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Economic Evaluation of Local Vaccine Production vs. Finished Product Distribution:
The Biovac Case Study

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Abstract

The African pharmaceutical industry lacks the capacity to adequately supply the continent with essential medicines to combat the heavy disease burden that is grappling the continent. As a result, Africa relies heavily on imported medicines and vaccines to meet the growing needs of the population. Local pharmaceutical production promises to provide a sustainable solution to public health, industrial development and socio-economic issues on the continent. However, local pharmaceutical production does not make economic sense if the industry is unable to competitively produce quality medicine at prices that are comparable to or better than those of imported medicine. The aim of this study was to evaluate whether locally filling a multivalent vaccine used in paediatric immunization is economically viable when compared to the same vaccine currently imported semi-finished for labelling, packaging and distribution. Can a South African vaccine manufacturer produce the same vaccine cheaper than it currently imports? The objectives were to determine the production costs for both semi-finished product and local vaccine filling operations and to assess which option makes economic sense to pursue. The sub-objectives were to establish the extent and impact of the market size and demand for this vaccine on the decision to pursue local production versus importation. A case study approach was adopted as a research method to gain an in-depth understanding of the economic and production factors within the context of vaccine manufacturing with The Biologicals and Vaccines Institute of Southern Africa (Biovac) as a unit of analysis. Multiple sources of data were used to collect data for analysis. The study found that local production of this vaccine is economically viable and more favourable over imported product at current annual demand of 4.5 million doses. Local vaccine filling operations break-even point was found to be at 1.3 million doses when compared to 2.6 million doses for imported semi-finished product Whilst economies of scale cannot be disregarded for long-term profitability, this study found that economic viability can be achieved with an annual demand of 4.5million doses. The aim of this study was accomplished. This study contributes to the body of knowledge on local pharmaceutical production and serves as a baseline for further research in this area.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

AIDS   Acquired Immunodeficiency Syndrome

AU   The African Union

AUC   The African Union Commission

Biovac   Biologicals and Vaccines Institute of Southern Africa (Pty) Ltd

cGMP   current Good Manufacturing Practice

EPI   Expanded Programme on Immunization

GAVI   Global Alliance for Vaccines and Immunization

HIV   Human Immunodeficiency Virus

IFC   International Finance Corporation

LFV   Locally Filled Vaccine

PMPA   Pharmaceutical Manufacturing Plan of Africa

SFP   Semi-Finished Product

UNCTAD   United Nations Conference on Trade and Development

UNIDO   United Nations Industrial Development Agency

WHO   World Health Organization

CHAPTER ONE: Introduction

1.1 Introduction

The reliance on imported medicines in Africa remains unsustainably high with an estimated 25 to 30 percent of essential medicines consumed in Africa being produced within the continent (African Development Bank, 2014). As a result of low production capacity the continent is susceptible to drug supply shortages, limited access to essential medicine and inability to swiftly respond to pandemic disease outbreaks. The disproportionate number of deaths due to acute shortage of the influenza vaccine in Africa during the 2009 H1N1 flu pandemic outbreak (Dawood et al., 2012) and the recent Ebola outbreaks in North and West Africa are examples demonstrating the unpreparedness to respond to epidemic outbreaks and heavy reliance on imported medicines.

Local production of medicines on the African continent promises to reduce dependency on imported drugs, improve access to medicines and create a sustainable response to drug supply shortages (African Union and UNIDO, 2012). To effectively reduce import dependency and address drug supply shortages in Africa, the continent must create a competitive, sustainable pharmaceutical industry that can reliably supply quality, affordable medicine. However, in light of current competition from foreign manufacturers, the viability of the local pharmaceutical industry lies in price competition (Wilson et al., 2012) and the ability of the industry to produce quality products at costs that are less than, or at least competitive, to those of foreign manufactures (Taylor et al., 2009).

The decision whether to produce locally or to continue with importation is complex (Kaplan and Laing, 2005) and requires a thorough assessment of the feasibility of either option. This is to ensure that such an undertaking will be economically viable given that local manufacturing may not necessarily be cheaper than importation (UNCTAD, 2011). This case study assesses the economic viability of a locally produced vaccine when compared to the same vaccine currently imported semi-finished for labelling, packaging and distribution.

The rest of this chapter is divided into the following sections: Section 1.2 discusses the motivation for the study, which is followed by Section 1.3 summarising the focus of the study; Section 1.4 discusses the problem statement; Section 1.5 states the objectives of the study;

Section 1.6 states imitations of the study and Section 1.7 will summarise this chapter and give an overview of the dissertation.

1.2   Motivation for the Study:

South Africa aims to improve its preparedness to respond to pandemic disease outbreaks (Dulnier, 2010) and reduce the dependency on imported vaccines by resuscitating vaccine manufacturing capability through the establishment of The Biologicals and Vaccines Institute of Southern Africa (Biovac). Over the past decade Biovac has sourced, imported and distributed vaccines for the national immunization programme and is now preparing to integrate the formulation and filling operations into the current importing and distribution business model (Dulnier, 2010).

This study had to be conducted because the current costing model for Biovac is based on sourcing and distribution of imported vaccines. No formal cost-analysis study has been conducted by Biovac on local vaccine filling activities from formulated bulk liquid product. Biovac will use the information from this study to develop a costing model for fill/finish operations. With the Company attracting technology transfer partners for collaboration in various projects, understanding the vaccine production costs and associated market dynamics will enable Biovac to make informed decisions on which strategy, if pursued, will be economically viable.

The decision on which imported vaccines are to be prioritised for local production can be made with more certainty if the production costs and market dynamics of either option is better understood. Because of limited human vaccine manufacturing operations in South Africa, there is a gap in the available literature on the production costs and capability to manufacture affordable, high quality vaccines. The extent to which the input costs are applicable to the viability of local production is not well defined and therefore there is limited reference to use as a baseline in the manufacturing of vaccines within the South African context.

 There are different views regarding the feasibility of local vaccine manufacturing. According to Kaplan and Laing (2005), local manufacturing may not be feasible in all developing countries if the economies of scale of production are insufficient. However, the extent of the requirement for economies of scale is not well defined in the literature. It has been estimated that up to 60

% of vaccine production costs are fixed and requires economies of scale to recoup some of the costs (Baumann, 2009). Again there is no distinction whether this figure refers to the production of monovalent or polyvalent vaccines or whether these are high cost or low cost vaccines.

1.3   Focus of the Study:

This study will focus on the production and infrastructural costs to assess whether Biovac can competitively produce quality vaccines more favourably than imported vaccines. The input costs associated with producing a single unit of vaccine from imported formulated bulk were analysed and compared to the costs of importing a fully finished vaccine for labelling and distribution. Direct and indirect costs of production as well as fixed and variable costs were identified and assessed to determine the extent to which they have an effect on the final price of a vaccine under different market conditions.

Since Biovac processes do not currently include antigen production and formulation, the costs of producing the antigens or the effect of locally producing vaccines from the antigen stage to finished product was not assessed as part of this study. The distribution and marketing costs of either a locally produced or imported vaccine is the same as the finished product is stored and packed in the same configuration therefore the study will not focus on these common costs.

1.4   Problem Statement:

Despite the dominant status of the South African pharmaceutical industry in Africa, in terms of annual production and the number of pharmaceutical manufacturers in the country (SEATINI and CEHURD, 2013), there is no human vaccine manufacturing capability in South Africa. As a result, South Africa remains the only member of the group of developing countries among them Brazil, Russia, India, China and South Africa (BRICS) to import all vaccines to support the national immunization programme (Kaddar et al., 2014). Despite having no vaccine manufacturing capability, South Africa is considered an early adopter of new vaccines financed by national government mainly through taxation (Blecher et al., 2012). It can therefore be expected that as newer vaccines are adopted by government for the immunization programme, there will be more pressure on the allocated vaccine budget.

Establishing vaccine manufacturing capability in South Africa could reduce trade deficit resulting from importation of pharmaceuticals, however such an investment undertaking requires a thorough assessment to determine its viability and profitability. When calculating the cost of a single unit of vaccine one must take into account the input costs such as the costs of establishing a vaccine manufacturing facility (Bate, 2008), developmental and production costs, cost and skill of labour, shipping and raw material (Lee and McGlone, 2010). Taking all of the above into account, the following pertinent questions remain to be answered:

- Is local vaccine manufacturing a viable option in South Africa?
- Can Biovac locally produce quality vaccines at a more favourable cost than currently imported?

1.5 Objectives of the Study

The aim of this study was to evaluate economic viability of Locally Filled Vaccine (LFV) when compared to imported, Semi-finished product for packaging and distribution (SFP).

The objectives of this study were:

i. To ascertain the manufacturing costs of a LFV versus SFP;
ii. To determine the level of economic activity for which LFV is preferred when compared to SFP;
iii. To determine the desirable market size for which one option is preferred over the other;
iv. To determine the level of investment needed for both options – LFV vs. SFP; and
v. To determine the effect of changing the key variables such as the selling price and the cost of imported product (SFP or formulated bulk) on the viability of either option.

1.6 Limitations of the Study

The LFV that was used to collect data was a technology transfer product candidate that is currently not commercially available in the South African market but has undergone stability testing and awaits approval by the regulatory authority. This means that this product has undergone the full manufacturing cycle, however, the costs of the primary and secondary packaging materials may change by the time the product is registered on the market. The SFP that was used for comparison in this study is registered and available in the market.

4

The cost price used is the current price of the product in the market on the government tender.

1.7　Summary and Overview of the Dissertation

This chapter discussed the motivation for the study, the problem statement and the focus of the study. The objectives and the limitations of the study were also stated in this chapter.

The next chapter, Chapter 2, will discuss the literature review of local pharmaceutical production. In particular, the drivers for local production and key considerations for successful local pharmaceutical production are discussed with more emphasis on vaccine manufacturing.

Chapter 3 outlines the case study research methodology that was employed in this study as well as data collection methods, data analysis tools and finally the issues of validity and reliability.

Chapter 4 presents and analyses the findings obtained using the methodology in Chapter 3.

Chapter 5 summarises the findings, makes recommendations and conclusion.

Chapter 6 will discuss the concluding remarks and make recommendations for future studies.

CHAPTER TWO: Literature Review

2.1   Introduction

Many solutions have been proposed to solve the issues of access to affordable, quality medicine, which is a threat to public health and budgets of national governments in Africa. Local pharmaceutical production emerges as one of the key solutions that promise benefits that are beyond access to medicine. It is therefore not surprising that local production is receiving support from political heads and multilateral organizations (UNCTAD, 2011;UNIDO, 2013) as a sustainable solution to reduce heavy reliance on imported medicines. Currently, affordability and quality of medicine remain a challenge for many African countries to the extent that they rely on donor funding to access medicine. This is particularly evident when it comes to vaccines donated by the Global Alliance on Vaccination and Immunizations (GAVI) and the funding of medicines needed to treat malaria, HIV and AIDS.

Despite the benefits that stand to be realized, there are key challenges that need to be overcome and considerations that must be taken into account in order for local production to be viable. These considerations relate to cost disadvantages and competitiveness of the pharmaceutical industry across the continent, the capability and capacity to embark on such an undertaking. The focus of this review will be on the key drivers behind the support to boost local production capacity and the key considerations for the successful establishment of local production in Africa within the context of South Africa.

The aim of this study was to evaluate economic viability of locally produced vaccines in South Africa as opposed to importing them semi-finished for sale and distribution. Although there are varying degree of pharmaceutical production across the African continent, vaccine production is almost non-existent with Senegal as the only human vaccine manufacturer producing a single vaccine against Yellow Fever for the domestic market. Therefore, there is limited literature available on local vaccine manufacturing in Africa. As a result, this chapter begins with the background on the issues surrounding local production and local production overview and definition. This is followed by the drivers and key considerations for establishing local production in the context of this study. A summary will conclude this chapter.

2.2   Background

The support for the developing countries to increase public access to essential medicine and reduce the dependency on imported medicine through local production is broadening. In Africa, the adoption of the Pharmaceutical Manufacturing Plan for Africa (PMPA) by the Heads of African Governments is a clear indication of the political commitment to boost local production capacity of essential medicine on the continent (African Union and UNIDO, 2012; African Development Bank, 2014). From a political and policy levels, establishing local pharmaceutical production promises to improve public health by increasing the security of drug supply and access to affordable medicines (WHO, 2011); promote industrial development and socio-economic stimulation through economic diversification from agricultural production and mineral extraction (UNIDO, 2013).

Despite the benefits and the high level support, competitive pharmaceutical production is complex and capital intensive (GlaxoSmithKline, 2011) and therefore requires careful consideration before embarking on such an investment undertaking. The primary considerations relate to investment cost associated with setting up a GMP-compliant manufacturing facility, access to technology and "know-how", skilled labour force, setting up a quality assurance system and the long lead times from drug discovery to commercialisation which can take approximately 10 – 15 years (IFPMA, 2011). With all these factors taken into consideration, the issue of cost of medicine and affordability cannot be ignored when considering the vast economic disparities between African countries (World Bank, 2014).

It is against this background that Kaplan and Laing (2005) supported by Bate (2008) have argued that local production may not be a viable option for all countries despite the benefits. Whilst other countries can manufacture, others should focus on streamlining their procurement and supply chain processes (Kaplan and Laing, 2005). This sentiment is shared by Bate (2008) who also concluded that it is difficult to sustain the argument for local production given the lack of resources and technical capacity to competitively produce affordable, high quality medicines in most developing countries.

2.3   Local Production Overview

2.3.1   Defining Local Production

According to the World Health Organization report (WHO, 2011), local production may be defined and better understood in terms of territorial location and ownership of the manufacturing facility. Under the territorial definition, it is implied that production of medicine takes place in a developing or least-developed country and is subject to national jurisdiction irrespective of who owns the facility. For example; the manufacturing operations of a foreign owned company, such as Pfizer (American company) or Sanofi-Aventis (French-owned), operating in South Africa maybe considered "local" irrespective of where it is controlled or the location of its headquarters.

The second definition of local production is in terms of ownership. Under this definition, it is implied that production operations will be considered "local" if the nationals have more than a majority of ownership in the firm. This definition has limitations in that the operations of a foreign owned company are excluded and considered foreign yet they take place within the said country. For the purposes of this study the territorial definition of local production has been adopted as it takes into account all manufacturing operations taking place in a country irrespective of ownership.

2.3.2   Forms of Local Production

Local production occurs at different levels of sophistication and hence the categorization of different forms is done in terms of simplicity of operations undertaken. There are three broad categories used to describe different forms of local production; namely tertiary, secondary and primary levels of production (WHO, 2011). Tertiary manufacturing is the simplest of all production categories that generally involves the labelling and packaging of formulated or SFP. This form of local production is commonly found in the least developed or low-income countries. Secondary manufacturing is more sophisticated than tertiary as it involves the mixing of raw materials and formulation of different dosage forms. This form of manufacturing is most prevalent in the so-called middle-income countries. However, the raw materials used in secondary manufacturing are usually produced by the industrialized and large developing

8

countries such as India and China where significant levels of the primary manufacturing take place.

The primary manufacturing involves the manufacturing of active pharmaceutical ingredients, intermediaries and excipients. According to the World Health Organization (WHO, 2011, pg12), the primary production used to be concentrated in just five industrialized countries – The United States of America, Germany, France, The United Kingdom and Japan. However, the picture has changed with China and India's competitive ability to produce API's. Other smaller developing countries like South Africa have some capability to produce certain raw materials. Although South Africa has some capability to produce raw materials, the majority of the raw materials used in formulating medicines are imported from countries abroad (Bennet, 2014).

2.3.3 Local Production of medicine in Africa

Literature review of the African pharmaceutical Industry confirms the presence of local production activities across the continent that are dominated by a handful of countries (Abbott, 2011) supplying a combined output of 25 to 30% of the continent's needs (Iñarra, 2015). According to the summary by Abbott (2011), based on the International Finance Corporation (IFC) annual report (World Bank, 2007), the African pharmaceutical industry is dominated by South Africa, Ghana, Nigeria, Kenya and North Africa. The South African pharmaceutical industry is considered as the most developed in the Sub-Saharan region and North Africa (Bennet, 2014) with South Africa alone responsible for the large majority of the manufacturing output (Abbott, 2011). This indicates vast differences in the capabilities of local production between the African countries and their abilities to provide essential medicines that will satisfy the needs of the population.

Despite Africa being described in the McKinsey Report (Holt et al., 2015, p2) as the world's fastest –growing economic region, the pharmaceutical industry remains weak and is biased to produce generic medicines (Holt et al., 2015) and copy drugs under licence (WESGRO, 2012). This weakness is evident when taking into account that, in global terms, the African pharmaceutical industry was worth an estimated US $23.1 billion in 2011 or less than 2% of the global market (African Development Bank, 2014, p1). To put this number into perspective, The European Federation of Pharmaceutical Industries and Associations estimated that Africa

9

combined with Asia and Australia – excluding Japan – contributed to global sales of only 13.7% in 2012 (EFPIA, 2012) and 16.6% in 2014 (EFPIA, 2015). The small size of the pharmaceutical industry in Africa may be interpreted as a good indication of the potential economic growth when considering that the disease pattern is expected to shift from communicable to chronic or "lifestyle" diseases over the next decade (de-Graft Aitkins et al., 2010). Based on the current situation; if the disease burden actually shifts as expected, it is difficult to imagine how the industry will be able to cope with additional demand and competition from cheaper medicines imported from India.

The above scenario presents some worrying scenarios. Firstly, too much focus on the production of generics and copy drugs indicates more emphasis on treatment rather than prevention of diseases through vaccination. Secondly, the production of generics at a large scale implies that the local producers are paying less attention to the research and development of new drugs to fight diseases that are more prevalent or disproportionately affect Africa. This could be interpreted to mean that the local industry is dependent on research expertise from outside the continent. With most countries limited to secondary and tertiary manufacturing – formulation, packaging and labelling – the transition to primary manufacturing could prove to be costly even if countries are interested in pursuing more sophisticated forms of production. Thirdly, limited research and development leaves Africa unable to respond the pandemic disease outbreaks as there could be slow progress with research on drugs to combat diseases affecting Africa. The shortages of the H1N1 influenza vaccine in 2009 (Dawood et al., 2012) and the unavailability of vaccine against the recent deadly Ebola outbreaks in West Africa(Holt et al., 2015) precisely demonstrate this point.

Finally, the African continent presents some unique disparities in local production. According to the African Development Bank (2015), the importation rate in Senegal is 80% with the majority of imports coming from India. Interestingly, Senegal is the only African country that has human vaccine manufacturing ability yet the country with the most developed pharmaceutical production capability (South Africa) does not produce vaccines for human use. As a result of producing a limited range of pharmaceuticals against a rising disease and shifting disease burden profile (de-Graft Aitkins et al., 2010), the local pharmaceutical industry will

continue to lack the adequate capacity to meet the growing needs of the continent. This leaves Africa heavily reliant on life-saving medicines and vaccines imported from abroad.

2.3.4 Local Production and the Pharmaceutical Industry in South Africa

South Africa is home to both local and multinational pharmaceutical manufactures that produce a wide range of pharmaceuticals for local demand and export (WESGRO, 2012). The multinational pharmaceuticals in the country include Pfizer (USA), Fresenius-Kabi (Germany), Sanofi (France), Johnson & Johnson (USA) and GlaxoSmithKline (United Kingdom) whilst the top local manufacturers include Aspen and Adcock Ingram (Kudlinski, 2013). The country has a well-developed pharmaceutical industry with all forms of local production – mainly secondary and tertiary with limited primary production – taking place. South Africa has the largest pharmaceutical market in Africa although multinationals continue to dominate the industry according to the Gauteng Growth Development Agency (GGDA, 2014).

South Africa is a net importer of pharmaceuticals and this places a heavy burden on the trade balance. Previously, the pharmaceutical industry catered for about 64% of the local medicine requirements and this has decreased due to an increase in imported medicine (GGDA, 2014). The Department of Trade and Industry (DTI) estimated that South Africa imported more than 65% of its pharmaceuticals and this was the 5th largest contributor to the South African trade deficit in 2013 (Kudlinski, 2013) The figures are startling in that, according to DTI, 85% of the imported pharmaceuticals in 2011 were in finished dosage form from India, Germany, United Kingdom, France and Italy (Kudlinski, 2013). Over the past decade, the reliance on imported medicine has continued to grow and this is a concern to government as it increases the risk to security of supply.

Like in many African countries that promote local production, the pharmaceutical industry in South Africa is mainly focused on the production of generic medicine (Zhan, 2014) and copy drugs under licence (WESGRO, 2012). According to the WESGRO report (2012), in 2011 the generic drug sales accounted for 29% in revenue and more than 50% in volume whilst patented drugs accounted for 59% of revenue. There is expectation that the market for generic drugs will continue to grow having grown at an average compounded annual growth rate of 22.3% between 2004 and 2011 (Holt et al., 2015).

Although South Africa dominates the African pharmaceutical industry in both annual production and the number of pharmaceutical manufacturers in the country (SEATINI and CEHURD, 2013), the country lags behind its peers in the BRICS group of countries (Brazil, Russia, India, China, South Africa) particularly when it comes to vaccine manufacturing. Until 1993 South Africa produced vaccines locally using out-dated technology and in 2014 South Africa remained the only member of the BRICS countries to import all vaccines for the national immunization programme (Kaddar et al., 2014). Meanwhile, in the corresponding period, the Chinese vaccine industry had developed rapidly to more than 40 vaccine manufacturers in 2010 (Hendriks et al., 2010). This is a far cry when considering that South Africa has the most developed pharmaceutical industry in Africa.

This section on local production overview suggests that the African pharmaceutical industry is weak and is focusing on generic medicines with limited research and development into diseases endemic to the continent. The local pharmaceutical industry is under pressure from competition from imports which are coming from India and other industrialized countries because of the growing reliance on imported medicine.

2.4   Drivers behind Local Production in Africa

Although arguments against the promotion of local production in every country have been presented (Kaplan and Laing, 2005) there is a strong support for local production in hope that it will improve public health (WHO, 2011), promote industrial development (UNIDO, 2013) and economic growth (Taylor et al., 2009). This section will discuss disease burden, access to affordable medicine, security of supply and socio-economic benefits as drivers behind the promotion of local production.

2.4.1 Disease Burden

While there are many diseases that affect Africa, specific diseases such as Malaria, HIV/AIDS, Tuberculosis, Cholera, Ebola and other tropical diseases are more prevalent or disproportionately affect Africa than any other part of the world. The disease burden is severe across the continent and there is no indication that the situation is getting better (de-Graft Aitkins et al., 2010). The continent is faced with a dual burden of disease due to an increase in both communicable and chronic disease (IHME, 2013). It is estimated that about 75% of

HIV/AIDS cases and 90% of deaths due to malaria occur in Africa (African Development Bank, 2014) including "more than 50% of the global deaths of children under the age of five" (African Union and UNIDO, 2012, page12). HIV/AIDS, Malaria and TB account for more than 5 million deaths per year, or about 50 % of all infectious disease deaths (Foster et al., 2006).

As recent as a decade ago, predictions of higher diabetes prevalence were rife that, by 2020, the disease burden will shift from infectious diseases to chronic or so-called lifestyle diseases (Foster et al., 2006) owing to Africa's widespread economic growth and the rise of the middle class (Bennet, 2014). Recent studies have confirmed that the disease burden is already shifting from communicable to chronic and lifestyle diseases such as diabetes, cardiovascular, cancers and depression (de-Graft Aitkins et al., 2010). A study conducted by the Institute of Human Metrics and Evaluation (IHME, 2013) confirmed an increase in the prevalence of non-communicable diseases between 1990 and 2010. The study found that incidents of diabetes, low back pain and depression increased by 88%, 65% and 61% respectively during this period. It is therefore not surprising that the South African pharmaceutical industry focusing on producing generic medicines against lifestyle diseases such as cardiovascular diseases, diabetes and antiretroviral (Kudlinski, 2013).

The shift in disease pattern will also require a shift of focus for many governments especially taking into account that many rely on foreign aid to combat diseases such as malaria, HIV/AIDS and national immunization programmes. The emergence of chronic diseases on the African continent will put a financial strain on many national governments as more medicine will need to be imported. Whilst this may be welcome news for the local industry as it will stimulate growth and unlock untapped markets, it is unlikely to be welcome by governments in poorer countries. In sub-Saharan Africa the prevalence of chronic diseases could not have come at a worst time as the region is faced with both communicable and non-communicable diseases (de-Graft Aitkins et al., 2010).

2.4.2 Access to affordable medicine

According to the World Health Organization, at least 30 percent of the world's population lacks access to essential medicines and in some countries in Africa, the number may be as high as 50 percent (Bate, 2008). The lack of access to essential medicines and vaccines in developing

countries is one of the reasons for the efforts to encourage local production of essential medicines that are either in short supply or treat other poverty related, tropical and neglected diseases (UNCTAD, 2011). With this approach there will be more assurance that essential medicines are produced closer to where they are needed.

Access to medicine and affordability of medicine may have different meanings and thus must be tackled separately. Access is concerned with physically getting the right medicine to the right person for the treatment of a properly diagnosed ailment. Affordability is concerned with the ability to pay for the required medicine. Many factors may be attributable to a lack of access to medicine. For example, the basic transport infrastructure may be lacking and thus the medical facilities become unreachable or medicine cannot reach the people who need it. Even worse, where it does reach the people, the quality can no longer be guaranteed as with a case with vaccines. In certain instances, people have to travel long distances to reach public health facilities.

Most importantly, limited access to medicine and high prices may fuel the presence of counterfeit medicines (Alfadl et al., 2013) which has been a serious problem in Africa for many years (Laroche et al., 2005). The issue of high prices is sometime difficult to comprehend because it is not directly linked to manufacturers charging high prices. Other forces are at play. For example, taxes, duties, transport costs and mark-ups by middlemen add to the cost of medicine even when manufacturers have lowered their prices (Bate, 2008). It is estimated that about 30% of medicines on the African continent are counterfeits with an estimated 100,000 people losing their lives because of counterfeit medicines (Leon, 2014, pg1). The dangers are life threatening and devastating when taking into account, for example, that a patient taking counterfeit malaria tablets stand to lose their lives when infected with the virus.

The other aspect limiting access to medicine is affordability of imported medicine by national governments. This is the ability of the governments to pay for the medicines to reach the people who need them. Vaccines for national immunization programmes illustrate this concept well. The African economies are vastly different in that there are those countries that are classified by the World Bank as upper middle income countries who can afford to pay for vaccines through taxation (Blecher et al., 2012). On the other hand, the poorest countries rely on funding

to supply the vaccines to their populations from organizations such as the Global Alliance for Vaccine and Immunization (GAVI) if they meet the stipulated requirements (Brenzel et al., 2006) such as the country's gross national income per capita of less than $1500. The dilemma facing countries on the verge of graduating from the donation programmes is how best to fund these vaccines and not put their populations at risk when the funding dries out and most importantly how best to prepare themselves for the transition from donor funding to self-procurement.

2.4.3 Security of Supply

Heavy reliance on imported medicine is the biggest threat to access to medicine and continuous drug supply. In Africa, essential drug supply shortages are a real threat because even when the country can afford to pay for the required medicines or vaccines, there is no assurance that the medicine will be available when needed. Even when the medicine eventually becomes available, it can take longer for it to reach the end user due to long supply chains among other things. Local production may alleviate the problem of medicine supply shortages and allow Africa to take course towards breaking away from depending on imported medicine to treat diseases that are grappling the continent. Manufacturing closer to home may shorten the lead times and supply chains to ensure the medicine reach the patients on time.

The target for many countries is to be self-sufficient with regards to supplying locally produced medicines and less reliance on imported medicines. However, the reality is that self-sufficiency is rare and very few countries can supply more than 85% of their market needs through local production (Kaplan and Laing, 2005). Arguably, it may be worth the effort for many developing countries to target and aim to supply at least 50% of their market through local production or to target to purchase from neighbouring countries as opposed to importing from overseas.

Despite the target of self-sufficiency, drug shortages continue to occur and affect many countries across the globe. These shortages are mainly attributable to manufacturing or production problems (Palmer, 2014), companies leaving the marketplace and changes in manufacturing recommendations such as implementation of stringent cGMP (NNII, 2006). Therefore, even if the vaccines were locally manufactured, production problems could still affect drug supply. Drug supply shortages become even more critical in pandemic situations

such as the shortage of influenza vaccines in 2006 (Ulmer et al., 2006) and again in 2010 during the H1N1 influenza outbreak. The Ebola outbreak in 2014 demonstrated three critical points; 1) Africa is totally dependent on foreign aid; 2) the medicine to treat tropical diseases that predominantly affect Africa are unavailable and; 3) the African governments are not prepared nor are able to effectively deal with pandemic situations. This had a devastating effect on the economies of the affected countries (Holt et al., 2015).

