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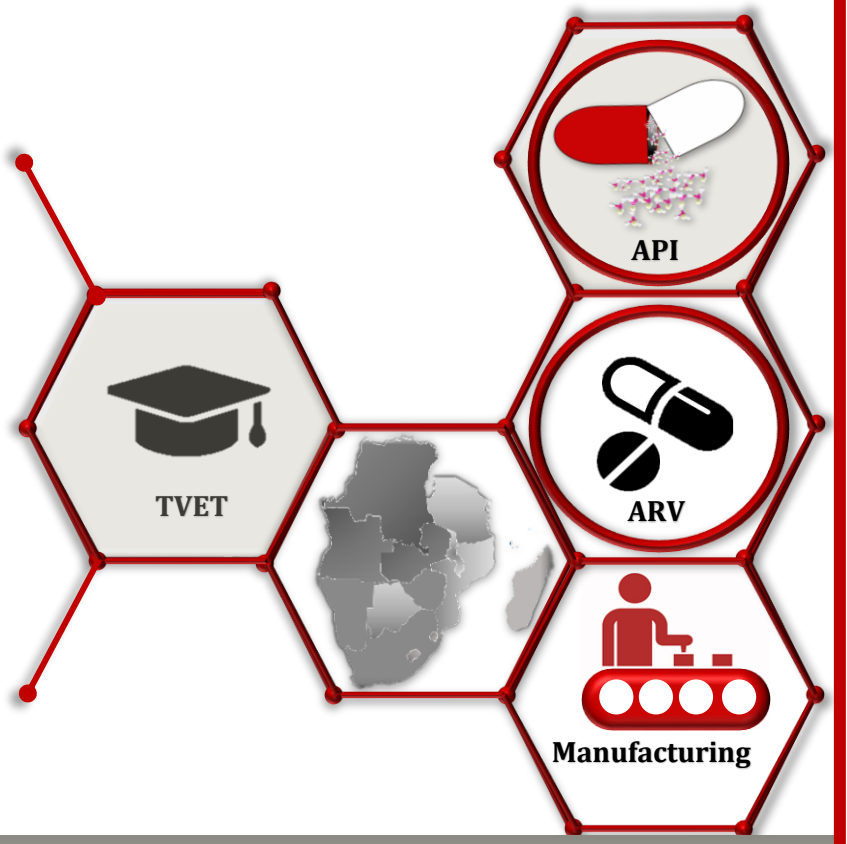


**Support towards Industrialization and the Productive Sectors (SIPS) in the SADC Region**

# ANTIRETROVIRAL VALUE CHAIN INCEPTION REPORT


Picture: Pixaby/ Ivabalk

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# ABBREVIATIONS

| | |
|---|---|
| AIDS | Acquired Immune Deficiency Syndrome |
| API | Active Pharmaceutical Ingredient |
| ART | Anti-Retroviral Therapy |
| ARV | Anti-Retroviral |
| BSc | Bachelor of Science |
| CAPA | Corrective and Preventive Action |
| CEO | Chief Executive Officer |
| CESARE | Cooperation for the Enhancement of Southern African Development Community Regional Economic Integration |
| cGMP | Current Good Manufacturing Practices |
| CHAI | Clinton Health Access Initiative |
| CMS/ NMS | Central Medical Store/ National Medical Store |
| COGS | Cost of Goods Supplied |
| D&L | Distribution and Logistics |
| DRC | Democratic Republic of Congo |
| EBIDTA | Earnings Before Interest Depreciation Tax and Amortisation |
| EMEA | European Medicines Evaluation agency |
| EU | European Union |
| FDF | Final Dosage Formulation |
| GF | Global Fund |
| GIZ | Deutsche Gesellschaft für Internationale Zusammenarbeit |
| GMP | Good Manufacturing Practice |
| HIV | Human Immunodeficiency Virus |
| ILO | International Labour Organization |
| KOL | Key Opinion Leader |
| LMIC | Low- and Middle-Income Country |
| MSc | Master of Science |
| MNC | Multinational company |
| NMRA | National Medicines Regulatory Authority |
| NQF | National Qualification Framework |
| NRA | National Regulatory Authority |
| OPEX | Operational Expenses |
| PEPFAR | President's Emergency Plan for AIDS Relief |
| PQR | Price and Quality Report |
| QMS | Quality Management Systems |
| R&D | Research and Development |
| SADC | Southern African Development Community |
| SHD | Directorate of Social and Human Development |
| SIPS | Support Towards Industrialization and the Productive Sectors |
| SRA | Stringent Regulatory Authority |
| TB | Tuberculosis |
| TLD | Tenofovir, Lamivudine and Dolutegravir |
| TVET | Technical and Vocational Education and Training |
| UNAIDS | Joint United Nations Programme on HIV/AIDS |

| | |
|---|---|
| UNIDO | United Nations Industrial Development Organization |
| US FDA | United States Food and Drug Administration |
| USAID | United States Agency for International Development |
| VAT | Value Added Tax |
| VC | Value Chain |
| WHO | World Health Organization |
| WHO PQ | World Health Organization Prequalification Scheme |
| Yft/Ypt | Years Full Time/ Years Part Time |

# EXECUTIVE SUMMARY

SADC's joint action, "Support towards Industrialisation and the Productive Sectors" (SIPS) is a Programme supported by the EU and the German government. The programme supports the SADC secretariat by contributing to the performance and growth of selected industrial value chains within the region. Specifically, the private sector component of the SIPS joint action is aimed at enhancing private sector participation in the regional antiretroviral/ pharmaceutical sector, the COVID-19-relevant medical and pharmaceutical products (CMPP) sector and the leather sector.

The aim within the SIPS inception phase was to conduct a detailed mapping and analysis of the antiretroviral (ARV) value chain within the SADC region using a multidimensional approach encompassing economic, social, environmental, and institutional considerations. This allowed a situational baseline of the ARV value chain to be established and identify gaps or areas for possible intervention by the SIPS joint action. The results will be used to devise innovative and refined approaches for the sustainable development of the ARV value chain within SADC. The key stakeholders within the ARV value chain – the ARV manufacturers and companies involved in other segments of the value chain, national private sector associations, central/national medical stores, academic and technical, vocational education and training institutions - were identified and data were collected using qualitative interviews and desk reviews of available information. The COVID-19 pandemic was a limiting factor as site visits and face-to-face interactions were not possible. Following the initial phases of interviews and data collection, a stakeholder workshop was conducted to validate the findings, which would be used to refine the implementation strategy.

The donor market for ARVs represents the largest market by size for the region while the public market presents an opportunity for value capture due to accessibility by local manufacturers. The private market in the region (except South Africa) is very small relative to the other two markets. The potential for additional value capture lies in manufacturing operations including excipient and packaging material production as logistics and distribution activities are already localized. Manufacturers identified in the member states have different capabilities for ARV manufacture. Although there is currently no ARV API manufacturer in the region, capable pilot manufacturing projects have been identified. There is a general lack of comprehensive market data within the region including an overview of regional tender data. There are several academic and TVET institutions offering courses identified as relevant to pharmaceutical manufacture, however, there is a lack of skilled industrial pharmacy personnel with expertise being sourced from outside the region.

Going forward, one of the proposed interventions is the establishment of national/ regional portals for publishing relevant market data such as active tenders within the region. Databases for the national/ central medical stores in member states, manufacturers in the ARV value chain and academic and TVET institutions offering training are currently being compiled. The SIPS joint action will also evaluate the possible promotion of the identified API manufacture projects including establishing intra-regional linkage with ARV manufacturers. SIPS will also aim to facilitate active ARV manufacturers to improve business operations efficiency, attain acceptable standards of GMP and establishment of robust quality management systems in line with international standards, making

WHO prequalification a long-term possibility. To address the lack of skilled industrial pharmaceutical personnel in the region, dialogue between industry and academic institutions to improve skills development in the region will be explored. To ensure the sustainability of any interventions, particularly for manufacturers, SIPS will facilitate access to affordable, flexible and innovative financing arrangements for spearheading ARV manufacturing projects, an intervention that would be further supported by the manufacturers achieving manufacturing and business efficiency.

Government commitment from member states by ensuring alignment of regulatory and procurement policies with industry preparedness together with long-term commitments to national/ regional procurement are needed to allow for increased industrialisation, inter-regional trade of goods, services and experts, job creation, equity in value chain promotion, and academic and skills development.

# 1. INTRODUCTION

## CESARE and SIPS

The programme, "Cooperation for the Enhancement of Southern African Development Community (SADC) Regional Economic Integration" (CESARE) supports the SADC Secretariat and its member states in the areas of economic development and good governance. Its main cooperation partner is the SADC Secretariat in Gaborone, Botswana. The programme is further implemented in cooperation with national governments of SADC member states as well as relevant national-level stakeholders, in particular private sector companies, relevant industry associations and civil society.

Within the CESARE framework, one of the four measures of the programme is the joint action "Support Towards Industrialization and the Productive Sectors (SIPS) in the SADC region". This Private Sector Development Action is financed by the EU and the German Government. GIZ is responsible for the implementation of two result areas of SIPS: (1) "To enhance the Private Sector Participation in the regional pharmaceutical and medical value chains (VC)" and (2) "To enhance the Private Sector Participation in the Regional Leather Value Chain". The expected outputs for the regional pharmaceutical value chain are enhancement of private sector participation in anti-retroviral (ARV) and COVID-19-relevant medical and pharmaceutical products (CMPP) value chains (result areas 2.1 and 2.2 respectively).

This report relates to the ARV result area of the SIPS project, which is result area 2.1 of the project.

By facilitating the development and governance of the regional anti-retroviral value chain for the pharmaceutical sector, it is expected that member states will be encouraged to address ongoing obstacles for regional integration, as well as to support the private sector regarding enhancing and upgrading production processes.

SIPS result area 1, which is implemented by the SADC Secretariat, ensures that the policy, regulatory and operational environment at the national and regional level for the development of both targeted value chains (i.e. the ARV and leather value chains) are beneficial. Result areas 2 and 3, which are implemented by GIZ, aim to enhance the participation of the private sector in the antiretroviral (ARV) and leather value chains. For these result areas, SIPS facilitates the collaboration between private sector stakeholders, supports the creation of clusters and collective practices that will benefit the strategic position of the private sector.

With the provision of capacity building and technical assistance to the private sector, SIPS is supporting (a) the move towards meeting international production standards, (b) improved understanding and respect of intellectual property rights, and (c) improved transfer of knowledge and knowhow.

Thus, in terms of the ARV component of the project, the specific objective of the SIPS Action is to improve the performance and growth of this regional value chain and related services, with the output being enhanced private sector participation in the regional Anti-retroviral (ARV) value chain.

## Overview of HIV prevalence, treatment and ARV manufacturing

The impact of HIV still resonates across the world, over 5 decades after it emerged as a major disease threat. In 2019, approximately 38 million people were living with HIV/AIDS worldwide, and an estimated 1.7 million new infections during that year. It is estimated that 81% of HIV positive individuals knew their status in 2019, with the remaining 19% (about 7.1 million people) unaware of their status[1].

Currently, there are effective antiretroviral therapies (ART) that do not completely cure the infection but offer long term remission and reduction in viral load. ART's have allowed most HIV positive individuals to lead normal lives and avoid the development of full-blown AIDS. First-line treatment for HIV is through combination therapy which uses multiple active pharmaceutical ingredients (APIs). Although these therapies are widely available, and there has been a significant decline in the number of new HIV infections, it remains a major infectious disease risk. It is important to highlight that, of the infected individuals, an estimated 25.4 million (67%) have access to antiretroviral therapy, meaning that 12.6 million people are not treated.

When considering the worldwide prevalence of HIV/AIDS, it becomes clear that by far the highest burden resides within the African continent, particularly Sub-Saharan Africa where approximately 67% of HIV positive cases are found. Furthermore, the highest disease burden is prevalent in the SADC region. According to 2020 data,[2] over 20 million individuals in East and Southern Africa were HIV positive, representing over 54% of the total worldwide population, with the vast majority (17 million people) in the SADC region.

It is also important to highlight the UNAIDS 90-90-90 strategy[3] to combat HIV/AIDS and help to end the epidemic, whereby:

- By 2020, 90% of all people living with HIV will know their HIV status.
- By 2020, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy.
- By 2020, 90% of all people receiving antiretroviral therapy will have viral suppression.

Antiretroviral therapies are a vital element within the essential medicines recommended for use in SADC countries, given the ongoing HIV prevalence and incidence in the region. Given that the majority of ARVs used in SADC are imported, there is a clear economic opportunity for the region by increasing the local capture of this market.

Pharmaceutical manufacturing is relatively capital intensive due to its highly technical and highly regulated nature. It is also shaped by an ever-shifting intellectual property and medical landscape as new ARVs are developed and then recommended for use. Roughly $1.3B is spent on ARVs in SADC each year (see Figure 5 below) by an overlapping patchwork of global donors, national governments,

[1] See https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics.

[2] See https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

[3] See https://www.unaids.org/en/resources/909090.

and private citizens. While margins on ARVs may be tight compared to other generic pharmaceuticals, there is fierce competition and well-established procurement strategies.

