a new facility are whether or not to use **single use technology (SUT)** and whether the facility will be **stick-built** (constructed on site from scratch) or **modular** (constructed offsite and brought in as discreet pieces to be assembled on site).

These methodologies and some of their extensive advantages and disadvantages are further explored in Appendix 2. For the purposes of understanding the examples: SUT allows for lower initial costs but increases operating costs, modular facilities are more expensive but faster to install than stick-built facilities, and modular facilities may be the only available option in countries without a local workforce with the specialized construction skills needed to build a vaccine facility.

It is extremely important to carry out and heed the recommendations from a robust front end feasibility study that is continuously updated.

Form/fill only facilities can take 1-3 years less to complete and typically cost less than half as much as fully integrated facilities.

Timelines and costs for any facility are also heavily dependent on the type and size of facility to be constructed.

5. Challenges

Newcomers to vaccine production will face significant barriers to entry. Some of the challenges to consider are listed here, and an expanded list of challenges and considerations can be found in Appendix 2.

Initial Investment

Any vaccine production facility requires significant capital, of an order of tens or hundreds of millions of dollars for a commercial production facility. See the appendices for detailed breakdowns of initial investment costs to consider.

Operating Costs

Vaccine production facilities have relatively high operating costs, especially for raw materials, skilled personnel and to continuously operate the utilities and **clean rooms**. Many of these costs occur even when product is not being manufactured. A large proportion of the operating costs is attributed to fixed cost that is a function of the facility design.

Project Durations

Getting commercial production up and running for a fully integrated facility takes years even if everything goes according to plan. During this time, there is usually no or very limited income until both product registration and commercialization are complete.

Industrial Cluster

Lack of other vaccine manufacturers in the region makes it hard to get supplies, skilled workers and technical support.

Competition

There is enormous global pressure to continuously lower vaccine pricing. Many

older and larger firms have already paid off their facilities and can sell some portion of their production volume near or at the cost of goods. The private and developed world markets that offer the most profit face intense competition from established and well-reputed companies.

Limited Partnership Opportunities

Vaccine production is difficult and many companies will be reluctant to invest resources to transfer their knowledge or supply product to a new and unproven company who could be a competitor.

Hiring and Training Personnel

Hiring foreign experts to work in key facility positions is often necessary. Many may expect salaries on par with their current position or may have to be paid an additional premium depending on the desirability of the facility location. Local skilled workers will require significant training which may include being sent abroad for months at a time. Companies around the world tend to underestimate the time and cost of finding and training their local and expat workforce.

Changes to the Landscape Over Time

Given the lengthy development process there is a risk that a well documented need at the time of starting a project may no longer be a need by the time the vaccine is approved, resulting in a smaller or absent market. Developers should therefore assess the projected needs on a continual basis.

A number of other factors need be taken into account during the evaluation and planning process, and have significant impact on the overall probability of project success.

6. Next Steps

Further information and additional reading

This white paper contains three appendices with further information:

Appendix 1 contains more details of the facilities referenced above in the scenario analysis, complete with cost breakdowns and timelines. This is no substitute for conducting a detailed analysis and verifying costs with vendors, but these analyses describe the methodology behind the examples described in section 4, providing the reader with an idea of how estimates should be built.

Appendix 2 includes a list of many (but not all) the “Other Considerations” to be investigated further as part of a preliminary feasibility study. It is highly recommended to consult with vaccine experts at this stage since the exact scope of a project will vary considerably from country to country and product to product in ways that cannot be covered in this primer.

Appendix 3 contains a glossary of terms.

Two related documents, described in section 1, provide additional reading material:

VMPA Study: Vaccine Manufacturing and Procurement in Africa (2017)

Commercialising vaccines: A methodology to identify potential market opportunities and conduct outline assessments (2017)

Enlisting of experts to inform decision making

As outlined in this paper, there are common, usually adopted approaches when considering the establishment of vaccine manufacturing and certain elements will always need to be included. These steps, as well as others which come into play, involve the input of expertise and bespoke analysis given the highly specialized and technical nature of vaccine manufacturing and the nature and dynamics of vaccine procurement. Therefore, concrete next steps in the process typically involve engagement with appropriate sources to receive the required input and allow well informed, strategically sound decision making.