Although local production promises to improve the security of supply, the argument for self-sufficiency remains difficult to sustain especially with Africa largely dependent on imported raw material supply.

2.4.4 Socio-economic Benefits

The African Union's Action Plan for the Accelerated Industrial Development of Africa (African Union, 2007) highlights the link between industrial development, economic growth and social development. The report also highlights the challenge of transforming African economies from resource-dependent to dynamic, diversified industrial economies. This sentiment is evident in the UNIDO's Industrial Development Report (IDR, 2013) which also promotes industrialization and economic diversification from agricultural and mineral extraction economies.

Local production is seen as a means to promote industrialization which presents the opportunity to diversify the economy and introduce other service sectors that will contribute towards a wide employment base (IDR, 2013). Local pharmaceutical production offers a mix of jobs and employment opportunities on a wide scale between low-end technology in packaging operations to high-end technology in research and development. Because high end jobs require skills in mathematics, science and engineering (IDR, 2013), there is a strong argument that local production will encourage investment in skills development and education as the manufacturing industry matures and becomes more sophisticated. This in turn has a potential to stimulate economic growth and create a substantial domestic market (IDR, 2013).

The African Union has emphasized that the industrialization in Africa must be anchored on building human capacity by investing in health, education and training. There is also

recognition that industrial development policies should be designed to enhance the science, technology and innovative capacity which is lacking in many African countries (African Union, 2007). As industrialization matures, it can be expected that there will be more exports generated which will have a positive impact on the balance of trade.

2.5   Considerations for Establishing Local Production Capacity

There are two major conflicting views regarding local pharmaceutical production in Africa. Firstly, there is a view by the Heads of State and Governments (African Union and UNIDO, 2012), the World Health Organization (WHO, 2011) and its allied organizations (UNCTAD, 2011, UNIDO, 2013) that the promotion of local production is a sustainable means to address the public health and socio-economic issues that are grappling the continent. The second opposing view as presented by Kaplan and Laing (2005) and supported by Bate (2008) puts forward the argument that local production may not be feasible for every country to pursue. This section discusses key considerations that must be in place in order for local production to be viable.

2.5.1   Infrastructural Development and Funding

The competitiveness and viability of local production rests on the availability of an efficient infrastructure (roads, communications, water and electricity) and financing. However, basic infrastructure on the continent is either lacking or inadequate hence the infrastructural development has been a priority of the African Union for more than a decade (African Union, 2007). Reliable supply of water and electricity are the cornerstone of pharmaceutical manufacturing such that any disruption in either of these utilities immediately results in a loss of competitiveness. Complex pharmaceutical formulations and cleaning regimes require availability of high quality water and electricity to run the sophisticated machinery.

The delivery of manufacturing supplies as well and final product to the patients demands adequate road infrastructure. Not only is the lack of basic infrastructure a problem for the manufactures, poor road and transport infrastructure will hinder access to medicine if the patients are unable to access healthcare facilities. Unreliable supply of electricity means the

manufacturers must have back-up power supply through the use of generators and pay for additional fuel costs.

Financing is key to industrial development (African Union, 2007) and a major consideration in the development of physical infrastructure required to set up local production operations – that is, the construction of the manufacturing facility. However, financing still remains a major constraint to the industrial development in Africa particularly for small and medium enterprises who are perceived to be risky by the formal banking systems (UNESC et al., 2013). The start-up costs of building a pharmaceutical plant that complies with international quality standards could cost millions of dollars and is therefore considered a major investment undertaking (Bate, 2008).

Once the facility has been built, additional costs to actually run and maintain the facility must be taken into account. Secondly, the hidden costs of maintaining the plant during the initial time of non-productivity whilst waiting for the regulatory authorities to assess and approve the facility as well as those products expected to be produced in that facility must be considered. Finally, consideration must be made to the allocation of funding for research and development to ensure a pipeline of drugs to be produced in the years to come. However, taking into account lead times from discovery to registration may take between 10 – 15 years and cost up to USD 1.38 billion to develop a single medicine (IFPMA, 2011), it is not unexpected that Africa lags behind in this regard. It is for this reason that Kaplan and Laing (2005), Bate (2008) and Slamet (2012) have argued that local production may not be feasible for certain countries.

Without adequate funding it is difficult to imagine any progress with regards to infrastructural development. With Africa being home to some of the poorest countries in the world, according to the World Bank classification system, and funding being hard to come by; the argument for local production becomes difficult to sustain (Bate, 2008). It is therefore not surprising that most countries in Africa concentrate their efforts on simple formulations which involve labelling and packaging.

Funding remains a big challenge in Africa and a stumbling block to local production (SEATINI and CEHURD, 2013). Despite the challenges with funding on the African continent, each country must evaluate its own situation and make an informed investment decision whether or

not local production is a viable option. South Africa already has a well-developed pharmaceutical industry, a robust banking system and a stable political climate which suggests that it may be more favourable to embark on local production than it would be in poorer countries such as Lesotho or Swaziland.

2.5.2 Human Resource Constraints

Although local production promises socio-economic benefits of employment and skill development, pharmaceutical manufacturing is complex and capital intensive as opposed to labour intensive. The processes involved in pharmaceutical production require specialized, highly trained personnel which are in short supply in many African countries (GlaxoSmithKline, 2011). The expected increase in employment rates is unlikely to be realized by the masses because of the specialization requirements of the pharmaceutical industry. Therefore in order for the industry to be competitive, careful consideration must be given to the availability of appropriately skilled personnel to carry out sophisticated tasks required in pharmaceutical production (Saleh, 2014).

The issue of skills availability and skills development becomes more critical as the industry evolves from tertiary to primary production where strong skills in research science, engineering and business management are required (IDR, 2013). Skills development for primary manufacturing is crucial; however, as mentioned in the previous section, funding is required for research and development. According to GlaxoSmithKline (2011) highly specialized staff is necessary to carry out research and development as well as high-tech manufacturing. Sadly, the World Health Report of 2006 (WHO, 2006) reported a crisis in human health in more than 57 countries especially in pharmaceutical health. The availability of scientific research skills and infrastructure cannot be overemphasized.

Central to the issue of availability of skilled personnel is whether the country has university faculties that are producing graduates with qualifications in the sciences particularly pharmacy/pharmacology, chemistry, microbiology, engineering and management (IDR, 2013, Kaplan and Laing, 2005). The quality of science education is crucial in ensuring that graduates are able to support research and development as the industry matures and moves towards primary production. South Africa is home to some of the world renowned universities with a

strong base in science, business and research. These include the Rhodes University School of Pharmacy, The University of Cape Town, Wits University, University of KwaZulu-Natal and a number of technology universities across the country all of which excel in the fields of science and research.

Because skills development takes time and effort (IDR,2013), technology transfer may be a solution in boosting local production capacity and facilitation of technical "know-how" transfer (GlaxoSmithKline, 2011). Technology has many benefits in that the recipient of technology transfer gains expertise, support and inherits a quality system from an established manufacturer. As beneficial as it may be to use technology transfer as a vehicle to accelerate skills transfer, careful attention must be paid to selecting a partner with a mutual benefit. For example, technology transfer partners may impose market/territory restrictions which may hamper the profitability of the local manufactures. Secondly, technology transfer is lengthy and may be expensive depending on the nature and complication of the technology being transferred. The costs of technology transfer may include travelling costs for training, new equipment, trial material and material for validation. All these costs are usually incurred before any product can be approved for sale to the market and someone has to pay for it.

2.5.3 Quality of Medicine and Regulatory Oversight

The quality of medicine and regulatory oversight go hand-in-hand as poor regulation of medicine pose a serious threat to public health and may result in the presence of sub-standard or counterfeit medicine on the market (Kaplan and Laing, 2005). It is the responsibility of the regulatory agencies to verify compliance with good manufacturing practices by manufacturers; to oversee the drug registration process and to ensure that drugs that are not registered or produced in GMP-compliant facilities do not reach the market (UNCTAD, 2011). The regulatory agency conducts facility inspections, reviews registration dossiers and issues licences and give market authorization to the manufacturers. Sadly, in many developing countries, including Africa, the regulatory oversight is not up to the required standard despite the presence of regulatory agencies in almost all countries (WHO, 2012).

Weak regulatory oversight in many countries results in the presence of sub-standard or counterfeit medicine finding their way into the market and have a devastating effect on human

health, economic relations and quality of life (Leon, 2014). A weak regulatory framework and a lack of access to medicine due to high prices are some of the reasons that are responsible for counterfeit medicine on the market. The problem of counterfeit medicine is not only an African problem as it also affects countries with the most robust regulatory systems; however, Africa is estimated to have over 25 percent of counterfeit medicine in circulation (Leon, 2014, pg1). Weak regulatory oversight also results in many countries not complying with GMP principles sighting costs associated with upgrading to GMP inadvertently compromising on quality standards.

There is a lack of regulatory harmonization across the African continent resulting in each country stipulating its own regulatory requirements which can also act as a barrier to registering medicines on the African continent (Narsai et al., 2012). Because of weak or poor regulation, many countries in Africa do not subscribe to internationally recognized quality standards such as those stipulated by the World Health Organization (WHO) for prequalification; the African countries are unable to benefit from economies of scale by selling to the WHO. It is for this reason that the African Union has recognized that inability to meet international standards is hampering competitiveness of the local industry as well as global competitiveness (African Union, 2007). The AU further recognizes that failure to meet global standards is a barrier to taking advantage of the benefits of market access for processed and manufactured goods.

2.5.4   Market Dynamics and Competitiveness

Arguments against local production in developing countries, particularly in Africa, suggest that the market size does not justify the investment undertaking. This argument is strongly supported by Kaplan and Laing (2005) who have indicated that countries with smaller economies should abandon local production ambitions due to a lack of economies of scale. From an investment perspective, the companies need to break even and generate profits to be able to recoup their investment (GlaxoSmithKline, 2011). The argument further suggests that small companies in small economies cannot enjoy economies of scale that large companies in developed countries do hence they cannot compete in price or quality (Kaplan and Laing, 2005). According to this argument, the suggestion is that smaller countries should rather abandon the idea of local manufacturing altogether and purchase medicines from large developing countries such as Brazil and India.

The above argument almost sounds convincing but is loosely constructed with a few loopholes that are left hanging. Firstly, the definition of a small economy and small company does not come through from the above argument. If African pharmaceutical manufacturers are producing essential medicines to satisfy the needs of their population, they do not have to be as big as the multinationals. Given the infrastructural and financial constraints facing the African manufacturers, the argument to remain within limits of your resources seems more plausible. Secondly, it is widely acknowledged that manufacturing medicines locally may not always be cheaper than importing them (UNCATD, 2011). However, with an increasing "dual burden of diseases" in Africa (IDR, 2013) the point at which local manufacturing will be more beneficial over importation is fast approaching and this has not yet been explored. Finally, the suggestion that African economies should buy from countries with large economies is a step in the wrong direction as it suggests that Africa will never break free from importation dependence. It also defeats the purpose of establishing local production to stimulate industrial development on the continent.

A simulation study conducted in Ghana showed that economies of scale are not an absolute necessity and that countries with smaller economies can generate profits despite certain cost disadvantages (Chaudhuri, 2013). According to Chaudhuri (2013), producing with cost disadvantages does not lead to higher prices of neither medicine nor does it render local production to be unviable. The most startling conclusion from this study is that the role of economies of scale is over-exaggerated. According to the United Nations Conference on Trade and Development (UNCTAD, 2011) cost disadvantages may be improved by introduction of incentives such as tax breaks, duty-free importation on active raw materials and tax holidays until profitability sate has been reached.

2.6 Chapter Summary

High disease burden, heavy reliance on imported medicines and the desire by many African countries to become self –sufficient with regards to medicine supply are key factors driving the support local pharmaceutical production. Whilst there is a case for supporting local production, there are strong arguments that seem to suggest that local production may not be a viable option for many African countries to an extent that each country needs to assess its case based on merit and circumstances affecting individual countries.

Literature reveal that Africa lacks the capacity to produce human vaccines for paediatric immunization programmes. There are numerous cost disadvantages that must be addresses for local production to be successful. These include the availability of basic infrastructure (water and electricity); availability of skilled staff with relevant skills in subjects such as chemistry, pharmacy and business management; fragmented and weak regulatory framework in many countries has an impact on the availability of high quality of medicines; relatively small markets and high production input costs result in low profit margins that may discourage potential investors; lack of funding for research and development results in heavy reliance on imported active raw materials for secondary production which encourages the pharmaceutical companies to focus more attention on producing generic medicines.

Whilst many factors affect the viability of local production, this study will focus on the production costs and market dynamics to ascertain whether local production of vaccines can be carried out in South Africa more favourably than importing SFP.

Taking into account the factors discussed in this review, Chapter 3 will describe the methodology that was employed in determining economic viability of a locally produced vaccine when compared to imported semi-finished.

CHAPTER THREE: Research Methodology

3.1 Introduction

This chapter presents the research methodology used in the study. The chapter begins by restating the aims and objectives of the study followed by the description of the research design and methodology; the location of the study, sampling, data collection and data analysis methods. The chapter concludes with a discussion of the measures taken to enhance the validity and reliability of the study.

3.2 Aim and Objectives of the study

The aim of this study was to evaluate economic viability of LFV when compared to SFP.

The objectives of this study were:

i. To ascertain the manufacturing costs of LFV versus SFP;
ii. To determine the level of economic activity for which LFV is preferred when compared to SFP;
iii. To determine the desirable market size for which one option is preferred over the other;
iv. To determine the level of investment needed for both options – LFV vs. SFP;
v. To determine the effect of changing the key variables such as the selling price, cost of labour, raw materials and bulk product on the viability of either option.

3.3 Location of the Study and Selection of Participants

3.3.1 Location of the Study

The study was conducted at The Biologicals and Vaccines Institute of Southern Africa (Biovac) in Cape Town. Biovac is a Public Private Partnership (PPP) entity that was established in 2003 to revive the development and manufacture of vaccines and biological products in South Africa. The Company employs more than 180 employees at its plant in Cape Town across the following departments: Manufacturing, Quality Control, Quality Assurance, Supply Chain, Regulatory Affairs, Business Development, Finance and Human Resources.

With no human vaccine manufacturing capacity in South Africa, vaccines that support the Extended Programme on immunization (EPI) are sourced abroad and imported either fully-finished or semi-finished for local packaging and distribution into the South African public market. To date, Biovac has made significant progress in re-establishing vaccine manufacturing capability by investing in world-class infrastructure and skills development. This has enabled Biovac to enter into technology transfer agreements with various international vaccine manufactures to locally produce vaccines in the newly commissioned multipurpose manufacturing facility in Cape Town.

The approval of the locally produced vaccines will enable Biovac to become the only approved human vaccine manufacturer in the Southern African region.

3.3.2 Selection of the Participants

The manufacturing of LFV and SFP requires input from seven (7) business units which include Production, Quality Assurance, Quality Control, Supply Chain, Regulatory Affairs, Finance and Human Resources departments. In order to achieve the objectives of this study, individuals possessing intimate knowledge and understanding of the vaccine manufacturing and support processes as they pertain to Biovac were selected to provide specific information. The Heads of each operational department were approached by the researcher to identify individual(s) within their departments who were knowledgeable in Biovac processes and systems and could be considered subject matter experts. The role of the identified participant was to provide the required information to be analysed by the researcher and to identify key informants for the research. Individuals from each department formed the basis of a focus group. The core of the focus group was made up of Section Heads (middle managers) from 7 business units who possessed both the process knowledge and authority to second subordinates to provide information to the researcher.

Non-probability, purposive sampling using the judgement technique was used to select the participants of this study. Purposive sampling design is used to obtain information confined in a specific target group or type of people either because they are the only ones who have it or they conform to a criteria set out by the researcher (Sekaran and Bougie, 2013). Within the context of this study, few participants could be selected based on their experience in vaccine

25

manufacturing and knowledge of the Biovac processes. The judgement technique was utilized to select the participants who were in the best position to provide the required information necessary.

Although, according to Sekaran and Bougie (2013), judgement sampling may limit the generalizability of the findings, it is the only viable sampling method when the required information can only be sourced from a handful of individuals who are subject matter experts. In this study the judgement sampling technique was used specifically because very few individuals, within Biovac, could provide the required information on the specific inputs required to support vaccine production processes.

Although the information pertaining to the manufacturing and support services was obtained from the section heads, or designates, these individuals were themselves not the subjects of the study since the aim of the study was to assess the costs associated with manufacturing and support operations.

3.4 Research Design and Methodology

3.4.1 Purpose of the Study

The purpose of this study was to explore and gain an in-depth understanding of the Biovac production cost factors associated with LFV and SFP operations. In order to conduct this study, the costs of a multivalent SFP were compared to the costs of LFV produced from formulated bulk product (antigen). This study had to be conducted because the current costing model for Biovac is based on sourcing and distribution of imported vaccines. No formal cost analysis study has been conducted by Biovac on LFV activities.

3.4.2 Research Approach

A single case study approach was selected as the research strategy for this study to explore and gain an in-depth understanding of the Biovac production processes and associated costs.

This case study follows a qualitative approach to solve the research question. The qualitative approach is exploratory in nature and is used when the researcher wants to gain a deeper understanding of the problem within a specific setting through first-hand experience (Sekaran

and Bougie, 2013). According to Rowley (2014) single case studies are appropriate to use where the case is extreme or unique and Biovac is a unique case where single case study is applicable.

Case study research is defined as an in-depth study of a particular situation, or event, or problem within its real-life context where the researcher utilizes multiple sources for data collection but has little or no control over the events as they unfold (Yin, 1994). In a case study the "case" may be an individual, or a group, or the organization, or a department within the organization that the researcher is interested in (Rowley, 2014, Sekaran and Bougie, 2013). In the case study methodology, the researcher selects the case and conducts a detailed contextual analysis to gain an in-depth understanding of the phenomenon to be studied as opposed to making generic statistical conclusions based on quantitative data.

Case studies have a prominent place in management studies and organizational theory as a form of data collection and a type of unstructured analysis (Schnell, 1992) and are particularly useful for analysing and solving practical business problems in their contextual setting (Dul and Hack, 2008). The case study approach was deemed appropriate to apply in this research as the aim was not to make statistical inferences about the vaccine manufacturing industry costs but to gain a holistic view of the cost factors as they pertain specifically to Biovac as a business.

The advantages of using case study as a research method lies is the ability to use multiple data sources to collect both qualitative and quantitative data for analysis and interpretation of the problem within its environment with minimal interference from the researcher (Sekaran and Bougie, 2013). Sources of data may include but not limited to archival records, interviews, physical artefacts, direct observations, and participant-observation with each data source contributing to the researcher's understanding of the phenomenon (Baxter and Jack, 2008). The captured qualitative accounts may reveal and explain complexities that may not be captured through experimental and survey research (Zainal, 2007).

Case study research approach is not without criticism. Critics of this methodology have argued that case studies may provide little basis for scientific generalisation because of the dependency from a single case and may lack rigour because the researcher may have allowed bias views to influence the direction of the findings (Yin, 1994). It has also been argued that conducting case studies may be time consuming and generate too much data that may prove to be a challenge to

analyse. Whilst scientific generalizability is an important factor in research, this study aimed at finding information about one specific organization, Biovac. Using multiple sources of data collection methods has enhanced the credibility of this study to deal with the issue of bias within the study. Finally, focusing the attention to the research question has allowed collection of relevant, manageable data.

3.4.3 Data Collection Strategies

The qualitative nature of this study called for a combination of data collection strategies to provide insight into the research problem from different angles. Both primary (first-hand) and secondary (existing) sources were used in data collection.

Data were collected using 1) Focus group discussions and interviews with a total of 6 "key informants"; 2) Document Studies; and 3) Observation methods.

3.4.3.1 Focus Group Discussions and Interviews with individuals

The focus group was formed by departmental section heads or designates (middle management) representing Production, Quality Assurance, Finance, Supply Chain and Project Management Office. The participants in the focus group were selected using a judgemental sampling method (Sekaran and Bougie, 2013) based on their experience and intimate knowledge of the vaccine manufacturing operations; the authority level as managers to be able to provide the required information and give direction to their subordinates to provide further details required in the study.

A total of 3 Team meetings were scheduled at monthly intervals with the members of the Focus group with additional ad hoc meetings with individuals from the group to provide clarity and specific information. Group meetings took place at the Company premises during normal working hours whilst individual interviews took place at a mutual venue as agreed. The Focus Group discussions provided first hand opinions and interpretation of the overview of Biovac production processes. Interviews with "key informants" (individual employees) were conducted to provide detailed information on the process overview obtained from the Focus Group discussions and to allow for further follow up to clarify concepts and check for reliability of data.

3.4.3.2 Document Studies

Existing Company records were studied to extract information to enable process analysis on manufacturing and packaging operations, in-bound transportation cost factors. The records consulted included:

- Manufacturing and Packaging Records – batch records, standard operating procedures, log books and work instructions
- Financial Databases – Financial records with data on costs of raw materials, salary bands per job category, equipment depreciation, budgets and actual spent for the years 2014 and 2015
- Project financial information – to supplement and correlate information supplied by various departments.

Sensitive business information was handled with care in order to ensure confidentiality and ethical considerations.

3.4.3.3 Observation Methods

Observation methods provide a useful tool to collect data on actions and behaviour (Sekaran and Bougie, 2013). Observations require the researcher to go into the field to collect first-hand data. In this study, observations were made within the production environment in order to gain insight into manufacturing inputs required in the study. The aim of using this method was to observe and record the production processes; to confirm the components and labour used in manufacturing as provided by the participants of the focus group and key informants; and to gain an in-depth understanding and confirm the accuracy of the Biovac production processes.

Both forms of observation methods – participant and non-participants – were used in this study. As a participant, the researcher made arrangements to spend time with production operators inside the manufacturing facility learning various aspects of the production processes whilst making notes of the critical operational information. This method of observation was utilised specifically when vial filling operations similar to those of the case study vaccines were undertaken. As a non-participant, the researcher observed the manufacturing processes using

the closed circuit cameras installed for this purpose as and when it was required to verify process information such as start and finish times of certain processes. The cameras are always switched on and the operators are aware that anyone could be watching at any given time. This provided the opportunity for the researcher to request permission to observe the operations as and when required.

3.5   Data Collection Procedure

Data collection was conducted with the research objectives in mind to ensure a logical flow of information from the first objective to the last objective. As a result, more time was allocated to understanding and capturing the various processes within the vaccine value chain in order to fulfil objective 1 (determination of production costs). The information obtained here was used to fulfil objective 2 (determination of favourable option to pursue based on economic activity) and objective 3 (determination of the desirable market size to generate revenue), as well as objective 5 (evaluation of the effect of changing key variables on profitability). Objective 4 (Cost of investment) was independent of data collected from objective 1.

3.5.1 Objective 1: Determination of the manufacturing costs of LFV and SFP

Process Flow Mapping

Data used to describe, analyse and cost the manufacturing processes were collected using a combination of sources, namely: focus group, interviews, company records and observations. Group discussions and interviews were critical in mapping the production processes and identifying which records to be studied as well as to confirm which processes to be observed for data collection. The extraction of information from Company financial records and process observation provided the key numerical information that was required to evaluate the economic viability of locally produced vaccines.

Initially, three Focus group meetings were scheduled over the period of 3 months to provide the overview of the manufacturing processes as they pertain to semi-finished imported vaccines and local formulation and filling activities. The aim of the first meeting was to initiate the group discussion to describe and give an overview of the operational activities at Biovac. The second meeting was scheduled by the researcher to present the initial results to the participants of the

focus group based on the discussions from the first meeting. This presented the opportunity for both the researcher and the subject matter experts to check if the information from the first meeting was captured accurately and for the group to ratify the process information first hand.

A third meeting with the focus group was scheduled to present the final framework to be used in collecting detailed data and to present the picture that had emerged from the initial analysis. Between the first and the third meeting, interviews with the identified key informants, observations and archival data were collected by the researcher. After the third meeting the research focussed mainly on the Company record extraction and observation techniques to collect numerical data.

The information on process maps was grouped into various cost centres based on the activities mapped and was verified through focus group discussions, manufacturing records review and individual interviews.

Collection of Batch Processing Data

The collection of batch processing data for both LFV and SFP was necessary in order to understand the total duration of each operation. Relevant data was collected from the discussions with the Focus Group and verified by studying the manufacturing batch records as well as through process observations. This data enabled the researcher to calculate the theoretical production capacity of this facility; the calculation of direct labour; the batch size to be filled and packed; the components required for each operation which in turn will enable the computation of raw materials required per batch. Data was collected on component preparation and cleaning times; components used in filling and packaging operations; labour usage and requirements for each process stage; theoretical capacity of the manufacturing site; equipment filling speeds and in-bound transportation costs of bulk liquid and finished product.

The duration of processing a single batch was computed by using data collected for a standard batch size of imported formulated bulk (83 Litres) for filling into single-dose glass vials using the automated vial filling machine at 10,000 units per hour and a manual packaging process that is currently in place.

The following assumptions were made in the calculation:

- Out of the 52 weeks in a year; there are 8 days a month allocated to weekends which translates to approximately 96 days per annum (equivalent to 13 weeks). With the exclusion of public holidays, approximately 38 working weeks available for production.
- Only a single product is filled in vials at this site over 38 weeks;
- All available resources are channelled to producing this product;
- The manual packaging operational capacity is fixed at 350 units packed per operator per hour for either LFV or SFP;
- The quantity of the product filled is equal to the product to be packed;

Collection of Process costing data

Data on the cost of components used in manufacturing (filling and packaging); equipment costs and depreciation; manufacturing overheads and labour costs were collected by the researcher through interviews and extracted from company financial and project records.

Cost of Production

The method used to calculate the costs of producing a single unit (dose) of LFV was similar for the SFP although the inputs varied. Variable costs per unit (dose) were calculated by dividing the costs per batch by the number of units per batch; fixed costs were computed per annum.

Total Fixed Costs were computed by adding direct costs (transportation, raw materials, etc.) and indirect costs (costs of labour, electricity, water, etc.).

Total Fixed costs per dose were calculated based on the known total annual demand of this product at 4.5 million doses per year. Different scenarios were simulated under different demands such as at theoretical capacity of Biovac.

Locally produced vaccine cost inputs

The cost of formulated bulk transportation, the cost of formulated bulk, the cost of raw materials, cost of product testing, equipment depreciation as supplied by the Finance Manager, direct and indirect labour and energy costs per batch including the packaging operations were taken into account in this calculation.

The cost of product per batch was calculated using the contract price per litre in the supplier's foreign currency and converted into South African Rands (ZAR) to obtain the cost of bulk product per litre. With the known delivered volume of bulk product, the total cost per batch was calculated by multiplying the volume and the ZAR product per litre. To variable cost per dose was calculated by dividing the total cost per batch with the average number of units per batch as calculated in Table 4.5 above.

The depreciation costs of critical equipment used in production were extracted from the company financial records.

The overhead costs were computed by extracting financial information on indirect costs related to manufacturing as supplied by the finance manager. From the focus group interviews, a percentage activity was allocated to production with the final overhead rate expressed as a percentage of the total indirect costs.

Imported SFP cost inputs

The costs of SFP, transportation, raw materials, product testing, direct and indirect labour costs were taken into account when calculating the input costs. Depreciation on the equipment used in the manual packaging of the SFP was not calculated as the equipment used was more than 10 years old and the remaining value was negligible to have a significant impact on the cost of production.

The unit cost of SFP was provided by the finance department and was multiplied by the average batch size of 119,000 units to calculate the estimated total cost of product.

A similar approach was followed when calculating the overhead costs relevant to SFP.

3.5.2 Objective 2: Determination of favourable option to pursue for LFV and SFP

Point of indifference or Pivot Point

This is the point at which the total cost to produce a certain number of doses is irrelevant of whether the vaccine is manufactured locally or imported semi-finished. This point is significant in that it could be used to determine which option is more favourable under different market conditions (low or high market demand). On either side of this point one option (LFV or SFP)

is expected to be more favourable than the other. In this study, the researcher is interested to determine the number of doses required to reach the point of indifference and extrapolate whether the point at which the LFV option is economically more viable than the SFP option.

To determine this point, variable costs per dose and fixed costs (Total Cost) of each unit produced up to 5 million doses were calculated. A chart depicting Total Cost (y-axis) vs. Number of doses (x-axis) was plotted on the same axis for both LFV and SFP using the formula:

Y = mx + c, where Y = Total Cost of production; m = variable cost per dose (Slope);

x = number of doses and c = Fixed Cost (y-intercept);

The point at which the two curves cross each other is the indifference point.