Despite these and other barriers to entry, a significant pharmaceutical industry exists in SADC. Due to the prevalence of HIV in the region, ARV manufacturing should be a key component of the pharmaceutical sector within the SADC region. There are opportunities to increase value capture along the approximately $1.3B value chain by increasing the procurement of locally manufactured products and reducing reliance on imports.

The pharmaceutical industry in South Africa is the most developed in the region, therefore the country will mainly be used as a benchmark for any opportunities for value capture related to the local manufacture of ARVs within SADC.

## Structure of the Report

This report examines the opportunities and challenges relating to ARV production in SADC, and the wider ARV value chain and discusses potential next steps to strengthen the concerned private sector.

Given the complexity of the industry and the market, and the challenges that exist, it is structured to assess the different facets relating to the ARV value chain. The report reviews the prevalence of HIV in SADC and discusses data challenges in this regard in Chapter 2 and then considers the ARV procurement process and provides an overview of the market in Chapter 3. It then provides an overview of current ARV manufacturing in SADC, with a country-by-country review where data is readily available in Chapter 4.

To produce ARV medicines according to international standards, certified production facilities, as well as highly qualified personnel, are required. Chapter 5 gives an overview of pharmaceutical production training opportunities within the SADC region.
There are various other factors, considerations and strategic components which are important to discuss in the context of enhancing ARV manufacture and increasing value chain capture. Some of these represent challenges and constraints, while others are important to provide an environment supporting industrial growth and development of the pharmaceutical sector. These aspects are reviewed in Chapter 6. The areas covered here are regulation and GMP, policies, donor-related aspects (given the impact of donors on the ARV market in particular), the importance of market data, and the potential to address one of the biggest costs drivers in ARV production, API purchasing, through pooled procurement.

Chapter 7 draws together the report conclusions and discusses potential next steps, considering each of the market areas in turn, therefore the public market, donor-driven market and private market.

Additional information and data related to the ARV market, an analysis of local value capture related to tablet manufacturing (the most common form of ARV medication), discussion of API production options, and donor sales data (specifically, Global Fund sales to African companies) is provided in the appendices to the report.

## Approach and Methods

The inception phase started with detailed mapping and profiling of the ARV value chain in each of the SADC Member States. This included identification of the key players, the bottlenecks at each stage of the value chain and how the various processes and stakeholders are interlinked. The purpose was to establish a situational baseline for the current performance of the value chain and to identify areas for possible intervention for the SIPS joint action. Furthermore, the analysis was meant to identify gaps between regional standards in the value chain when compared to the international standards in aspects of product quality, business practices and service delivery.

Relevant private-sector ARV manufacturers in the pharmaceutical value chain in all SADC Member States were identified through relevant publications (for example policy documents, research data, donor data as referenced throughout this report), relevant ministries in the Member States, respective pharmaceutical associations in the region, and personal business contacts. The purpose was to develop a database of the companies and to ascertain current and planned operations in relation to ARV production, manufacturing capacity, regulatory status, current markets for production, expansion plans, barriers to manufacture within the region (economic, technical, legal or other) etc. Data was sought using desk review of the relevant documentation, qualitative interviews with the companies and other key stakeholders within the region. Furthermore, SMEs in other segments of the ARV value chain, that is, manufacturers of excipients, pharmaceutical raw materials such as solvents, and packaging materials were identified, and data related to capacity, current market (ARV and non-ARV related) was gathered. The same methods of data collection as for the ARV manufacturers were applied. The interactions with both ARV manufacturers and other companies relevant to the ARV value chain (for example, excipient manufacturers) were also used to gather data on intra-regional trade relations within this value chain to approximate the potential for sustainable value capture by intra-regional trade.

In order to apply the multidimensional approach to analysing the value chain, stakeholders within the region providing education and training relevant to pharmaceutical manufacturing within the SADC region, for example, industrial pharmacy, together with national private sector associations were identified. The purpose was to assess their capacity to improve skill development in the pharmaceutical sector. Online research and qualitative interviews were used to collect data on existing programmes in academic and TVET institutions. Still, in line with the human resource element of the health sector, the policies and regulatory mechanisms in place for the trade in services of human resources for health within SADC (country and regional level), the general availability of skilled personnel in the region as well as of barriers to the movement of professionals in the development of regional pharmaceutical value chain in the SADC region were analysed. Qualitative interviews were conducted with relevant ministry representatives from the SADC Member States and the pharmaceutical industry.

Short-term experts were responsible for conducting the research under the supervision of the SIPS team. In all aspects of the inception phase, COVID-19 travel restrictions were a limitation to site visits and face to face interviews with stakeholders, therefore nearly all interactions had to be conducted online.

The last step of the consultative process involved the participation of the relevant ARV value chain stakeholders in a virtual workshop to validate the findings and provide further information and/or recommendations to the collated findings. The workshop was held virtually on the 21st of September 2021 and the draft inception report was shared with stakeholders prior to the workshop for their review, comments and inputs. Feedback was provided during the meeting and via an online feedback tool which is annexed in Appendix V. The responses were classified according to the corresponding chapter in the inception report and incorporated in the inception report accordingly. In general, most respondents agreed with the findings of the report and valuable input was gathered through the process to refine the proposed interventions. All comments and inputs from respondents were documented and are included in the annex.

# 2. PREVALENCE OF HIV IN SADC MEMBER STATES

According to UNAIDS, as of 2018, approximately 17 million people were living with HIV/AIDS across SADC. While UNAIDS is only able to estimate the total number of people living with HIV/AIDS, they provide a precise figure of 11,266,052 for those people living with HIV/AIDS and receiving Antiretroviral Treatment (ART) throughout SADC member states. As Table 1 depicts below, the prevalence of the disease and uptake of ART is not equally distributed throughout the region.

Table 1: 2018 UNAIDS data for the HIV/AIDS disease burden and prevalence of ART throughout the SADC region (includes a range of error for some numbers)[4,5,6].

| Country | Number of people living with HIV Population (all Ages) | People Living with HIV Receiving ART (Total #) | People Living with HIV Receiving ART (%) | HIV Prevalence in Adults 15-49 (%) |
|---|---|---|---|---|
| **South Africa** | 7,700,000 [7100000 - 8300000] | 4,788,139 | 62 [57 - 66] | 20.4 [17.4 - 22.5] |
| **Mozambique** | 2,200,000 [1700000 - 2700000] | 1,212,562 | 56 [44 - 68] | 12.6 [10 - 15.7] |
| **Zimbabwe** | 1,300,000 [1100000 - 1500000] | 1,150,543 | 88 [77 - 100] | 12.7 [10.8 - 14.5] |
| **United Republic of Tanzania** | 1,600,000 [1400000 - 1700000] | 1,108,728 | 71 [64 - 78] | 4.6 [4 - 5.1] |
| **Zambia** | 1,200,000 [1100000 - 1400000] | 964,689 | 78 [69 - 88] | 11.3 [10 - 12.6] |
| **Malawi** | 1,000,000 [940000 - 1100000] | 814,275 | 78 [70 - 84] | 9.2 [8 - 10] |
| **Botswana** | 370,000 [330000 - 400000] | 307,377 | 83 [75 - 90] | 20.3 [17.3 - 21.8] |
| **Democratic Republic of the Congo** | 450,000 [370000 - 530000] | 256,486 | 57 [47 - 67] | 0.8 [0.6 - 0.9] |
| **Lesotho** | 340,000 [320000 - 360000] | 206,298 | 61 [57 - 65] | 23.6 [21.2 - 24.7] |
| **Namibia** | 200,000 [190000 - 220000] | 184,245 | 92 [84 - 99] | 11.8 [10.6 - 12.7] |
| **Eswatini** | 210,000 [190000 - 220000] | 177,156 | 86 [80 - 94] | 27.3 [25.1 - 29] |
| **Angola** | 330,000 [290000 - 390000] | 88,734 | 27 [23 - 31] | 2 [1.7 - 2.3] |

[4] See https://aidsinfo.unaids.org/.

[5] Figures are based on modelled HIV estimates. Please see the "Annex on methods" from "Seizing the moment—Tackling entrenched inequalities to end epidemics" for more information on HIV estimates methodology.

[6] For Seychelles, UNAIDS only reported the total number of people receiving ART.

| Country | Number of people living with HIV Population (all Ages) | People Living with HIV Receiving ART (Total #) | People Living with HIV Receiving ART (%) | HIV Prevalence in Adults 15-49 (%) |
|---|---|---|---|---|
| **Madagascar** | 39,000 [30000 - 55000] | 3,510 | 9 [7 - 13] | 0.3 [0.2 - 0.4] |
| **Mauritius** | 13,000 [10000 - 15000] | 2,756 | 22 [18 - 26] | 1.3 [1.1 - 1.5] |
| **Seychelles** | N/A | 554 | N/A | N/A |
| **Comoros** | 200 [100-500] | 60 | 48 [26 - 86] | 0.1 [0.1 - 0.1] |
| **SADC Total** | **Approx. 17,000,000** | **11,266,112** | | |

The SADC region has a disproportionally high disease burden as it accounts for 45% of the worldwide disease burden.[7] South Africa has the highest disease burden, an estimated 17% of the total HIV population in SADC is in South Africa. South Africa has the highest number of people living with HIV/AIDS in the region (45% of SADC's total) with the largest population of people on ART (43% of SADC's total) and the largest number of people living with HIV/AIDS who are not receiving ART (51% of SADC's total). For this reason, South Africa constitutes much of the HIV/AIDS treatment picture in SADC.

Figure 1 summarises the data on HIV prevalence in SADC in 2020. South Africa (SA) continues to dominate global HIV prevalence figures with 7,7 million people living with HIV, followed by Mozambique, Tanzania, Zimbabwe, and Zambia, which together account for more than 80% of the affected population in the SADC region. South Africa accounted for more than 240,000 of the region's new infections in 2018 while five other countries accounted for 43% of new infections: Mozambique (150,000), Tanzania (72,000), Zambia (48,000), Malawi (38,000), and Zimbabwe (38,000).[8]

The graph in Figure 1 indicates the burden of disease for SADC member states and provides more detail on the prevalence of HIV in all SADC countries.

[7] Bertoldi, A., Walwyn, D., Marais, S., Cloete, L, van Lieshout, B., Dean, G.N., & Stanco, R. (2020). SADC pharma pre-feasibility study, Prepared for the Southern African Development Community (SADC).
[8] UNAIDS 'AIDSinfo'.

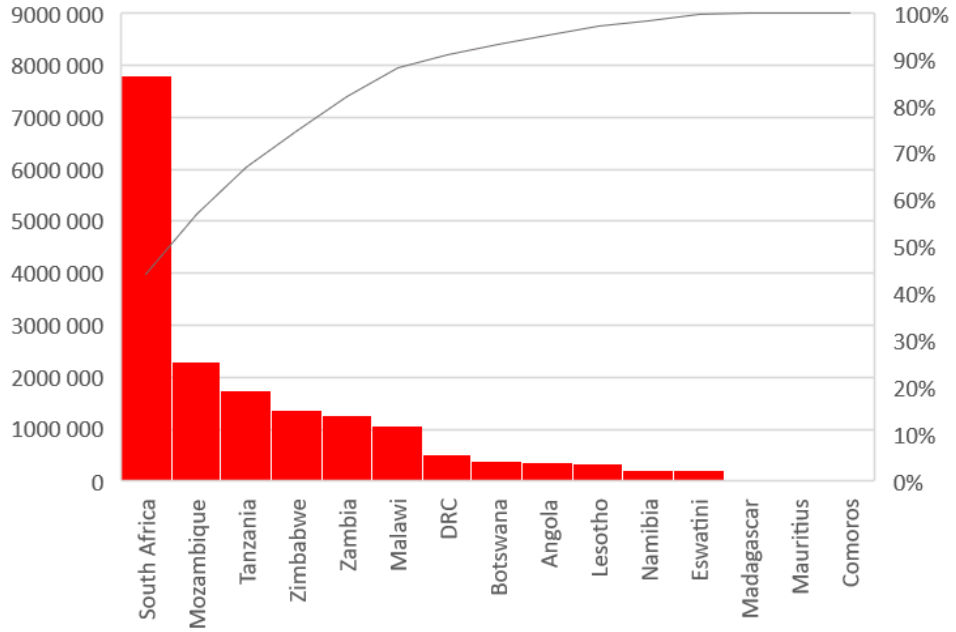



Figure 1:Pareto graph of HIV burden of disease in SADC in 2020

In terms of proportion of the general population, Botswana, Eswatini, Lesotho and South Africa have the highest HIV prevalence relative to their population (17%, 18%, 16% and 13%, respectively). The lowest proportion is in the Indian Ocean islands (Comoros, Madagascar, Mauritius and Seychelles), Angola and the Democratic Republic of Congo which all have a prevalence of 1% or less as depicted in Figure 2.