In particular, there are three key types of expertise that would need to be engaged to work through this list of “Other Considerations”:

Vaccines Markets and Commercial Specialist

- Forecast global competitive and demand landscape in the vaccines industry at the time of commercial launch of planned facility + 5 to 10 years.
- Assess likely competition, target markets, future market demand, expected pricing and potential partners.

Vaccines Facility and Manufacturing Specialist

- Help determine your facility scope, costs, size and capability.
- Help determine the technical merit of potential Technology Transfer Partners.
- Lead cost analyses to determine which types of technology (SUT, Pre-sterilized vials and syringes, modular construction, etc) to use.
- Lead early facility cost, timeline and COG estimation work.

Vaccines Development and Registration Specialist

- Help to determine and manage regulatory agency expectations for product development and filing in your target market(s).
- Help to determine cost and duration of any product development work that may be necessary.
- Engage regulatory agency in early, science-based discussions on their expectations to register the product in the market.

The above list is not an exhaustive one, and other areas of expertise are also likely to be required as the decision making process evolves, but it represents a logical start to the analytical work required.

Readers may want to refer to further related documents including the VMPA Study: Vaccine Manufacturing and Procurement in Africa.

More due diligence beyond the scope of this document should be carried out, much of which will require experienced vaccine experts.

Appendix 1: Scenario analysis: consideration of project time and investment cost

A set of four different project scenarios was compiled in order to give the reader general guidelines for the work necessary to complete a small commercial vaccines production facility. The range in scope and size of the projects depicted here can be used to create a rough estimate of the project cost and duration necessary for many of the types of facilities a company new to vaccine manufacturing may be considering. Whilst there is no replacement for conducting one's own bespoke project estimate, these examples may give the reader a broad estimate that can be used prior to beginning the first stage of FEL. The four types of facility are as follows:

1. Low volume / fully integrated
2. Low volume / form/fill only
3. High volume / fully integrated
4. High volume / form/fill only (adapted from high volume / fully integrated scenario)

Scenarios 1 & 2: Low Volume Facilities

This section will explore a “generic” low volume facility. Generic in this case indicating that it could be built in a range of countries, producing a relatively simple liquid vaccine, with a bulk facility of average fermentation efficiency. Changing any of these factors can significantly affect the final cost. A modular build was chosen for the example since the cost of modular facilities is relatively static between countries.

Facility Details:

- 10 million dose/year production
- 1-3 valent product
- Liquid filled product in a single dose vial or syringe
- Modular build
- Manual visual inspection and packaging

The same facility will be considered in both fully integrated (producing bulk antigen) and form/fill only configurations to best show how costs and project durations differ.

Facility Costs:

Table 3: A detailed breakdown of the various costs[^] associated with building these facilities

	Description	Size (Bulk)	Cost (Bulk) [^]	Size (F/F only)	Cost (F/F only) [^]
Bulk Facility	Modular facility with single use bioreactors	2 x 2,000-4,000L Bioreactors	\$ 20 000 000	N/A	N/A
Form/Fill	Modular facility with traditional filler and stainless steel formulations area	200-300 VPM filling machine	\$ 12 500 000	200-300 VPM filling machine	\$ 12 500 000
Inspection and Packaging	Stick built* light duty industrial building	~100 m2	\$ 500 000	~100 m2	\$ 500 000
Warehouse	Stick built* general warehouse and cold storage area	2500 m2 warehouse, 100 m2 cold storage	\$ 3 000 000	1000 m2 warehouse, 100 m2 cold storage	\$ 2 000 000
QA/QC Lab	Stick built* facility with imported analytical equipment	100 m2	\$ 1 000 000	65 m2	\$ 650 000
Office Building	Stick built* office for ~ half of skilled work force	10 m2 per person: 500 m2	\$ 1 000 000	10 m2 per person: 320 m2	\$ 640 000
Labour	Gradual ramp up to full employment over the course of the project (see below)	~ 130 people	\$ 5 015 000	~ 64 people	\$ 2 950 000
Total Facility Cost:			\$ 43 015 000		\$ 19 240 000
OOM -30% to 50% estimate:			\$ 30.1 - 64.5m		\$ 13.7 – 28.9m