3.5.3   Objective 3: Determination of the desirable market size for each option

Break-even Point Analysis

The desirable market size will be determined by the number of doses required to break-even. The break-even point is a neutral point where the cost of production equals the revenue generated. It is used to determine the point at which the number of units sold will cover the operational expenses and generate a profit. The selling price of the SFP and LFV was assumed to be the same as this is the single exit price on tender. The break-even point was calculated using the variable cost per dose and fixed costs which in turn were used to compute the contribution margin.

Using the contribution margin and total fixed costs, the Total Profit gained from each unit produced up to 5 million doses was calculated. A chart depicting Profit (y-axis) vs. Number of doses (x-axis) was plotted on the same axis for both LFV and SFP using the formula:

Y = mx + c, where Y = Total Profit; m = Contribution Margin (Slope); x = number of doses and c = Total Fixed Cost (y-intercept);

The break-even point was reached at a point where each curve crossed the horizontal axis.

3.5.4 Objective 4: Determination of the level of investment required for LFV & SFP

The investment requirements for locally filled and imported vaccines differ. This section will estimate the cost of setting up a facility from the ground up. With the Company having first built a facility suitable for imported vaccines (Cold Storage, Packaging and quality Control testing) then built a new facility for formulation and filling; the actual cost was accurately calculated from the data that was collected from the archival projects and financial records.

The cost of bringing the product into the facility was estimated from technology transfer projects with external partners by analysing the actual project expenditure on each project from inception to submission of a product dossier for registration. In particular, the costs were analysed and grouped according to the following categories:

- Infrastructural Costs – Physical Buildings (Packaging, Formulation, Utilities, Warehouse and Cold Room Storage and Quality Control Laboratories)

- Plant & Equipment – Automated Filling Machines, Washers, Autoclaved and Utilities

- Technology Transfer Components – Product-specific Equipment, Qualification & Validation, Regulatory, Bulk Product Transportation and Consultant Fees

The foreign currency fluctuations and today's cost of borrowing were not taken into account

3.5.5 Objective 5: Assessment of the effect of changing variables on profitability

Objectives 1 to 3 were concerned about understanding the production cost and market dynamics under static conditions. This objective aimed to test the resilience of either LFV or SFP operations by introducing the stress factors which are known to occur in the vaccine business. Firstly, the SFP and formulated bulk are imported from a European supplier and are therefore subject to currency fluctuations between the South African Rand and the Euro. The resilience to external forces had to be tested for the most favourable option as per objectives 2 and 3. Secondly, the prices of vaccines are known to drop either due to entry of competitor products or due to unaffordable prices (Spier and Milstien, 2009). It was therefore critical that both semi-

finished and LFV were subjected to these external factors and assess the impact on profitability and to determine which option is able to better withstand these factors.

By using the production cost information from objectives 1 to 3, the cost of product (Formulated bulk and SFP) was increased by 25% while the selling price which is currently known was reduced by 20% and the effects on profitability and resilience were analysed. The percentage manipulations were adjusted in parallel up to a point where only one option indicated viability under duress.

3.6 Data Analysis

The data collected from multiple sources had to be coded and categorized to give meaningfulness. Data selection, coding and categorization is known as data reduction (Sekaran and Bougie, 2013). It helps to give ideas on how data may be displayed as well as to draw conclusions based on patterns. Once the data has been coded, the next stage in the analysis is data presentation as a matrix or graphical form to illustrate the patterns as they are developing.

Data Coding
The unit of analysis in this study was the entire organization as this was a case study. As a result, an insurmountable amount of data was collected. Relevant data was selected and coded as either direct or indirect cost. These direct and indirect costs were further classified into either fixed or variable costs.

Data Categorization
The second stage of analysis was the mapping of the manufacturing processes for both SFP and LFV with the production costs associated with both processes described and classified into cost centres. Through repetition of data from multiple sources, the main cost drivers emerged as transportation of SFP or formulated bulk costs (for LFV), raw materials, labour, equipment depreciation, utility and product testing costs.

During this stage of data analysis, patterns and relationships between the data began to emerge which at times necessitated categories to be broken down into sub-categories.

Data Display and Analysis

The data that had been coded and categorised into cost pools was captured and displayed in a tabular matrix using Microsoft Excel Spreadsheet. With further analysis, formulae and graphs were computed from the data to easily read patterns and make conclusions.

Data Stress testing

In order to test the robustness of the model, the cost of formulated product and the selling price were deliberately increased and decreased by between 10 and 25%. Further analysis was conducted on the effect of this manipulation.

3.7   Issues of Trustworthiness

Although case study research methodology is widely used in management studies and organizational theory (Schnell, 1992) because of its flexibility in the use of multiple sources of data to enhance credibility (Baxter and Jack, 2008, Yin, 2012), the method may be subject to criticism. The researcher took careful consideration when conducting this study to ensure the credibility of the study.

To enhance the credibility of this study, the researcher used multiple sources of data to converge them into the research. Within the context of this study, a focus group made up of company section heads that are familiar with the intricacies of vaccine production was formed. This group provided valuable information on the overview of the processes. Because of the level of authority within this middle management group, each member was able to select individuals from their teams who could be interviewed or guide the researcher into the facility to observe the processes as they unfold. The information that was provided by members of the focus group was verified through observations and review of manufacturing and financial records for accuracy.

A series of meetings with the focus groups were setup as well as presentations to the research and development team (academic team) were used as a means to interrogate the robustness of the research methodology and approach. Data relating to costs were collected from projects and verified against archived financial records whilst data on processes and process maps were verified through approved standard operating procedures and observation of the processes. An

audit trail of the presentation slides to various groups (focus groups, management and research and development team), the meeting requests and summary of discussions were kept by the researcher for reference and as part of the audit trail. This team provided valuable input on the best approach and course to be taken in order to ensure the researcher remained within the scope of the study.

3.8 Ethical Considerations

Ethical considerations were observed at all times when this research was conducted. Active research only commenced after the Ethical Clearance Certificate was issued by the University of KwaZulu-Natal. Permission to conduct the study was sought and granted in writing by the Chief Executive Officer of Biovac. In conducting this research study within a commercial entity, the researcher had to take great care not divulge company secrets such as supplier information, trade secrets and sensitive information without explicit permission to do so. The permission letter reiterated that access to confidential Company information needed to be treated in a confidential and appropriate manner as outlined in the Company's Policies and procedure.

As this was a case study research, observations took place within the work setting and it was imperative to demonstrate respect to the production schedule and request for permission to have access to restricted areas within the facility, Company records and time for interviews. Although this was a case study on the entity, key informants and the focus group members had the option not to participate and this was emphasized during on-going progress report-back meetings.

3.9 Limitations of the Study

Assumption that only one product is produced on the site annually. The effect on the production costs if more products are added onto the facility was not assessed.

The effect of foreign exchange currency fluctuations on the original cost when the equipment was purchased was not taken into account. Instead, the cost of production and other related costs will be reported in the local currency (the South African Rand).

3.10 Summary

This chapter discussed the case study research methodology that was employed by the researcher when conducting this study. The selection of middle managers as subject matter experts proved to be invaluable in ensuring the accuracy and the robustness of data collection procedures. Multiple sources of data from company financial and project records, standard operating procedures, individual interviews as well as direct and indirect observations were used in the study to collect and verify information provided by the Focus Group members as well as the key informants.

The presentations to various groups within the organization enhanced the credibility of the study. Ethical considerations were also employed by first obtaining permission to conduct the study at the Company site and undertaking to maintain confidentiality of sensitive information that the researcher may have obtained special access such as personnel salaries and Company supplier database and trade secrets (contracts).

Chapter 4 will present the findings resulting from data collected in this chapter. The findings will be presented systematically to align with the objectives as presented in this chapter.

CHAPTER FOUR: Findings

4.1 Introduction

The aim of this study was to evaluate whether local production of vaccines, in South Africa, is economically viable when compared to imported vaccines using Biovac as a case study. This chapter presents and discusses the results of the data analysis from Chapter 3. This study entailed the collection and sifting through tremendous amounts of data from different sources over a period of 4 months in order to achieve the goals and objectives of the study.

The results are narrated and presented in tabulation and graphical form as appropriate.

This chapter is organized with the research problem in mind and with the findings presented in accordance to research questions raised in Chapters 1 and 3 as follows:

- Section 4.2.1 will report on the demographics of the Unit of Analysis
- Section 4.2.2 will report the findings on the unit cost of production;
- Section 4.2.3 will report findings on the point where LFV is favourable over SFP (The point of indifference);
- Section 4.2.4 will report on the findings relating to market size for which one option is desirable over the other (Break-even Analysis);
- Section 4.2.5 will report the investment costs required for each option – LFV and SFP;
- Section 4.2.6 will report the findings on the effects of changing key variables such as the cost of product and a drop in price on the profitability of either of the options.
- Section 4.2.7 will summarise the findings of this chapter and introduce Chapter 5.

4.2 Presentation of Findings

4.2.1 Demographics of the Unit of Analysis

The Biologicals and Vaccines Institute of Southern Africa (Biovac) is a pharmaceutical manufacturing company based in Cape Town with a workforce of approximately 180 employees. The core business of Biovac is vaccine manufacturing. The company was formed in 2003 as a Public Private Partnership (PPP) between the South African Government and The Biovac Consortium. Since 2003, more than R700 million has been invested in infrastructural and skills development in order to realize the company's ambitions of becoming a fully-fledged

vaccine manufacturer on the African continent. Since inception, Biovac has recruited a wide mix of skilled personnel to support the current operations of vaccine distribution, basic Research and Development as well as future expansion operations. By 2014, the skill set was mixed with Company employing 9 personnel with PhD qualifications on the high end and 30 with matriculation and below as summarised in Table 4.1 below.

Table 4.1: Biovac Skill Set in 2014 (Permanent Employees)

Qualifications	No. of people
Matric & Below	30
Certificates & Diplomas	34
Bachelor's Degree	20
Honours Degree	10
Master Degree	13
PhD	9

Source: Adapted from Biovac Presentation**:** Retention Policies and Models for the Local Workforce

The headcount per department is shown in figure 4.1 below. The figure shows that the highest numbers of people are employed in Production, Quality Control, Logistics, Engineering and Research and Development departments.
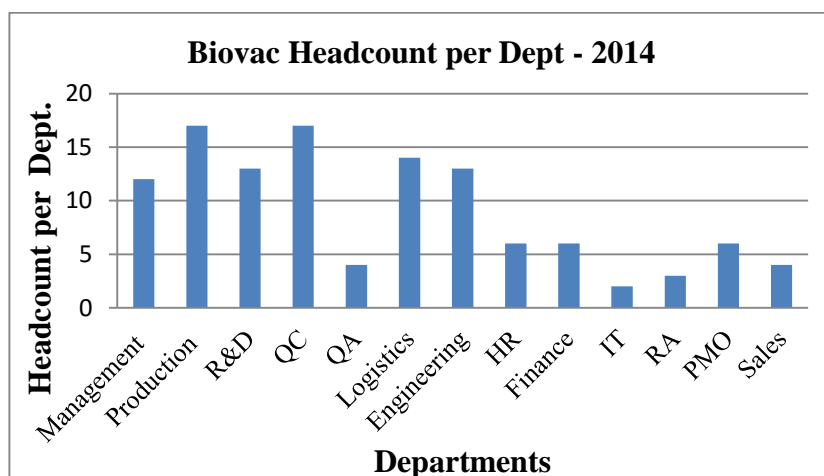
Figure 4.1: Biovac Headcount per Department

Source: Adapted from Biovac Presentation**:** Retention Policies and Models for the Local Workforce

4.2.2 Objective 1: Unit Cost of Production

The determination of the unit cost of production was conducted in a multistep approach involving: 1) process flow mapping and identifying the relevant cost centre (pools), cost activities and classification; 2) Batch process information and theoretical capacity for aseptic filling and manual packaging operations; 3) Computation of cost activities and classification; 4) Indirect cost allocation of manufacturing and administrative overheads and; 5) the cost of producing a single unit of vaccine under various demand scenarios.

Process Flow Mapping and Cost Categories

The manufacturing process overview was developed from the description and identification of activities involved in both local filling and semi-finished importation operations. Due to the complexity of the vaccine manufacturing operations, data collected was reduced and categorized into main cost centre activities and further subdivided into relevant costs per activity. Each cost activity was classified as either fixed or variable as described in Table 4.2 below.

Table 4.2: Process Steps for SFP and LFV

Semi-Finished Product	Locally Filled Vaccine		
Cost Centre/ Pool	Cost Centre/ Pool	Cost Activities	Cost Classification
Finished Product Handling	Bulk Liquid Handling	Transportation	Variable
		Raw Materials	Variable
		Labour	Fixed
	Aseptic Filling	Raw Materials	Variable
		Labour	Fixed
		Equip. Depr.	Fixed
		Direct Electricity	Variable
Viewing	Viewing	Labour	Fixed
		Equip. Depr.	Fixed
Labeling & Packaging	Labeling & Packaging	Raw Materials	Variable
		Labour	Fixed
		Equip. Depr.	Fixed
		Direct Electricity	Variable
Quality Control	Quality Control	Consumables	Variable
		Labour	Fixed
		Commissioned Testing	Variable

There are four steps involved in the processing of an imported vaccine and five for a locally produced vaccine. These steps are grouped vertically into cost centres. The manufacturing steps are similar between LFV and SFP operations with the additional aseptic filling step for the LFV.

The cost centres for SFP are product handling from supplier to Biovac; product inspection; labelling and packaging and quality control testing. The LFV cost centres were found to be same as in SFP with the addition of the aseptic filling cost centre. In both SFP and LFV the common cost activities were:

- Transportation Costs – Freight Charges, Customs Clearance and Agents Fees
- Raw Materials (SFP or Formulated Bulk Liquid) – Cost of Product and Insurance
- Direct Electricity – power consumption required to power the equipment
- Quality Control Testing – consumables and testing commissioned testing
- Labour Costs – all labour costs across the cost centres including indirect labour
- Equipment Depreciation – Significantly costly equipment depreciation (Automated filling lines, washers and autoclaves)

Batch Process Information and Theoretical Capacity Calculations

Aseptic Filling

The company subscribes to batch manufacturing method of operation. In order to fill one batch of product, a single batch of formulated bulk liquid must be dispensed into single, sterile vials. The formulated bulk product for LFV is shipped sterile to Biovac in a sealed stainless steel tank with a volume of 83 litres (L) which is dispensed to single vials with a target 0.68 millilitres per vial.

A single batch of finished product filled from 83 litres of formulated bulk into single dose vials at a rate of 10,000 vials per hour is expected to have a theoretical yield of approximately 122,000 unit doses. A 2% rejection rate allowed to account for start-up samples, product testing (quality control), in-process checks, product lost due to start-up and the product left in the 3-meter line between the formulated bulk tank and the filling line, the final quantity expected to be transferred to packaging is approximately 119,000 doses. Although the actual filling time

required to fill and empty the formulated bulk tank is approximately 12 hours, the total batch processing time (filling operations) is 19 hours as shown in Table 4.3 below.

Table 4.3: Batch Process Information (Aseptic Filling)

Batch Process Information (Aseptic Filling)		
Formulated Bulk Size	83	Litres
Fill Volume per dose	0.68	mL
Batch Size	122059	units
Batch Size (2% Scrap)	119618	units
Filling Capacity	10000	units/hour
Filling time	12	hours
Setup Time	4	hours
Cleaning Time	3	hours
Total Process Time	**19**	**hours**

It takes approximately 4 hours to prepare for the aseptic filling of a batch. This is the time it takes to perform the cleaning and sanitisation of the filling line, the aseptic connections between the filling line and the formulated bulk product and the time to allow the filling suite to return to a state of "rest". Upon completion of the filling process, the disposable filling components are discarded as per approved procedures. The filling machine and the filling suite are cleaned over a period of 3 hours.

Theoretical Annual Filling Capacity

The filling line has a theoretical capacity of 63.8 million batches per year at 10,000 vials per hour. This capacity is achieved over 38 production weeks and takes into account the machine will not be utilised during planned maintenance shutdown, Christmas holiday time and on public holidays. As presented in Table 4.4 below, 63.8 million doses equate to a total of 523 batches that could be filled on the vial filling line.

Table 4.4: Theoretical Filling Capacity

Theoretical Filling Capacity		
Production Weeks	38	Weeks
Production Days	266	Days per Annum
Production Hours	6384	Hours per Annum
Annual Filling Capacity	63,840,000	Doses per Annum
No. of batches/annum	**523**	**batches**

The annual demand for this product is 4.5 million doses which equates to a spare capacity of 59.3 million doses under the study assumptions. The annual demand of 4.5 million doses is equivalent to 38 batches to be filled per annum versus a maximum theoretical capacity of 523 batches. Based on the theoretical capacity of the filling line and the stated demand, the utilization capacity of this filling line is approximately 7% per annum for this product.

Packaging Operations

The manual packaging process for both LFV and the current SFP is the same and take the same duration to complete both operations. Each unit filled or imported has to undergo a manual visual inspection before it can be labelled and packed. Table 4.5 below summarises the duration of the packaging process

Table 4.5: Batch Process Information (Manual Packaging)

Batch Process Information (Manual Packaging)			
Parameter	Daily Capacity	Duration/ Quantity	Unit of measure
Batch Size		119 618	Doses
Visual Inspection Capacity/hour	2100	14	hours
Labeling Capacity/hour	6000	5	hours
Packaging Capacity/hour	1750	9	hours
Total Process Time		28	hours
Batch processing Days		**4**	**days**

The visual inspection process is performed by 7 operators at an average of 300 vials viewed per hour and takes approximately 14 hours to complete. This equates to 2 working days on a single shift of 7 working hours (Excludes tea and lunch breaks). The labelling is carried out

using an old automatic labelling machine which has the capability to encode the batch and expiry date at an output of 6000 vials per hour over 5 hours.

The packaging operation takes approximately 9 hours when carried out by 8 operators with an average packaging rate of 250 vials per hour. The total average packaging time is approximately 4 days for a single batch of product.

Cost Activity and Computation of Unit Cost of Production

From data collection and process overview, the main cost drivers for both LFV and SFPs were transport, raw materials, product cost (either formulated bulk or SFP), quality control testing and labour costs. Of these cost drivers, the cost of transport, raw materials and cost of product emerged the highest. Table 4.6 below presents a detailed account of the various costs associated with LFV and SFPs as per data collected.

Table 4.6: Summary Costs behaviour per batch and per dose

Summary Cost Behaviour							
Cost Drivers		**Locally Filled Vaccine Costs**			**Semi-Finished Vaccine Costs**		
Cost Activity	Cost Type	Per Batch	Variable Costs/dose	Fixed Costs per Annum	Per Batch	Variable Costs/dose	Fixed Costs per Annum
Transport	Variable	R 192,287	R 1.58		R 403,725	R 3.31	
Raw Materials	Variable	R 280,340	R 2.34		R 63,566	R 1.06	
Cost of Product	Variable	R 11,961,765	R 100.00		R 8,779,971	R 157.00	
Direct Energy	Variable	R 4,979	R 0.04				
QC Testing	Variable	R 90,738	R 0.74		R 22,392	R 0.18	
Depreciation	Fixed			R 3,097,307			
All Labour	Fixed			R 8,023,794			R 5,069,243
Total variable Cost per Dose		**R 104.70**			**R 161.55**		
Total Direct Fixed Cost				**R 11,121,101**			**R 5,069,243**
Manufacturing Overheads				R 14,065,742			R 2,168,850
Administration Overheads				R 84,269,765			R 54,318,980
Total indirect cost				**R 98,335,506**			**R 56,487,830**
Total Fixed Costs				**R 109,456,607**			**R 61,557,073**
Total Fixed Costs/dose (4.5 million doses)		**R 24.32**			**R 13.68**		
Total Fixed Costs/dose (2 million doses)		R 54.73			R 30.78		
Total Fixed Costs/dose (76 million doses)		R 1.71			R 0.96		

Source: Author compiled using data from Biovac documents and interviews:

The cost of transporting 83L formulated bulk from a supplier in Europe to Cape Town was R192, 287 whilst the cost of transporting SFP from the same supplier was R403, 725. The cost of transporting SFP is more than double the cost of transporting 83 Litres of formulated bulk for LFV operations because it is more complex and expensive to transport SFP in vials packed into shippers and airfreighted from Europe to South Africa. The sheer weight and volume of shipping a full container under cold-chain conditions with SFP is expected to cost substantially more than transporting a single, stainless steel tank containing 83 Litres of product from Europe to South Africa (R1.58 per dose bulk product when compared to R3.31 for SFP). The cost of transport is made up of freight charges, customs clearance fees and agent forwarding charges.

The cost of raw materials required to process a batch of a LFV was R280, 340 whilst the cost of raw materials required for a SFP was R63, 566. The costs of raw materials for a LFV are more than four times the costs of raw materials required to complete a SFP. The raw material costs for a LFV are R2.34 per dose whilst for a SFP the raw material costs are R1.06. This is a difference of only 50% between the dosage forms however; this is expected at a dose level since the raw material costs of a LFV are in addition to those of an imported product. The cost of raw materials for SFP included the labels, cartons, package inserts and shippers. In addition, the raw materials for a LFV includes glass vials, gamma irradiated rubber stopper and the aluminium seal cap. All these items are imported into the country.

At the time of conducting the study, the cost price of a single dose of SFP was R157 before processing. This translates to R8, 779, 971 per batch of 119,000 units. The cost of purchasing formulated bulk (83L) was calculated to be R11, 961,765 per batch which translates to R100 per dose filled locally. The unit cost per dose of a SFP costs at least 50% more (at R157) than a LFV at R100 per dose when compared to the SFP at R157 per dose as per contract price. For both options of this product, the product cost accounted for more than 90% of the variable cost per dose.

Direct energy costs to drive the filling line, autoclaves and automated washers were found to be significantly low at less than 5 cents per dose. Direct energy was only calculated for the LFV

and not on the manual packaging operation as there is only one low capacity labelling line used in this process and the power consumption is considered insignificant.

The cost of quality control testing of a LFV was four times that of a SFP. It cost R90, 738 to test a batch of a locally produced vaccine (R0.74 per dose) when compared to R22, 392 to test a batch of a SFP (R0.18 per dose). The quality control testing for LFV includes full batch testing whilst the SFP batch includes selected tests which are limited.

Fixed depreciation costs using a straight-line method for the major equipment used directly during the filling process were calculated as fixed costs at R3 million whilst the total cost of labour that is directly involved in the production of the batch was R8 million for the LFV and R5 million for the SFP. This is a cost difference of R3 million (60% difference) that is required per annum to produce vaccines locally.

The total variable cost per dose for a LFV is R104.70 when compared to R161.55 for the SFP. This is a cost difference of R56.85 per unit between a LFV and the imported product. However, the total fixed costs for a LFV are R109 million when compared to R61.5 million for the SFP. The total fixed costs per dose for the LFV at annual demand of 4.5million doses were R24.32 when compared to R13.68 for the SFP. This is a difference of almost 80% between the two products. At full theoretical capacity of 63.8 million doses per year, the fixed cost per dose drops from R24.32 to R1.71 for the LFV and R13.68 to R0.96 for the imported vaccine. The fixed cost per dose for both products drop significantly with an increase in the number of doses produced. At 2 million doses (approximately half the annual demand), the fixed cost per dose are more than double those of the annual demand.

4.2.3 Objective 2: Level of economic activity favourable to LFV vs. SFP

The second objective of this study was to determine the level of economic activity for which LFV option is preferred when compared to SFP. This was achieved by first determining the point at which the total cost of producing a LFV is less than the total cost of producing a SFP.

Figure 4.2 below is a graphical representation of the total costs incurred in the production of LFV and the SFP when plotted against the number of doses of vaccines sold.
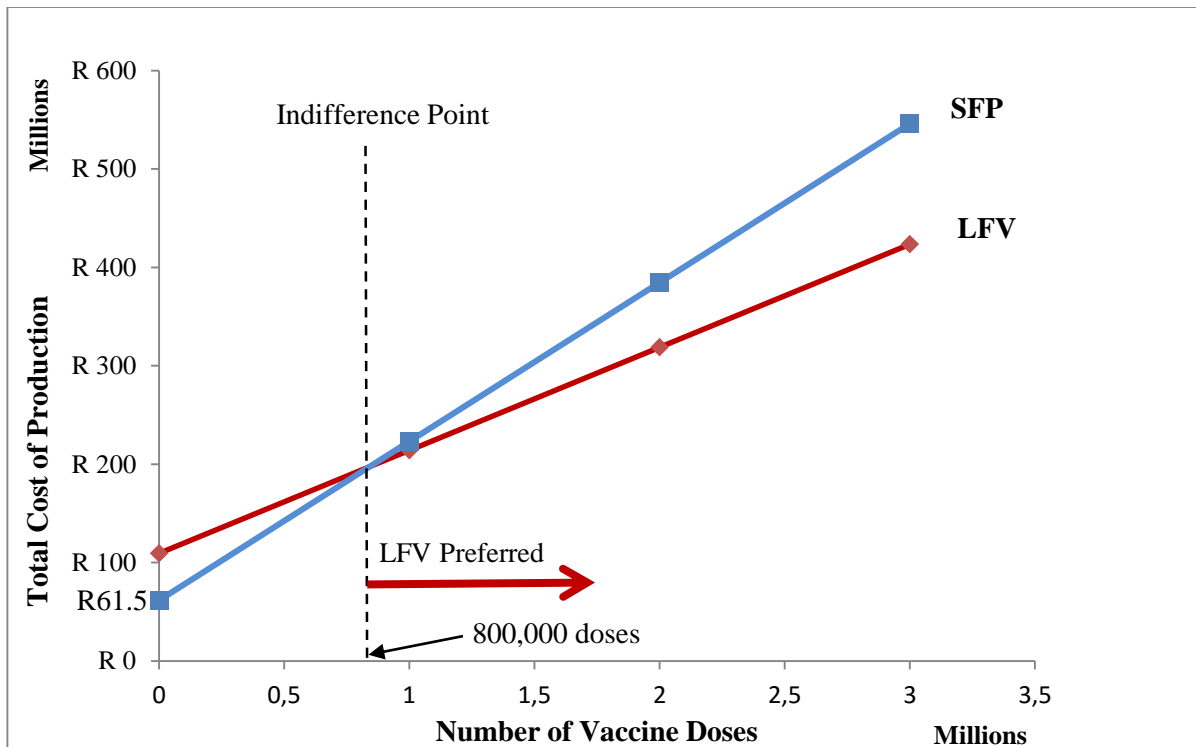
Figure 4.2: Point of Indifference

In figure 4.2 above, the cost behaviours of LFV and SFP are plotted on the same axis. The total cost of production is plotted along the Y-axis and the number of vaccine doses is plotted along the X-axis. The Y-intercept for each curve represents the respective fixed costs of each option. The curve depicting SFP is plotted in blue and labelled SFP whilst the curve depicting LFV is plotted in dark red and labelled LFV. The slopes of each of the curves represent the variable cost per dose which translates to the total cost of production for each vaccine sold. The variable cost per dose for SFP (R161.55) is higher than for LFV (R104.70) hence the cost of production increases at different rates which are shown by a steeper curve for the SFP when compared to the LFV curve.

The black dotted line indicates the point at which the LFV and SFP curves intersect at 800,000 doses. At this point, the costs of production for either option is the same. This point is also referred to as the point of indifference. It is observed from the curves that the total fixed cost of LFV is initially higher R109 million than the fixed cost of a SFP at R61.5 million up to 800, 000 doses (point of indifference). Beyond this point, the costs of LFV remain below the costs of importing a SFP. That is, beyond 800, 000 doses it becomes more favourable to locally

produce the vaccine than to import it semi-finished. This does not mean that either option will generate positive revenue (profit) beyond 800, 000 doses.

When taking into account the break-even analysis of each option as calculated in table 4.7 below, the break-even point for LFV is 1.3 million doses and 2. 6 million doses for the SFP. Therefore, this confirms that at 800,000 doses sold the company would be operating at a loss for both options. The profit maximising level of R109 million for LFV is reached at 2.4 million doses while the profit maximising level for SFP will never be realised within the annual demand of 4.5 million doses (see figure 4.7 below).

4.2.4 Objective 3: Determination of the desirable market size (Break-even Point)

The selling price for both LFV and SFP is the same at R185.00 per dose (current selling price of SFP). Table 4.7 summarises the break-even analysis for the LFV and the SFP.