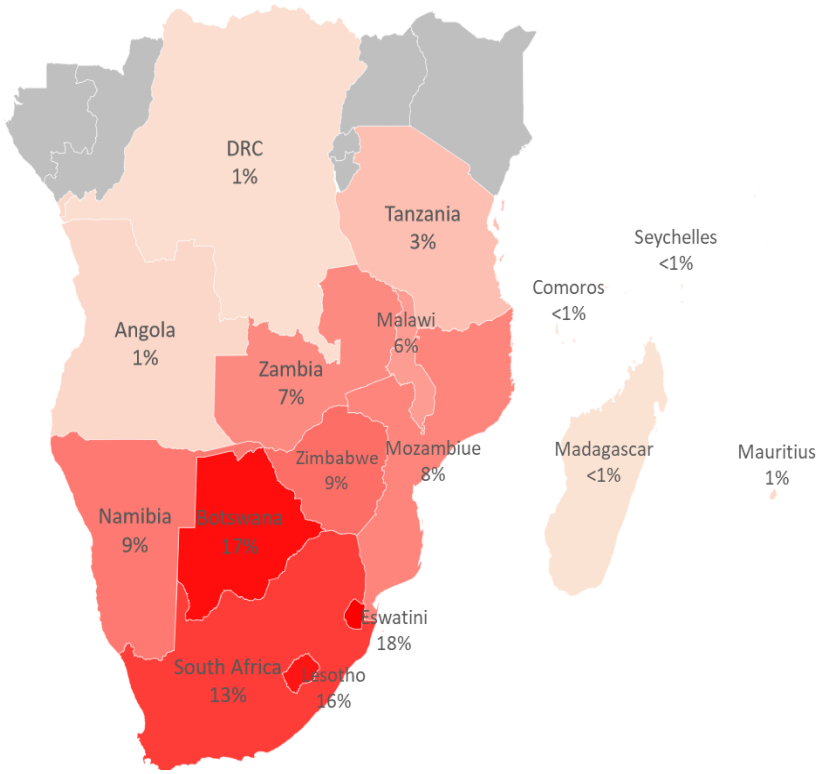



Figure 2: HIV prevalence in SADC

To evaluate the market for antiretrovirals (ARVs) in the region, we must first determine not only where they are being consumed in high quantities, but also where there are still large populations of patients who are not on treatment. South Africa constitutes a large portion of people not yet on treatment in the region, therefore, it is important to investigate what is happening in the other SADC countries by analysing their data without South Africa's. Figure 3 plots the total number of existing people receiving ART against those who are still not receiving ART for all SADC countries outside of South Africa.

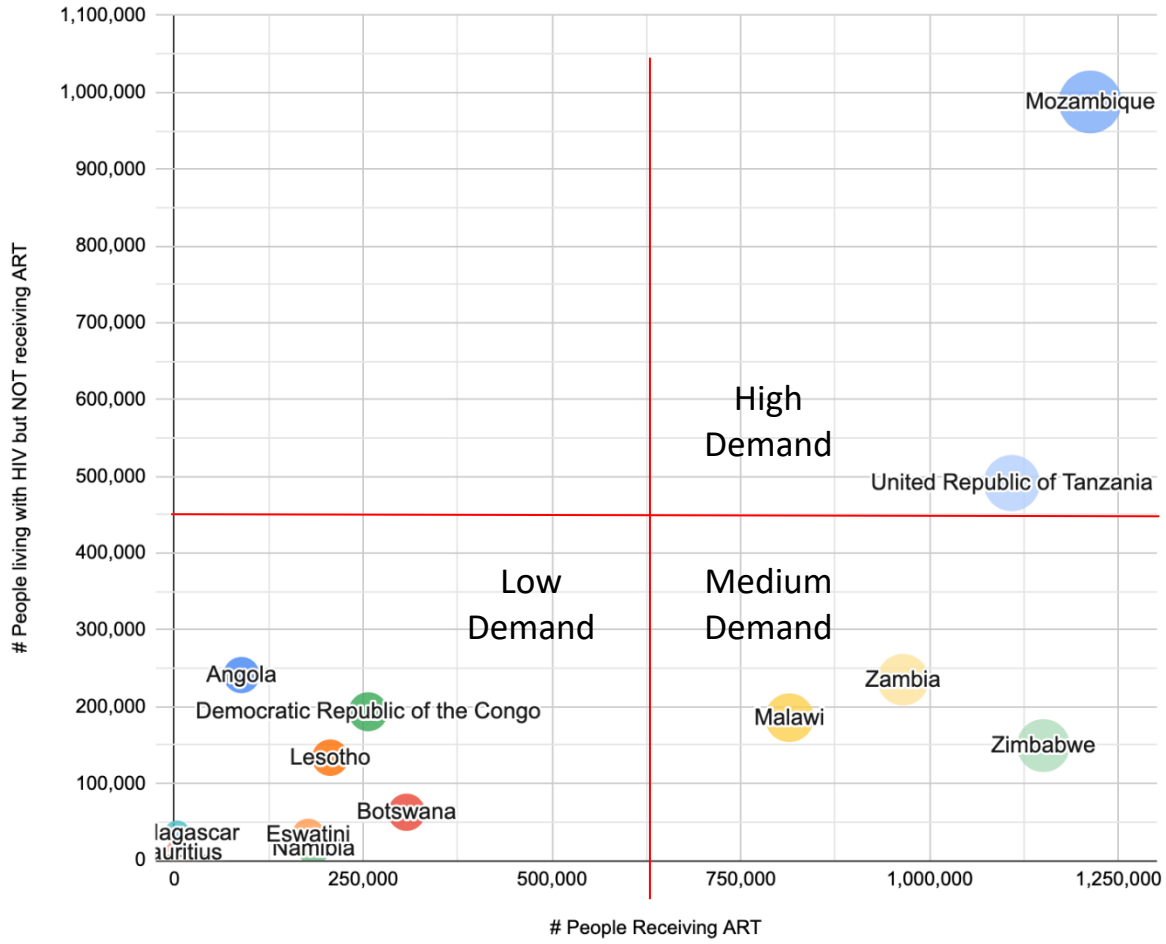



Figure 3: Number of receiving ART vs number of People living with HIV but not receiving treatment for each country in SADC, excluding South Africa.

In Figure 3, Mozambique and Tanzania are shown as large existing users of ARVs (over 1 million patients each). In addition, both countries have a high proportion of HIV positive individuals who currently are not on treatment (approximately 1 million and 500,000 respectively), thereby justifying the need for ARVs in these countries. Figure 3 also illustrates that Malawi, Zimbabwe, and Zambia have sizeable existing ARV usage, but due to their countries high ART coverage rate, not many people are still in need of ARVs as in the case of Tanzania and Mozambique. It is difficult to get a clear picture of what is happening in the rest of the countries from Figure 3 alone.

Figure 4 shows that 81% of the SADC ARV utilization outside of South Africa lies in the five countries discussed above: Mozambique, Tanzania, Malawi, Zimbabwe, and Zambia.

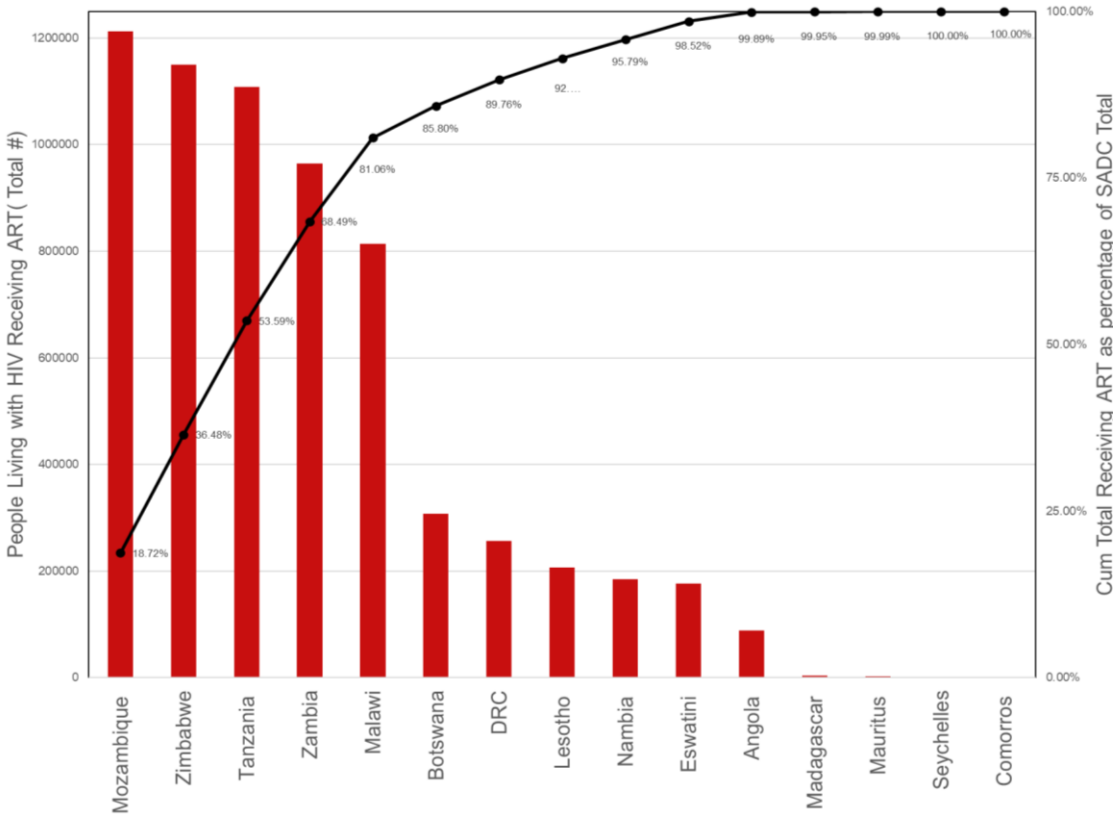



Figure 4: Number of people receiving ART in each country except for South Africa[9].

[9] See https://aidsinfo.unaids.org/

Figure 5 shows that the same 5 countries plus Angola and the Democratic Republic of Congo represent 90% of the estimated unmet requirement for ARVs that still exists in SADC outside of South Africa.

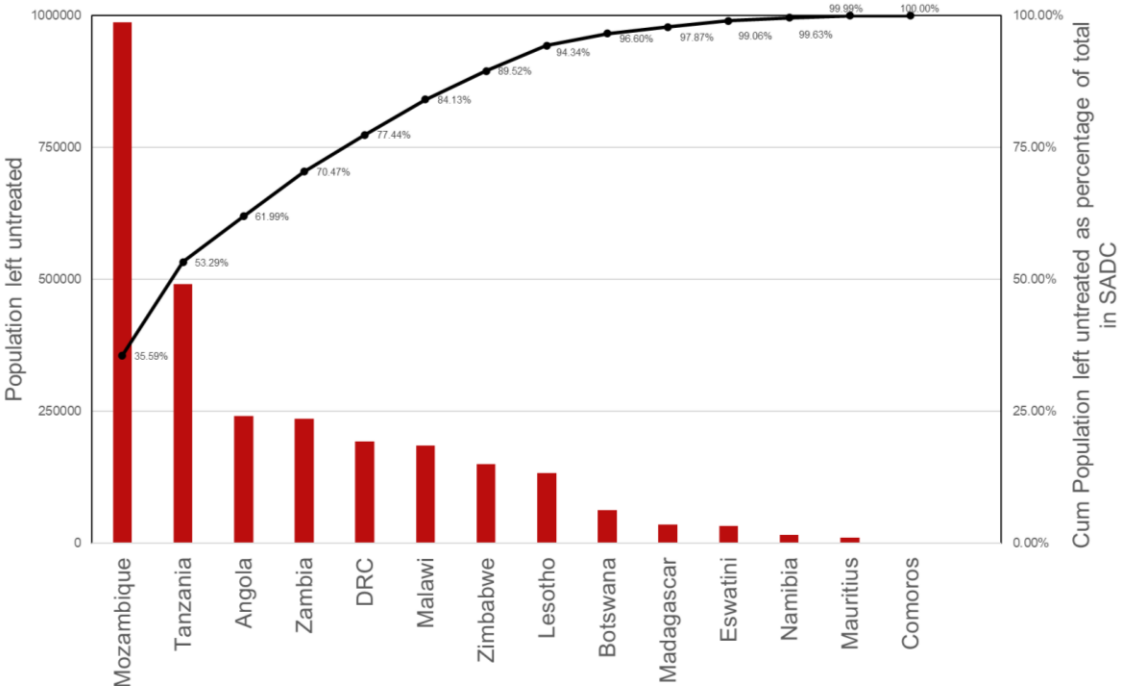



Figure 5: Estimated number of people living with HIV/AIDS but not receiving ART in each country except for South Africa[10].

From this data, it is possible to divide all the countries in the region into 4 groups based on the size of their existing and unmet need for ARVs:

**Group 1**: High existing demand and high unmet need: South Africa, Mozambique, Tanzania

**Group 2**: High existing demand with medium unmet need: Malawi, Zimbabwe, Zambia

**Group 3**: Medium total population living with HIV/AIDS regardless of ART coverage rate: Angola, Democratic Republic of Congo, Lesotho, Namibia, Botswana, and Eswatini

**Group 4**: Low total population living with HIV/AIDS regardless of ART coverage rate: Comoros, Madagascar, Mauritius, Seychelles[11]

[10] Ibid.

[11] Please note: there is no UNAIDS estimate for the total number of people living with HIV/AIDS in Seychelles and for that reason, it wasn't possible to include them in Figures 2 and 4. But with a total population of roughly 100,000, Seychelles clearly belongs in Group 4.