*Stick-built prices are based on AECOM Construction Handbook³ pricing

[^] These costs include:

- Equipment purchase
- Engineering costs
- Module construction and installation
- Basic process development and validation (see project duration section below)

They explicitly exclude the following, which will be briefly discussed in Appendix 2:

- Land purchase and development costs
- Permitting costs and durations
- Facility operating and carrying costs
- Clinical trials or other advanced product development or registration activities
- Inflation, the time value of money, borrowing costs, depreciation and taxes

This is not an exhaustive list of all potential project costs

³ Africa Property & Construction Cost Guide 2017, www.aecom.com

Labour Costs:

The cost of labour has been estimated for two shifts a day and a skeleton night crew on an annual basis. To estimate the labour costs pre-production, a percentage of the final full employment cost is used, increasing as the facility nears completion.

For the purposes of this case study, a typical wage found in middle-income countries for skilled (\$25 000 pa) and unskilled (\$10 000 pa) labour was used. In practice, the cost of labour will vary significantly between countries.

Table 4: Employee Numbers and Costs

	Bulk and Form/Fill Facility (number of employees/dept)	Form/Fill only Facility (number of employees/dept)
General Labour	20	15
Total Unskilled	20	15
Admin and Management	18	12
Production	67	36
Quality	15	10
Tech Ops/Engineer	10	6
Total Skilled	110	64
Total Annual Cost:	\$ 2.95 m	\$1.75 m

Project Duration:

The project durations depicted represent the time from start of Basis of Design to the start of commercial production. This timeline shows the minimum possible time to get both the bulk and form/fill facility up and running: 4.5 years. In this case, the project is structured so both facilities start production at the same time (i.e. not via backwards integration). This is typically how a project would be structured for a company that has developed a vaccine and is building capacity to supply the initial commercial launch of a new product.

It would be highly unlikely that a technology transfer would be structured in this way. Most local producers would find this to be too much work to take on at once and may opt for a **backwards integration** strategy. In practice, this means they would stagger the building of each facility – the form/fill facility is constructed first and thus will start operating before the bulk antigen facility. The gap of time between the form/fill only and fully integrated production can vary according to the project execution strategy. Because of this variation in how long the project could be, the decision was made to depict the overall timeline in the manner below so the reader could determine for themselves the required gap between the two phases of the project. See Appendix 2 for some advantages and disadvantages of backwards integration.

In any case, the timeline for each facility on its own should be considered a best-case scenario with a moderate level of process development/definition and minimal time for validation and registration. Late changes in design, difficult process development, breaking the project into three or more phases (i.e. packaging first, then form/fill, then bulk antigen) or the requirement for more detailed clinical data can extend or even double this timeline. Conditions external to the project such as a delay in the award of a government tender or a lack of funding mid-project can also cause delays.

Table 5: Breakdown and comparison of construction timelines for bulk versus form/fill facilities

	Year 1		Year 2		Year 3		Year 4		Year 5		Year 6	
% full employment	10%	15%	20%	25%	30%	40%	50%	50%	100%			
Bulk Facility (4.5 years)	Facility Design											
		Facility Construction										
			C & Q									
						Process Qual.**						
							Process Def.***					
								Validation and Registration				
										Start Production		
Form/Fill Facility (3.5 years)								Validation and Registration				
							Process Definition					
							Process Qual.**					
						C & Q*						
				Facility Construction								
			Facility Design									
% of full employment			20%	30%	30%	40%	50%	50%	100%			

*Commissioning and Qualification

**Process Qualification

***Process Definition

Scenarios 3 & 4: High Volume Facilities

As an example of a high volume facility, using publicly available figures, this scenario will consider an actual case study - the currently ongoing technology transfer started in 2013 between a major pharmaceutical company and a prominent semi-public South American biopharmaceutical producer. References used are listed at the end of the section.