Table 4.7: Break-even Analysis of LFV vs. SFP

	LFV	**SFP**
Sales/Dose	R 185.00	R 185.00
Variable cost/Dose	R 104.70	R 161.55
Contribution Margin	**R 80.30**	**R 23.45**
Total Fixed Costs	R 109,456,607	R 61,557,073
Doses to Break-even	**1,363,150**	**2,625,234**
Total Costs per dose (F+V)	R 129.03	R 175.23
Profit/Loss per Dose (2 million Doses)	**R25.57**	**-R7.30**
Profit/Loss per dose (at 4.5 million doses)	**R 55.97**	**R 9.77**

The variable cost per dose of LFV is significantly lower than for the SFP at R104.70 and R161.55 respectively. The lower variable cost per dose corresponds with a higher contribution margin of R80.30 for the LFV when compared to a much lower contribution margin of R23.45 for the SFP. The total fixed costs for each option vary significantly with fixed costs accounting for R109.5million for LFV when compared to R61.5million for SFP. The break-even point for both LFV and SFP was found to be below the annual demand of 4.5million doses.

The number of doses required to break-even for the LFV was 1.3million compared to 2.6million for the SFP. The total cost per dose for LFV was lower at R129.03 when compared to R175.23 for the SFP. This resulted in a significant profit per dose of R55.97 per dose of locally produced unit when compared to R9.77 per dose if 4.5 million doses are produced. An analysis of 2 million doses results in a loss of R7.30 per dose for the SFP and a profit of R25.57 per dose for the LFV as shown in table 4.7.

Figure 4.3 below is a graphical presentation of the results on the effect of profit generated per dose sold for the LFV and the SFP.

Figure 4.3: Break-even Analysis of LFV vs. SFP

By plotting the curve depicting Profit on the Y-axis against the number of doses sold the curve above emerges. The Y-intercept for each curve represents the fixed costs. The slopes of each of the curves represent the contribution margin per dose which translates to profit generated with each sale. The break-even point for both LFV and SFP is the point where each of the curves cross the X-axis at zero as indicated in figure 4.3 above. Below the x-axis depicts LFV or SFP curve is generating losses whilst above the x-axis depicts profit generation. The annual demand

for this product on the South African market is 4.5 million doses and this point is marked on by the red dotted line.

The fixed costs for LFV are more than those of the SFP however; the slopes of each curve differ markedly. That is, the LVF curve is steeper than the SFP curve which means the higher the contribution margin, the steeper the curve and the faster the rate of profit generation. By observing the two curves, it takes less than a million doses for the LFV and SFP curves to cross each other and reach a point where the cost of importing the SFP equals the cost of producing locally. However, both LFV and SFP options are not profitable at this point. At the LFV break-even point of 1.3million doses, the SFP option is not generating a profit and is still at a loss of approximately R30 million. When the SFP reaches break-even point at 2.6million doses, the LFV option has already generated a profit of approximately R90 million.

At the annual demand of 4.5 million doses, the profit generated by the LFV is approximately R250 million compared to a profit of approximately R45million generated by the SFP option.

4.2.5 Objective 4: Investment costs

The analysis of the investment costs showed that R745 million has been invested over 10 years into establishing local manufacturing operations. A further breakdown of the costs reveals that R375 million is required for investment into SFP operations as opposed to a total of R745 million required for LFV operations. From the findings, almost twice (1.98 times) the investment amount is required for LFV operations than semi-finished. The investment amounts exclude the cost of labour incurred from 2003 to 2014 for both manufacturing options. Because Biovac was established on an existing site (formerly, The State Vaccines Institute) the costs of acquiring the land, excavations and electrification is excluded from the calculated investment costs.

The major investment costs for SFP were attributable to setting up of the Cold Room Storage infrastructure, Quality Control laboratories, Packaging Halls and the Administration buildings. Of these costs, the Quality Control laboratory constituted the bulk of the costs at R240 million whilst the construction of the warehouse building was the least. The warehouse cost included

the refrigeration infrastructure for vaccine storage. The major investment costs are summarised in Table 4.8 below.

Table 4.8: Investment Cost Summary

Cost Category	Item Description	Item Cost
Infrastructure	API, Formulation & Filling	R300 million
	Quality Control Laboratories	R240 million
	Packaging Hall	100 million
	Warehouse & Utility	R30 million
Plant & Equipment	Automated Filling Line	R34 million
	Washers & Autoclaves	R12.5 million
	Cleanroom Structures	R2.5 million
Technology Transfer	Product for Local Filling	R17 million

The investment cost of setting up local filling operations alone were R300 million excluding the equipment to be used inside the Cleanrooms. The cost of constructing the formulation and filling suites was more than the combined cost of setting up operations for a SFP. Of this amount (R300 million), approximately 10% was allocated to the purchasing of a high speed automated aseptic filling machine at a cost of R34 million. Less than 5% of the cost went to the purchasing of autoclaves and automatic washers which are crucial in ensuring consistent cleaning and disinfection of pathogens before and after filling operations.

4.2.6 Objective 5: Effect of changing Cost of Product and Selling Price

Increasing Cost of Product

Figure 4.4 below demonstrates the effect of increasing the cost of formulated bulk by 25% on the profitability of local vaccine filling operations.
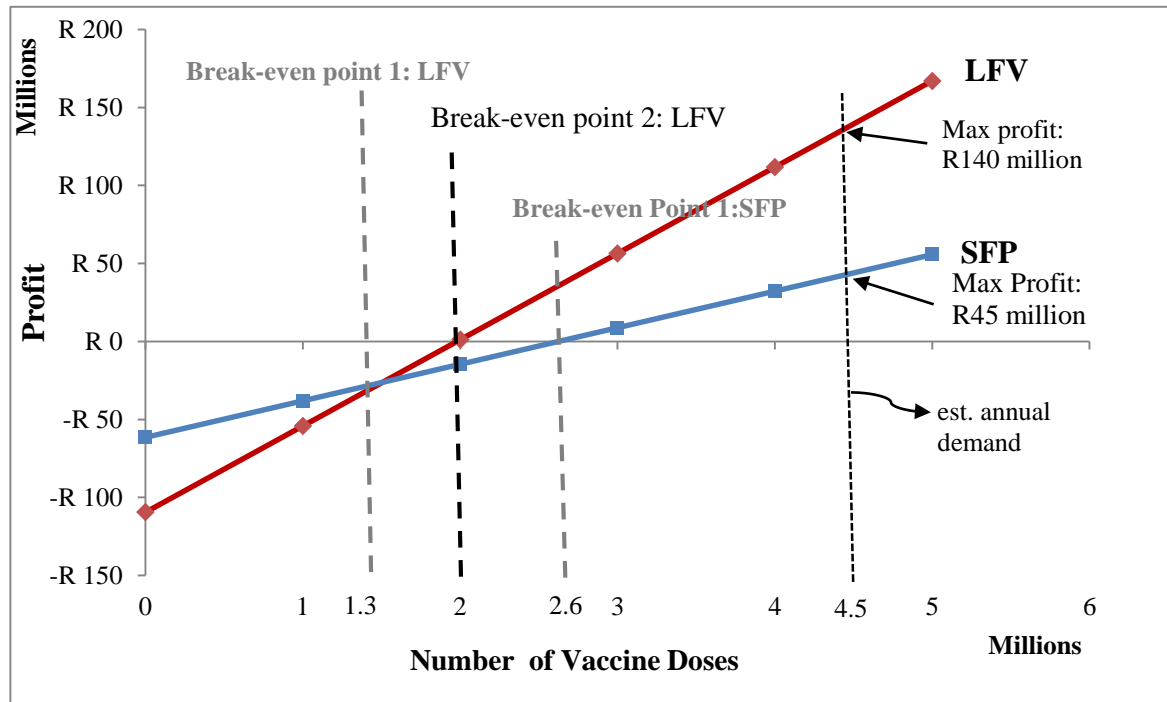
Figure 4.4: Effect of increasing Cost of Product on profitability for LFV

The findings show that increasing the cost of formulated bulk for LFV by 25% moves the break-even point curve to shift to the right from 1.3 million doses (break-even point 1: LFV) to 1.98 million doses (break-even point 2: LFV). Notably, the new break-even point for LFV is reached before the break-even point for SFP (Break-even point 1: SFP) which occurs at 2.6 million doses.

A 25% increase in the cost of formulated bulk product resulted in a drop in profit per dose for LFV from R55.97 to R30.97 which equates to a profit drop of R25 per dose (45% decline). This results in a net profit of 16% from local filling operations as opposed to a profit of 12% from SFP. Consequently, the effect on total profit from LFV operations drops to approximately R140 million (from R250 million) at 4.5 million doses produced.

Figure 4.5 below shows the effect of increasing the cost of formulated bulk product by 25% on the point of indifference.
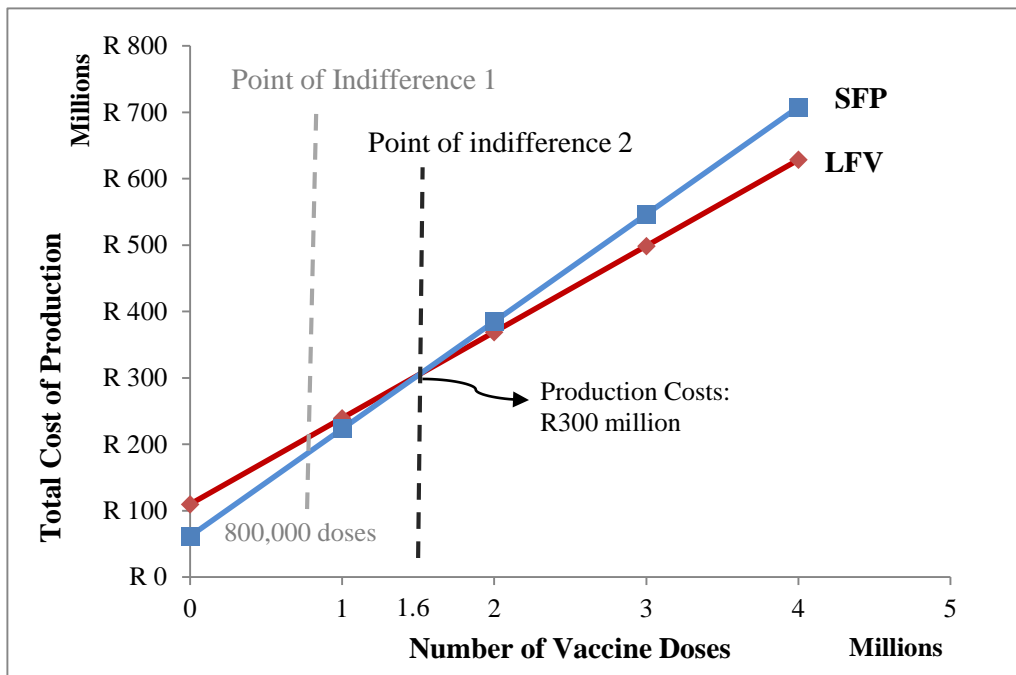
Figure 4.5: Point of Indifference after increasing Cost of Product for LFV

The effect of increasing the cost of formulated bulk product on the indifference point is a shift of the break-even point to the right from the original 800, 000 doses to 1.6 million doses. Not shown in the above curves, increasing results in a break-even point of 7.9 million doses which is beyond the annual demand of this product. This figure indicates that local filling operations are favourable over semi-finished operations even with a 25% increase in the cost of product at 4.5 million doses. This supports earlier findings that LFV operations are more resilient to price fluctuations and are favourable over SFP if the demand is expected to be more than 1.6 million doses per annum.

Reduction in Selling Price:

The selling price of a SFP was R185 per dose. Findings showed that reducing the selling price of a SFP by 10% from R185 to R175.75 per dose resulted in 4.3 million doses to break even when compared to 2.6million doses if the selling price remained unchanged. The findings show that beyond a 10% reduction in the selling price for SFP, this option will not break even at the

current annual demand of 4.5 million doses per annum. The price was only reduced by 10% for SFP, instead of 20%, to avoid analysing a result from a selling price per dose of R148 which is below the variable cost per dose of R161.55.

A 20% reduction in the LFV selling price from R185 to R148 breaks even at 2.5 million doses resulting in profit of R18.97 per dose as shown in the break-even analysis in Table 4.9 and Figure 4.6 below.

Table 4.9: Break-even Analysis after a drop in product selling price

Break-even Analysis after Selling Price Reduction		
	LFV	**SFP**
Sales per Dose	**R 148.00**	**R 175.75**
Variable cost/Dose	R 104.70	R 161.55
Contribution Margin	R 43.30	R 14.20
Total Fixed Costs	R 109,456,607	R 61,557,073
Doses to Break-even	**2,528,052**	**4,335,549**
Total Costs per dose (F+V)	R 129.03	R 175.23
Profit per dose (4.5 million dose capacity)	**R 18.97**	**R 0.52**

The findings in Table 4.9 showed that the profit per dose generated by LFV operations after a 20% reduction in the selling price is 32 times more than the profit per dose generated from SFP operations. The findings reveal that a 20% selling price reduction results is a drop of almost 50% (from R80 to R43) for the LFV operations and remained profitable. This is in contrast to a drop of 60% in profit margin from only a 10% drop in the selling price for the SFP. These findings are consistent with those observed on the effect of increasing the cost of product in that in both instances in that LFV option is more resilient to price fluctuations. SFP is sensitive to external market forces which can easily render the operations to be unprofitable in the long term.

Figure 4.6 below illustrates the effect of reducing the selling price by 20% for LFV and 10% for SFP.
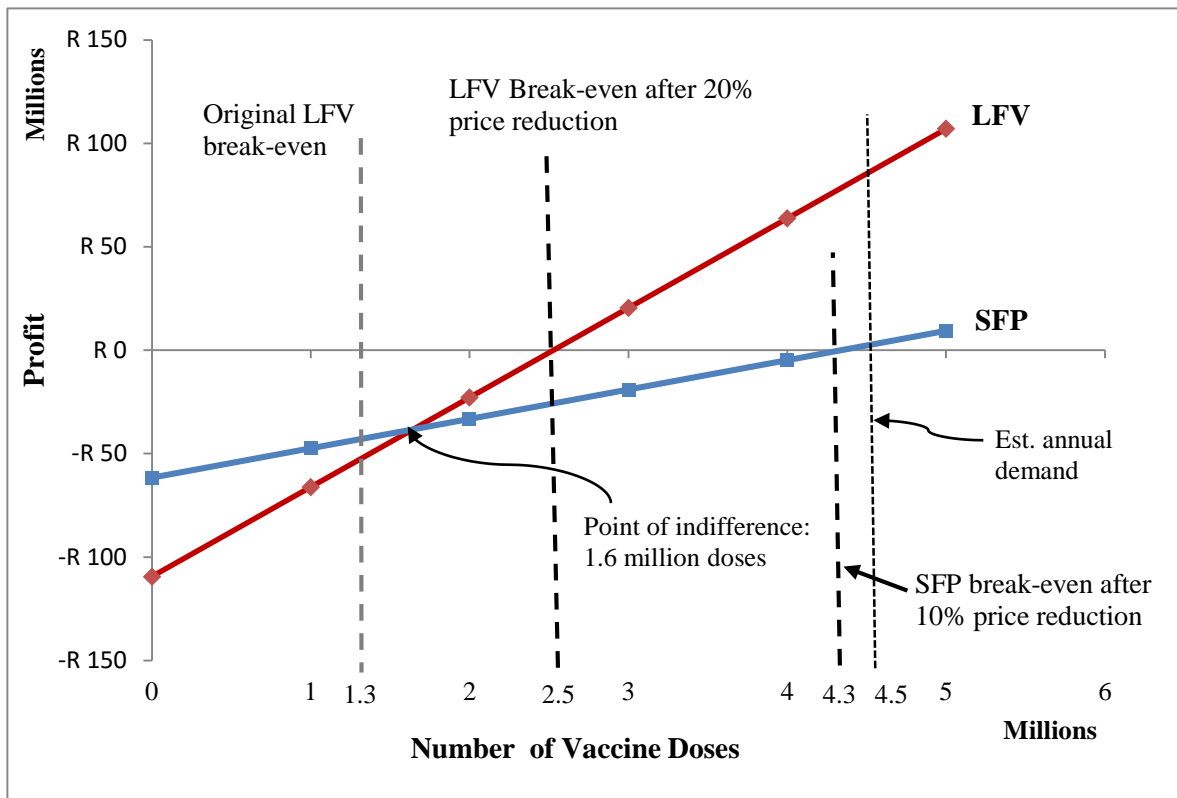
Figure 4.6: Effect of reducing Selling Price on profitability

Figure 4.6 shows that LFV operations break-even ahead of SFP operations.

Reducing the selling price of SFP by 10% causes the curve to shift to the right resulting in a break-even of 4.3 million doses which reduced the profit per dose to R0.52 (R104,000 total profit) if 4.5 million doses are sold.

Reducing the selling price of LFV by 20% causes the curve to shift to the right resulting in a break-even of 2.5 million doses which reduced the profit per dose to R18,97 if 4.5 million doses are sold. Under the selling price scenarios above, LFV is preferred over SFP beyond a demand of 1.6 million doses per annum the

4.3   Summary of Findings

The major findings from this study show that LFV operations from formulated bulk product is more favourable than SFP beyond 800,000 doses sold when the estimated annual demand is 4.5 million doses. The break-even point for LFV operations is reached at 1.3 million doses which is less than half the estimated annual demand of 4.5 million doses for this product. This is in stark contrast to the break-even point of SFP which is reached at 2.6 million doses. From the study, an estimated demand of 4.5 million doses per annum may be expected to generate a profit of approximately R250 million for LFV when compared to R50 million for the SFP. The study seems to suggest less reliance on large markets for LFV operations than SFP, at current annual demand, as demonstrated by the effect of price fluctuations on the break-even point and profitability of either of the options.

The major cost factors for both options were identified to be inbound transportation and cost of product. The study found that there are more inherent cost disadvantages for SFP than LFV operations. The cost of transporting SFP is more than double the cost of transporting the formulated bulk for LFV production whilst SFP seemed to show more sensitivity to price fluctuations. For example, a 10% reduction in the selling price of SFP resulted in a 60% reduction in the contribution margin and a break-even point of 4.3 million doses when compared with a 20% reduction in the selling price of LFV which reached break-even point at 2.6 million doses. This is particularly concerning for a product that is imported in foreign currency and may be subjected to future exchange rate fluctuations.

The cost of product for both LFV and SFP options remain significantly high and accounts for more than 90% of the total variable cost per dose.

The investment costs to set up LFV operations were calculated to be R745 million as opposed to R330 million required to set up SFP operations.

Chapter 5 will provide a discussion of the findings from this Chapter.

CHAPTER FIVE: Discussion

5.1 Introduction

The aim of this study was to evaluate economic viability of a LFV when compared to the same vaccine that is currently imported as a SFP for labelling, packaging and distribution. The objectives were to determine the production costs for both options followed by a thorough analysis on which option is favourable to pursue under which conditions. A case study approach was followed in conducting this study in order to gain an in-depth contextual analysis of the Biovac processes and cost factors using multiple sources of data. This chapter will discuss the findings in relation to the key consideration that were highlighted in the literature review in chapter 2 within the context of Biovac. In particular, the production costs, skills availability, economies of scale and their effect on profitability and finally the findings on the investment cost requirements will be discussed. The Chapter will conclude with a summary.

5.1.1. Cost of Production and Price of Finished Product

The literature review in Chapter 2 highlighted the drivers behind the support for local production as heavy disease burden, lack of access to affordable medicine, security of supply and the socio-economic benefits that stand to be realized. Those who argued against local production (Kaplan and Laing, 2005; Bate, 2008) cited lack of skilled personnel, economies of scale (small markets), cost disadvantages and lack of competitiveness of the local pharmaceutical industry. That is, the viability of local production rests on the ability of local manufacturers to produce quality medicine at competitive or better prices than imported medicine. Within the context of this study, the production costs of a LFV were compared to the costs of a SFP to determine the viability of local vaccine production in South Africa.

In-bound Transport Costs

The cost of transporting formulated bulk product is significantly less than the cost of transporting SFP. Formulated bulk product is transported in a 100L stainless steel vessel that is inside a self-cooling container. On the other hand, the filed vials are packed in trays which are stacked inside insulated shipper boxes that are filled with dry ice. Dry ice is used to ensure that that cold chain is maintained from the supplier to Biovac. As a result, shipment of SFP is bulky and requires a standard shipping container. Because the packaging configuration of

formulated bulk takes up less space and requires less pre-shipment handling, it is expected that the shipment costs would be less.

Cape Town is a port of entry for Formulated bulk and SFPs which are then transported for 15 kilometres to Biovac in a refrigerated truck. The shipping costs would be expected to be more if either the formulated bulk or the SFP were to be delivered to a land-locked country. This additional cost of transport would be added to the price of medicine. All else being equal, it is likely that the cost of the same product in a landlocked country would be more than it would be in South Africa.

Cost of Testing (Quality Control)

The cost of testing LFV is substantially more than testing a SFP. The SFP is delivered with a certificate of analysis that confirms that all tests have been performed in accordance to procedure with only the potency and product identification that remain to be tested on finished product. Formulated bulk product requires additional testing steps from delivery to finished product. These steps include bulk sample testing, in-process and finished product testing which includes sterility testing and potency at each step of the process. It is therefore expected that the testing costs would be more for LFVs when compared to SFP.

In instances where the laboratory infrastructure is not in place to complete all tests required, the Company may send certain samples to external, approved laboratories to conduct such tests on behalf of the Company. External testing comes at a cost, therefore, a cost-benefit analysis on which tests are to be carried out in-house or to be outsourced is usually done based on the available skill, complexity of the test, cost of equipment and frequency of the testing requirement.

Raw Materials Costs

The costs of raw materials that are required to process formulated bulk are twice as much as those required for processing SFP. SFP is delivered as naked vials (unlabelled product) and undergoes labelling and final packaging. Over and above, the LFV requires specialised type of glass vials, gamma-irradiated rubber stoppers and aluminium seals which are imported abroad in foreign currency. Once the product is filled, it undergoes the same process as a SFP. The cost of raw materials per dose is however not twice as much for LFV versus SFP because the total

cost is an average of total cost divided by the number of units filled. The importation of glass vials and rubber stoppers could be subject to foreign currency fluctuations resulting in annual cost variations

Cost of Production – LFV vs. SFP

When analysing the cost of product, the following becomes evident: The cost of SFP is R157 per dose as per contract which translates to R8.7 million per batch. The cost of formulated bulk product is R11.9 million as per contract which translates to R100 per dose of filled product.

SFP and LFV present different sets of challenges that may have an effect on the cost of each option. Firstly, the risks of product failure due to sterility and low potency remain with the supplier of the SFP up to the point of delivery to Biovac. Over and above, the product supplier would have incurred additional cost of quality assurance on the process as well as raw materials used in the product also remain with the supplier. Secondly, the same risk of batch failure due to sterility pose a major concern as the responsibility shifts from the product supplier to the manufacturer. Vaccine manufacturing requires aseptic handling which means there is no terminally sterilisation step once the product is in the final container. The manufacturer not only has to be vigilant about product handling to prevent loss of potency and product contamination during processing but also has to prove through validation that the product can be handled from delivery right through processing into finished product.

Another finding that may appear as a cause for concern is the low utilization capacity of 7% which suggests that the filing suites will be utilized for a time equivalent to a few weeks in a year. Even when taking into account aseptic validation activities that take place during year, the utilisation capacity remains low. This presents an opportunity to bring additional products through contract manufacturing of other compatible products and indicates that the filling line is not a bottleneck. This will help to improve the higher utilisation capacity.

5.1.2. Availability of Skilled Labour and Cost of Labour

Personnel employed at Biovac possess a skill base that ranges from very low skill with no formal qualification all the way up to Master's and PhD level. The spread of skill and expertise support the low tech, tertiary operations with semi-skilled personnel through to aseptic filling

operations with skilled personnel and research and development with highly skilled personnel with Honour's, Master's and PhD degrees. The Universities of Stellenbosch, Cape Town and the Western Cape are some of the tertiary institutions providing support to Biovac in skills development and other research collaborations.

The labour requirements for SFP operations are less than those of LFV in terms of the operator skill and the simplicity of the operations. The skill requirement for tertiary production operators is low-tech and does not require a tertiary qualification. On the other hand, secondary production (aseptic formulation and filling) requires a higher level of expertise especially in microbiology background. This is evident in the mix of skill set that is utilised for local filling operations. As long as Biovac is able to recruit and retain the right kind of skilled personnel and continually train them in topics such as validation, aseptic processing, good manufacturing practices and quality assurance; local production operations will receive the required support and ensure that local filling operations remain sustainable.

5.1.3. Economies of Scale on Profitability and Sustainability

Under current conditions, local vaccine filling from imported bulk is favourable if the demand is estimated beyond 1.3 million doses. For the product under study, the demand for SFP is currently at 4.5 million doses per annum and therefore renders this option profitable. However, the SFP seemed to be more sensitive to selling price fluctuations as was shown that a 10% reduction in the selling price resulted in a break-even of 4.3 million doses which is not sustainable, unprofitable and risky in the long term. This is concerning when taking into account that this product is imported in foreign currency and hence is subject to currency fluctuations. Secondly, with vaccine prices known to drop with time as more competition enters the market (Spier and Milstien, 2009), the sensitivity of the SFP to price does not seem to favour this option for long term sustainability Therefore, the findings support local production of this vaccine.

The economies of scale for this product appear to be exaggerated with profitability being achieved with 1.3 million doses which coincides with a point where the number of doses for imported vaccine is not even profitable. This finding is in line with a study that was conducted in Ghana by Chaudhuri (2013) which also showed that local production in small countries with small markets can be profitable despite the cost disadvantages.

The findings of this study confirmed the issue of high fixed costs in vaccines (Baumann, 2009) in that the fixed cost per dose reduced with the increasing number of doses. This effect of this phenomenon was more noticeable with SFP. This suggest that although the definition of economies of scale is not very clear; when it comes to the profitability of SFP operations, the more doses that can be sold the lower the average fixed cost per dose that can be realised. Perhaps one way to improve profitability would be to expand to regional markets. For South Africa, expansion into the Southern African Developing Countries (SADC) region which includes Namibia, Botswana, Zimbabwe, Swaziland, Lesotho, and Mozambique could potentially unlock untapped markets in the region and result in a higher annual demand for this product. In turn, this will could have a positive impact on the current equipment utilisation which is currently at 5.6%.

5.1.4. Investment Costs

Infrastructural Costs

The findings in Chapter 4 confirmed that there are different levels of investment requirements for secondary and tertiary production operations. The infrastructural investment began a decade ago and to date more than R700 million has been invested into the reestablishment of local vaccine manufacturing. The setup costs for tertiary operations (labelling and packaging) were substantially low at R375 million when compared to R745 million total investment cost for secondary and tertiary operations. This implies that the requirements for LFV operations are twice as much as the requirements for SFP operations. This was not surprising as the infrastructural cost of the formulation and filling suites alone were R300 million excluding plant and equipment.

Vaccines are sensitive to heat and therefore the investment into the warehouse and cold room storage is required upfront before any labelling and packaging can take place. Being heat sensitive, testing for potency on delivery and of finished product is critical to prevent processing of product that may not meet the quality standard hence the quality assurance infrastructural requirement. Quality control laboratories require sophisticated equipment which also adds to the cost of the product.

The presence of the cold chain and testing infrastructure not only does it allow for labelling and packaging operations to continue but serve as building blocks for more products to be brought into the facility. In addition, it serves as a footprint for expansion into more complex operations such as formulation and filling whilst generating revenue. The model of backward integration which was adopted by Biovac showed that other countries who are interested in establishing local pharmaceutical manufacturing can begin by investing in simpler operations to generate revenue and increase the level of investment into more complex operations over time.

The findings revealed that the profit margins from SFP operations are lower than those for LFV which may be an indication of the ability to recoup the investment costs from operations. The findings showed that importing SFP will generate a profit of 10%, excluding distribution and marketing costs, whilst the LFV operations can be expected to generate a profit of about 43% under the same conditions. It can be concluded from the findings that LFV operations, under current conditions, are more favourable for this product over the SFP. From an investment point of view, LFV operations indicate a better return on investment and a high probability to being able to recoup the investment costs. This means the formal banking sector is likely to fund this kind of operation.