# 3. ARV VALUE CHAIN IN SADC MEMBER STATES

## Value of ARV Procurement Channels

ARVs are procured in SADC through three main channels:

1) Donors
2) National Government Tenders
3) Private Market Purchases

The two main donors in the region are the President's Emergency Plan for AIDS Relief (PEPFAR) and Global Fund. PEPFAR, funded by the US government only buys products that are approved for use by the United States Food and Drug Administration Agency (US FDA). In contrast, Global Fund requires either WHO Pre-Qualification or authorization for use by a Stringent Regulatory Authority (SRA) (such as US FDA, Health Canada or National Regulatory Agencies from EU Countries) for the products they wish to supply. In both cases, approval for use or registration by a National Regulatory Authority in SADC alone is insufficient for a company to supply ARVs through these donors. In most SADC countries, donors procure the majority of ARVs used in the country.

National Governments also procure a sizable amount of the ARVs in SADC. To supply government tenders, the product must first be registered with the local NMRA. In general, WHO PQ or approval by an SRA is not required although most countries may prefer it. In most cases, these government tenders give preference to domestic producers of ARVs, mostly in the form of price preferences. Importers of finished products, both from within SADC and from outside of SADC, do not enjoy this same preference in most cases. Typically, without a price preference, local SADC ARV manufacturers can't compete on price with Indian and Chinese manufacturers. Consequently, there are few examples of government ARV tenders in one SADC country being won by a manufacturer in another SADC country. The main exception being South African manufacturers, who regularly win government ARV tenders in countries such as Lesotho and eSwatini.

Private insurance or out of pocket purchases of ARVs, in general, are very small in all countries, except for South Africa.

The value of each of these procurement channels has been estimated from various data sources below in Table 2. For a detailed explanation of the sources of this data please see Appendix A.

Table 2: Estimated value of the ARV market in each country by procurement channel. Compiled using data from 2017-2020

| Country | Breakdown of Procurement Channels | | | Total |
|---|---|---|---|---|
| | Donor | Public | Private | |
| **ANGOLA** | $6,268,048 | $2,730,403 | $0[f] | $8,998,451 |
| **BOTSWANA** | $4,960,014 | $30,096,785 | $0[f] | $35,056,798 |
| **COMOROS** | $7,635 | $0 | $0[f] | $7,635 |
| **DR CONGO** | $18,168,578 | $0[a] | $0[f] | $26,289,815 |
| **ESWATINI** | $8,681,270 | $13,500,000[c] | $0[f] | $22,181,270 |
| **LESOTHO** | $6,678,348 | $17,108,861 | $0[f] | $23,787,209 |
| **MADAGASCAR** | $165,899 | $174,489 | $19,388 | $359,775 |
| **MALAWI** | $58,534,170[a] | $0 | $0[f] | $83,463,188[a] |
| **MAURITIUS** | $0 | $282,490 | $0[f] | $282,490 |
| **MOZAMBIQUE** | $73,728,832[a] | $0[e] | $0[f] | $124,287,605[a] |
| **NAMIBIA** | $5,105,329 | $13,000,000[c] | $0[f] | $18,885,113[a] |
| **SEYCHELLES** | $0 | $160,927 | $0[f] | $160,927 |
| **SOUTH AFRICA** | $15,085,163 | $583,568,758 | $90,000,000[c] | $688,653,921 |
| **TANZANIA** | $86,676,870 | $26,967,750[a] | $0[f] | $113,644,620 |
| **ZAMBIA** | $71,488,348 | $17,500,000[c] | $0[f] | $88,988,348 |
| **ZIMBABWE** | $110,082,431[a] | $20,500,000[b] | $0[f] | $130,582,431 |
| **Total[d]** | **$465,630,934** | **$733,711,699** | **$90,019,388** | **$1,365,629,595** |

**Notes:**

a: Denotes values that need more due diligence to verify (See Appendix A),

b: Whilst there are issues related to government funding of their national ARV tender (according to recent industry feedback), there is an expectation that the tender will be approximately $19-22M/year in the near future.

c: Estimates based on interviews with local SADC producers.

d: The total figure should be regarded as 'best estimates' as there are uncertainties regarding the accuracy of data constituting the donor and private market channels.

e: According to local firms, there will be a public tender of approximately $5-10M in the near future.

f: The private markets have been reported as zero as they are small in each case or there is no reliable date except for South Africa.

As the data in Table 2 contains several estimations, it is not possible to make complete and accurate comparisons. However, this represents, according to the data available, a tool to consider and contrast the different public markets and the following grouping can be drawn, looking at comparative public market value:

- South Africa: $583M of ARV sales; 80% of total SADC public market value
- Botswana, and Zimbabwe: $20-30M sales per country; under 5% of total SADC market value per country
- Lesotho, eSwatini, Namibia, Zambia: $10-20M sales per country; under 2.5% of total SADC market value per country
- Mozambique: $3-10M sales per country
- Angola, Comoros, DRC, Madagascar, Malawi, Mauritius, Seychelles: Under $3M sales per country; 1% or less of total SADC market value per country
- Tanzania: to be confirmed.

Given the data weaknesses that exist, these groupings may change significantly if more accurate data can be obtained.

There are countries with very significant public ARV procurement programs, which can be a significant enabler for the domestic production of ARVs. However, a sizable national ARV tender alone is not enough to catalyse the creation of the pharmaceutical industry as explained throughout Chapter 4. For example, despite the sizable annual tender in Lesotho, there are currently no pharmaceutical manufacturers there. Furthermore, some countries with local pharmaceutical manufacturers, such as Tanzania, Namibia, and Zimbabwe, are not producing sizeable volumes of ARVs domestically. This is in part because margins for ARVs are so small, but also due to other factors such as delays in payment and other tender related issues as described in Chapter 4.

## Value Capture Opportunities along the ARV Production Value Chain

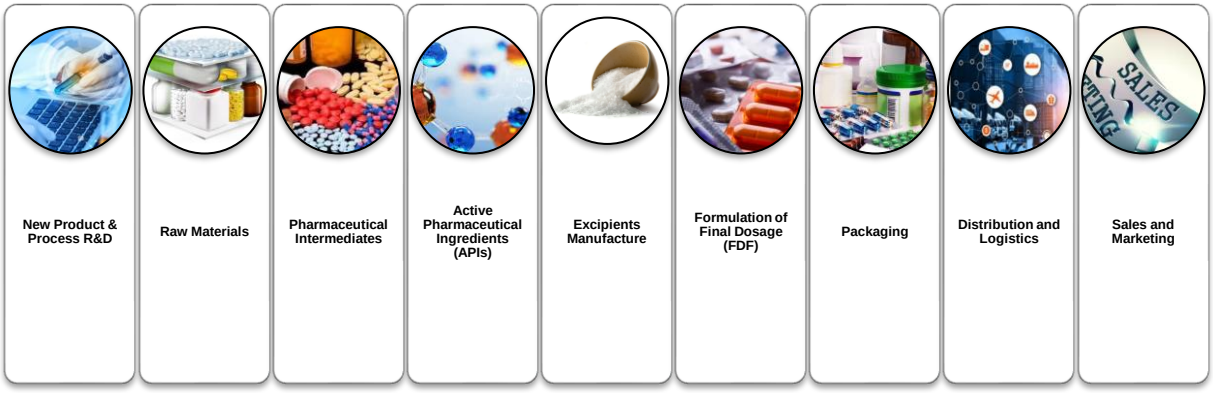



Figure 6: Value Chain for ARV Production

Figure 6 depicts the typical value chain for pharmaceutical products including ARVs. All estimates below exclude any local price preference. The analysis below excludes three sections of the value chain for which an actual value capture was not estimated: Sales and Marketing, Distribution and Logistics (D&L) and New Product Research & Development (R&D).

The ARV value chain has nine segments of which the manufacturing process constitutes six of these segments. These stages of the value chain are: New Products and Process R&D, Raw materials/reagents, Pharmaceutical Intermediates, Active Pharmaceutical Ingredients (APIs) and the formulated Final Dosage Form (FDF). In addition, FDFs often include excipients that could also potentially be manufactured in the SADC region. Lastly, there are packaging and labelling requirements for the FDFs.

The definitions of the above-mentioned value chain concepts including a detailed analysis of each segment, within the region are further defined below.

**New Product & Process R&D:** Research and Development (R&D) into new products used in ARVs (e.g. APIs) as well as new and novel processes for manufacturing the pharmaceutical products.

New Product R&D activities are also largely discounted here because it is highly unlikely any new ARV products will be developed in SADC over the period of this project. There is also a substantial pipeline of new ARV APIs globally and there is very little need to focus on new product development. This is due to the relative dearth of R&D capabilities in SADC and the large competitive advantage in spending

and experience multinationals firms have in this area. For instance, Mylan alone spent over $704.5M[12] on R&D in 2018. Instead, any new R&D activities in SADC could be focused on improving the efficiency of manufacturing operations which will then be rolled into the manufacturing value capture. Furthermore, due to transfer pricing, tax sheltering and other corporate accounting strategies applied to a portfolio of R&D projects, it is not a straightforward exercise to estimate the value that would be generated by new product intellectual property. However, SADC could pursue R&D that improves cost-effective manufacturing processes of ARV APIs as these have a large cost contribution on the FDF.

**Raw Materials:** A general term used to denote reagents, catalysts and solvents intended for use in the production of API Starting Materials (Pharmaceutical Intermediates).

These are generally commoditised fine chemicals and commodity chemicals sourced from chemical manufacturers. Raw materials include solvents, reagents, and catalysts. These are generally produced by bulk commodity chemical companies such as SASOL in South Africa. These chemicals are normally sold at world parity prices (USD prices) and other than a small saving in transport or shipping cost, there would be no major comparative advantage to source these products within the SADC region as it would not have a substantive impact on the final ARV prices.

**Pharmaceutical Intermediate (API Starting Material)**: A raw material, intermediate, that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API.
An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house. API Starting Materials are normally of defined chemical properties and structure. Pharmaceutical intermediates are often also custom manufactured for API producers. The regulatory requirements for producing pharmaceutical intermediates are less onerous than for APIs. Several companies in India and China produce Pharmaceutical Intermediates for use in ARV APIs at affordable prices. Although there are Fine Chemical Companies in South Africa, no company in SADC is presently producing any Pharmaceutical Intermediates for ARV API manufacture. All API facilities could conceivably produce their Pharmaceutical Intermediates in-house.

**Active Pharmaceutical Ingredient (API)**: Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the formulated drug product or FDF. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or function of the body.

[12] See http://newsroom.mylan.com/2019-02-26-Mylan-Reports-Fourth-Quarter-and-Full-Year-2018-Results-and-Provides-2019-Guidance.

**API Production**

ARV APIs make up approximately 70% to 80% of the cost of the ARV FDFs.[13] As such it becomes very difficult for any company operating in the latter stages of the value chain (formulation and packaging) to compete with players that are fully back integrated within the value chain and produce their own ARV APIs. These companies can offer the final ARV FDF typically at a discount of 10% to 15% to any of the local suppliers that import the APIs, normally from the very same players.

There are still several barriers to entry for API to be made in Africa at large scale using traditional batch manufacturing processes (Please see Appendix C). These barriers vary between countries but include in-country regulatory capability, regulatory harmonisation, finance, skills, and the cost of cGMP or WHO PQ infrastructure. The most important barriers are input costs and a lack of long term guaranteed demand.

In recent years, there have been new promising technologies such as continuous flow chemistry techniques as well as more efficient chemical synthesis pathways which Africa could leverage to leapfrog into the production of APIs. However, flow chemistry technologies have mostly been successfully implemented at small or pilot-scale by a few multinationals, often at great cost. In many cases, these technologies have been implemented in pilot-scale facilities to increase the plants' flexibility and product's speed to market, rather than to compete on the open market. Additionally, discussions with the Medicines for All Institute at Virginia Commonwealth University[14] and a recent article[15] by a group of South African researchers reviewing the feasibility of API production in Africa, indicated that commercial-scale production of ARV APIs using these technologies may still be a few years away.

There is a possibility for a small producer of API to rely solely on large economies of scale to bring its COGs in line with the rest of the industry. The ability to produce smaller volumes may also further insulate them from shifting treatment protocols since they may still be able to compete with a portfolio of products at these smaller volume levels. One such project is being evaluated for South Africa but due to strict confidentiality, details on the project are scarce. However, the plan will be to use batch manufacturing combined with novel synthesis routes to produce a portfolio of APIs which would be sold to local manufacturers. To combat the ever-changing ARV regimen changes and slim margins, the company plans to produce ARVs along with other generic medicine APIs such as those for tuberculosis which have more stable, long term demand profiles and higher margins.

Even if an API was being produced in Africa using new technologies, many of the barriers depicted in Appendix C would still exist such as the need for more ARV FDF manufacturers in Africa, fragmented demand for APIs in Africa, shipping and logistics around the continent, availability of the other APIs

[13] Interviews with ARV FDF manufacturers in SADC.

[14] According to their website, https://medicines4all.vcu.edu/about/our-mission/: "The Medicines for All Institute (M4ALL), based at Virginia Commonwealth University College of Engineering in Richmond, Virginia, is committed to improving global access to high-quality medications by driving down production costs. By re-imagining manufacturing processes, the institute's chemical engineers and chemists optimize active pharmaceutical ingredient production and provide open access to manufacturers around the world to enhance the security of medicine supply chains. The institute was founded in 2017 with funding from the Bill & Melinda Gates Foundation."