Facility details:

- 30 million dose/year production
- 4 valent product
- Liquid filled product in a single dose vial or syringe
- Stick built facility situated on existing site with other vaccine production

This example was chosen as an upper limit to what is feasible for a newcomer. This producer has an established track record as an experienced manufacturer of vaccines and other sterile biologics, and thus is an obvious contender for a technology transfer – an advantage that a newcomer to the sector

may not have. They also have the advantage of a relatively mature market both from a regulatory agency perspective and the presence of a local cluster in biologics.

This example is of a fully integrated facility, however a rough rule of thumb is that the cost of a form/fill facility is approximately 35 – 45% of its fully integrated counterpart.

Facility Details and Costs:

The annual reports state that the new facility would cost approximately \$150m. It is projected to produce 30 million doses/year of a 4-valent vaccine. It is important to note that while this is approximately three times as costly and three times as productive as our low-volume example, the costs involved do not scale linearly. See Appendix 2: Other Considerations for further explanation.

In this case, some factors that may contribute to the relatively high facility cost include:

- **Stainless Steel Facilities.** High output operations tend to use stainless steel bulk and form/fill which incur a higher upfront cost. Additionally, as the existing technology transfer process is in stainless steel, it is most likely to be tech-transferred in the same way.
- **Large Bulk Facilities.** The vaccine being produced is a quadrivalent **recombinant** vaccine, which requires relatively large bulk facilities.
- **Location.** The facility is being built in a relatively high cost location, which affects labour and construction costs, especially for stick-built buildings.

This cost most likely contains all equipment and construction costs to build on the existing site. However, as the existing site is large and semi-public, it is unlikely that the local partner faced an additional land purchase cost.

Labour Costs:

The South American producer is well-supported by the government of its host country. As this support extends to many staff members' salaries, they have most likely not been included in the final cost. Additionally, although there will be a sizable amount of work required from the technology transfer partner and their staff, these costs and salaries are also not included in the cost estimate.

Project Duration:

It appears that the technology transfer has been structured as a reverse integration in 4 stages:

1. Importation of finished product
2. Local testing and release of imported product
3. Form/Fill and Packaging
4. Bulk antigen production

In 2013, it was estimated that the technology transfer would take 5 years to complete. Recent articles indicate that the process may be moving even more slowly. In general, 5 years is an aggressive approach for this type of deal. A typical estimate for this type of work would be closer to 7-10 years to complete full localization, which seems to be more aligned with the current progress.

As of the latter half of 2016, the second stage of the technology transfer had been completed. This shows that even an experienced company with many advantages may still wrestle with high costs and expanding timelines.

References

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Appendix 2: Other Considerations

Newcomers to vaccine production face significant challenges, even if they pass the initial feasibility assessment.

This Appendix will explore other considerations to keep in mind with the help of vaccine experts. This is not an exhaustive list but can be used as a starting point, from which a vaccine expert will be able to expand.

Backwards Integration

As mentioned in the main document, many new vaccine manufacturers choose to use backwards integration when starting a new facility. Working in this way is recommended and comes with many advantages. Vaccine producers often stagger the timeline of each stage.

Advantages of backwards integration:

Faster Return on Investment: Projects at the lower end of the value chain are faster and cheaper to implement. By completing them first, the facility can start bringing in money sooner.

Lower regulations burden: Regulations are more stringent further up the production chain.

Step-by-step learning: Each new process builds on previous knowledge. The technology transfer partner may also insist on a delay so the new producer can prove they are performing well enough to move further up the value chain.