The finding that LFV operations provide a higher probability to recoup investment costs when compared to SFP is confirmed by the analysis into the effect of price fluctuations. This analysis showed lower profit margins of R9.77 per dose at 4.5 million doses sold for SFP and sensitivity to price fluctuations can be translated to mean that more than a decade that may be required to recoup the investment costs of simple tertiary production operations. LFV operations, on the other hand, are able to repay the investment costs in approximately 4 years with a profit margin of R55 per dose. Even when the selling price drops by 20%, LFV is still favoured over SFP.

Technology Transfer Costs

This refers to the costs associated with bringing a new product into the facility. There are three considerations to be taken into account when selecting a technology transfer partner to ensure a mutual benefit. Firstly, the selection of the product(s) to be produced in the facility must be compatible with the available infrastructure in order to contain investment costs. Secondly, because pharmaceutical production is highly regulated, the product may not be sold to the

market before licensing and registration approval from the local regulatory agency has been obtained.

Finally, whilst technology transfer may speed up the process knowledge and improve personnel skill level, it cost money and someone has to pay for it. Selecting a mutually compatible partner is critical to ensure fair distribution of costs. For example, this technology transfer required an investment of approximately R17 million. However, this cost could have been in excess of R30 million without the technology transfer partner bearing the costs of active raw materials and training. Transferring technical know-how requires competent project management skills as this is an immense investment undertaking before the product can be sold into the market.

5.2 Summary

The break-even point for LFV operations is reached at 1.3 million doses sold when compared to SFP operations with a break-even point of 2.6 million doses. Taking into account the current annual demand of this product at 4.5 million doses, LFV operations can be expected to generate a profit of R250 million when compared to R50 million expected from SFP. The finding from the study seems to suggest that profitability can be achieved from relatively small markets.

The investment requirements for setting up LFV were found to be approximately twice as much as those required to setup SFP operations, however the potentially higher profit margins justify such an investment undertaking. Whilst the SFP investment setup costs may seem favourable initially, the demonstrated sensitivity of this option to price fluctuations remains a concern for a product that is imported abroad and is subject to foreign exchange rate uncertainties.

For Biovac, the option of LFV is preferred and must pursued in order to realise demonstrated profits.

Chapter will highlight and discuss significant conclusions from this study and make recommendations for future studies.

CHAPTER SIX: Conclusions and Recommendations

6.1 Introduction

The aim of this study was to evaluate, using Biovac as a case study, whether LVF is economically viable when compared to SFP. The objectives were to determine the costs of production of each option and to assess which option was favourable under which conditions and to determine the investment requirements for each of the options. This Chapter provides the implications of this research as well as recommendations for future studies based on the findings.

6.2 Significant Conclusions from the Study

The major conclusion from this study is that LFV production may be economically viable and more preferable to imported SFP. The cost of formulated bulk and SFP constituted more than 80% of the total cost of production however; the profit margins from LFV operations were shown to be substantially higher than those that stand to be realised from processing SFP. For example, at 4.5 million doses, LFV operations can be expected to generate a profit of R250 million when compared to R50 million profit that may be expected from SFP. As a result of low profit margins that are generated from SFP, this manufacturing option is the least favourable between the two and is sensitive to price fluctuations (10% story and currency effects). The conclusion is that SFP option may not be viable for long-term sustainability of the organization.

The second conclusion from findings showed that LFV operations of high-end multivalent vaccines are economically viable even with low volumes of 4.5 million doses. Whilst pursuing LFV has been demonstrated to be cheaper and more profitable than SFP, it is important to take note that in this option; the risk of batch failure shifts from the overseas supplier to the local manufacturer. high batch failure rate may have negative financial implications which the local manufacturer may not have been exposed to when processing SFP. Therefore, significant amount of time in training and validation may be required to ensure the risk of batch failure due to process inconsistencies is minimised.

Although the study did not assess economic viability from antigen production and formulation, the findings suggest that LFV from locally produced antigens may be even cheaper. This takes into account that local production will eliminate transport and formulated bulk costs. However, this level of operation requires additional product handling expertise and may expose the organization to even higher risks of batch failures at multiple levels of operation over and above the skill requirements for processing product at this level. It is within this context that a conclusion can be drawn that security of supply may take years to be realised, if not decades, as Africa continues to be dependent on imported formulated bulk to carry out local filling operations. This suggests that the African continent still remains vulnerable to supply shortages. This is contrary to the notion of establishing local manufacturing operations to reduce dependency on imports.

6.3   Implications of this Research

This study provides an assessment tool for Biovac management to use when assessing the viability of a project proposal from a potential technology transfer partner. With the production costs associated with processing SFP and LFV from formulated bulk known, determining the number of doses required to break-even (profitability) and the extent of the profitability (at anticipated demand) of the proposed option is now possible. This will allow management to strategize on which vaccines or compatible products to pursue and more importantly which information to use in the assessment.

The findings from this study suggest that economies of scale are a key consideration for profit generation and may not necessarily be an absolute requirement for countries or governments who want to produce locally to meet local demand. As shown by the findings, the break-even point of a locally produced vaccine with an annual demand of 4.5 million doses could be reached with 1.6 million doses sold. However, economies of scale cannot be disregarded as they can provide a cushion against external forces such as a drop in the selling price or an increase in the cost of product as per the findings on the resilience of the SFP option.

With the African Union supporting local production across Africa as a means to stimulate industrial development and economic growth, other countries that may be interested in pursuing vaccine production and sterile manufacturing can use this study as a baseline to gauge the level

of investment required for such an undertaking. Other countries will be able to use findings from this study on manufacturing costs to make decisions which cost factors to subsidise in efforts to lower costs to the end user.

6.4   Limitations and Recommendations for Future Studies

This study was the first of its kind in South Africa with regards to human vaccine production with the findings and conclusions drawn from a single case study. Due to the general limitations of the case study and a single unit of analysis, the findings may be difficult to apply generically across other pharmaceutical manufacturing operations. Because this study focussed on the production costs to evaluate economic viability, perhaps other studies could focus on the impact of other types of costs such as opportunity and sunk costs on the profitability of the organization.

Secondly, this case study focused on multivalent vaccine production to draw conclusion on the viability of LFV operations. This presented a limitation in that the study did not consider whether a low cost vaccine with a lower or higher demand will also be a viable option to pursue when compared with SFP. However, this study has laid a foundation for future similar studies on economic viability of any pharmaceutical operations. For Biovac to get a complete picture on which vaccines to continue importing or to consider for local manufacturing, through technology transfer, an internal study must be carried out to include monovalent and low cost vaccines. Carrying out a study of this nature will allow Biovac to develop a matrix of the type of products to be pursued for local production based on set of well-defined criteria. Such criteria could involve assessing the effect of adding other products on the existing infrastructure to increase the equipment utilization rates which are currently below 10%.

Finally, the duration of the technology transfer for this product was almost 3 years due to regulatory requirements for validation prior to product licensing. Perhaps a study focussing on comparing the opportunity costs due to time lost while waiting for regulatory approval and licensing for either SFP or LFV may justify or prove to the contrary the viability of local production. The study will need to focus from an investment point of view.

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Abstract The African pharmaceutical industry lacks the capacity to adequately supply the continent with essential medicines to combat the heavy disease burden that is grappling the continent. As a result, Africa relies heavily on imported medicines and vaccines to meet the growing needs of the population. Local pharmaceutical production promises to provide a sustainable solution to public health, industrial development and socio- economic issues on the continent. However, Local pharmaceutical production does not make economic sense if the industry is unable to competitively produce quality medicine at prices that are comparable to or better than those of imported medicine. The aim of this study was to evaluate whether locally filling a multivalent vaccine used in paediatric immunization is economically viable when compared to the same vaccine currently imported semi-finished for labelling, packaging and distribution. Can a South African vaccine manufacturer produce the same vaccine cheaper than it currently imports? The objectives were to determine the production costs for both semi-finished product and local vaccine filling operations and to assess which option makes economic sense to

pursue. The sub-objectives were to establish the extent and impact to which the market size and demand for this vaccine on the decision to pursue local production versus importation. A case study approach was adopted as a research method to gain an in-depth understanding of the economic and production factors within the context of vaccine manufacturing with The

[1]**Biologicals and Vaccines Institute of Southern Africa (Biovac)** as **a** unit of

analysis. Multiple sources of data were used to collect data which was analysed in detail. The findings from the study showed that local vaccine filling operations of this product were favourable over importation of semi-finished product when the demand exceeded 800,000 doses per annum. The local filling operations were found to be economically viable beyond 1.3 million doses as opposed to 2.6 million doses for semi-finished product. The aim of this study was accomplished. This study contributes to local production body of knowledge and serves as a baseline for economic evaluation of local vaccine production operations versus importation as no formal study has been conducted in Africa i CHAPTER ONE: Introduction 1.1 Introduction The reliance on imported medicines in Africa remains unsustainably high with an estimated 25 to 30 percent of essential medicines consumed in Africa being produced within the continent (African Development Bank, 2014). As a result of low production capacity the continent is susceptible to drug supply shortages, limited access to essential medicine and inability to swiftly respond to pandemic disease outbreaks. The disproportionate number of deaths due to acute shortage of the influenza vaccine in Africa during the 2009 H1N1 flu pandemic outbreak (Dawood et al., 2012) and the recent Ebola outbreaks in North and West Africa are examples demonstrating the unpreparedness to respond to pandemic outbreaks and heavy reliance on imported medicines. Local production of medicines on the African continent promises to reduce dependency on imported drugs, improve access to medicines and create a sustainable response to drug supply shortages (African Union and UNIDO, 2012). To effectively reduce import dependency and address drug supply shortages in Africa, the continent must create a competitive, sustainable pharmaceutical industry that can reliably supply quality, affordable medicine. However, in light of current competition from foreign manufacturers, the viability of the local pharmaceutical industry lies in price competition (Wilson et al., 2012) and the ability of the industry to produce quality products at costs that are less than, or at least competitive, to those of foreign manufactures (Taylor et al., 2009). The decision whether to produce locally or to continue with importation is complex (Kaplan and Laing, 2005) and requires a thorough assessment of the feasibility of either option. This is to ensure that such an undertaking will be economically viable given that local manufacturing may not necessarily be cheaper than importation (UNCTAD, 2011). This case study assesses the economic viability of a locally produced vaccine when compared to the same

vaccine currently imported semi-finished for labelling, packaging and distribution. The 19rest of this chapter is divided into the following sections: Section 1.2 discusses the Motivation for the study, which 3is followed by Section 1.3 summarising the Focus of the study; Section 1.4 discusses the problem statement; Section 1.5 States the Objectives of the 2 Study; Section 1.6 States Limitations of the Study and Section 1.7 which is the Summary of this Chapter and an overview of the next Chapters to follow in the thesis. 1.2 Motivation for the Study: South Africa aims to improve its preparedness to respond to pandemic disease outbreaks (Dulnier, 2010) and reduce the dependency on imported vaccines by resuscitating vaccine manufacturing capability through the establishment 1of The Biologicals and Vaccines Institute of Southern Africa (Biovac). Over the past decade Biovac has sourced, imported and distributed vaccines for the national immunization program and is now preparing to integrate the formulation and filling operations into the current importing and distribution business model (Dulnier, 2010). This study had to be conducted because the current costing model for Biovac is based on sourcing and distribution of imported vaccines. No formal cost-analysis study has been conducted by Biovac on local vaccine filling activities from formulated bulk liquid product. Biovac will use the information from this study to develop a costing model for fill/finish operations. With the Company attracting technology transfer partners for collaboration in various projects, understanding the vaccine production costs and associated market dynamics will enable Biovac to make informed decisions on which strategy, if pursued, will be economically viable. The decision on which imported vaccines are to be prioritised for local production can be made with more certainty if the production costs and market dynamics of either option is better understood. Because of limited human vaccine manufacturing operations in Africa, there is a gap in the available literature on the production costs and capability to manufacture affordable, high quality vaccines. The extent to which the input costs are applicable to the viability of local production is not well defined and therefore there is limited reference to use as a baseline in the manufacturing of vaccines within the South African context. There are different views regarding the feasibility of local vaccine

manufacturing. According to Kaplan and Laing (2005), local manufacturing may not be feasible in all developing countries if the economies of scale of production are insufficient. However, the extent of the requirement for economies of scale is not well defined in the literature. It has been estimated 3 that up to 60 % of vaccine production costs are fixed and requires economies of scale to recoup some of the costs (Baumann, 2009). Again there is no distinction whether this figure refers to the production of monovalent or polyvalent vaccines or whether these are high cost or low cost vaccines. 1.3 Focus of the study: This study will focus on the production and infrastructural costs to assess whether Biovac can competitively produce quality vaccines more favourably than imported vaccines. The input costs associated with producing a single unit of vaccine from imported formulated bulk were analysed and compared to the costs of importing a fully finished vaccine for labelling and distribution. Direct and indirect costs of production as well as fixed and variable costs were identified and assessed to determine the extent to which they have an effect on the final price of a vaccine under different market conditions. Since Biovac processes do not currently include antigen production and formulation, the costs of producing the antigens or the effect of locally producing vaccines from the antigen stage to finished product was not assessed as part of this study. The distribution and marketing costs of either a locally produced or imported vaccine is the same as the finished product is stored and packed in the same configuration therefore the study will not focus on these common costs. 1.4 Problem Statement: Despite the dominant status of the South African pharmaceutical industry across the continent in terms of annual production and the number of pharmaceutical manufacturers in the country (SEATINI and CEHURD, 2013), there is no human vaccine manufacturing capability in South Africa. As a result, South Africa remains the only member of the BRICS countries to import all vaccines to support the national immunization programme (Kaddar et al., 2014). Despite having no vaccine manufacturing capability, South Africa is considered an early adopter of new vaccines financed by national government mainly through taxation (Blecher et al., 2012). It can therefore be expected that as newer vaccines are adopted by government for the immunization program, there will be more pressure on the allocated vaccine budget. Establishing vaccine manufacturing capability in South Africa could reduce trade deficit resulting from importation of pharmaceuticals, however such an investment undertaking requires a thorough assessment to determine its viability and profitability. When calculating the cost of a single unit of vaccine one must take into account the input costs such as the costs of establishing a vaccine manufacturing facility (Bate, 2008), developmental and production costs, cost and skill of labour, shipping and raw material (Lee and McGlone, 2010). Taking all of the above into account, the following pertinent questions remain to be answered: ? Is vaccine manufacturing a viable option on the African continent? ? Can Biovac locally produce quality vaccines at a more favourable cost than

82

they are currently imported? 1.5 Objectives of the Study The objectives and the sub-objectives of this study were as follows: a. To ascertain the manufacturing costs of a locally produced vaccine (Fill and finish) and imported vaccine for labeling and packaging; b. To determine the level of economic activity for which local production is preferred compared to importation and distribution of finished vaccine product c. To determine the market size for which one option is preferred over the other; d. To determine the level of investment needed for both options – local production vs. importation; and e. To determine the effect of changing the key variables such as the selling price and the cost of imported product (Semi-finished or formulated bulk) on the viability of either option. 1.6 Limitations of the study The locally produced vaccine that was used to collect data was a technology transfer product candidate that is currently not commercially available in the South African market but has undergone stability testing and awaits approval by the regulatory authority. This means that this product has undergone the full manufacturing cycle, however, the costs of the primary 5 and secondary packaging materials may change by the time the product is registered on the market. The semi-finished product (SFP) that was used for comparison in this study is registered and available in the market. The cost price used is the current price of the product in the market on the government tender. 1.7 Summary This chapter discussed the

12**motivation for the study, the problem statement** and **the focus of the study.**

The objectives and the **limitations of the study** were also stated **in**   this chapter, The

next chapter, Chapter 2, will discuss the literature review of local pharmaceutical production. In particular, the drivers for local production and key considerations for successful local pharmaceutical production are discussed with more emphasis on vaccine manufacturing. Chapter 3 outlines the case study research methodology that was employed in this study as well as data collection methods, data analysis tools and finally the issues of validity and reliability. Chapter 4 presents and analyses the findings obtained using the methodology in Chapter 3 Chapter 5 summarises the findings, makes recommendations and conclusion. Chapter 6 will discuss the concluding remarks and make recommendations for future studies. CHAPTER TWO: Literature Review 2.1 Introduction Many solutions have been proposed to solve the issues of access to affordable, quality medicine, which is a threat to public health and budgets of national governments in Africa. Local pharmaceutical production emerges as one of the key solutions that promise benefits that are beyond access to medicine. It is therefore not surprising that local production is receiving support from political heads and multilateral organizations (UNCTAD, 2011;UNIDO, 2013) as a sustainable solution to reduce heavy reliance on imported medicines. Currently, affordability and quality of medicine remain a challenge for many African countries to

the extent that they rely on donor funding to access medicine. This is particularly evident when it comes to vaccines donated by the Global Alliance on Vaccination and Immunizations (GAVI) and the funding of medicines needed to treat malaria, HIV and AIDS. Despite the benefits that stand to be realized, there are key challenges that need to be overcome and considerations that must

37**be taken into account in order** for local production **to be** viable. These

considerations relate to cost disadvantages and competitiveness of the pharmaceutical industry across the continent, the capability and capacity to embark on such an undertaking. The focus of this review will be on the key drivers behind the support to boost local production capacity and the key considerations for the successful establishment of local production in Africa. The aim of this study was to evaluate economic viability of locally produced vaccines in South Africa as opposed to importing them semi-finished for sale and distribution. Although there are varying degree of pharmaceutical production across the African continent, vaccine production is almost non-existent with Senegal as the only human vaccine manufacturer producing a single vaccine against Yellow Fever for the domestic market. Therefore, there is limited literature available on local vaccine manufacturing in Africa. As a result, this chapter begins with the background on the issues surrounding local production and local production overview and definition. This is followed by the drivers and key considerations for establishing local production in the context of this study. A summary will conclude this chapter. 2.2 Background The support for the developing countries to increase public access to essential medicine and reduce the dependency on imported medicine through local production is broadening. In Africa, the adoption of the Pharmaceutical Manufacturing Plan for Africa (PMPA) by the Heads of African Governments is a clear indication of the political commitment to boost local production capacity of essential medicine on the continent (African Union and UNIDO, 2012; African Development Bank, 2014). From a political and policy levels, establishing local pharmaceutical production promises to improve public health by increasing the security of drug supply and access to affordable medicines (WHO, 2011); promote industrial development and socio-economic stimulation through economic diversification from agricultural production and mineral extraction (UNIDO, 2013). Despite the benefits and the high level support, competitive pharmaceutical production is complex and capital intensive (GlaxoSmithKline, 2011) and therefore requires careful consideration before embarking on such an investment undertaking. The primary considerations relate to investment cost associated with setting up a GMP-compliant manufacturing facility, access to technology and "know-how", skilled labour force, setting up a quality assurance system and the long lead times from drug discovery to commercialisation which can take approximately 10 – 15 years (IFPMA, 2011). With all these factors taken into consideration, the issue of cost of medicine and affordability cannot be ignored

when considering the vast economic disparities between African countries (World Bank, 2014). It is against this background that Kaplan and Laing (2005) supported by Bate (2008) have argued that local production may not be a viable option for all countries despite the benefits. Whilst other countries can manufacture, others should focus on streamlining their procurement and supply chain processes (Kaplan and Laing, 2005). This sentiment is shared by Bate (2008) who also concluded that it is difficult to sustain the argument for local production given the lack of resources and technical capacity to competitively produce affordable, high quality medicines in most developing countries. 2.3 Local Production Overview 2.3.1 Defining Local Production According to the World Health Organization report (WHO, 2011), local production may be defined and better understood in terms of territorial location and ownership of the manufacturing facility. Under the territorial definition, it is implied that production of medicine takes place in a developing or least-developed country and is subject to national jurisdiction irrespective of who owns the facility. For example; the manufacturing operations of a foreign owned company, such as Pfizer (American company) or Sanofi-Aventis (French- owned), operating in South Africa maybe considered "local" irrespective of where it is controlled or the location of its headquarters. The second definition of local production is in terms of ownership. Under this definition, it is implied that production operations will be considered "local" if the nationals have more than a majority of ownership in the firm. This definition has limitations in that the operations of a foreign owned company are excluded and considered foreign yet they take place within the said country. For the purposes of this study the territorial definition of local production has been adopted as it takes into account all manufacturing operations taking place in a country irrespective of ownership. 2.3.2 Forms of Local Production Local production occurs at different levels of sophistication and hence the categorization of different forms is done in terms of simplicity of operations undertaken. There are three broad categories used to describe different forms of local production; namely tertiary, secondary and primary levels of production (WHO, 2011). Tertiary manufacturing is the simplest of all production categories that generally involves the labelling and packaging of formulated or semi-finished product. This form of local production is commonly found in the least developed or low-income countries. Secondary manufacturing is more sophisticated than tertiary as it involves the mixing of raw materials and formulation of different dosage forms. This form of manufacturing is most prevalent in the so-called middle-income countries. However, the raw materials used in secondary manufacturing are usually produced by the industrialized and large developing countries such as India and China where significant levels of the primary manufacturing takes place. The primary manufacturing involves the manufacturing of active pharmaceutical ingredients, intermediaries and excipients. According to the WHO World medicine report, the primary production used to be concentrated in just five industrialized countries – The

85

25United States of America, Germany, France, The United Kingdom and

Japan. However, the picture has changed with China and India's competitive ability to

produce API's. Other smaller developing countries like South Africa have some capability to produce certain raw materials. Although South Africa has some capability to produce raw materials, the majority of the raw materials used in formulating medicines are imported from countries abroad (Bennet, 2014). 2.3.3 Local Production of medicine in Africa Literature review of the African pharmaceutical Industry confirms the presence of local production activities across the continent that are dominated by a handful of countries (Abbott, 2011) supplying a combined output of 25 to 30% of the continent's needs (Iñarra, 2015). According to the International Finance Corporation (IFC) annual report (World Bank, 2007) as summarised by Abbott (2011), the pharmaceutical industry on the continent is dominated by South Africa, Ghana, Nigeria, Kenya and North Africa. The South African pharmaceutical industry is considered as the most developed in the Sub-Saharan region and North Africa (Bennet, 2014) with South Africa responsible for more than 70% of the manufacturing output (Abbott, 2011). This indicates vast differences in the capabilities of local production between the African countries and their abilities to provide essential medicines that will satisfy the needs of the population. Despite Africa being described in the McKinsey Report (Holt et al., 2015) as the world's fastest –growing economic region, the pharmaceutical industry remains weak and is biased to produce generic medicines (Holt et al., 2015) and copy drugs under licence (WESGRO, 2012). This weakness is evident when taking into account that, in global terms, the African pharmaceutical industry was worth an estimated US $23.1 billion in 2011 or less than 2% of the global market (African Development Bank, 2014). To put this number into perspective, The European Federation of Pharmaceutical Industries and Associations estimated that Africa combined with Asia and Australia – excluding Japan – contributed to global sales of only 13.7% in 2012 (EFPIA, 2012) and 16.6% in 2014 (EFPIA, 2015). The small size of the pharmaceutical industry in Africa may be interpreted as a good indication of the potential economic growth when considering that the disease pattern is expected to shift from communicable to chronic or "lifestyle" diseases over the next decade (de-Graft Aitkins et al., 2010). Based on the current situation; if the disease burden actually shifts as expected, it is difficult to imagine how the industry will be able to cope with additional demand and competition from cheaper medicines imported from India. The above scenario presents some worrying scenarios. Firstly, too much focus on the production of generics and copy drugs indicates more emphasis on treatment rather than prevention of diseases through vaccination. Secondly, the production of generics at a large scale implies that the local producers are paying

less attention to the research and development of new drugs to fight diseases that are more prevalent or disproportionately affect Africa. This could be interpreted to mean that the local industry is dependent on research expertise from outside the continent. With most countries limited to secondary and tertiary manufacturing – formulation, packaging and labelling – the transition to primary manufacturing could prove to be costly even if countries are interested in pursuing more sophisticated forms of production. Thirdly, limited research and development leaves Africa unable to respond the pandemic disease outbreaks as there could be slow progress with research on drugs to combat diseases affecting Africa. The shortages of the H1N1 influenza vaccine in 2009 and the unavailability of vaccine against the recent deadly Ebola outbreaks in West Africa precisely demonstrate this point. Finally, the African continent presents some unique disparities in local production. According to the African Development Bank (2015), the importation rate in Senegal is 80% with the majority of imports coming from India. Interestingly, Senegal is

the only African country that has human vaccine manufacturing ability yet the 36**country**

with the most developed pharmaceutical production **capability (South Africa)** does

not produce vaccines for human use. As a result of producing a limited range of pharmaceuticals against a rising disease and shifting disease burden profile (de-Graft Aitkins et al., 2010), the local pharmaceutical industry will continue to lack the adequate capacity to meet the growing needs of the continent. This leaves Africa heavily reliant on life-saving medicines and vaccines imported from abroad. 2.3.4 Local Production and the Pharmaceutical Industry in South Africa South Africa is home to both local and multinational pharmaceutical manufactures that produce a wide range of pharmaceuticals for local demand and export (WESGRO, 2012). The multinational pharmaceuticals in the country include Pfizer (USA), Fresenius-Kabi (Germany), Sanofi (France), Johnson & Johnson (USA) and GlaxoSmithKline (United Kingdom) whilst the top local manufacturers include Aspen and Adcock Ingram (Kudlinski, 2013). The country has a well-developed pharmaceutical industry with all forms of local production – mainly secondary and Tertiary with limited primary production – taking place. South Africa has the largest pharmaceutical market in Africa although multinationals continue to dominate the industry according to the Gauteng Growth Development Agency (GGDA, 2014). South Africa is a net importer of pharmaceuticals and this places a heavy burden on the trade balance. Previously, the pharmaceutical industry catered for about 64% of the local medicine requirements and this has decreased due to an increased in imported medicine (GGDA, 2014). According to the department of Trade and Industry (DTI), in 2013 South Africa imported 65% of its pharmaceuticals and this was the 5th largest contributor to the South African trade deficit (Kudlinski, 2013). The figures are

startling in that, according to DTI, 85% of the imported pharmaceuticals in 2011 were in finished dosage form from India, Germany, United Kingdom, France and Italy (Kudlinski, 2013). Over the past decade, the reliance on imported medicine has continued to grow and this is a concern to government as it increases the risk to security of supply. Like in many African countries that promote local production, the pharmaceutical industry in South Africa is mainly focused on the production of generic medicine (Zhan, 2014) and copy drugs under licence (WESGRO, 2012). According to the WESGRO report (2012), in 2011 the generic drug sales accounted for 29% in revenue and more than 50% in volume whilst patented drugs accounted for 59% of revenue. There is expectation that the market for generic drugs will continue to grow having grown

32**at an average** compounded **annual** growth **rate of** 22.3% **between** 2004 **and** 2011

(Holt et al., 2015). Although South Africa dominates the African pharmaceutical industry in both annual production and the number of pharmaceutical manufacturers in the country (SEATINI and CEHURD, 2013), the country lags behind its peers in 26**the BRICS group of countries**

(Brazil, Russia, India, China, South Africa) particularly when it comes to vaccine

manufacturing. Until 1993 South Africa produced vaccines locally using out-dated technology and in 2014 South Africa remained the only member of the BRICS countries to import all vaccines for the national immunization programme (Kaddar et al., 2014). Meanwhile, in the corresponding period, the Chinese vaccine industry had developed rapidly to more than 40 vaccine manufacturers in 2010 (Hendriks et al., 2010). This is a far cry when considering that South Africa has the most developed pharmaceutical industry. This section on local production overview suggests that the African industry is weak and is focusing on generic medicines with limited research and development into diseases endemic to the continent. The local pharmaceutical industry is under pressure from competition from imports which are coming from India and other industrialized countries because of the growing reliance on imported medicine. 2.4 Drivers behind Local Production in Africa Although arguments against the promotion of local production in every country have been presented (Kaplan and Laing, 2005) there is a strong support for local production in hope that it will improve public health (WHO, 2011), promote industrial development (UNIDO, 2013) and economic growth (Taylor et al., 2009). This section will discuss disease burden, access to affordable medicine, security of supply and socio-economic benefits as drivers behind the promotion of local production. 2.4.1 Disease Burden While there are many diseases that affect Africa, specific diseases such as Malaria, HIV/AIDS, Tuberculosis, Cholera, Ebola and other tropical diseases are more prevalent or disproportionately affect Africa than any other part

of the world. The disease burden is severe across the continent and there is no indication that the situation is getting better (de-Graft Aitkins et al., 2010). The continent is faced with a dual burden of disease due to an increase in both communicable and chronic disease (IHME, 2013). It is estimated that about 75% of **9HIV/AIDS cases and 90% of deaths due to malaria occur in Africa** including "more than **50% of the global deaths of** children **under** the age of **five".18HIV/AIDS, Malaria and TB account for more than 5 million deaths per year,** or about 50 % of all infectious disease deaths (Foster et al., 2006). As recent as a decade ago, predictions of higher diabetes prevalence were rife that, by 2020, the disease burden will shift from infectious diseases to chronic or so-called "lifestyle diseases" (Foster et al., 2006) owing to Africa's widespread economic growth and the rise of the middle class (Bennet, 2014). Recent studies have confirmed that the disease burden is already shifting from communicable to chronic and lifestyle diseases such as diabetes, cardiovascular, cancers and depression (de-Graft Aitkins et al., 2010). A study conducted by the Institute of Human Metrics and Evaluation (IHME, 2013) confirmed an increase in the prevalence of non-communicable diseases between 1990 and 2010. The study found that incidents **17of diabetes, low back pain and depression increased by 88%, 65% and 61% respectively** during this period. It is no longer a prediction, it is happening. The South African pharmaceutical industry is already focusing on producing generic medicines against cardiovascular diseases, diabetes and antiretroviral (Kudlinski, 2013). The shift in disease pattern will also require a shift of focus for many governments especially taking into account that many rely on foreign aid to combat diseases such as malaria, HIV/AIDS and national immunization programs. The emergence of chronic diseases on the African continent will put a financial strain on many national governments as more medicine will need to be imported. Whilst this may be welcome news for the local industry as it will stimulate growth and unlock untapped markets, it is unlikely to be welcome by governments in poorer countries. In sub-Saharan Africa the prevalence of chronic diseases could not have come at a worst time as the region is faced with both communicable and non-communicable diseases (de-Graft Aitkins et al., 2010). 2.4.2 Access to affordable medicine