[15] Landscape and opportunities for active pharmaceutical ingredient manufacturing in developing African economies; React. Chem. Eng., 2019,4, 457

for fixed-dose combination drugs and continually changing treatment regiments. For this reason, API production in Africa will not be the easiest or quickest means of expanding the local value capture of the ARV value chain but could be a possibility.

**Excipients**: Examples of excipients include fillers, extenders, diluents, wetting agents, solvents, emulsifiers, preservatives, flavours, absorption enhancers, sustained-release matrices, and colouring agents. For ARVs, these include products like Microcrystalline Cellulose, Lactose Monohydrate and Starch.

**Excipient Production**

Excipients are the various inactive ingredients used in a tablet to ensure the tablet stays intact and the API is stable and delivered in the prescribed manner. There are often 10 or more different excipients in a product and each product has a different formulation, often requiring different sets of excipients. For example, the common first line ARV TLD contains the following inactive ingredients[16]:

1. croscarmellose sodium,
2. lactose monohydrate,
3. mannitol,
4. microcrystalline cellulose,
5. povidone K 30,
6. pregelatinized starch,
7. sodium starch glycolate
8. sodium stearyl fumarate.
9. polyethylene glycol,
10. polyvinyl alcohol,
11. talc
12. titanium dioxide.

Other excipients used in other ARV formulations include:

1. Starch,
2. Magnesium stearate,
3. Sodium lauryl sulfate,
4. Sodium starch glycolate,
5. Croscarmellose sodium,
6. Colloidal silica,
7. Hydroxypropyl cellulose.

Excipients can account for between 3-5%[17] of the final product price although they are typically highly commoditized products, made in large bulk quantities and sold at razor-thin margins. While these may be "commodity" products, they require a higher quality level than the food or industrial grade version which may be used elsewhere. This, combined with the fact that there are so many different excipients

[16] See https://www.accessdata.fda.gov/drugsatfda_docs/pepfar/210787PI.pdf.

[17] Based on interviews with local SADC producers.

needed for one product, make the prospect of gaining a significant amount of additional local value capture from local excipient production unlikely.

**Final Dosage Formulation (FDF) Manufacturing Operations (Fully Manufacturing)**

Final Dosage Formulation (FDF) manufacturing facilities formulate products from API and excipients, form tablets or capsules and package them. Most ARV products are FDFs (i.e., tablets or capsules) and most government and donor tender products are packed into plastic jars rather than blister packs.

According to an estimate given by a SADC manufacturer, one can expect around 30% of the final purchase value of ARVs that are locally produced to be captured locally (see Appendix B for the full local value capture analysis). The local value capture comes in the form of OPEX, local packaging materials and other corporate expenses paid from Earnings Before Interest, Depreciation, Tax and Amortization (EBIDTA). OPEX will be mostly retained locally in the form of wages, utility payments, third-party services, etc. Expenses paid from EBIDTA would also mostly stay local unless a disproportionate amount of the financing or ownership structure resides outside of the country.

It may seem counterintuitive to go through all the additional hurdles to set up a full manufacturing facility instead of a packaging only facility for only an additional 7-11% increase in local content (i.e., 32-36% versus 25% local value capture). However, the truth is, local manufacturers are opting for full manufacturing as opposed to packaging only facilities to increase their gross margin and EBIDTA, not to increase local content. The gross margin on packaging only of ARVs is as low as 3-5%, while it is typically 20-25%[18] for full manufacturing (with these figures including any local price preferences that exist). The gross margins for full manufacturing of generic pharmaceuticals are even higher at 40-45%[18].

As mentioned before, full manufacturing facilities need significant production volumes and high-capacity utilization to achieve the economies of scale necessary to compete in price-sensitive markets. Because of this, the pricing example used to derive the estimates above is based on a facility with a capacity of 1 billion tablets/capsules per year. This facility will never be devoted to ARV production only for two reasons:

1) No country needs 1B ARV tablets per year except for South Africa, and even then, all of a country's ARV needs will never realistically be sourced from a single company, let alone a single facility.
2) The gross margin on ARVs is only roughly 20-25% due to intense global competition, while the gross margin for other generic pharmaceuticals is typically 40-45%.

Therefore, the most common approach for manufacturers is to devote only part of the production capacity to low margin, high volume products such as ARVs to keep the facility busy and operating near capacity. This keeps the cost of goods low by spreading the fixed costs over more units. The rest of the facility capacity is devoted to higher-value products with lower volumes or more variable demands, from which a disproportionate amount of the profit is derived. In short, ARVs give operational stability, while other products bring profit.

[18] Based on interviews with local SADC producers

Appendix B lays out a detailed explanation of the cost model used to calculate the local value capture inherent in full FDF manufacturing operations. Please note, the example there assumes the entire production capacity is devoted to ARV production throughout the year, which as discussed above is not representative of how most facilities would operate in practice. However, it does enable us to determine the rough value of local value capture from the full manufacturing of ARVs.

Appendix B also addresses estimates of the level of employment coming from ARV production. In summary, due to overall low levels of ARV production in SADC and the relatively low labour-intensive nature of pharmaceutical production, it is reasonable to assume that approximately 125-175 direct jobs[19] are devoted to ARV production, most of which are in South Africa. Therefore, even significant gains in localized ARV production over the next 3-5 years are likely to result in dozens of newly created roles directly manufacturing ARVs, rather than hundreds. Additionally, up to 2 new jobs could be created in firms supporting the local ARV manufacturers for each new job created at the pharmaceutical manufacturers according to one estimate by a local SADC manufacturer.

**Packaging Materials:** Packaging may be defined as the collection of different components (e.g. bottle, vial, closure, cap, ampoule, blister) which surround the pharmaceutical product from the time of production until its use. Packaging materials include printed material employed in the packaging of a pharmaceutical product, but not any outer packaging used for transportation or shipment.

**Packaging Only Manufacturing Operations**

Packaging only facilities receive shipments of loose tablets and capsules from abroad to be packaged into plastic bottles locally. Packaging only facilities are built when forecasted production volumes do not warrant the construction of a full formulation, tabletting and packaging facility. Therefore, one would tend to see them in countries with relatively small markets for the target products. According to one such manufacturer in Botswana, the final sales price is made up of:

- 70% = imported tablets or capsules (do not have any local content)
- 5% = imported packaging materials (plastic jars, product leaflets, etc.)
- 15% = locally sourced packaging materials (labels, corrugated boxes, etc.)
- 10% = Operational Expenses (OPEX) and gross margin (both mostly retained locally)

By adding the last two amounts together, one can estimate local value capture for a packaging only facility to be roughly 25% of the total sale price.

According to the same manufacturer in Botswana, the gross margin for this type of production is usually between 3-5% but some companies do this for almost no margin simply to keep their facility busy or for the prestige of winning a tender.

Packaging materials other than plastic jars tend to be sourced locally for most manufacturers. Printed corrugated boxes, tape and labels and product inserts suitable for use in the pharmaceutical industry are available locally in most countries. In some cases, companies do import their labels or product inserts, mostly from India, as part of a larger shipment of goods that must be imported. However, this is mostly seen as opportunistic purchases rather than done out of necessity.

[19] Based on the analysis in Appendix B.

The jars used to package ARVs however are typically imported and constitute roughly 5%[20] of the final product price. Companies reported that importing jars from South Africa was likely to be 2-5 times more expensive[20] than getting similar materials from India. However, there is a company in Zambia that is setting up a facility to produce jars locally, which they intend to sell to local production partners of an MNC ARV producer. This MNC has already carried out their first audit of the jar production facility. They plan to compete with imports by providing shorter lead times and having a similar total landed cost due to lower duties and shipping costs, an important cost factor in landlocked Zambia. This is the only such jar localization project that the team came across during discussions with local companies.

Shorter lead times will also help companies to carry lower inventories, tying up less working capital. Most companies do not consider or even know, the total landed cost when purchasing any materials. Unfortunately, while the total landed cost of a locally made jar may be cheaper, some customers may not factor these additional costs into their purchasing decisions and will need to be sold on the idea first.

**Distribution and Logistics**

D&L is already being carried out by local firms in each country regardless of where the ARVs are coming from and thus the value here has, and always will be, captured locally. While there were discussions with companies who handle D&L as part of their business, the focus of these discussions was on other value-added activities these companies performed such as manufacturing or sales and marketing.

**Sales and Marketing**

Local agents play a role in shaping the national ART guidelines which impact the public, private and donor markets in these countries. Local agents inform prescribers and Key Opinion Leaders (KOL) of the latest ART science and patient management using traditional pharmaceutical sales and marketing strategies such as:

1) Individual face to face meetings
2) Hosting local group meetings and seminars
3) Facilitating KOL attendance at regional and international meetings/conferences

Private market purchases are known to be heavily influenced by traditional sales and market programs. This is because both the patient and prescriber play a big role in determining which drugs are used. However, through influencing the national ART guidelines, agents ensure the newest and best-suited treatments are being procured at the National and Donor tender level. This not only improves health outcomes for those living with HIV/AIDS but curtails the dumping of older or less efficacious treatments. It also enables agents to indirectly influence Donor sourced supplies of ARVs in favour of the global firm they represent.

Agents can also play a pivotal role in national tenders by tendering on behalf of the global firm they represent. In some cases, this even entitles them to a price preference as a local company, even if they are importing a fully finished product.

[20] Based on interviews with local SADC producers.

Agents for foreign makers of ARVs are quite common throughout the region, even in countries where all or most of the ARVs are provided by Donors. The agents interviewed for this project declined to comment on the commission they received for their work and thus a local value capture could not be determined. Furthermore, shifting market dominance in the market resulting in the replacement of one company's agents for another's a zero-sum game and thus results in no further localization.

**Value Capture Overview**

Table 3: Overview of opportunities for local value capture at each step in the ARV value chain.

| Value Chain Step | Outlook on Additional Local Value Capture |
|---|---|
| New Product & Process R&D | New product development is unlikely to occur in SADC in the short term. A more viable alternative use for academia and research resources would be the development of improved efficiency or new and novel methods of API production and improved business processes at local firms. |
| Raw Materials | Companies like SASOL in South Africa produce raw materials for use in ARV API manufacture, as do companies like Illovo (e.g. ethanol). Prices are based on global market prices and local supply does not provide a cost benefit to ARV API manufacturers, apart from savings in transport cost. |
| Pharmaceutical Intermediates | No Fine Chemical Companies producing relevant ARV Pharmaceutical Intermediates exist in SADC, although existing API producers could potentially produce certain Pharmaceutical intermediates in-house. |
| API Manufacturing | No such operations exist for ARVs anywhere in Africa despite API being a large constituent of the final product cost. Possibility for a small, technologically advanced manufacturer to be established. |
| Excipient Manufacturing | No sizable operations exist in Africa, but excipients represent a small portion of the value chain. These are typically commodity products with small margins, and many are required for one product, making it unlikely any local production will be viable. |
| Full FDF Manufacturing | These operations exist throughout the region and capture approximately 20-30% of the total ARV price locally. Increased local market share here will result in additional value capture and thus should be a focus of this project. |
| Packaging Material Production | Jar production could be financially viable, especially if companies begin purchasing based on the total cost to procure rather than the lowest ex-factory cost. |
| Packaging Only Manufacturing | These operations exist throughout the region and capture approximately 25% of the total ARV price locally. Increased local market share here will result in additional value capture and thus should be a focus of this project. |
| Distribution and Logistics | Typical D&L company commissions are unknown but are fully localized already. Value could rise as the ARV market grows, but this is not guaranteed. |
| Sales and Marketing | Typical local agents' commissions are unknown but are fully localized already. Value could rise as the ARV market grows, but this is not guaranteed. |

It is not possible to determine the current local value capture for ARVs in the region however, the value capture estimates at various stages of the value chain enable the identification of where the best local value capture opportunities are for ARVs in SADC. It could also be possible to estimate the incremental value localized from any planned interventions by this project.

Lastly, it is necessary to determine where the local value capture is already near its peak for the environment currently in place in that country. To perform this type of analysis, a greater amount of market data is required, compared to the levels currently found in most SADC countries. The two exceptions, where there is sufficient data, are Botswana and South Africa. Therefore, the following example, for Botswana, is provided to demonstrate the next steps that could be taken:

In Botswana, roughly 60-80%[21] of the ARVs bought by the country are packed locally and the national tender is the main source of funding for ARVs. Since packaging only operations capture approximately 25% of the final value locally, one can conclude that roughly 15-20% of the total ARV value chain is captured (i.e., 60-80% x 25% = 15-20%).

Competing means of additional value capture could be:

1. Increase the proportion of ARVs being locally packaged.
2. Localize jar production or move to full manufacturing, however, there may not be enough volume to justify either in Botswana at this time.
3. Advocate for further consolidation of the industry or increased exports/imports with the rest of SADC were possible.

In summary, if there was a sufficient level of market data for all SADC countries, an analysis like the above case could be carried out for each relevant territory.

[21] Based on interviews with local SADC producers.