Flexibility: Easier to change overall production strategy as one learns more.

Spread out the work: Executing one project at a time can greatly reduce project risk and complexity.

Disadvantages of backwards integration:

Restrictions: Technology transfer partners can impose restrictions on the quantity of product manufactured, or where the final product can be sold.

Lower margins: The most difficult processes and the last to be taught have the highest margins.

Supply insecurity: A facility working on the latter part of the production chain relies heavily on their supplier. Global shortages of a product may leave such a facility without a readily available supply.

Longer timeline: Each step of the process takes longer to get up and running, stretching out the total timeline.

Delayed know-how transfer: The local partner and country must wait longer to learn how to perform the most complex processes.

Changing circumstances

Many deals to localize some portion of vaccine production arise through a government agreeing to buy a sizeable amount of a vaccine at a relatively high price, offering exclusivity for a certain local entity and their technology transfer partner to produce this vaccine.

In theory, this is a win-win-win deal for all parties:

- Global technology transfer partner gets exclusivity and does not have to compete for tenders in future years.
- Local company gets a guaranteed revenue stream and an interested technology transfer partner.
- Government ensures investment in local industry, accesses new and better technology and builds a platform for a new industry sector in their country.

However, in the time it takes to build this new facility (5-10 years), the government may decide to scrap the exclusivity or purchasing program or change the purchasing price due to a host of reasons out of the producer's control. Such reasons include a change of power, budget cuts or the arrival of cheaper competition on the open market.

Land purchase, permitting and development

Land costs and development costs vary widely from country to country and from location to location in a given country. In North America and Europe, it is not uncommon for the site purchase and land development to cost half as much as the total cost to deliver the production facility itself.

As land purchase and development can make up such a large percentage of the overall project cost, the chosen site for production must be extensively investigated. Costs for land development of a green field facility will usually exceed those for brown field facilities. Land development will include things like site terrain leveling, running connections to mains utilities to your production site, roads and other infrastructure such as walls and fencing.

Permitting costs and timelines also vary significantly between countries and should be taken into account during planning. *The World Bank: Doing Business* website is full of useful information about permitting around the world⁴.

Modular vs Stick Built Facilities

Facilities can be "stick-built", i.e., built on site by a construction crew, or modular, where individual pieces of the facility are built off site and then later assembled on site.

⁴ <http://www.doingbusiness.org/data/exploreeconomies/south-africa/dealing-with-construction-permits>

Modular facilities are more expensive but have several advantages.

- **More predictable costs:** The cost of traditional or “stick-built” facilities can vary widely across a single region, let alone globally. The cost of modular facilities, as they are built in a more controlled environment by experts, varies far less.
- **Less reliance on local environment:** In a country without other similar facilities, it may be difficult to find a construction company able to build the facility to the appropriate standards, as it relies on the ability to locally source not only high quality construction materials but also a highly skilled workforce with experience in dealing with the highly technical aspects of the construction project.
- **Convenience:** Most equipment is installed before shipping to site, so once the facility is assembled the construction is almost complete.
- **Faster:** Typically faster and more predictable construction timeline since they are built in a controlled environment by highly experienced people. Construction can actually begin while construction permits are being obtained.

In a situation where it is essential to start production as fast as possible, a modular facility can be a good choice. However, all things being equal, choosing a stick-built facility makes sense if it is possible to source all the skilled labour locally or if there is no need to pay a premium to complete construction at a faster rate.

Another option not mentioned in the main document is doing a retrofit of an existing facility. If it is possible to reuse sections of an existing facility, this can significantly lower initial investment costs and project timelines.

Operating Costs

Vaccine production facilities have high ongoing costs. Skilled personnel must be retained and utilities and clean rooms must be kept up and running. Many of these costs are incurred even whilst not manufacturing product, from the beginning of the project phase. Vaccines also require costly high-quality production inputs (consistent municipal utilities, raw materials, sterile consumables, etc), which can be difficult to obtain consistently in certain regions; companies have shut down because these operating costs were incorrectly calculated and not supported by the market price.