According to the 4**World Health Organization,** at least **30 percent of the world's population lacks access to** essential **medicines** and **in some countries in Africa, the number may be as high as 50 percent** (Bate, 2008). The 38**lack of access to essential medicines** and vaccines **in** developing countries is one of the reasons for the efforts to encourage local production of essential medicines that are either in short supply or treat other poverty related, tropical and neglected diseases (UNCTAD, 2011). With this approach there will be more assurance that essential medicines are produced closer to where they are needed. Access to medicine and affordability of medicine may have different meanings and thus must be tackled separately. Access is concerned with physically getting the right medicine to the right person for the treatment of a properly diagnosed ailment. Affordability is concerned with the ability to pay for the required medicine. Many factors may be attributable to a lack of access to medicine. For example, the basic transport infrastructure may be lacking and thus the medical facilities become unreachable or medicine cannot reach the people who need it. Even worse, where it does reach the people, the quality can no longer be guaranteed as with a case with vaccines. In certain instances, people have to travel long distances to reach public health facilities. Most importantly, limited access to medicine and high prices may fuel the presence of counterfeit medicines (Alfadl et al., 2013) which has been a serious problem in Africa for many years (Laroche et al., 2005). The issue of high prices is sometime difficult to comprehend because it is not directly linked to manufacturers charging high prices. Other forces are at play. For example, taxes, duties, transport costs and mark-ups by middlemen add to the cost of medicine even when manufacturers have lowered their prices (Bate, 2008). It is estimated that about 30% of medicines on the African continent are counterfeits with an estimated 100,000 people losing their lives because of counterfeit medicines (Leon, 2014). The dangers are life threatening and devastating when taking into account, for example, that a patient taking counterfeit malaria tablets stand to lose their lives when infected with the virus. The other aspect limiting access to medicine is affordability of imported medicine by national governments. This is the ability of the governments to pay for the medicines to reach the people who need them. Vaccines for national immunization programs illustrate this concept well. The African economies are vastly different in that there are those countries that are classified by the World Bank as upper middle income countries who can afford to pay for vaccines through taxation (Blecher et al., 2012). On the other hand, the poorest countries rely on funding to supply the vaccines to their

populations from organizations such as the Global Alliance for Vaccine and Immunization (GAVI) if they meet the stipulated requirements (Brenzel et al., 2006) such as the country's gross national income per capita of less than $1500. The dilemma facing countries on the verge of graduating from the program is how best to fund these vaccines and not put their populations at risk when the funding dries out. Most importantly how best to prepare themselves for the transition from donor funding to self-procurement. 2.4.3 Security of Supply Heavy reliance on imported medicine is the biggest threat to access to medicine and continuous drug supply. In Africa, essential drug supply shortages are a real threat because even when the country can afford to pay for the required medicines or vaccines, there is no assurance that the medicine will be available when needed. Even when the medicine eventually becomes available, it can take longer for it to reach the end user due to long supply chains among other things. Local production may alleviate the problem of medicine supply shortages and allow Africa to take course towards breaking away from depending on imported medicine to treat diseases that are grappling the continent. Manufacturing closer to home may shorten the lead times and supply chains to ensure the medicine reach the patients on time. The target for many countries is to be self-sufficient with regards to supplying locally produced medicines and less reliance on imported medicines. However, the reality is that self- sufficiency is rare and very few countries can supply more than 85% of their market needs through local production (Kaplan and Laing, 2005). Arguably, it may be worth the effort for many developing countries to target and aim to supply at least 50% of their market through local production or to target to purchase from neighbouring countries as opposed to importing from overseas. Despite the target of self-sufficiency, drug shortages continue to occur and affect many countries across the globe. These shortages are mainly attributable to manufacturing or production problems (Palmer, 2014), companies leaving the marketplace and changes in manufacturing recommendations such as implementation of stringent cGMP (NNii, 2006). Therefore even if the vaccines were locally manufactured, production problems could still affect drug supply. Drug supply shortages become even more critical in pandemic situations such as the shortage of influenza vaccines in 2006 (Ulmer et al., 2006) and again in 2010 during the H1N1 influenza outbreak. The Ebola outbreak in 2014 demonstrated three critical points; 1) Africa is totally dependent on foreign aid; 2) the medicine to treat tropical diseases that predominantly affect Africa are unavailable and; 3) the African governments are not prepared nor are able to effectively deal with pandemic situations. This had a devastating effect on the economies of the affected countries (Holt et al., 2015). Although local production promises to improve the security of supply, the argument for self- sufficiency remains difficult to sustain especially with Africa largely dependent on imported raw material supply. 2.4.4 Socio-economic Benefits The

2 African Union's Action Plan for the Accelerated Industrial Development of

Africa (African Union, 2007) highlights the link between industrial development, economic

growth and social development. The report also highlights the challenge of transforming African economies from resource-dependent to dynamic, diversified industrial economies. This sentiment is evident in the UNIDO's Industrial Development Report (IDR, 2013) which also promotes industrialization and economic diversification from agricultural and mineral extraction economies. Local production is seen as a means to promote industrialization which presents the opportunity to diversify the economy and introduce other service sectors that will contribute towards a wide employment base (IDR, 2013). Local pharmaceutical production offers a mix of jobs and employment opportunities on a wide scale between low-end technology in packaging operations to high-end technology in research and development. Because high end jobs require skills in mathematics, science and engineering (IDR, 2013), there is a strong argument that local production will encourage investment in skills development and education as the manufacturing industry matures and becomes more sophisticated. This in turn has a potential to stimulate economic growth and create a substantial domestic market (IDR, 2013). The African Union has

emphasized that the industrialization in Africa **must be anchored on** building **human**

capacity by investing **in health, education and training.** There is also recognition that

industrial development policies should be designed to enhance the science, technology and innovative capacity which is lacking in many African countries (African Union, 2007). As industrialization matures, it can be expected that there will be more exports generated which will have a positive impact on the balance of trade. 2.5 Considerations for Establishing Local Production Capacity There are two major conflicting views regarding local pharmaceutical production in Africa. Firstly, there is a view by the Heads of State and Governments (African Union and UNIDO, 2012), the World Health Organization (WHO, 2011) and its allied organizations (UNCTAD, 2011, UNIDO, 2013) that the promotion of local production is a sustainable means to address the public health and socio-economic issues that are grappling the continent. The second opposing view as presented by Kaplan and Laing (2005) and supported by Bate (2008) puts forward the argument that local production may not be feasible for every country to pursue. This section discusses key considerations that must be in place in order for local production to be viable. 2.5.1 Infrastructural Development and Funding The competitiveness and viability of local production rests on the availability of an efficient infrastructure (roads,

communications, water and electricity) and financing. However, basic infrastructure on the continent is either lacking or inadequate hence the infrastructural development has been a priority of the African Union for more than a decade (African Union, 2007). Reliable supply of water and electricity are the cornerstone of pharmaceutical manufacturing such that any disruption in either of these utilities immediately results in a loss of competitiveness. Complex pharmaceutical formulations and cleaning regimes require availability of high quality water and electricity to run the sophisticated machinery. The delivery of manufacturing supplies as well and final product to the patients demands adequate road infrastructure. Not only is the lack of basic infrastructure a problem for the manufactures, poor road and transport infrastructure will hinder access to medicine if the patients are unable to access healthcare facilities. Unreliable supply of electricity means the manufacturers must have back-up power supply through the use of generators and pay for additional fuel costs. Financing is key to industrial development (African Union, 2007) and a major consideration in the development of physical infrastructure required to set up local production operations – that is, the construction of the manufacturing facility. However, financing still remains a major constraint to the industrial development in Africa particularly for small and medium enterprises who are perceived to be risky by the formal banking systems (UNESC et al., 2013). The start-up costs of building a pharmaceutical plant that complies with international quality standards could cost millions of dollars and is therefore considered a major investment undertaking (Bate, 2008). Once the facility has been built, additional costs to actually run and maintain the facility must be taken into account. Secondly, the hidden costs of maintaining the plant during the initial time of non-productivity whilst waiting for the regulatory authorities to assess and approve the facility as well as those products expected to be produced in that facility must be considered. Finally, consideration must be made to the allocation of funding for research and development to ensure a pipeline of drugs to be produced in the years to come. However, taking into account lead times from discovery to registration may take between 10 – 15 years and cost up to USD 1.38 billion to develop a single medicine (IFPMA, 2011), it is not unexpected that Africa lags behind in this regard. It is for this reason that Kaplan and Laing (2005), Bate (2008) and Slamet (2012) have argued that for certain countries local production may not be feasible. Without adequate funding it is difficult to imagine any progress with regards to infrastructural development. With Africa being home to some of the poorest countries in the world, according to the World Bank classification system, and funding being hard to come by; the argument for local production becomes difficult to sustain (Bate, 2008). It is therefore not surprising that most countries in Africa concentrate their efforts on simple formulations which involve labelling and packaging. Funding remains a big challenge in Africa and a stumbling block to local production (SEATINI and CEHURD, 2013). Despite the challenges with funding on the African continent,

each country must evaluate its own situation and make an informed investment decision whether or not local production is a viable option. South Africa already has a well- developed pharmaceutical industry, a robust banking system and a stable political climate which suggests that it may be more favourable to embark on local production than it would be in poorer countries such as Lesotho or Swaziland. 2.5.2 Human Resource Constraints Although local production promises socio-economic benefits of employment and skill development, pharmaceutical manufacturing is complex and capital intensive as opposed to labour intensive. The processes involved in pharmaceutical production require specialized, highly trained personnel which are in short supply in many African countries (GlaxoSmithKline, 2011). The expected increase in employment rates is unlikely to be realized by the masses because of the specialization requirements of the pharmaceutical industry. Therefore in order for the industry to be competitive, careful consideration must be given to the availability of appropriately skilled personnel to carry out sophisticated tasks required in pharmaceutical production (Saleh, 2014). The issue of skills availability and skills development becomes more critical as the industry evolves from tertiary to primary production where strong skills in research science, engineering and business management are required (IDR, 2013). Skills development for primary manufacturing is crucial; however, as mentioned in the previous section, funding is required for research and development. According to GlaxoSmithKline (2011) highly specialized staff is necessary to carry out research and development as well as high-tech manufacturing. Sadly, the World Health Report of 2006 (WHO, 2006) reported a crisis in human health in more than 57 countries especially in pharmaceutical health. The availability of scientific research skills and infrastructure cannot be overemphasized. Central to the issue of availability of skilled personnel is whether the country has university faculties that are producing graduates with qualifications in the sciences particularly pharmacy/pharmacology, chemistry, microbiology, engineering and management (IDR, 2013, Kaplan and Laing, 2005). The quality of science education is crucial in ensuring that graduates are able to support research and development as the industry matures and moves towards primary production. South Africa is home to some of the world renowned universities with a strong base in science, business and research. These include the Rhodes University School of Pharmacy, The University of Cape Town, Wits University, University of KwaZulu- Natal and a number of technology universities across the country all of which excel in the fields of science and research. Because skills development takes time and effort (IDR,2013), technology transfer may be a solution in boosting local production capacity and facilitation of technical "know-how" transfer (GlaxoSmithKline, 2011). Technology has many benefits in that the recipient of technology transfer gains expertise, support and inherits a quality system from an established manufacturer. As beneficial as it may be to use technology transfer as a vehicle to accelerate

94

skills transfer, careful attention must be paid to selecting a partner with a mutual benefit. For example, technology transfer partners may impose market/territory restrictions which may hamper the profitability of the local manufactures. Secondly, technology transfer is lengthy and may be expensive 30**depending on the nature** and complication **of the technology being transferred. The** costs of technology transfer may include travelling costs for training, new equipment, trial material and material for validation. All these costs are usually incurred before any product can be approved for sale to the market and someone has to pay for it. 2.5.3 Quality of Medicine and Regulatory Oversight The quality of medicine and regulatory oversight go hand-in-hand as poor regulation of medicine pose a serious threat to public health and may result in the presence of sub-standard or counterfeit medicine on the market (Kaplan and Laing, 2005). It is the responsibility of the regulatory agencies to verify compliance with good manufacturing practices by manufacturers; to oversee the drug registration process and to ensure that drugs that are not registered or produced in GMP-compliant facilities do not reach the market (UNCTAD, 2011). The regulatory agency conducts facility inspections, reviews registration dossiers and 21 issues licences and give market authorization to the manufacturers. Sadly, in many developing countries including Africa the regulatory oversight is not up to the required standard despite the presence of regulatory agencies in almost all countries (WHO, 2012). Weak regulatory oversight in many countries results in the presence of sub-standard or counterfeit medicine finding their way into the market and have a devastating effect on human health, economic relations and quality of life (Leon, 2014). A weak regulatory framework and a lack of access to medicine due to high prices are some of the reasons that are responsible for counterfeit medicine on the market. The problem of counterfeit medicine is not only an African problem as it also affects countries with the most robust regulatory systems; however, Africa is estimated to have as much as 30% of counterfeit medicine in circulation (Leon, 2014). Weak regulatory oversight also results in many countries not complying with GMP principles sighting costs associated with upgrading to GMP inadvertently compromising on quality standards. There is a lack of regulatory harmonization across the African continent resulting in each country stipulating its own regulatory requirements which can also act as a barrier to registering medicines on the African continent (Narsai et al., 2012). Because of weak or poor regulation, many countries in Africa do not subscribe to internationally recognized quality standards such as those stipulated by the World Health Organization (WHO) for prequalification; the African countries are unable to benefit from economies of scale by selling to the WHO. It is for this reason that the African Union has recognized that inability to meet international standards is hampering competitiveness of the

local industry as well as global competitiveness (African Union, 2007). The AU further recognizes that failure to meet global standards is **2a barrier to taking advantage of the benefits of market access for processed and manufactured goods.** 2.5.4 Market Dynamics and Competitiveness Arguments against local production in developing countries, particularly in Africa, suggest that the market size does not justify the investment undertaking. This argument is strongly supported by Kaplan and Laing (2005) who have indicated that countries with smaller economies should abandon local production ambitions due to a lack of economies of scale. From an investment perspective, the companies need to break even and generate profits to be able to recoup their investment (GlaxoSmithKline, 2011). The argument further suggests that small companies in small economies cannot enjoy economies of scale that large companies in developed countries do hence they cannot compete in price or quality (Kaplan and Laing, 2005). According to this argument, the suggestion is that smaller countries should rather abandon the idea of local manufacturing altogether and purchase medicines from large developing countries such as Brazil and India. The above argument almost sounds convincing but is loosely constructed with a few loopholes that are left hanging. Firstly, the definition of a small economy and small company does not come through from the above argument. If African pharmaceutical manufacturers are producing essential medicines to satisfy the needs of their population, they do not have to be as big as the multinationals. Given the infrastructural and financial constraints facing the African manufacturers, the argument to remain within limits of your resources seems more plausible. Secondly, it is widely acknowledged that manufacturing medicines locally may not always be cheaper than importing them (UNCATD, 2011). However, with an increasing "dual burden of diseases" in Africa (IDR, 2013) the point at which local manufacturing will be more beneficial over importation is fast approaching and this has not yet been explored. Finally, the suggestion that African economies should buy from countries with large economies is a step in the wrong direction as it suggests that Africa will never break free from importation dependence. It also defeats the purpose of establishing local production to stimulate industrial development on the continent. A simulation study conducted in Ghana showed that economies of scale are not an absolute necessity and that countries with smaller economies can generate profits despite certain cost disadvantages (Chaudhuri, 2013). According to Chaudhuri (2013), producing with cost disadvantages does not lead to higher prices of neither medicine nor does it render local production to be unviable. The most startling conclusion is that the role of economies of scale is over-exaggerated. **8According to the United Nations Conference on Trade and**

96

Development (UNCTAD, 2011) cost disadvantages may be improved by introduction of incentives such as tax breaks, duty-free importation on active raw materials and tax holidays until profitability sate has been reached. 2.6 Summary This chapter discussed local production from an African context and identified the key drivers behind the support to boost local production as well as key considerations to be taken into account for successful establishment of local production. Aim of this study was to evaluate whether it would be economically viable to produce vaccines in South Africa by comparing primary production costs (semi-finished imported) versus a secondary production cost (locally filled vaccine). Based on the literature review, the disease burden in South Africa is no different to other African countries and the same considerations for local production to be successful are applicable to vaccine manufacturing. Specific considerations are scarcity of skills, reliance on active raw materials for secondary production, funding for research and development, market dynamics and the cost of production. Taking into account the factors discussed in this review, Chapter 3 will describe the methodology that was employed in determining economic viability of a locally produced vaccine when compared to one that is imported semi-finished. 5**CHAPTER THREE: Research Methodology 3.1**

Introduction This chapter presents the research methodology used in the study. The chapter begins by restating **the** aims and objectives of the study followed by the 6**description of the research design** and methodology; **the** location **of the** study, sampling, data collection and data analysis methods. The chapter concludes with a discussion of the measures taken to 10**enhance the validity and reliability of the study.** 3.2

10**Aim and Objectives of the study The aim of this study** was **to** evaluate economic viability **of** locally filled vaccine (LFV) when compared to imported, semi-finished vaccine for packaging and distribution (SFP). The objectives of this study were: i. To ascertain the manufacturing costs of a locally produced vaccine (LFV) versus imported vaccine for labeling and packaging (SFP); ii. To determine the level of economic activity for which local vaccine production is preferred when compared to importation and distribution of finished vaccine product; iii. To

97

determine the desirable market size for which one option is preferred over the other; iv. To determine the level of investment needed for both options – local production vs. importation of vaccines. v. To determine the effect of changing the key variables such as the selling price, cost of labour, raw materials and bulk product on the viability of either option. 3.3 Location of the Study and Selection of Participants 5**3.3. 1 Location of** the **Study The** study **was conducted** at 1**The Biologicals and Vaccines Institute of Southern Africa (Biovac)** in Pinelands, Cape Town. Biovac is a Public Private Partnership (PPP) entity that was established in 2003 to revive the development and manufacture of vaccines and biological products in South Africa. The Company employs more than 180 employees at its plant in Cape Town across the following departments: Manufacturing, Quality Control, Quality Assurance, Supply Chain, Regulatory Affairs, Business Development, Finance and Human Resources. With no human vaccine manufacturing capacity in South Africa, vaccines that support the Extended Program on immunization (EPI) are sourced abroad and imported either fully- finished or semi-finished for local packaging and distribution into the South African public market. To date, Biovac has made significant progress in re-establishing vaccine manufacturing capability by investing in world-class infrastructure and skills development. This has enabled Biovac to enter into technology transfer agreements with various international vaccine manufactures to locally produce vaccines in the newly commissioned multipurpose manufacturing facility in Cape Town. The approval of the locally produced vaccines will enable Biovac to become the only approved human vaccine manufacturer in the Southern African region. 3.3.2 Selection of the Participants The participants had to possess intimate knowledge and understanding of the vaccine manufacturing (formulation, filling and packaging), quality control & assurance, supply chain, financial controls and project management processes as they pertain to Biovac. The Section Heads of each operational department were approached to identify a subject matter expert within their department who was knowledgeable in Biovac processes and systems. The role of the identified participant was to provide the required information to be analysed by the researcher. Non-probability, purposive sampling using the judgement technique was used to select the participants of this study. Purposive sampling design is used to obtain information confined in a specific target group or type of people either because they are the only ones who have it or they conform to a criteria set out by the researcher (Sekaran and Bougie, 2013). Within the context of this study, few participants could be selected based on their experience in vaccine manufacturing and knowledge of the Biovac processes. The judgement technique was utilized to select the participants who were in the best position to provide the required information necessary.

Although, according to Sekaran and Bougie (2013), judgement sampling may limit the generalizability of the findings, it is the only viable sampling method when the required information can only be sourced from a handful of individuals who are subject matter experts. In this study the judgement sampling technique was used specifically because very few individuals, within Biovac, could provide the required information on the specific inputs required to support vaccine production processes. The selected participants (subject matter experts) represented the respective operational departments to provide the required information but were themselves not subjects of the study. 3.4 Research Design and Methodology 22**3.4.1 Purpose of** the

Study The purpose of this study was **to** explore and gain an in-depth understanding of the Biovac production cost factors associated with local vaccine manufacturing (LFV) when compared to imported semi-finished vaccine operations. In order to conduct this study, the costs of manufacturing imported semi-finished multivalent vaccine (SFP) were compared to the costs of locally manufacturing the same vaccine from formulated bulk product. This study had to be conducted because the current costing model for Biovac is based on sourcing and distribution of imported vaccines. No formal cost analysis study has been conducted by Biovac on LFV activities. 3.4.2 Research Approach A single case study approach was selected as the research strategy for 8**this study to explore and** gain **an** in-depth **understanding of the** Biovac production processes **and** associated costs. This case study follows a qualitative approach to solve the research question. The qualitative approach is exploratory in nature and is used when the researcher wants to gain a deeper understanding of the problem within a specific setting through first-hand experience (Sekaran and Bougie, 2013). According to Rowley (2014) single case studies are appropriate to use where the case is extreme or unique and Biovac is a unique case where single case study is applicable. Case study research is defined as an in-depth study of a particular situation, or event, or problem within its real-life context where the researcher utilizes multiple sources for data collection but has little or no control over the events as they unfold (Yin, 1994). In a case study the "case" may be an individual, or a group, or the organization, or a department within the organization 23**that the researcher is**

interested in (Rowley, 2014, **Sekaran** and **Bougie, 2013).** In **the case study**

methodology the researcher selects the case and conducts a detailed contextual analysis 6**to gain an** in-depth **understanding of the phenomenon to** be studied as opposed to making generic statistical conclusions based on quantitative data. Case studies have a prominent place in 15**management studies and organizational theory as a form of data collection and a type of unstructured analysis** (Schnell, 1992) and are particularly useful for analysing and solving practical business problems in their contextual setting (Dul and Hack, 2008). The case study approach was deemed appropriate to apply in this research as the aim was not to make statistical inferences about the vaccine manufacturing industry costs but to gain a holistic view of the cost factors as they pertain specifically to Biovac as a business. The advantages of using case study as a research method lies is the ability to use multiple data sources to 29**collect both** qualitative **and** quantitative **data for analysis** and interpretation **of the problem** within its environment with minimal interference from the researcher (Sekaran and Bougie, 2013). Sources of data 16**may include but not limited to archival records, interviews, physical artefacts, direct observations, and participant-observation** with each **data** source 28 21**contributing to the researcher's understanding of the phenomenon (Baxter and Jack, 2008).** The captured qualitative accounts may reveal and explain complexities that 20**may not be captured through experimental** and **survey research (Zainal, 2007). Case study research** approach is not without criticism. Critics of this methodology have 11**argued that case studies** may **provide little basis for scientific generalisation**

because of **the** dependency from a single case and may lack rigour because the researcher may have allowed 11**bias views to influence the direction of the findings** (Yin, 1994). It has also been argued that conducting case studies may be time consuming and generate too much data that may prove to be a challenge to analyse. Whilst scientific generalizability is an important factor in research, this study aimed at finding information about one specific organization, Biovac. Using multiple sources of data collection methods has enhanced the credibility of this study to deal with the issue of bias within the study. Finally, focusing the attention to the research question has allowed collection of relevant, manageable data. 3.4.3 Data Collection Strategies The qualitative nature of this study called for a combination of data collection strategies to provide insight into the research problem from different angles. Both primary (first-hand) and secondary (existing) sources were used in data collection. Data were collected using 1) Focus group discussions and Interviews with "key informants"; 2) Document Studies; and 3) Observation methods. 3.4.3.1 Focus Group Discussions and Interviews with individuals The focus group was formed by departmental section heads (middle management) representing Production, Quality, Finance, Supply Chain and Project Management Office. The participants in the focus group were selected using a judgemental sampling method (Sekaran and Bougie, 2013) based on their experience and intimate knowledge of the vaccine manufacturing operations; the authority level as managers to be able to provide the required information and give direction to their subordinates to provide further details required in the study. Focus group discussions provided first hand opinions and interpretation of the overview of Biovac production processes. Interviews with "key informants" (individual employees) were conducted to provide detailed information on the process overview obtained from the Focus Group discussions and to allow for further follow up to clarify concepts and check for reliability of data. 3.4.3.2 Document Studies Existing Company records were studied to extract information to enable process analysis on manufacturing and packaging operations, in-bound transportation cost factors. The records consulted included: ? Manufacturing and Packaging Records – batch records, standard operating procedures, log books and work instructions ? Financial Databases – Financial records with data on costs of raw materials, salary bands per job category, equipment depreciation, budgets and actual spent for the years 2014 and 2015 ? Project financial information – to supplement and correlate information supplied by various departments. Sensitive business information was handled with care in order to ensure confidentiality and ethical considerations. 3.4.3.3 Observation Methods Observation methods provide a useful tool to collect data on actions and behaviour (Sekaran and Bougie, 2013). Observations require the researcher

to go into the field to collect first- hand data. In this study, observations were made within the production environment in order to gain insight into manufacturing inputs required in the study. The aim of using this method was to observe and record the production processes; to confirm the components and labour used in manufacturing as provided by the participants of the focus group and key informants; and to gain an in-depth understanding and confirm the accuracy of the Biovac production processes. Both forms of observation methods – participant and non-participants – were used in this study. As a participant, the researcher spent time with the operators learning various aspects of the production processes. As a non-participant, the researcher observed the processes using the closed circuit cameras installed for this purpose. The cameras are always switched on and the operators are aware that anyone could be watching at any given time. This provided the opportunity for the researcher to request permission to observe the operations as and when required. 3.5 Data Collection Procedure Data collection was conducted with the research objectives in mind to ensure a logical flow of information from the first objective to the last objective. As a result more time was allocated to understanding and capturing the various processes within the vaccine value chain in order to fulfil objective 1 (determination of production costs). The information obtained here was used to fulfil objective 2 (determination of favourable option to pursue based on economic activity) and objective 3 (determination of the desirable market size to generate revenue), as well as objective 5 (evaluation of the effect of changing key variables on profitability). Objective 4 (Cost of investment) was independent of data collected from objective 1. 3.5.1 Objective 1: Determination of the manufacturing costs of LFV and SFP Process Flow Mapping Data used to describe, analyse and cost the manufacturing processes were collected using a combination of sources, namely: focus group, interviews, company records and observations. Group discussions and interviews were critical in mapping the production processes and identifying which records to be studied as well as to confirm which processes to be observed for data collection. The extraction of information from Company financial records and process observation provided the key numerical information that was required to evaluate the economic viability of locally produced vaccines. Initially, three Focus group meetings were scheduled over the period of 3 months to provide the overview of the manufacturing processes as they pertain to semi-finished imported vaccines and local formulation and filling activities. The aim of the first meeting was to initiate the group discussion to describe and give an overview of the operational activities at Biovac. The second meeting was scheduled by the researcher to present the initial results to the participants of the focus group based on the discussions from the first meeting. This presented the opportunity for both the researcher and the subject matter experts to check if the information from the first meeting was captured accurately and for the group to ratify the process information first