# 4. MANUFACTURING OVERVIEW

## Review of ARV manufacturing in SADC

There is significant diversity across SADC regarding ARV manufacturing and related value chains. This is not surprising, given large variability over several parameters that impact the business and market environments within individual countries including:

- Variations in population size
- Economic strength and GDP
- Other geopolitical factors and relative levels of stability
- Variations in HIV prevalence and the size of the untreated market
- Relative levels of industrial development

A combination of these and other factors have led to a diverse range of capability and size within SADC regarding pharmaceutical manufacturing. This has, in turn, created different opportunities within the specific field of HIV medicines.

In simple terms, the business opportunities relating directly to the manufacturing process can be broken down into various categories, reflecting the dynamics of pharmaceutical product supply and demand:

- Importers and local agents
- Pharmaceutical product manufacturers (that is, producers of finished products)
    - Full manufacturers
    - Packaging only manufacturers (those receiving bulk product or primary packaged product and completing the manufacturing process)
- API and/or intermediate manufacturers
- Manufacturers of excipients and other raw materials
- Jar manufacturers (important in the ARV arena as most products are supplied in plastic jars)

There is considerable diversity across SADC when considering the level of manufacturing within these categories, and the following points should be noted:

- Many countries have one or more manufacturers, whilst some do not have any.
- South Africa represents by far the largest pharmaceutical manufacturing base, with a greater industry value, size and number of employees than all the other SADC countries put together.
- Within other manufacturing countries, different models are followed in terms of the level of manufacturing conducted - that is, full manufacturing versus packaging only.
- Importantly, some manufacturers are locally owned whereas others are subsidiaries of multinational companies and can be either partly or wholly owned.
- Most countries have one or more importers. Importers are likely to work with a variety of manufacturers, many of which are from India, whilst local agents represent either multinational companies or other medium-large manufacturers based outside the continent, particularly Indian manufacturers.

A large proportion of ARVs are supplied by donors and then distributed by national governments through local Non-Governmental Organizations. This leaves little incentive for local manufacture of ARV APIs and or ARV FDFs. As a result, the number of companies that operate in the manufacturing value chain of ARVs in the region is limited.

Companies operating in the latter stages of the value chain (formulation and packaging) therefore find it difficult to compete with players that are fully back-integrated in producing their own ARV APIs. When tendering, those who import APIs and excipients and then formulate are unable to compete with a company that is manufactures their own API. The latter can offer the final ARV FDF typically at a discount of 10% to 15% to any of the local suppliers that import the APIs, normally from the very same players. The companies that have a fully integrated value chain and produce the APIs include Hetero, Mylan (Viatris), Cipla, Aurobindo and Laurus, and most of the ARV APIs and FDFs supplied into the SADC market originate from these players, whether it be directly, or indirectly through agreements with 3rd parties or via donors.

Partnerships with these API and ARV producers are the predominant means of localizing ARVs successfully in the region. This has resulted in local producers of ARV FDFs forging relationships with these fully integrated players, sometimes on an exclusive basis. Most distributors of products simply buy from these players and distribute in the SADC region. Some of these players even established their own subsidiaries in SADC (essentially as distributors) to compete with other local companies in any tenders issued. In such situations, companies may supply bulk tablets for local packaging, or they may have an agreement for supply of API for a particular product that is licensed for local manufacture by the SADC-based partner. Such arrangements enable the multinational partner to gain access to the local ARV market, usually with preferential terms for national tenders and enable local manufacturers to keep pace with the ever-changing ARV treatment regimens without having to invest in the development of new products. However, since none of the locally manufactured products in the region (other than two from Aspen in South Africa) have WHO-PQ, these partnerships are only being formed in countries with sizeable national tender markets as local products without WHO-PQ do not qualify for Donor-funded tenders even if the API or finished tablets the local manufacturers are receiving do.

Many pharmaceutical manufacturers do not make only ARVs. The other products that are made - typically off patent generics across a range of therapeutic areas - are less likely to involve a technology partner as this approach is not required for most pharmaceutical products.

## Potential for ARV API manufacture in SADC

ARV APIs are classified according to their mode of action into several classes namely: nucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors, fusion inhibitors, integrase inhibitors, entry inhibitors (or CCR-5 blockers) and maturation inhibitors. First line regimens typically consist of 2 NRTIs combined with 1 NNRTI.

APIs within a class often have structural similarities (apart from the NNRTIs). Since the mode of action differs in each class, APIs belonging to different ARV classes, typically have vastly different chemical structures.

From an API manufacturer's perspective, this translates into hugely different process steps in the manufacturing of the APIs belonging to different structural classes. This further implies that, should a manufacturer erect a single-purpose, dedicated API facility to manufacture one specific API, the likelihood of that plant being capable of manufacturing another API, from a different ARV class, without further capital investment, is very low. On the other hand, there are examples of multi-purpose plants manufacturing ARV APIs from different classes. Furthermore, when the originator of an ARV enters the market, the process for manufacturing of the API, is often not fully optimised from a cost perspective. When an ARV is patent protected, improvement of the manufacturing process of the API continues with a view to lower overall cost of production. Manufacturing of APIs is also increasingly outsourced to contract manufacturers, who further innovate around the process.

One key input into the overall manufacturing cost of an API is the cost of raw materials, and API manufacturers build competitive advantages through strategic sourcing of raw materials. This, in turn, stimulates fine chemical intermediate manufacturers to produce bulk quantities of intermediates, used as raw materials in the API manufacturing, at extremely competitive prices. These factors contribute to the dramatic drop in prices of APIs by the time patents expire and generic APIs are produced. As fine chemical intermediate manufacturing capacity comes online, and the price of key intermediates decreases, API producers often change their manufacturing processes to start with a later, more advanced intermediate in the process sequence. This frees up manufacturing capacity and shortens manufacturing batch times.

Access to API at a competitive price is crucial for any ARV manufacturer in the SADC region and this often necessitates exclusive / non-competing arrangements with the major API producers. However, only one company (in South Africa) was identified in the SADC region that is capable of, and willing to produce ARV APIs. It is however unlikely that any company would ever target high volume-low margin APIs, as this requires substantial capital investment, and requires competing with existing producers (mostly in India) with fully depreciated capital investments. ARV API production in SADC would only be potentially viable for:

- Newer APIs (e.g., dolutegravir),
- Those with smaller volumes and higher margins (e.g., darunavir, nevirapine) or
- Existing APIs when a substantial technological innovation allows the competitive production of such an API (e.g., tenofovir produced using continuous flow chemistry techniques as was alluded to in recent review articles).[22]
- Lastly, since substantial capital investment would be required, any company would want to produce ARV APIs that have a substantial lifetime in prescribed regimens and would be unlikely substituted in the near future (these include tenofovir, dolutegravir and lamivudine).

Additionally, any API plant that a company invests in would have to be sufficiently multi-purpose to allow a ready switch between ARV APIs without a substantial capital investment, should treatment regimens change, and newer APIs be required.

[22] See https://researchspace.csir.co.za/dspace/handle/10204/11403.

## APIs for current and future ARTs

Newer generation combination treatments have reduced side effects and complex treatment regimens have been combined into single-tablet fixed-dose combinations which greatly contribute to adherence due to the increased ease of administration. The most recent recommendations for ART are for the fixed- dose combination (FDC) of tenofovir disoproxil fumarate (TDF), lamivudine (3TC) and dolutegravir (DTG). This is also known as TLD and is the combination that was considered in the SADC feasibility study. Emtricitabine (FTC) can be used as an alternative to lamivudine (3TC) and efavirenz (EFV) as an alternative to dolutegravir (DTG).[23] This gives a combination of tenofovir disoproxil fumarate (TDF), lamivudine (3TC) and efavirenz (EFV) as an alternative first- line regimen and it is referred to as TLE. The active ingredients for TLD and efavirenz are discussed in more detail below:

**Tenofovir Disoproxil Fumarate**

Tenofovir Disoproxil Fumarate (TDF) belongs to the therapeutic class HIV-1 nucleotide reverse transcriptase inhibitor, indicated for first- and second line, for adults and adolescents according to the WHO 2006 guidelines. It was first approved by the US FDA in October 2001 and is included in the WHO EML. Although tenofovir was discovered and patented in 1985, Gilead later applied for additional patents on a new form of the drug, tenofovir disoproxil fumarate. These later patents expired in 2018. Tenofovir Alafenamide (TAF) is also under consideration as an alternative to TDF. The synthesis for TDF and TAF are very similar with some changes in the latter parts of the process therefore cost of manufacture are very similar and any API producer would be able to make the switch from TDF to TAF if the need arises. However, TDF is still preferred in the first line regimens TLE and TLD. Recent articles on the adverse effects reported resulting in increased obesity primarily amongst women when TAF is used, means that TDF will probably remain the preferred API in the near future.[24]

**Efavirenz**

Efavirenz (EFV) belongs to the non-nucleoside reverse transcriptase inhibitors therapeutic class and is indicated for first and second line, for adults, adolescents and children. It was first approved by US Food and Drug Administration (FDA) on 17th September 1998 and is included in the WHO Model List of Essential Medicines. EFV was developed by Dupont Pharma and is now marketed by Bristol-Myers-Squibb, but Merck has the marketing license in several countries. Although there is a desire to switch from the TLE regimen (containing EFV) to the newer TLD regimen (with DTG replacing EFV), many physicians are reluctant to switch patients that are doing well on a TLE regimen. This means EFV will remain an important API in the near future.

EFV is a classic example of the progression of the API manufacturing process, as it approaches patent expiry (expired in 2013). The EFV process patented by Merck in 1993, started with simple raw materials; namely parachloroaniline and cyclopropyl methyl ketone and utilised a 12-step chemical process. The patented process is fairly inefficient as it produces a racemic mixture of EFV isomers, which are separated at the end of the process using a chemical resolution method. This means that at least 50% of EFV manufactured cannot be recovered and, instead, is turned into waste at a late stage of the manufacturing process.

[23] See https://www.who.int/publications/i/item/WHO-CDS-HIV-18.51.

[24] See https://www.aidsmap.com/news/nov-2019/advance-study-shows-high-frequency-major-weight-gain-women-receiving-dolutegravir-taf.

The manufacturing process has since evolved with the more common starting material now being 1-(2-amino-5-chlorophenyl)-2,2,2-trifluoroethanone and cyclopropyl acetylene which produces EFV in a four chemical step process that is highly selective to the desired isomer. The substantially shorter synthesis route also reduces the fully absorbed cost of EFV, due to the requirement for less production capacity with the fewer process steps. Raw material cost saving and lower effluent treatment cost further contribute to the fact that the price of the EFV API dropped substantially since it was first produced using the patented procedure (by at least three-fold). For the higher volume APIs such as EFV, further cost reductions could also be achieved by building dedicated single-purpose plants.

Comparison of three new process technologies for EFV highlights how small changes in process routes have vastly different effluent profiles. In one case, chlorinated organics are produced as a waste by-product, on a ton for ton basis with EFV, resulting in very high disposal cost. One raw material change in another process results in 360 kg sodium chloride effluent per ton of EFV being replaced with 760 kg chloroform per ton of product. These two by-products have vastly different disposal requirements and cost implications, depending on plant location.

**Dolutegravir**

Dolutegravir is a second-generation HIV integrase strand transfer inhibitor (INSTI) and the most recent antiretroviral approved for treatment of HIV-1 infection. Dolutegravir in combination with two nucleoside reverse transcriptase inhibitors is one of the preferred regimens recommended by WHO. Its synthesis involves the reaction of (R)-3-aminobutanol (1) with 3-benzyloxy-4-oxo-1-(2-oxoethyl)-1,4-dihydropyridine- 2,5-dicarboxylic acid 2-methyl ester. Later, the (R)-3-aminobutanol became a key intermediate for the synthesis of Dolutegravir sodium.

**Lamivudine (3TC)**

Lamivudine (3TC) is an important component of the first-line regiment for antiretroviral treatment (ART). Although it is one of the oldest active pharmaceutical ingredients (APIs) of ART, it has maintained this position because it is effective, has few side effects, and is highly affordable. In some territories in SADC emtricitabine (FTC) is preferred to 3TC but comes at a slightly higher cost. The processes for manufacture of 3TC and FTC are quite different as is the cost of manufacture. The SADC study[25] focused on 3TC, as the total market demand for 3TC within the Southern African Development Countries (SADC) is expected to reach 600 tonnes per annum (Tpa) by the end of 2022, which is large by global standards and a significant portion of the total domestic active pharmaceutical ingredient (API) market.

[25] Bertoldi, A., Walwyn, D., Marais, S., Cloete, L, van Lieshout, B., Dean, G.N., & Stanco, R. (2020). SADC pharma pre-feasibility study, Prepared for the Southern African Development Community (SADC).

## Excipients

### Background

Excipients are the additives that are combined with the pharmacologically active substances in the formulation to give the final pharmaceutical products such as tablets or syrups. The main purpose of adding them is to increase the bulk of the formulation along with imparting desired properties.[26]
There are several excipients used in the final formulation of ARV FDFs as listed above. The following points were noted in the interviews with key excipient producers:

- Only two of the identified stakeholders manufacture excipients at a grade suitable for pharmaceutical use.
- None of the big companies exclusively focus on manufacturing excipients for ARV production.
- The smaller traders sell based on a specification and price and do not know the end-use of the products in detail.
- There are other multi-national companies that import, and trade chemicals (including excipients) produced by their principals at factories elsewhere in Asia and Europe.
- Many traders and sellers of food-grade excipients do not sell Pharma-grade excipients.
- In some cases, traders of food-grade excipients sell proprietary blends of pharmaceutical excipients, but these are all imported on-demand, and they do not manufacture any locally.