Single dose vs multi dose vials

The cost estimates in this document are based on single dose vials or syringes. Many vaccines are filled into multi-dose vials (anywhere from 5-20 doses per vial), which allow a lot of increase in capacity without changing the filling equipment. Most commercial fillers can fill both single and multi dose vials.

Single Use Technology (SUT) vs stainless steel systems

In a traditional vaccine manufacturing facility, everything that would come in contact with the product would be made of stainless steel. This would include all production vessels, transfer piping and process control instrumentation.

However, advances over the past 10-15 years have made it possible to replace many of these stainless steel systems with single use plastic and polymer film systems. Another relatively new innovation is pre-washed and pre-sterilized RTU primary containers (i.e. vials and syringes). Choosing between stainless and these single use technologies (SUT) is a crucial calculation for a new producer.

Advantages of SUT:

Lower upfront cost: Using SUT and RTU primary containers can drastically cut upfront costs.

Faster set up: Standardized design units are quicker and easier to set up than equivalent stainless steel facilities.

Easy expansion: Facility capacity can be quickly expanded by simply adding additional units.

Reduced facility scope: The combination of using more single use equipment and RTU primary containers allows new facilities to remove the requirement for all on-site cleaning and sterilizing equipment.

Disadvantages of SUT:

Higher variable operating cost: Each new batch of vaccines requires new disposable equipment. This higher operating cost can eclipse the initial cost savings.

Continued supply chain risk: Using SUT equipment for bulk and form/fill requires repeated ordering of new parts. If a supplier experiences difficulty in meeting demand, production is at risk.

In general, the amount of batches of vaccine that a particular facility produces determines whether stainless steel or SUT is preferable. A small number of annual batches is better suited to SUT while for large numbers, stainless steel is more cost effective. Numbers of batches do not necessarily reflect overall production volume: a high capacity facility can produce a large volume of product in few batches and vice versa.

Choosing between SUT and stainless is a complicated decision with many contributing factors. A Total Cost of Ownership Analysis is necessary to determine the best set up.

The need for multiple facilities

It is not possible to produce all vaccines in a single facility for two main reasons. The first is that the equipment needed to produce vaccines varies from product to product. The second is that the production of some vaccines needs to be segregated completely from areas producing other types of vaccines. This can result in segregated production areas or even separate facilities.

Different Bulk Fermentations: Different antigen fermentation methods mean that not all antigens will use the same fermentation or purification equipment and technology. Producing various antigens may even require dedicated facilities, as in the case of spore forming toxoids.

Lyophilized vaccines: In some cases vaccines are not stable in liquid forms even with the best refrigeration and stabilizers. In this case, they typically will be freeze dried or lyophilized. The lyophilization process adds another layer of complexity to the form/fill facility and cold chain, and it also requires the addition of a lyophilizer to freeze dry products immediately after they have been filled into vials.

Biocontamination and safety considerations: For safety reasons, some vaccines cannot be made in the same facility. Two common examples are:

1. Live and inactivated vaccines need to be made in separate production facilities according to most national regulations.
2. Products with varying biosafety levels require different degrees of containment precautions to be set in place both in the design of the facility and its operation. In some cases, this may also result in the need for separate facilities.

Process and Product Development

Our case study in Appendix 1 includes basic process development work (water runs, placebo runs and validation runs) followed by minimal product registration data gathering (process characterization, product equivalency testing, stability, etc) that doesn't include trials in humans. This assumes that these tests will be run by local employees (some who have prior experience with this) with guidance from the technology transfer partner. It does not include any payments that a technology transfer partner may request in exchange for their people's time or the hiring of a validation company to perform this.