hand. A third meeting with the focus group was scheduled to present the final framework to be used in collecting detailed data and to present the picture that had emerged from the initial analysis. Between the first and the third meeting, interviews with the identified key informants, observations and archival data were collected by the researcher. After the third meeting the research focussed mainly on the Company record extraction and observation techniques to collect numerical data. The information on process maps was grouped into various cost centres based on the activities mapped and was verified through focus group discussions, manufacturing records review and individual interviews. Collection of Batch Processing Data The collection of batch processing data for both LFV and SFP was necessary in order to understand the total duration of each operation. This data will enable the researcher to calculate the theoretical production capacity of this facility; the calculation of direct labour; the batch size to be filled and packed; the components required for each operation which in turn will enable the computation of raw materials required per batch. Data was collected on component preparation and cleaning times; components used in filling and packaging operations; labour usage and requirements for each process stage; theoretical capacity of the manufacturing site; equipment filling speeds and in-bound transportation costs of bulk liquid and finished product. The duration of processing a single batch was computed by using data collected for a standard batch size of imported formulated bulk (83 Litres) for filling into single-dose glass vials using the automated vial filling machine at 10,000 units per hour and a manual packaging process that is currently in place. 32 The following assumptions were made in the calculation: ? Out of the 52 weeks in a year, there are 38 working weeks available for production when the public holidays, weekends and annual maintenance shutdown are excluded; ? Only a single product is filled in vials at this site over 38 weeks; ? All available resources are channelled to producing this product; ? The manual packaging operational capacity is fixed at 350 units packed per operator per hour for either locally filled or imported semi-finished product; ? The quantity of the product filled is equal to the product to be packed; Collection of Process costing data Data on the cost of components used in manufacturing (filling and packaging); equipment costs and depreciation; manufacturing overheads and labour costs were collected by the researcher through interviews and company financial record extraction. Cost of Production The method used to calculate the costs of producing a single unit (dose) of a locally produced vaccine was similar for the semi-finished imported product although the inputs varied. Variable costs per unit (dose) were calculated by dividing the costs per batch by the number of units per batch; fixed costs were computed per annum. Total Fixed Costs were computed by adding direct and indirect costs. Total Fixed costs per dose were calculated based on the known total annual demand of this product at 4.5 million doses per year. Different scenarios were simulated under different demands such as at

theoretical capacity of Biovac. Locally produced vaccine cost inputs The cost of formulated bulk transportation, the cost of formulated bulk, the cost of raw materials, cost of product testing, equipment depreciation using the straight line method, direct and indirect labour and energy costs per batch including the packaging operations were taken into account in this calculation. Imported semi-finished vaccine cost inputs The costs of semi-finished product, transportation, raw materials, product testing, direct and indirect labour costs were taken into account when calculating the input costs. The cost of equipment depreciation was not calculated as the equipment used in manual operations was more than 10 years old and the remaining value was negligible. 3.5.2 Objective 2: Determination of favourable option to pursue for LFV and SFP Point of indifference or Pivot Point This is the point at which the total cost to produce a certain number of doses is irrelevant of whether the vaccine is manufactured locally or imported semi-finished. This point is significant in that it could be used to determine which option is more favourable under different market conditions (low or high market demand). On either side of this point one option (LFV or SFP) is expected to be more favourable than the other. In this study, the researcher is interested to determine the number of doses required to reach the point of indifference and extrapolate whether the point at which the LFV option is economically more viable than the SFP option. To determine this point, variable costs per dose and fixed costs (Total Cost) of each unit produced up to 5 million doses were calculated. A chart depicting Total Cost (y-axis) vs. Number of doses (x-axis) was plotted on the same axis for both LFV and SFP using the formula: $Y = mx + c$, where Y = Total Cost of production; m = variable cost per dose (Slope); x = number of doses and c = Fixed Cost (y-intercept); The point at which the two curves cross each other is the indifference point. 3.5.3 Objective 3: Determination of the desirable market size for each option Break-even Point Analysis The desirable market size will be determined by the number of doses required to break-even. The break-even point is a neutral point where the cost of production equals the revenue generated. It is used to determine the point at which the number of units sold will cover the operational expenses and generate a profit. The selling price of the SFP and LFV was assumed to be the same as this is the single exit price on tender. The break-even point was calculated using the variable cost per dose and fixed costs which in turn were used to compute the contribution margin. Using the contribution margin and total fixed costs, the Total Profit gained from each unit produced up to 5 million doses was calculated. A chart depicting Profit (y-axis) vs. Number of doses (x-axis) was plotted on the same axis for both LFV and SFP using the formula: $Y = mx + c$, where Y = Total Profit; m = Contribution Margin (Slope); x = number of doses and c = Total Fixed Cost (y-intercept); The break-even point was reached at a point where each curve crossed the horizontal axis. 3.5.4 Objective 4: Determination of the level of investment required for LFV & SFP The investment requirements for locally filled and imported

104

vaccines differ. This section will estimate the cost of setting up a facility from the ground up. With the Company having first built a facility suitable for imported vaccines (Cold Storage, Packaging and quality Control testing) then built a new facility for formulation and filling; the actual cost was accurately calculated from the data that was collected from the archival projects and financial records. The cost of bringing the product into the facility was estimated from technology transfer projects with external partners by analysing the actual project expenditure on each project from inception to submission of a product dossier for registration. In particular, the costs were analysed and grouped according to the following categories: ? Infrastructural Costs – Physical Buildings (Packaging, Formulation, Utilities, Warehouse and Cold Room Storage and Quality Control Laboratories) ? Plant & Equipment – Automated Filling Machines, Washers, Autoclaved and Utilities ? Technology Transfer Components – Product-specific Equipment, Qualification & Validation, Regulatory, Bulk Product Transportation and Consultant Fees The foreign currency fluctuations and today's cost of borrowing were not taken into account 3.5.5 Objective 5: Assessment of the effect of changing variables on profitability Objectives 1 to 3 were concerned about understanding the production cost and market dynamics under static conditions. This objective aimed to test the resilience of either locally filled vaccine or semi-finished operations by introducing the stress factors which are known to occur in the vaccine business. Firstly, the semi-finished product and formulated bulk are imported from a European supplier and are therefore

subject to 33**currency fluctuations between the** South African Rand **and the Euro.**

The resilience to external forces had to be tested for the most favourable option as per

objectives 2 and 3. Secondly, the prices of vaccines are known to drop either due to entry of competitor products or due to unaffordable prices (Spier and Milstien, 2009). It was therefore critical that both semi-finished and locally filled vaccines were subjected to these external factors and assess the impact on profitability and to determine which option is able to better withstand these factors. By using the production cost information from objectives 1 to 3, the cost of product (Formulated bulk and semi-finished product) was increased by 25% while the selling price which is currently known was reduced by 20% and the effects on profitability and resilience were analysed. The percentage manipulations were adjusted in parallel up to a point where only one option indicated viability under duress. 3.6 Data Analysis The data collected from multiple sources had to be coded and categorized to give meaningfulness. Data selection, coding and categorization is known as data reduction (Sekaran and Bougie, 2013). It helps to give ideas on how data may be displayed as well as to draw conclusions based on patterns. Once the data has been coded, the next stage in the analysis is data presentation as a matrix or graphical form to

illustrate the patterns as they are developing. Data Coding The unit of analysis in this study was the entire organization as this was a case study. As a result, an insurmountable amount of data was collected. Relevant data was selected and coded as either direct or indirect cost. These direct and indirect costs were further classified into either fixed or variable costs. Data Categorization The second stage of analysis was the mapping of the manufacturing processes for both imported semi-finished (SFP) and locally produced vaccines (LFV) with the production costs associated with both processes described and classified into cost centres. Through repetition of data from multiple sources, the main cost drivers emerged as transportation of semi- finished product (SFP) or formulated bulk (LFV) costs, raw materials, labour, equipment depreciation, utility and product testing costs. During this stage of data analysis, patterns and relationships between the data began to emerge which at times necessitated categories to be broken down into sub-categories. Data Display and Analysis The data that had been coded and categorised into cost pools 31**was captured and** displayed **in a** tabular matrix using **Microsoft Excel Spreadsheet.** With further analysis, formulae and graphs were computed from the data to easily read patterns and make conclusions. Data Stress testing In order to test the robustness and the integrity of the model, the cost of formulated product and the selling price were deliberately increased and decreased by between 10 and 25%. Further analysis was conducted on the effect of this manipulation. 3.7 Issues of Trustworthiness Although case study research methodology is widely used in management studies and organizational theory (Schnell, 1992) because of its flexibility in the use of multiple sources of data to enhance credibility (Baxter and Jack, 2008, Yin, 2012), the method may be subject to criticism. The researcher took careful consideration when conducting this study to ensure the credibility of the study. To enhance the 6**credibility of this** study, **the researcher used** multiple sources **of data** to converge them into the research. Within the context of this study, a focus group made up of company section heads that are familiar with the intricacies of vaccine production was formed. This group provided valuable information on the overview of the processes. Because of the level of authority within this middle management group, each member was able to select individuals from their teams who could be interviewed or guide the researcher into the facility to observe the processes as they unfold. The information that was provided by members of the focus group was verified through observations and review of manufacturing and financial records for accuracy. A series of meetings with the focus groups were setup as well as presentations to the research and development team (academic team) were used as a means to interrogate the robustness of the

research methodology and approach. Data relating to costs were collected from projects and verified against archived financial records whilst data on processes and process maps were verified through approved standard operating procedures and observation of the processes. An audit trail of the presentation slides to various groups (focus groups, management and research and development team), the meeting requests and summary of discussions were kept by the researcher for reference and as part of the audit trail. This team provided valuable input on the best approach and course to be taken in order to ensure the researcher remained within the scope of the study. 3.8 Ethical Considerations Ethical considerations were observed at all times when this research was conducted. Active research only commenced after the Ethical Clearance Certificate was issued by the University of KwaZulu-Natal. Permission to conduct the study was sought and granted in writing by the 38 Chief Executive Officer. In conducting this research study within a commercial entity, the researcher had to take great care not divulge company secrets such as supplier information, trade secrets and sensitive information without explicit permission to do so. The permission letter reiterated that access to confidential Company information needed to be treated in a confidential and appropriate manner as outlined in the Company's Policies and procedure. As this was a case study research, observations took place within the work setting and it was imperative to demonstrate respect to the production schedule and request for permission to have access to restricted areas within the facility, Company records and time for interviews. Although this was a case study on the entity, key informants and the focus group members had the option not to participate and this was emphasized during on-going progress report- back meetings. 3.9 Limitations of the Study Assumption that only one product is produced on the site annually. The effect on the production costs if more products are added onto the facility was not assessed. The effect of foreign exchange currency fluctuations on the original cost when the equipment was purchased was not taken into account. Instead, the cost of production and other related costs will be reported in the local currency (the South African Rand). 3.10 Summary This chapter discussed the case study research methodology that was employed by the researcher when conducting this study. The researcher began by stating the aim and the objectives of the study and described the location of the study as well as the manner in which the participants were selected. Research design methodology description including data collection strategies, detailed data collection procedures and data analysis description were discussed. Finally the issues of trustworthiness and ethical considerations employed in the study taken into account in the study were discussed towards the end of the chapter. Chapter 4 will present the findings resulting from data collected in this chapter. The findings will be presented systematically to align with the objectives as presented in this chapter. CHAPTER FOUR: Findings 4.1 Introduction The aim of this study was to evaluate whether local production of vaccines, in South

Africa, is economically viable when compared to imported vaccines using Biovac as a case study.

14**This chapter presents** and discusses **the results of the data analysis** from Chapter 3. This study entailed the collection and sifting through tremendous amounts of data from different sources over a period of 4 months 27**in order to achieve the** goals and **objectives of the study.** The results are narrated and presented in tabulation and graphical form as appropriate. This chapter is organized with the research problem in mind and with the findings presented in accordance to research questions raised in Chapters 1 and 3 as follows: ? Section 4.2.1 will report on the demographics of the Unit of Analysis ? Section 4.2.2 will report the findings on the unit cost of production; ? Section 4.2.3 will report findings on the point where local production is favourable over an imported vaccine (The point of indifference); ? Section 4.2.4 will report on the findings relating to market size for which one option is desirable over the other (Break-even Analysis); ? Section 4.2.5 will report the investment costs required for each option – Locally Filled Vaccine and Semi-finished Product; ? Section 4.2.6 will report the findings on the effects of changing key variables such as the cost of product and a drop in price on the profitability of either of the options. ? Section 4.2.7 will summarise the findings of this chapter and introduce Chapter 5. 4.2 Presentation of Findings 4.2.1 Demographics of the Unit of Analysis The 1**Biologicals and Vaccines Institute of Southern Africa (Biovac) is a** pharmaceutical manufacturing company based in Cape Town with a workforce of approximately 180 employees. The core business of Biovac is vaccine manufacturing. The company was formed in 2003 as 1**a Public Private Partnership (PPP) between the South African Government and The Biovac Consortium.** Since 2003, more than R700 million has been invested in infrastructural 40 and skills development in order to realize company's ambitions of becoming a fully-fledged vaccine manufacturer on the African continent. Since inception, the Company has recruited a wide mix of skilled personnel to support the current operations of vaccine distribution, basic Research and Development as well as future expansion operations. By 2014, the skill set was mixed with Company employing 9 personnel with PhD qualifications on the high end and 30 with matriculation and below as summarised in Table 4.1

below. Table 4.1: Biovac Skill Set in 2014 (Permanent Employees) Qualifications No. of people Matric & Below 30 Certificates & Diplomas 34 Bachelor's Degree 20 Honours Degree 10 Master Degree 13 PhD 9 The headcount per department is shown in figure 4.1 below. The figure shows that the highest numbers of people are employed in Production, Quality Control, Logistics, Engineering and Research and Development departments. Biovac Headcount per Dept - 2014 Headcount per Dept. 18 16 14 12 10 8 6 4 2 0 Departments Figure 4.1: Biovac Headcount per Department Adapted from Biovac Presentation: Retention Policies and Models for the Local Workforce 4.2.2 Unit Cost of Production The determination of the unit cost of production was conducted in a multistep approach involving: 1) process flow mapping and identifying the relevant cost centre (pools), cost activities and classification; 2) Batch process information and theoretical capacity for aseptic filling and manual packaging operations; 3) Computation of cost activities and classification; 4) Indirect cost allocation of manufacturing and administrative overheads and; 5) the cost of producing a single unit of vaccine under various demand scenarios. Process Flow Mapping and Cost Categories The manufacturing process overview was developed from the description and identification of activities involved in both local filling and semi-finished importation operations. Due to the complexity of the vaccine manufacturing operations, data collected was reduced and categorized into main cost centre activities and further subdivided into relevant costs per activity. Each cost activity was classified as either fixed or variable as described in Table 4.2 below. Table 4.2: Process Steps for SFP and LFV Semi-Finished Product Locally Filled Vaccine Cost Centre/ Pool Cost Centre/ Pool Cost Activities Cost Classification Finished Product Handling Bulk Liquid Handling Transportation Raw Materials Labour Variable Variable Fixed Aseptic Filling Raw Materials Labour Eq. Depreciation Direct Electricity Variable Fixed Fixed Variable Viewing Viewing Labour Eq. Depreciation Fixed Fixed Labeling & Packaging Labeling & Packaging Raw Materials Labour Eq. Depreciation Direct Electricity Variable Fixed Fixed Variable Quality Control Quality Control Consumables Labour Commissioned Testing Variable Fixed Variable There are four steps involved in the processing of an imported vaccine and five for a locally produced vaccine. These steps are grouped vertically into cost centres. The manufacturing steps are similar between LFV and SFP operations with the additional aseptic filling step for the LFV. The cost centres for SFP are product handling from supplier to Biovac; product inspection; labelling and packaging and quality control testing. The LFV cost centres were found to be same as in SFP with the addition of the aseptic filling cost centre. In both SFP and LFV the common cost activities were: ? Transportation Costs – Freight Charges, Customs Clearance and Agents Fees ? Raw Materials (SFP or Formulated Bulk Liquid) – Cost of Product and Insurance ? Direct Electricity – power consumption required to power the equipment ? Quality Control Testing – consumables and testing commissioned testing ? Labour Costs – all

labour costs across the cost centres including indirect labour ? Equipment Depreciation –
Significantly costly equipment depreciation (Automated filling lines, washers and autoclaves)
Batch Process Information and Theoretical Capacity Calculations Aseptic Filling The company
subscribes to batch manufacturing method of operation. In order to fill one batch of product, a
single batch of formulated bulk liquid must be dispensed into single, sterile vials. The batch size
for the product under consideration equals 83 litres of formulated bulk that is received by the
Company ready for dispensing pending quality assurance approval. The required dose to be
administered to a patient is 0.5 millilitres (ml) however 0.68 ml is the target fill volume in order to
account for the residual volume of product that remains on the syringe when the vaccine is
administered. A single batch of finished product filled from 83 litres of formulated bulk into single
dose vials at a rate of 10,000 vials per hour is expected to have a theoretical yield of
approximately 122,000 unit doses. With a 2% rejection rate allowed to account for start-up
samples, product testing (quality control), in-process checks, product lost due to start-up and the
product left in the 3 meter line between the formulated bulk tank and the filling line, the final
quantity 43 expected to be transferred to packaging is approximately 119,000 doses. Although
the actual filling time required to fill and empty the formulated bulk tank is approximately 12 hours,
the total batch processing time (filling operations) requires approximately 19 hours to complete as
shown in Table 4.3 below. Table 4.3: Batch Process Information (Aseptic Filling) Batch Process
Information (Aseptic Filling) Formulated Bulk Size 83 Litres Fill Volume per dose 0.68 mL Batch
Size 122059 units Batch Size (2% Scrap) 119618 units Filling Capacity 10000 units/hour Filling
time 12 hours Setup Time 4 hours Cleaning Time 3 hours Total Process Time 19 hours It takes
approximately 4 hours to prepare for the aseptic filling of a batch. This is the time it takes to
perform the cleaning and sanitisation of the filling line, the aseptic connections between the filling
line and the formulated bulk product and the time to allow the filling suite to return to a state of
"rest". Upon completion of the filling process, the disposable filling components are discarded as
per approved procedures. The filling machine and the filling suite are cleaned over a period of 3
hours. Theoretical Annual Filling Capacity The filling line has a theoretical capacity of 63.8 million
batches per year at 10,000 vials per hour. This capacity is achieved over 38 production weeks
and takes into account the machine will not be utilised during planned maintenance shutdown,
Christmas holiday time and on public holidays. As presented in Table 4.4 below, 63.8 million
doses equates to a total of 523 batches that could be filled on the vial filling line. Table 4.4:
Theoretical Filling Capacity Theoretical Filling Capacity Production Weeks 38 Weeks Production
Days 266 Days per Annum Production Hours 6384 Hours per Annum Annual Filling Capacity
63,840,000 Doses per Annum No. of batches/annum 523 batches The annual demand for this
product is 4, 500, 000 doses which equates to a spare capacity of 59.3 million doses. The annual

demand of 4.5 million doses is equivalent to 38 batches required to be filled per annum. Based on the theoretical capacity of the filling line and the stated demand, the utilization capacity of this filling line is approximately 7% per annum for this product. Packaging Operations The manual packaging process for both locally filled vaccine and the current semi-finished product is the same and take the same duration to complete both operations. Each unit filled or imported has to undergo a manual visual inspection before it can be labelled and packed. Table 4.5 below summarises the duration of the packaging process Table 4.5: Batch Process Information (Manual Packaging) Batch Process Information (Manual Packaging) Parameter Batch Size Daily Capacity Duration/ Quantity 119 618 Unit of measure Doses Visual Inspection Capacity/hour 2100 14 hours Labeling Capacity/hour 6000 5 hours Packaging Capacity/hour 1750 9 hours Total Process Time 28 hours Batch processing Days 4 days The visual inspection process is performed by 7 operators at an average of 300 vials viewed per hour and takes approximately 14 hours to complete. This equates to 2 working days on a single shift of 7 working hours (Excludes tea and lunch breaks). The labelling is carried out 45 using an old automatic labelling machine which has the capability to encode the batch and expiry date at an output of 6000 vials per hour over 5 hours. The packaging operation takes approximately 9 hours when carried out by 8 operators with an average packaging rate of 250 vials per hour. The total packaging time is approximately 4 days for a single batch of product. Cost Activity and Computation of Unit Cost of Production From data collection and process overview, the main cost drivers for both locally filled and semi-finished vaccines were transport, raw materials, product cost (either formulated bulk or semi-finished product), quality control testing and labour costs. Of these cost drivers, the cost of transport, raw materials and cost of product emerged the highest. Table 4.6 below presents a detailed account of the various costs associated with locally filled and semi-finished vaccines as per data collected. Table 4.6: Summary Costs behaviour per batch and per dose Summary Cost Behaviour Cost Drivers Locally Filled Vaccine Costs Semi-Finished Vaccine Costs Cost Activity Cost Type Per Batch Variable Costs/dose Fixed Costs per Annum Per Batch Variable Costs/dose Fixed Costs per Annum Transport Variable R 192,287 R 1.58 R 403,725 R 3.31 Raw Materials Variable R 280,340 R 2.34 R 63,566 R 1.06 Cost of Product Variable Direct Energy Variable R 11,961,765 R 4,979 R 100.00 R 0.04 R 8,779,971 R 157.00 QC Testing Variable R 90,738 R 0.74 R 22,392 R 0.18 Depreciation Fixed R 3,097,307 All Labour Fixed R 8,023,794 R 5,069,243 Total variable Cost per Dose R 104.70 R 161.55 Total Direct Fixed Cost R 11,121,101 R 5,069,243 Manufacturing Overheads R 14,065,742 R 2,168,850 Administration Overheads Total indirect cost R 84,269,765 R 98,335,506 R 54,318,980 R 56,487,830 Total Fixed Costs R 109,456,607 R 61,557,073 Total Fixed Costs/dose (4.5 million doses) Total Fixed Costs/dose (2 million doses) Total Fixed Costs/dose (76 million doses) R 24.32 R 54.73 R 1.71 R 13.68 R 30.78

R 0.96 The cost of transporting 83L formulated bulk from a supplier in Europe to Cape Town was R192, 287 whilst the 39cost of transporting semi-finished product from the same supplier was 46 R403, 725. The cost of transporting semi-finished product is more than double the cost of transporting 83 Litres of formulated bulk for local filling operations. Transporting 83L from Europe to South Africa cost R1.58 per dose when compared to R3.31 for semi-finished vaccine. The cost of transport is made up of freight charges, customs clearance fees and agent forwarding charges. The cost of raw materials required to process a batch of a locally filled vaccine was R280, 340 whilst the cost of raw materials required for a semi-finished product was R63, 566. The costs of raw materials for a locally filled vaccine are more than four times the costs of raw materials required to complete a semi-finished product. The raw material costs for a locally filled vaccine are R2.34 per dose whilst for a semi-finished product the raw material costs are R1.06. This is a difference of only 50% between the dosage forms however; this is expected at a dose level since the raw material costs of a locally filled vaccine are in addition to those of an imported product. The cost of raw materials for semi-finished vaccines included the labels, cartons, package inserts and shippers. In addition, the raw materials for a locally filled vaccine includes glass vials, gamma irradiated rubber stopper and the aluminium seal cap. All these items are imported into the country. A single dose of semi-finished product costs R157 before processing. This translates to R8, 779, 971 per batch of 119,000 units. The cost of purchasing formulated bulk (83L) was calculated to be R11, 961,765 per batch which translates to R100 per dose filled locally. The unit cost per dose of a semi-finished product costs at least 50% more (at R157) than a locally filled vaccine at R100 per dose when compared to the semi-finished product at R157 per dose as per contract price. For both options of this product, the product cost accounted for more than 90% of the cost per dose. Direct energy costs to drive the filling line, autoclaves and automated washers were found to be significantly low at less than 5 cents per dose. Direct energy was only calculated for the locally filled vaccine and not on the manual packaging operation as there is only one low capacity labelling line used in this process and the power consumption is considered insignificant. The cost of quality control testing of a locally finished vaccine was four times that of a semi- finished vaccine. It cost R90, 738 to test a batch of a locally produced vaccine (R0.74 per dose) when compared to R22, 392 to test a batch of a semi-finished product (R0.18 per dose). The quality control testing for locally filled vaccine includes full batch testing whilst the semi-finished batch includes selected tests which are limited. Fixed depreciation costs using a straight-line method for the major equipment used directly during the filling process were calculated as fixed costs at R3 million whilst the total cost of labour that is directly involved in the production of the batch was R8 million for the locally filled vaccine and R5

million for the semi-finished vaccine. This is a cost difference of R3 million (60% difference) that is required per annum to produce vaccines locally. The total variable cost per dose for a locally filled vaccine is R104.70 when compared to R161.55 for the semi-finished product. This is a cost difference of R56.85 per unit between a locally filled vaccine and the imported product. However the total fixed costs for a locally filled vaccine are R109 million when compared to R61.5 million for the semi-finished product. The total fixed costs per dose for the locally filled vaccine at annual demand of 4.5million doses were R24.32 when compared to R13.68 for the semi-finished imported vaccine. This is a difference of almost 80% between the two products. At full theoretical capacity of 63.8 million doses per year, the fixed cost per dose drops from R24.32 to R1.71 for the locally filled vaccine and R13.68 to R0.96 for the imported vaccine. The fixed cost per dose for both products drop significantly with an increase in the number of doses produced. At 2 million doses (approximately half the annual demand), the fixed cost per dose are more than double those of the annual demand. 4.2.3 Objective 2: Level of economic activity favourable to LFV vs.