### Key Constraints

Excipients are manufactured by large commodity chemical companies, often as a more refined version for an existing bulk chemical. There are no dedicated excipient manufacturers in SADC, but some of the large commodity chemical companies could potentially produce these. However, in our interviews, it was found that even those do not manufacture excipients. In general, excipient suppliers will sell these products to a specific company but do not know the products end-use.

Given the lack of a strong ARV manufacturing value chain within the region, there is currently no incentive for the players in other parts of the value chain such as excipient manufacture and bottle/packaging operations to support ARV production as there is low revenue potential. Instead, players are opting to leave manufacturing and venturing into another segment of the value chain through exclusive marketing and distribution agreements with the Asian API producers.

In conclusion, there are no excipients produced in the SADC region for use in the ARV value chain exclusively.

[26] Mousumi Kar, Yashu Chourasiya, Rahul Maheshwari, Rakesh K. Tekade, Chapter 2 - Current Developments in Excipient Science: Implication of Quantitative Selection of Each Excipient in Product Development, Editor(s): Rakesh K. Tekade, In Advances in Pharmaceutical Product Development and Research, Basic Fundamentals of Drug Delivery, Academic Press, 2019, Pages 29-83,
ISBN 9780128179093, https://doi.org/10.1016/B978-0-12-817909-3.00002-9.

## Bottling and Packaging

**Background**

There are three types of packaging: primary, secondary, and tertiary. Each type of packaging has unique requirements, risks, and intended use.

***Primary packaging*** is designed to provide protection from excessive transmission of moisture or solvents into or out of the product, provide light protection for the product, provide additional microbiological protection by protecting the product from microbial intrusion, and provide protection from excessive transmission of reactive gases (atmospheric oxygen, inert headspace filler gas, or other organic vapours) into or out of the product. Examples of primary packaging include vials, syringes, ampules, stoppers, closures, bottles, pouches, and blisters.

The ISO standard, "15378:2017 Primary packaging materials for medicinal products — Particular requirements for the application of ISO 9001:2015, regarding good manufacturing practice (GMP)" specifies GMP principles in production and control of primary packaging materials and these are important for the safety of a patient receiving the medicinal product because of the direct contact between the packaging materials and the product.

***Secondary packaging****'s* main purpose is for branding display, logistical purposes, and protecting and collating individual units during storage. Secondary packaging also includes packaging purposely made to display multiple product units for sale, which speeds restocking from storeroom to shelf; this packaging includes retail-ready packaging, shelf-ready packaging, or countertop display units. Examples of secondary packaging include pouches, boxes, and trays.

***Tertiary packaging*** facilitates the protection, handling, and transportation of a series of sales units or secondary packages to group everything into unit loads during transit. This type of packaging is rarely seen by the consumer. Examples of tertiary packaging include boxes, totes, shrink wrap, and pallets.

Stakeholders indicated that they import all the packaging requirements but are open to procuring in SADC region if price and quality is acceptable. Several companies in the SADC region were identified that could supply the key stakeholders interviewed with bottling and packaging however it is uncertain if they comply with the cGMP requirements. A list of these companies can be found in Appendix C.

Companies like Avacare Health indicated their willingness to buy packaging from local suppliers provided the price and quality was favourable but admitted to currently importing all packaging from Mylan India.

**Key Constraints**

Although several suppliers could potentially supply local formulators with packaging materials, a general comment from the industry is that the price for local packaging material is often not competitive to imports from China and India and can sometimes be 2 to 5 times more expensive. In addition, they prefer procuring from suppliers that have the necessary quality systems, and often these are from their technology partners.

These findings suggest that local suppliers of packaging materials could supply ARV FDFs producers but need to get their pricing competitive and ensure compliance with regulatory requirements.

## Distribution

Many additional traders/distributors receive imported ARV FDFs from one of the donor agencies and then distribute it through the health system. Many other distributors serve the public and private

sector who import ARV FDFs from Asia and distribute these. As alluded to previously under excipient constraints, some market players are venturing into the later stages of the ARV value chain through exclusive marketing and distribution agreements with the larger API producers in Asia. Exclusive arrangements with these large Asian API producers in specific countries is one way to minimise competition from the very same players that provide the APIs however, competition with other distributors of products from other suppliers remain a concern.

ARV manufacturing activities in the SADC region are limited to formulation and packaging. ARV FDFs are only manufactured in South Africa and the largest producer stopped production in 2020. A key factor that contributes to the lack of ARV manufacturing in the region is the low margins on the FDFs and the reliance on imported ARV APIs as well as issues related to the public market where often payment terms are not favourable and tenders that are awarded do not always translate into sales of ARVs. Ultimately, most ARVs are imported and then supplied and distributed by donors.

## Country-by-country summary of manufacturing

When considering current ARV and general pharmaceutical manufacturing in SADC, it is not possible, overall, to group countries into some distinct categories, apart from a few exceptions. However, the following observations can be made, and conclusions can be drawn:

- **South Africa** This represents by far the largest SADC country in terms of the current public market (see figure 5), which with a value of $583M in 2019 represents approximately 80% of the total SADC public ARV market by existing sales. This fact, combined with South Africa's long-established pharmaceutical industry, leads to the current situation where this country is the single largest manufacturer of ARVs in SADC. Recently some ARV manufacturers have announced their intention to exit the public ARV market and devote their existing capacity to other products. A new SAHPRA approved API facility built in South Africa has ARV APIs in their pipeline but likely not the ones used in the first- and second-line regimens.

- **Zambia** has established pharmaceutical manufacturing, including at least the packaging of ARVs. In some of Zambia's facilities, full manufacturing of pharmaceuticals takes place, starting with API and raw materials and ending with a finished, fully packaged product. Whilst it is known that packaging-only activities for ARV's takes place in at least one facility (as mentioned above), it is not clear as to whether there is full manufacturing of ARVs by other companies.

- **Zimbabwe** has a long-established pharmaceutical manufacturing industry that includes full manufacturing operations. While there used to be full manufacturing of ARVs in the past, discussions with local companies have indicated all ARV production has ceased. There are, however, plans for one company to build a new facility that will devote roughly one-third of its capacity to the production of ARVs (packaging only, rather than full production). There is the potential that, if this operation proves successful, other ARV manufacturers may follow suit and set up similar packaging-only facilities in the country.

- **Mozambique** has established pharmaceutical manufacturing but does not presently manufacture ARVs. It is, however, in the process of a technology transfer that will localize

tabletting and packaging of ARVs. Whilst the public market is currently very low or non-existent, there is an expectation that the public market size will grow to the region of $5-10M in the near term.

- **Botswana** has packaging only operations as opposed to full manufacturing operations, including ARV packaging (although in one instance there is a facility designed for full production which has not been utilised). As with the case of Zambia, Zimbabwe and other countries, its public markets are significantly smaller than South Africa, but still attractive to local firms.

- **Namibia** also has packaging only operations in common with its neighbour Botswana. The plant in Namibia packages ARVs and the one in Botswana may include ARV packaging in the future.

- **Lesotho, eSwatini.** Lesotho and eSwatini have been reported to have sizable public tenders as is the case with Namibia. One company has also started the process of establishing a new fully-fledged ARV FDF facility in eSwatini through a subsidiary. This plant will do formulation and packaging of ARVs, with APIs and excipients obtained from their technology partner. This plant will also export to South Africa and Lesotho. It is also worth noting that Lesotho did in the past, have pharmaceutical packaging operations.

- **Angola, DRC.** From our interactions with stakeholders, it appears as if DRC and Angola only distribute ARVs (from donor funds) via local distributors. All indications are that DRC and Angola have relatively small public markets.

- **Malawi, Tanzania.** From a manufacturing perspective, these countries can be grouped in that there is currently no ARVs production in either of these countries although they do have several pharmaceutical manufacturers. In Tanzania, individual companies have moved away from ARV production, whilst it is not clear that ARVs were ever manufactured there. Tanzania and Malawi also largely only distribute ARVs (from donor funds) via local distributors.

- **Comoros**, **Madagascar, Mauritius, Seychelles.** The island states, which all fall at the lower end in terms of the overall population and HIV positive populations, do not have a straightforward business rationale to support local ARV manufacturing when considering national need alone. This viewpoint applies to the Seychelles, Comoros, Mauritius and Madagascar, which for the purposes of analysing this country-by-country manufacturing status could be considered as a common group. This does not mean that manufacturing is not feasible in such territories, but it indicates that local market need is not in itself sufficient to commercially justify ARV manufacturing. In such cases, any new manufacturing operations would need, from the outset to target exports and other products as a significant portion of their business. In such situations, it is unlikely that operations would be set up unless prioritised by the Government. It is worth noting that although a state-owned packaging plant was launched in 2020 in Madagascar, no ARV production is envisaged for now but in theory, would be possible in the future. There are also plans to install an API facility in Madagascar but not for ARV APIs.

In summary, the pharmaceutical manufacturing landscape in SADC is diverse, as outlined above. A detailed analysis of ARV manufacturing capacities will be conducted in the next section.
Given the manufacturer dynamics discussed in this chapter, where do potential opportunities lie? The following operational scenarios are all relevant, and take into account both existing manufacturers and development projects:

1. Existing companies manufacturing ARVs and looking to expand production
2. Existing companies currently not manufacturing ARVs but with the potential to move into the market
3. New facility development projects (specifically, those with the potential to deliver in the short-medium term) that are either targeting ARV production or may consider it.

Of these three scenarios, the first two - those where there is an existing manufacturing facility - are more likely to deliver significant near-term impact given that new facility development projects would typically take two to five years to reach full operation. This considers the fact that for a new build project it generally takes 2-3+ years to plan, build, equip, validate and initiate production.

Taking into account the presence of either existing industry and/or defined new pharmaceutical manufacturing projects, it is possible to develop a set of countries where the more promising opportunities exist - from a manufacturing perspective, in terms of the ability to impact and capture a greater proportion of the ARV value chain. Whilst this list is not exhaustive, it serves to highlight those countries with the clearest potential opportunities. These countries, which all fall into categories 1 and 2 above, are Mozambique, Zimbabwe, Zambia, Botswana, Namibia, Tanzania and Malawi, as well as South Africa.

This list is not exhaustive as it is not known whether manufacturing exists or not, or previously existed, in other countries. In addition, it may be the case that the governments of other countries have a particular interest in stimulating the emergence of a pharmaceutical manufacturer and this could also raise the relative potential of other territories. Therefore, other SADC countries, for instance, DRC, Angola, eSwatini and Lesotho may also be relevant however the opportunity needs to be more clearly defined and better understood in this third bracket.

In SADC most activities are in the distribution part of the value chain, with some packaging operations in South Africa, Zambia, Namibia and Botswana and FDF facilities in South Africa. Table 4 provides the country breakdown with regards to their current capabilities in the ARV value chain.

Table 4: SADC Country Capability in ARV Value Chain

| Country | Raw Materials | Pharmaceutical Intermediates | API manufacture | Excipient manufacture | Final dose formulation | Bottling and Packaging | Distribution |
|---|---|---|---|---|---|---|---|
| Angola | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 |
| Botswana | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 | 🟢 |
| Comoros | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 |
| DRC | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 |
| Eswatini | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 |
| Lesotho | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 |
| Madagascar | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 |
| Malawi | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 |
| Mauritius | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 |
| Mozambique | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 |
| Namibia | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 | 🟢 |
| Seychelles | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 |
| South Africa | 🟢 | 🔴 | 🔴 | 🟢 | 🟢 | 🟢 | 🟢 |
| Tanzania | 🔴 | 🔴 | 🔴 | 🔴 | ⚫ | ⚫ | 🟢 |
| Zambia | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 | 🟢 |
| Zimbabwe | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟢 |

Key: 🟢 =Yes 🔴 = No ⚫ = Unknown

## Intra-Regional Trade

Low intra-SADC trade has been highlighted as a general concern on several occasions and efforts should be made to address the situation. One of the reasons that intra-regional trade on ARVs is low is linked to our findings that very limited ARV manufacturing occurs in the region with most happening in South Africa, Namibia and Botswana. Differences in regulations and policies also hinder intra-regional ARV trade and most ARVs are imported from India by companies who then distribute them within Member States, often through subsidiaries in a specific country.