The time and cost of this is highly dependent on the regulatory agency, the product that is being transferred, where its being transferred from and how much of the process is being transferred. Thus the timeline can range from around 1 year as depicted in the case study, to 5 or more years. Product development costs can range from just a few non-saleable production lots (as depicted above) to non-saleable production lots plus human studies with costs of millions of dollars.

Product Development/Clinical Trials

Product development costs must also be considered and are also not included in the main document. There are costs involved with production process development and conducting any product tests for product registration. These tests require product which cannot be later sold.

If clinical trials are required for a product, carrying out these trials can take multiple years with costs in the millions of dollars. The exact cost and duration of the trials depend on a number of factors which are beyond the scope of this document.

Appendix 3: Glossary

Adjuvant A substance that may be added to a vaccine to boost the immune system response to the target antigen.

Antigen A toxin or other foreign substance which induces an immune response in the body. In the context of vaccines, are several types of antigen including whole inactivated pathogen, attenuated pathogen, purified subunit derived from the pathogen, and recombinant antigens.

Backwards integration/Reverse integration A technology transfer regime which sees a local producer begin production at the end of the value chain then working back along the value chain to learn subsequent processes.

Bio-safety Level A set of bio-containment precautions required to isolate dangerous biological agents in certain areas of a facility or production room.

Birth cohort A group of people born during a particular period. In the context of vaccination, this is usually during a single year.

Clean rooms An environment, typically used in manufacturing, with a low level of environmental pollutants such as dust, airborne microbes, aerosol particles, and chemical vapours.

Cold chain The strict control and monitoring of the temperature of a vaccine starting during manufacturing and continuing all the way through to administration to the patient.

Cost of goods The cost of the materials used in creating the goods along with the direct labour costs used to produce the goods.

Front End Loading (FEL) A deliberate approach to build and verify a project's business case early in the project's lifecycle when the cost to alter or cancel the project is still relatively low.

GAVI Global Alliance for Vaccines and Immunization, a public-private global health partnership committed to increasing access to immunization in poor countries.

Inactivated vaccine A vaccine consisting of virus particles, bacteria, or other pathogens that have been grown in culture and then killed using a method such as heat or formaldehyde.

Live/attenuated vaccine A vaccine created by reducing the virulence of a pathogen, but still keeping it viable (or "live").

Lyophilization The creation of a stable preparation of a biologic substance by rapid freezing and dehydration of the frozen product under high vacuum.

Modular A construction method involving assembly of sections or modules of the overall facility or structure off-site. The individual module units are then transported and assembled on site.

Order of magnitude (OOM) Typically order of magnitude separates numbers by factors of ten (i.e. something costing thousands of dollars costs an order of magnitude more than something costing hundreds). With regards to the type of cost estimating in this document, it refers to a range of -30% to + 50% of a yet to be determined value.

PAHO The Pan American Health Organization, an international public health agency working to improve health and living standards of the people of the Americas.

Ready-to-use (RTU) Pre-washed and pre-sterilized production equipment or primary product containers (i.e. vials or syringes).

Recombinant vaccine A vaccine produced by inserting the DNA encoding an antigen (such as a bacterial surface protein) that stimulates an immune response into bacterial or mammalian cells, expressing the antigen in these cells and then purifying it from them.

Single-use Technology (SUT) Equipment that is only used once before disposal. This can range from filters that are bought **RTU** and then discarded after their use all the way to bioreactors that consist of a **RTU** bag that is used in conjunction with a reusable housing.

Stick built The typical construction method whereby a facility or structure is assembled piece-by-piece on site.

Technology transfer (tech transfer) The transfer of know-how and/or processes from a more experienced organization or company to a less experienced one.

Weighted Average Price An average price calculated from how much of a given product is bought at each price. If there is only one supplier of the product, then this price reflects the actual price paid to the supplier; if there is more than one supplier contracted for a product, individual prices are not determinable.

UNICEF The United Nations Children's Fund, a United Nations (UN) program headquartered in New York City that provides humanitarian and developmental assistance to children and mothers in developing countries.

Appendix 4: Acknowledgements

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