SFP The second 28**objective of this study was to determine the** level **of** economic

activity for which local production (LFV option) is preferred when compared to the importation of SFP. This was achieved by first determining the point at which the total cost of producing a LFV is less than the total cost of producing a SFP. Figure 4.2 below is a graphical representation of the total costs incurred in the production of LFV and the SFP when plotted against the number of doses of vaccines sold. 48 Millions R 600 Indifference Point SFP R 500 LFV R 400 Total Cost of

Prodcution 7**R 300 R 200 R 100** LFV Preferred R0 **0 0.5** 1 1.5 2 2.5 3 3.5 Number of

Vaccine Doses Millions Figure 4.2: Point of Indifference In figure 4.1 above, the cost behaviours of LFV and SFP are plotted on the same axis. The total cost of production is plotted along the Y-axis and the number of vaccine doses is plotted along the X-axis. The Y-intercept for each curve represents the respective fixed costs of each option. The curve depicting SFP is plotted in blue and labelled SFP whilst the curve depicting LFV is plotted in dark red and labelled LFV. The slopes of each of the curves represent the variable cost per dose which translates to the total cost of production for each vaccine sold. The variable cost per dose for SFP (R161.55) is higher than for LFV (R104.70) hence the cost of production increases at different rates which are shown by a steeper curve for the SFP when compared to the LFV curve. The black dotted line indicates the point at which the LFV and SFP curves intersect at 800,000 doses. At this point it does not matter whether this product is imported semi-finished or is manufactured locally since the costs of production is the same. This point is also referred to as the point of indifference. It is observed from the curves that the total fixed cost of a LFV is initially higher than the fixed cost of a SFP up
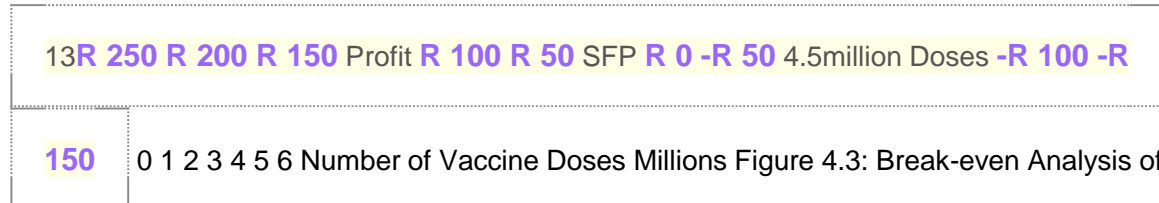
to 800, 000 doses (point of indifference). Beyond this point, the costs of local vaccine production remain below the costs of importing a SFP. That is, beyond 800, 000 doses it becomes more favourable to locally produce the vaccine than to import it semi-finished. This does not mean that either option will generate positive revenue (profit) beyond 800, 000 doses. When taking into account the break-even analysis of each option as calculated in table 4.6 below, the break-even point for LFV is 1.3 million doses and 2. 6 million doses for the SFP. Therefore this confirms that at 800,000 doses sold the company would be operating at a loss for both options. 4.2.4 Objective 3: Determination of the desirable market size (Break-even Point) The selling price for both locally filled vaccine (LFV) and semi-finished product (SFP) is the same at R185.00 per dose (current selling price of SFP). Table 4.7 summarises the break even analysis for the LFV and the SFP. Table 4.7: Break-even Analysis of LFV vs. SFP LFV SFP Sales/Dose R 185.00 R 185.00 Variable cost/Dose R 104.70 R 161.55 Contribution Margin R 80.30 R 23.45 Total Fixed Costs R 109,456,607 R 61,557,073 Doses to Break-even 1,363,150 2,625,234 Total Costs per dose (F+V) R 129.03 R 175.23 Profit per dose (4.5 million dose) R 55.97 R 9.77 The variable cost per dose of LFV is significantly lower than for the SFP at R104.70 and R161.55 respectively. The lower variable cost per dose corresponds with a higher contribution margin of R80.30 for the LFV when compared to a much lower contribution margin of R23.45 for the SFP. The total fixed costs for each option vary significantly with fixed costs accounting for R109.5million for LFV when compared to R61.5million for SFP. The break- even point for both LFV and SFP was found to be below the annual demand of 4.5million doses. The number of doses required to break-even for the LFV was 1.3million compared to 2.6million for the SFP. The total cost per dose for LFV was lower at R129.03 when compared to R175.23 for the SFP. This resulted in a significant profit per dose of R55.97 per dose of locally produced unit when compared to R9.77 per dose. An analysis of 2million doses results in a loss for the SFP and a profit of R25.57 for the LFV. Figure 4.3 below is a graphical presentation of the results on the effect of profit generated per dose sold for the LFV and the SFP. Millions R 350 R 300 Break-even Point for LFV Break-even Point for SFP LFV

13R 250 R 200 R 150 Profit R 100 R 50 SFP R 0 -R 50 4.5million Doses -R 100 -R

150 0 1 2 3 4 5 6 Number of Vaccine Doses Millions Figure 4.3: Break-even Analysis of

LFV vs. SFP By plotting the curve depicting Profit on the Y-axis against the number of doses sold the curve above emerges. The Y-intercept for each curve represents the fixed costs. The slopes of each of the curves represent the contribution margin per dose which translates to profit generated with each sale. The break-even point for both LFV and SFP is the point where each curve crosses the X-axis at zero. This point is shown on the graph by the black dotted line. Below

the X-axis there is no profit generated hence the numbers are negative and above the X-axis there is profit generated hence the numbers are positive. The annual demand for this product on the South African market is 4.5 million doses and this point is marked on by the red dotted line. The fixed costs for LFV are more than those of the SFP however; the slopes of each curve differ markedly. That is, the LVF curve is steeper than the SFP curve which means the higher the contribution margin, the steeper the curve and the faster the rate of profit generation. By observing the two curves, it takes less than a million doses for the LFV and SFP curves to cross each other and reach a point where the cost of importing the SFP equals the cost of producing locally. However, both LFV and SFP options are not profitable at this point. At the LFV break-even point of 1.3million doses, the SFP option is not generating a profit and is still at a loss of approximately R30 million. When the SFP reaches break-even point at 2.6million doses, the LFV option has already generated a profit of approximately R90 million. At the annual demand of 4.5 million doses, the profit generated by the LFV is approximately R250 million compared to a profit of approximately R45million generated by the SFP option. 4.2.5 Investment costs The analysis of the investment costs showed that more than R745 million has been invested into establishing local manufacturing operations. A further breakdown of the costs reveals that R375 million is required for investment into semi-finished operations as opposed to a total of R745 million required for local vaccine filling operations. From the findings, almost twice (1.98 times) the investment amount is required for locally filled vaccine operations than semi- finished. The investment amounts exclude the cost of labour that was incurred from 2003 to 2014. Because Biovac was established on an existing site (formerly, The State Vaccines Institute) the costs of acquiring the land, excavations and electrification is excluded from the calculated investment costs. The major investment costs for semi-finished product were attributable to setting up of the Cold Room Storage infrastructure, Quality Control laboratories, Packaging Halls and the Administration buildings. Of these costs, the Quality Control laboratory constituted the bulk of the costs at R240 million whilst the construction of the warehouse building was the least. The warehouse cost included the refrigeration infrastructure for vaccine storage. The major investment costs are summarised in Table 4.8 below. Table 4.8: Investment Cost Summary Cost Category Item Description Item Cost API, Formulation & Filling R300 million Infrastructure Quality Control Laboratories R240 million Packaging Hall 100 million Warehouse & Utility R30 million Automated Filling Line R34 million Plant & Equipment Washers & Autoclaves R12.5 million Cleanroom Structures R2.5 million Technology Transfer Product for Local Filling R17 million The investment cost of setting up local filling operations alone were R300 million excluding the equipment to be used inside the Cleanrooms. The cost of constructing the formulation and filling suites was more than the combined cost of setting up operations for a semi-finished product. Of

this amount (R300 million), approximately 10% was allocated to the purchasing of a high speed automated aseptic filling machine at a cost of R34 million. Less than 5% of the cost went to the purchasing of autoclaves and automatic washers which are crucial in ensuring consistent cleaning and disinfection of pathogens before and after filling operations. 4.2.6 Effect of changing Cost of Product and Selling Price Increasing Cost of Product Figure 4.4 below demonstrates the effect of increasing the cost of formulated bulk by 25% on the profitability of local vaccine filling operations. Millions R 200 R 150 Break-even point 1: LFV Break-even point 2: LFV LFV R 100 Profit R 50 R 0 SFP -R 100 Break-even Point 1:SFP -R 150 0 1 2 Number of Vaccine Doses 3 4 5 6 Millions Figure 4.4: Effect of increasing Cost of Product on profitability for LFV The findings show that increasing the cost of formulated bulk by 25% caused the break-even point curve to shift to the right from 1.3 million doses (Break-even point 1:LFV) to 1.98 million doses (break-even point 2: LFV). Notably, the new break-even point for LFV is reached before the break-even point for SFP (Break-even point 1: SFP) which occurs at 2.6 million doses. A 25% increase in the cost of formulated bulk product resulted in a drop in profit per dose for LFV from R55.97 to R30.97 which equates to a profit drop of R25 per dose (45% decline). This results in a net profit of 16% from local filling operations as opposed to a profit of 12% from semi-finished product. Consequently the total profit that can be realized from local filling operations is approximately R140 million compared to approximately R45 million that could be generated from semi-finished operations. Figure 4.5 below shows the effect of increasing the cost of formulated bulk product by 25% on the point of indifference. This figure indicates that local filling operations are favourable over semi-finished operations even with a 25% increase in the cost of product. Millions R 800

Point of Indifference 1 R 700 Point of indifference 2 7R 600 R 500 Total Cost R 400 R

300 R 200 R 100 R 0 0 1 2 3 4 5 Number of Vaccine Doses Millions Figure 4.5: Point of

Indifference after increasing Cost of Product for LFV Figure 4.5 shows the effect of increasing the cost of product on the indifference point as a shift to the right from the original 800, 000 doses to fewer than 1.6 million. On the contrary, by increasing the cost of semi-finished product by 25%; the break-even point was reached at 7.9 million doses which are beyond the annual demand for this product. This suggests that local vaccine filling operations are favourable over semi-finished if the demand is expected to be more than 1.6 million doses per annum. With the current demand of this product currently estimated to be 4.5 million doses, local production is favourable. Reduction in Selling Price: The selling price of a semi-finished vaccine was R185 per dose. Findings showed that dropping the selling price of a semi-finished product by 10% from R185 to R175.75 per dose required 4.3 million doses to break even as opposed to 2.6million doses if the

selling price remained unchanged. In contrast, a 20% reduction in the selling price of a locally filled vaccine from R185 to R148 required 2.5 million doses to break even as per break-even analysis curve in Table 4.9 and Figure 4.6 below. Table 4.9: Break-even Analysis after a drop in product selling price Break-even Analysis after Selling Price Reduction LFV SFP Sales per Dose R 148.00 R 175.75 Variable cost/Dose R 104.70 R 161.55 Contribution Margin R 43.30 R 14.20 Total Fixed Costs R 109,456,607 R 61,557,073 Doses to Break-even 2,528,052 4,335,549 Total Costs per dose (F+V) R 129.03 R 175.23 Profit per dose (4.5 million dose capacity) R 18.97 R 0.52 The findings in Table 4.9 showed that the profit per dose generated by local filling operations after a 20% reduction in the selling price is 32 times more than the profit per dose generated from semi-finished product operations. The findings reveal that a 20% selling price reduction results is a drop of almost 50% (from R80 to R43) for the locally filled vaccine operations and remained profitable. This is in contrast to a drop of 60% in profit margin from only a 10% drop in the selling price for the semi-finished product. These findings are consistent with those observed on the effect of increasing the cost of product in that in both instances; locally produced vaccine option is more resilient to price fluctuations. Semi-finished product is sensitive to external market forces which can easily render the operations to be unprofitable in the long term. Figure 4.6 below illustrates the effect of reducing the selling price by 20% for locally filled vaccine and 10% for semi-finished product. Millions R 150 R 100 Original LFV break-even LFV Break-even after 20% price reduction LFV R 50 SFP Break-even after 10% price reduction Profit R0 SFP -R 50 -R 100 Point of indifference -R 150 0 1 2 3 4 5 6 Number of Vaccine Doses Millions Figure 4.6: Effect of reducing Selling Price on profitability Figure 4.6 shows that locally filled vaccine operations break-even ahead of semi-finished product operations. The effect of the price reduction is a shift to the right in break-even points of both options (LFV & SFP) but the point of indifference is reached around 1.6 million doses indicating that local filling operations are favourable when the demand is more than 1.6 million doses. Under the selling price reduction scenarios described above, it was also noted that there is virtually no profit generated by the semi-finished operations at maximum annual demand of 4.5 million doses. This again is in contrast to a modest profit of approximately R50 million generated from local filling operations. 4.3 Summary This chapter analysed the findings on semi-finished and local vaccine filling operations. The findings showed that local vaccine filling, compared to semi-finished product, generates higher profits and is more favourable as a form of local production when the demand for this vaccine exceeds 800, 000 doses per annum. The findings also revealed that the low margins generated from semi-finished operations may be responsible for the high sensitivity to price fluctuations for this manufacturing option. As shown in the study, a 10% reduction in the selling price renders semi-finished operations unprofitable whereas the local filling operations are able to withstand price drop of

20% and still remain profitable. In this study, it was shown that local filling operations do not rely on economies of scale (or large markets) to be profitable; however when it comes to semi-finished product economies of scale may cushion the operations against operational losses due to external market forces. Chapter 5 will provide a discussion of the findings from this Chapter.

CHAPTER FIVE: **24Discussion 5.1 Introduction The** aim **of this study was to** evaluate economic viability **of** a locally filled vaccine when compared to the same vaccine that is currently imported as a semi-finished product for labelling, packaging and distribution. The objectives were to determine the production costs for both options followed by a thorough analysis on which option is favourable to pursue under which conditions. A case study approach was followed in conducting this study in order to gain an in-depth contextual analysis of the Biovac processes and cost factors using multiple sources of data. This chapter will discuss the findings in relation to the key consideration that were highlighted in the **14literature** **review in chapter 2** within **the** context **of** Biovac. In particular **the** production costs, skills availability, economies of scale and their effect on profitability and finally the findings on the investment cost requirements will be discussed. The Chapter will conclude with a summary.

5.1.1. Cost of Production and Price of Finished Product Literature review in Chapter 2 highlighted the drivers behind the support for local production as heavy disease burden, lack of access to affordable medicine, security of supply and the socio-economic benefits that stand to be realized. Those who argued against local production (Kaplan and Laing, 2005; Bate, 2008) cited lack of skilled personnel, economies of scale (small markets), cost disadvantages and lack of competitiveness of the local pharmaceutical industry. That is, the viability of local production rests on the ability of local manufacturers to produce quality medicine at competitive or better prices than imported medicine. Within the context of this study, the production costs of a locally filled vaccine were compared to the costs of a semi-finished product to determine the viability of local vaccine production in South Africa. In-bound transport Costs The cost of transporting formulated bulk product is significantly less than the cost of transporting semi-finished product for labelling and packaging. Formulated bulk product is transported in a 100L stainless steel vessel that is inside a self-cooling container. On the other hand, the filed vials are packed in trays which are stacked inside insulated shipper boxes that 59 are filled with dry ice. Dry ice is used to ensure that that cold chain is maintained from the supplier to Biovac. As a result, shipment of semi-finished product is bulky and requires a standard shipping container. Because the packaging

118

configuration of formulated bulk takes up less space and requires less pre-shipment handling, it is expected that the shipment costs would be less. Cape Town is a port of entry for Formulated bulk and semi-finished products which are then transported for 15 kilometres to Biovac in a refrigerated truck. The shipping costs would be expected to be more if either the formulated bulk or the semi-finished product were to be delivered to a land-locked country. This additional cost of transport would be added to the price of medicine. All else being equal, it is likely that the cost of the same product in a landlocked country would be more than it would be in South Africa. Cost of Testing (Quality Control) The cost of testing a locally filled vaccine is substantially more than testing a **35semi-finished product. The semi-finished product is** delivered with a certificate of analysis that confirms that all tests have been performed in accordance to procedure with only the potency and product identification that remain to be tested on finished product. Formulated bulk product requires additional testing steps from delivery to finished product. These steps include bulk sample testing, in-process and finished product testing which includes sterility testing and potency at each step of the process. It is therefore expected that the testing costs would be more for locally filled vaccines when compared to semi-finished product. In instances where the laboratory infrastructure is not in place to complete all tests required, the Company may send certain samples to external, approved laboratories to conduct such tests on behalf of the Company. External testing comes at a cost, therefore, a cost-benefit analysis on which tests are to be carried out in-house or to be outsourced is usually done based on the available skill, complexity of the test, cost of equipment and frequency of the testing requirement. Raw Materials Costs The costs of raw materials that are required to process formulated bulk are twice as much as those required for processing semi-finished product. Semi-finished product is delivered as 60 naked vials (unlabelled product) and undergoes labelling and final packaging. Over and above, the locally filled vaccine requires specialised type of glass vials, gamma-irradiated rubber stoppers and aluminium seals which are imported abroad in foreign currency. Once the product is filled, it undergoes the same process as a semi-finished product. The cost of raw materials per dose is however not twice as much for locally filled vaccine versus semi- finished product because the total cost is an average of total cost divided by the number of units filled. The importation of glass vials and rubber stoppers mean that these items are subject to foreign currency fluctuations and therefore the cost may vary throughout the year. Cost of Production – Locally Filled vaccine vs. Semi-finished Product When analysing the cost of product, the following becomes evident: The cost of semi-finished product is R157 per dose as per contract which translates to R8.7 million per batch. The cost of formulated bulk product is R11.9 million as per contract which translates to R100 per dose of filled product. The cost per dose of locally filled

vaccine is expected to be lower than semi- finished product as expected. Formulated bulk cost more than the semi-finished product however the variable cost per dose of a locally filled vaccine is far less the semi-finished product. Semi-finished product and LFV present different sets of challenges that may have an effect on the cost of each option. Firstly, the risks of product failure due to sterility and low potency remain with the supplier of the semi-finished product up to the point of delivery to Biovac. Over and above, the product supplier would have incurred additional cost of quality assurance on the process as well raw materials used in the product also remain with the supplier. Secondly, the same risk of batch failure due to sterility pose a major concern as the responsibility shifts from the product supplier to the manufacturer. Vaccine manufacturing requires aseptic handling which means there is no terminally sterilisation step once the product is in the final container. The manufacturer not only has to be vigilant about product handling to prevent loss of potency and product contamination during processing but also has to prove through validation that the product can be handled from delivery right through processing into finished product. Another finding that may appear as a cause for concern is the low utilization capacity of 5.6% which suggests that the filing suites will be utilized for an equivalent of only a few weeks in a year. Even when taking into account aseptic validation activities that take place during year, the utilisation capacity remains low. This presents an opportunity to bring additional products through contract manufacturing of other compatible products and indicates that the filling line is not a bottleneck. This will help to improve the higher utilisation capacity. 5.1.2. Availability of Skilled Labour and Cost of Labour Personnel employed at Biovac possess a skill base that ranges from very low skill with no formal qualification all the way up to Master's and PhD level. The spread of skill and expertise support the low tech, tertiary operations with semi-skilled personnel through to aseptic filling operations with skilled personnel and research and development with highly skilled personnel with Honour's, Master's and PhD degrees. The Universities of Stellenbosch, Cape Town and the Western Cape are some of the tertiary institutions providing support to Biovac in skills development and other research collaborations. The labour requirements for labelling and packaging of semi-finished product operations is less than the requirements for LFV in terms of the operator skill and the simplicity of the operations. The skill requirement for tertiary production operators is low-tech and does not require a tertiary qualification. On the other hand secondary production (aseptic formulation and filling) requires a higher level of expertise especially in microbiology background. This is evident in the mix of skill set that is utilised for local filling operations. As long as Biovac is able to recruit and retain the right kind of skilled personnel and continually train them in topics such as validation, aseptic processing, cGMP and quality assurance; local production operations will receive the required support and ensure that local filling operations remain sustainable. 5.1.3. Economies of Scale on

Profitability and Sustainability Under current conditions, local vaccine filling from imported bulk is favourable if the demand is estimated beyond 1.3 million doses. For the product under study, the demand for semi- finished product is currently at 4.5 million doses per annum and therefore this option is favourable. The semi-finished product seemed to be highly sensitive to price fluctuations and with a slight drop in the selling price resulting in non-profitability. This is concerning when taking into account that this product is imported in foreign currency and hence is subject to currency fluctuations. Secondly, with vaccine prices known to drop with time as more competition enters the market (Spier and Milstien, 2009), the sensitivity of the semi-finished product to price does not seem to favour this option for long term sustainability Therefore, the findings support local production of this vaccine. The economies of scale for this product appear to be exaggerated with profitability being achieved with 1.3 million doses which coincides with a point where the number of doses for imported vaccine is not even profitable. The argument for economies of scale was raised in Chapter 2 and a concern was raised by the researcher that there is no definition or an indication on what constitutes favourable economies of scale. This finding is 34 **in line with a study that was conducted** in Ghana by Chaudhuri (2013) which also showed that local production in small countries with small economies can be profitable despite the cost disadvantages. The findings confirmed the issue of high fixed costs in vaccines (Baumann, 2009) in that the fixed cost per dose reduced with the increasing number of doses. This effect of this phenomenon was more noticeable with semi-finished product. This suggest that although the definition of economies of scale is not very clear; when it comes to the profitability of semi- finished product operations the more doses that can be sold the lower the fixed cost per dose that can be realised. Perhaps one way to improve profitability would be to expand to regional markets. For South Africa, expansion into the Southern African Developing Countries (SADC) region which includes Namibia, Botswana, Zimbabwe, Swaziland, Lesotho, and Mozambique would unlock untapped markets. This will also increase the current production utilisation capacity of 5.6% to beyond 15%. Local production is able to repay the investment costs in approximately 4 years with a profit margin of R55/dose for LFV. Even when the selling price drops by 20% LFV is still favoured over SFP. 5.1.4. Investment Costs Infrastructural Costs The findings in Chapter 4 confirmed that there are different levels of investment requirements for secondary and tertiary production operations. The infrastructural investment began a decade ago and to date more than R700 million has been invested into the reestablishment of local vaccine manufacturing. The setup costs for tertiary operations (labelling and packaging) were substantially low at R375 million when compared to R745 million total investment cost for secondary and tertiary operations. This implies that the requirements for local vaccine filling

operations are twice as much as the requirements for semi-finished operations. This was not surprising as the infrastructural cost of the formulation and filling suites alone were R300 million excluding plant and equipment. Vaccines are sensitive to heat and therefore the investment into the warehouse and cold room storage is required upfront before any labelling and packaging can take place. Being heat sensitive, testing for potency on delivery and of finished product is critical to prevent processing of product that may not meet the quality standard hence the quality assurance infrastructural requirement. Quality control laboratories require sophisticated equipment which also adds to the cost of the product. The presence of the cold chain and testing infrastructure not only does it allow for labelling and packaging operations to continue but serve as building blocks for more products to be brought into the facility. In addition it serves as a footprint for expansion into more complex operations such as formulation and filling whilst generating revenue. The model of backward integration which was adopted by Biovac showed that other countries who are interested in establishing local pharmaceutical manufacturing can begin by investing in simpler operations to generate revenue and increase the level of investment into more complex operations over time. The findings revealed that the profit margins from semi-finished operations are lower than those for semi-finished product which translates to the ability to recoup the investment costs from operations. The findings showed that importing this vaccine will generate a profit of 10% before distribution and marketing costs whilst the local filling operations will generate 64 about 43% before distribution and marketing costs. It is clear from the findings that local filling operations, under current conditions, are highly favourable for this product over the imported vaccine. From an investment point of view, local filling operations indicate a better return on investment and a high probability to being able recoup the investment costs. This means the formal banking sector is likely to fund this kind of operation. This finding is supported by the analysis into the effect of price fluctuations which showed that a 10% drop in the selling price resulted in a break-even point of 4.3million doses for the semi-finished product as opposed to the local filling operations. This means it would take more than a decade to recoup the investment costs of simple tertiary production operations. On the other hand, even with a drop in selling price of as much as 20% for a locally filled vaccine this option remains favourable over the SFP both in terms of the point of indifference and break-even. Technology Transfer Costs This refers to the costs associated with bringing a new product into the facility. There are three considerations to be taken into account when selecting a technology transfer partner to ensure a mutual benefit. Firstly, the selection of the product(s) to be produced in the facility must be compatible with the available infrastructure in order to contain investment costs. Secondly, because pharmaceutical production is highly regulated, the product may not be sold to the market before licensing and registration approval from the local regulatory agency has been obtained.

Finally, whilst technology transfer may speed up the process knowledge and improve personnel skill level, it cost money and someone has to pay for it. Selecting a mutually compatible partner is critical to ensure fair distribution of costs. For example, this technology transfer required an investment of approximately R17 million. However this cost could have been in excess of R30 million without the technology transfer partner bearing the costs of active raw materials and training. Transferring technical know-how requires competent project management skills as this is an immense investment undertaking before the product can be sold into the market. 5.2 Summary The findings indicate that local vaccine filling operations from formulated bulk product is more favourable over imported semi-finished vaccine for labelling and packaging when the estimated demand exceeds 800, 000 doses. The profitability of local filling operations is reached at 1.3 million doses. This is less than half the annual demand of 4.5 million doses for this product. In contrast, the profitability of an imported semi-finished vaccine is reached at 2.6 million doses which is twice number of doses. In addition, at 4.5 million doses the semi- finished product is expected to generate a profit of approximately R50 million compared to a convincing R250 million for locally filled vaccine. Although the investment requirements for local vaccine filling operations were found to be approximately twice as much as those required for semi-finished product operations, the profit margins justify the investment undertaking. Furthermore, the semi-finished product seemed to show noticeable sensitivity to price fluctuations which is a concern for a product that is imported in foreign currency and is subject to exchange rate uncertainties. Finally, the concept of economies of scale in relation to profit generation seems to be over exaggerated as shown by the findings of this study as well as the study that was conducted in a smaller market in Ghana. CHAPTER SIX: Recommendations and Conclusions 6.1 Introduction The aim of this study was to evaluate, using Biovac as a case study, whether local vaccine production is economically viable when compared to importation of semi-finished product. The objectives were to determine the costs of production of each option and to assess which option was favourable under which conditions and to determine the investment requirements for each of the options. This Chapter provides the implications of this research as well as recommendations for future studies based on the findings. 6.2 Significant Conclusions from the Study The major conclusion from this study is that local vaccine production may be economically viable and more preferable to imported semi-finished product. The cost of formulated bulk and semi-finished product constituted more than 80% of the total cost of production however; the profit margins from local vaccine filling operations were shown to be substantially higher than those that stand to be realised from processing semi-finished product. As a result of low profit margins that are generated from semi-finished product, this manufacturing option is the least favourable between the two and is sensitive to price fluctuations. The conclusion is that this option may not be viable

for long sustainability of the organization. The second conclusion from findings showed that local production operations of high-end multivalent vaccines are economically viable even with low volumes. This finding must be interpreted with caution as it does not reveal that whilst being cheaper and profitable; the risk of batch failure shifts from the supplier to the local manufacturer. This may have massive financial implications which the local manufacturer may not have been exposed to when processing semi-finished product. Therefore significant amount of time in training and validation may be required to ensure the risk of batch failure due to process inconsistencies is minimised. Although the study did not assess economic viability from antigen production and formulation, the findings suggest that local filing from locally produced antigens may be even cheaper. This takes into account that local production will eliminate transport and formulated bulk costs however; this level of operation will require additional product handling and expose the organization to even higher risks of batch failure over and above the skill requirements for processing product at this level. It is within this context that a conclusion can be drawn that security of supply may take years to be realised, if not decades, as Africa continues to be dependent on imported formulated bulk to carry out local filling operations. This suggests that the African continent still remains vulnerable to supply shortages. This is contrary to the notion of establishing local manufacturing operations to reduce dependency on imports. 6.3 Implications of this Research This study provides an assessment tool for Biovac management to use when assessing the viability of a project proposal from a potential technology transfer partner. With the production costs associated with processing imported semi-finished product and local filling from formulated bulk know, determining the number of doses required to break-even (profitability) and the extent of the profitability (at anticipated demand) of the proposed option is now possible. This will allow management to strategize on which vaccines or compatible products to pursue and more importantly which information to use in the assessment. The findings from this study suggest that economies of scale are a key consideration for profit generation and may not necessarily be an absolute requirement for countries or governments who want to produce locally to meet local demand. As shown by the findings, the break-even point of a locally produced vaccine with an annual demand of 4.5 million doses could be reached with 1.6 million doses sold. However, economies of scale cannot be disregarded as they can provide a cushion against external forces such as a drop in the selling price or an increase in the cost of product as per the findings on the resilience of the semi-finished product option. With The African Union supporting local production across Africa as a means to stimulate industrial development and economic growth, other countries that may be interested in pursuing vaccine production and sterile manufacturing can use this study as a baseline to 68 gauge the level of investment required for such an undertaking. Other countries will be able to use findings from this study on manufacturing

124

costs to make decisions which cost factors to subsidise in efforts to lower costs to the end user. 6.4 Recommendations to solve the research problem This case study focused on multivalent vaccine production to draw conclusion on the viability of local vaccine filling operations. This presented a limitation in that the study did not consider whether a low cost vaccine with a lower or higher demand will also be a viable option to pursue when compared with imported semi-finished product. However, this study made it possible to determine economic viability of any operations. For Biovac to get a complete picture on which vaccines to continue importing or to consider manufacturing them locally, through technology transfer, an internal study must be carried out to include monovalent and low cost vaccines. Carrying out a study of this nature will allow Biovac to develop a matrix of the type of products to be pursued for local production based on set of well-defined criteria. Most importantly a study assessing the effect of adding other products on the existing infrastructure will be of benefit in that it can increase the utilization capacity which is currently below 10%. 6.5 Recommendations for Future Studies This study was a first of its kind on the African continent with regards to vaccine production but the findings and conclusions were drawn from a single case study. Due to the limitations of the study and a single unit of analysis, the findings may be difficult to apply generically across other pharmaceutical manufacturing operations. The focussed on the production costs to evaluate viability, perhaps other studies could focus more on other types of costs to evaluate the combined effect of mixed costs on the viability of local operations. Despite the limitations of the study, the findings showed some correlation with literature on the exaggeration of the effect of economies of scale. For example, the finding showing possibility profitability with relatively low volumes of vaccines sold correlated with the study conducted by Chaudhuri (2013) in Ghana which also showed similar results. Perhaps more 69 studies could be conducted to define what constitutes economies of scale in order to remove ambiguity in the current interpretation and definition. Finally, the duration of the technology transfer for this product was almost 3 years due to regulatory requirements for validation prior to product licensing. Perhaps a study focussing on comparing the opportunity costs the due to time lost while waiting for regulatory approval and licensing for either semi-finished or locally filled vaccine may justify or prove to the contrary the viability of local production. The study will need to focus from an investment point of view. 6.6 Summary The aim of the study to evaluate economic viability of local vaccine production was fulfilled. The research methodology and approach used to address the objectives was able to collect relevant data. From the findings presented in Chapter 4 and analysed in Chapter 5 the conclusion that is drawn from this study is that the local vaccine filling operations are a viable option when compared to imported semi-finished product under the conditions stated in the previous chapters. The recommendations made will enable Biovac to expand on the findings of this research 4 6 7 8 9 10 11 12 13 14 15 16

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