## Challenges

A **SADC Pre-Feasibility Study** concluded the following:[27]

- **There is a limited production of pharmaceutical products in the SADC region:** Current pharmaceutical manufacturing in the SADC region is limited and products utilised within the region are largely sourced from foreign locations, such as India and China.
- **Local production is inhibited by four main factors:**
    - **Political**: Current pharmaceutical initiatives in the SADC region such as pooled procurement and regulatory harmonization depend on strong political support in SADC Member States to be fully implemented. There is inadequate political commitment to a regional approach, in favour of domestic strategies.
    - **Economic**: Local ARV suppliers compete with Indian and Chinese suppliers of final dose formulations and rely on these same countries for imports of active pharmaceutical ingredients (APIs) and other raw materials. Manufacturers indicated that they are unable to compete on price with these Asian countries because their governments subsidise the labour and utilities needed for

[27] Bertoldi, A., Walwyn, D., Marais, S., Cloete, L, van Lieshout, B., Dean, G.N., & Stanco, R. (2020). SADC pharma pre-feasibility study, Prepared for the Southern African Development Community (SADC).

manufacturing. Another important economic obstacle is limited access to finance by local manufacturers.

- **Regulatory:** Regulation is a major stumbling block for prospective manufacturers, this includes registration of pharmaceutical products, the inexperience of local regulators, the need for WHO prequalification for supply to donors as well as the presence of a multitude of NMRAs that do not have a standardised approach across SADC.
- **Legal:** This includes parallel importation, insufficient counterfeit controls, contract enforcement and intellectual property protection laws, as well as corruption.

A variety of challenges exist for manufacturers working within SADC. Some of these are commonly experienced in the region and throughout Sub Saharan Africa as a whole, reflecting general issues facing pharmaceutical manufacturers and others are country specific. The challenges faced in the industry may also reflect a specific set of circumstances that are perennial or are only experienced at a certain point in time.
The following challenges are important to highlight and discuss:

1. **Manufacturing and operation-related**

**API.** This represents the biggest single cost of goods for ARV production. Manufacturers operating at WHO PQ standards face the added issue of having to source API from a suitably qualified supplier. Becoming somewhat tied to this supplier implies that they may face higher pricing on an ongoing basis as the cost and complexity of switching suppliers is a hurdle to competitive API sourcing.

Access can also be an issue for manufacturers requiring relatively small API qualities as the suppliers tend to favour clients that require larger orders.

**WHO Prequalification (WHO PQ).** Companies choosing to pursue WHO PQ, to access donor-funded tenders, need to both attain this standard and maintain it. Reaching WHO PQ is technically challenging, requires significant investment and typically takes significant time (minimally 2-3 years for the first product). The company must demonstrate the required standards across both its facility and its Quality Management Systems (QMS). A QMS also has cost implications and outsourcing of expertise may be required in some instances.

Maintaining WHO PQ requires ongoing investment. Taken together, there is a negative impact on COGS for companies operating at WHO PQ, reducing their profit margin. Consequentially while they can now apply for donor tenders, they become less competitive in local markets that do not require WHO PQ and their commercial strategy has to reflect this dynamic. Another challenge is that, even for companies reaching WHO PQ, there are no guarantees that they will be successful when applying for donor tenders (see Appendix D).

2. **Market and regulatory-related issues**

There are a variety of issues that can generally be grouped under this heading. These include:

**Changing drug regimens**. HIV treatment regimens change frequently as new products are developed, and different therapeutic drug combinations are recommended over time. The consequence of this is that companies often struggle to keep up with the current regimens, which is a particular issue for manufacturers working on donor tenders that require WHO PQ for each product or combination they wish to market. The current ARV regimens for a selection of SADC countries is shown in Figure 7. As can be seen, there is a wide range in both first-line treatments and second-line treatments across the countries. This fact, combined with the frequent regimen changes, complicates manufacturing planning and necessitates frequent new product development as purchasers change their requirements to meet updated ARV guidelines.

Table 5: Current ARV drug regimens for a range of SADC countries[28].

| Country | First Line: Adults and Adolescent | First Line: Children |
|---|---|---|
| **Botswana** | TVD + DTG | ABC + 3TC + EFV |
| **Eswatini** | TLD (TDF + 3TC + DTG) | 1. ABC + 3TC + LPV-r(< 3 yrs)<br>2. ABC + 3TC + EFV(3 <10 yrs) |
| **Lesotho** | TDF + 3TC + EFV | ABC + 3TC + EFV |
| **Namibia** | TDF(or TAF) + 3TC<br>(or FTC)+DTG | ABC + 3TC + DTG |
| **South Africa** | TLD (TDF + 3TC + DTG) | ABC + 3TC + DTG<br>(weight>35 kg) |
| **Zambia** | TDF (or TAFc ) + XTCd + DTGe | ABC + 3TC + LPV-r |
| **Zimbabwe** | TAF + 3TC + DTG | 2 NRTI + LPV-r |

**KEY - ARV Drug Acronyms**

| | |
|---|---|
| 3TC | lamivudine |
| ABC | abacavir |
| DTG | dolutegravir |
| EFV | efavirenz |
| FTC | emtricitabine |
| LPV | lopinavir |
| NRTI | nucleoside reverse transcriptase inhibitor |
| TAF | tenofovir alafenamide |
| TDF | tenofovir disoproxil fumarate |
| TLD | tenofovir + lamivudine + dolutegravir |
| TVD | Truvada (TDF + FTC) |
| XTC | 3TC or FTC |

[28] See SADC Secretariat.

**Regulatory-related challenges.** The lack of regulatory harmonisation across SADC has resulted in fragmented markets which makes entry into new territories time-consuming and complex, in terms of both a manufacturer receiving marketing authorisation and individual product registration.

**Lack of reliable, comprehensive market data**. Across Sub-Saharan Africa as a whole, and within SADC, there is a lack of reliable, comprehensive market data. This impacts manufacturers in several ways:

- Manufacturers cannot easily develop their market strategy and production plans.
- Manufacturers may miss out on market opportunities as they can be difficult to identify.
- Investors cannot easily understand the market opportunities that exist, making it less likely that they will support the local pharmaceutical industry.
- Potential partners may be less likely to form collaborations - for instance, product and technology transfer - since the market opportunities of doing so are not well understood and laid out.

In addition, Government and other procurement bodies face planning challenges as they may not have accurate market data to work with. The degree that this issue is present varies across SADC. For instance, there is generally good market information for South Africa. One other positive, when considering the ARV market when compared to other disease and therapeutic areas, is that the HIV market in its entirety is better served by international organisations meaning that, on average, it is more likely that HIV-related data can be obtained for a particular territory from these organisations. There is, however, still a strong case to improve market information in SADC.

### 3. Policy, Government-related and financial

Several challenges were identified that relate, directly or indirectly, to national and regional policymaking, and/or other Government-related interventions. These are discussed in the following section.

**Long payment cycles**. Manufacturers that conduct much of their business with national public procurement bodies, namely Ministries of Health, Central Medical Stores and comparable entities are particularly at risk of cash flow issues resulting from long payment cycles. This is a commonly faced challenge in many territories.

**Other payment or tender-related issues**. There are isolated examples of manufacturers in SADC reporting significantly longer delays, one example being a case of a company indicating that it is awaiting payment of over $30M for ARV deliveries made to a public procurement body over 2 years. There are also examples of tenders being awarded to local manufacturers but then not being followed up with actual order placements. Although this was only highlighted in one territory, it also represents an example of counterproductive practices that hinder local manufacturing. Further examples of challenges relating to tender execution include an extended legal dispute in one SADC country over the awarding of a recent tender. In this case, there was significant disruption to the orders as compared to the schedule set out in the tender, which may also impact the next tender cycle. Lastly, in another SADC country, there are allegations that a local manufacturer who won a tender on the premise that the product was produced locally, is importing the product fully finished. It is important to state that none of the above alleged tender issues has been fully examined therefore the details

remain to be established, but these examples serve to illustrate the potential complexities when working with the public sector, in particular.

**Need for Incentives.** It is generally accepted that, to stimulate the growth and development of local pharmaceutical manufacturing, governments may need to put incentive packages in place. The types of incentives used vary from country to country and may take the form of financial and non-financial instruments. When considering this approach, it is important to understand (a) whether incentives exist and (b) whether they are correctly implemented. Manufacturers in SADC indicated a general need to review the incentives in place since in some cases there was an apparent lack of incentives in operation and in others it was reported that they were not fully utilised by governments. A common incentive widely used in Sub-Saharan Africa and elsewhere is local price preference. This typically takes the form of a 10-20% premium paid to a local manufacturer above the price that would be paid to a manufacturer operating outside of the country in question. The use of this policy varies within SADC and was one of the most widely requested incentives by local manufacturers in the region. There are also examples of manufacturers indicating that in certain countries in SADC such a policy exists, but it is not in effect.

Table 6: Price preference reported for locally manufactured pharmaceutical products, for selected SADC countries.

| Country | Price preference reported[a] |
|---|---|
| Botswana | 15%[b] |
| Mozambique | 25% |
| Tanzania | 15% |
| Zambia | 15-20% |
| Zimbabwe | Up to 30[c]% |

[a] Percentages represent figures indicated by manufacturers and were not verified with the relevant Ministry of Industry/Trade

[b] Reported that whilst this preference is allowable under the relevant Government policies, in practice, it is not utilised

[c] The figure of up to 30% applies to Zimbabwe-based manufacturers where the product has 30% or more local content

Incentives are particularly important when considering WHO PQ and the additional costs associated with manufacturing at this standard and will be discussed in more detail in Chapter 5.

**Lack of flexible and affordable financing arrangements.** Despite the emphasis on stimulating production in the pharmaceutical sector, more still needs to be done to that effect. Along with other sectors such as agriculture and mining, financial packages or loans can be availed to pharmaceutical companies at preferential rates given the amount of investment required to either set up, expand or upgrade operations to meet the required specifications.

**Exchange rate related financial issues.** This is not an issue in countries with relatively stable currencies but causes significant financial challenges in territories where there is either a sudden weakness or volatility in its exchange rate or where there is a general weakness in the currency due to longer-term economic issues. In these instances, and, where there is an ongoing decline in the value of a currency

versus the world markets, manufacturers relying on public tenders can face severe economic difficulties. This is because API and other imported raw materials are charged in US dollars or an equivalent major currency whereas the finished product is billed in the local currency. In this instance, and especially when there are long government payment cycles, the profit margin on the product can be wiped out by the loss in value of the local currency by the time that the goods are paid for. This is less of an issue for manufacturers in countries that conduct most of their business with donors or export most of their products as, in these instances, both raw materials and finished goods are charged in a major currency.

## Impact of the Covid-19 pandemic

A few companies have indicated that there have been delays in upgrade projects and facility audits due to the inability of consultants and auditors to travel during the pandemic. In Namibia and Botswana some companies have reported being forced to stop operations due to economic challenges mainly caused by the pandemic, a situation which most likely also occurred in other SADC Member States. One company has also stated that they have stopped work on their project to start producing ARVs to focus on the production of Covid related hygiene materials. Lastly, in Botswana, the need for close coordination between the pharmaceutical manufacturers there and the government on supply needs has improved communication between them.

## Key findings

An over-arching finding thus far is that many manufacturers have "closed shop" and exited the ARV manufacturing space as a result of a combination of the above-highlighted challenges. In summary:

***Reasons for exit by ARV manufacturers:*** Some ARV manufacturers have exited or started exiting manufacturing operations. The reasons for this exit are summarised below:

- The profit margins of production are too low. APIs contribute 65% to 80% of the cost of ARV FDFs and generic companies (the ones listed below and who manufacture mostly in India) control this value chain and are therefore able to out-compete in local ARV tenders (on price). Those local companies that were successful in any SADC tenders all have supply agreements in place with these main suppliers of APIs from India and often import the final FDFs and package or distribute these locally.
- Some of the countries have low rates of HIV/AIDS and as a result, few individuals are on or seeking treatment and other countries are already receiving these drugs from donors (see Appendix A). There seems to be no value in them pursuing the local production of ARVs.
- The largely public market for ARVs requires substantial cash flow as payment terms from largely public tenders are not favourable and often lengthy delays are experienced in getting paid for ARV batches delivered. Many smaller companies do not have the necessary working capital to support this do not enter this market.
- WHO prequalification (PQ), another requirement by many of the public donors, is a lengthy and costly process which has resulted in certain ARV manufacturers exiting the market and prevented others from entering the market.

Existing pharmaceutical manufacturing companies in some cases are state-owned and require additional investment to meet WHO PQ criteria. Additionally, there are some skills gaps to support a

pharmaceutical manufacturing industry and local markets are too small to justify ARV manufacture. Due to the general economic situation in countries with high HIV prevalence, there is a heavy reliance on donors for supply of ARVs.

The condition in the sector is summarised using the technological innovation systems[29] (TIS) framework in Table 7.

Table 7: ARV Technological System of Innovation status summary

| Function | Status |
|---|---|
| **Resource mobilization** | Lack of adequate state or private financing in most SADC countries except for richer countries such as South Africa, Mauritius, Botswana and Namibia. |
| **Market formation** | The ARV market in countries with high HIV prevalence is dominated by the state in richer countries such as South Africa and by donors in poorer countries. State procurement is seen as bureaucratic by private sector manufacturers who feel they cannot rely on government orders on a low margin business that requires significant capital outlays and relatively high skilled labour. Government payment terms are not favourable and tenders that are awarded don't always translate into orders for ARVs.<br>Donors require WHO prequalification which is onerous for manufacturers in poorer countries.<br>The SADC market remains fragmented despite agreements on pooled procurement in SADC which has not yet come to fruition.<br>Both donor and government buyers buy at the lowest cost which is difficult for local suppliers to attain given incumbent suppliers' market position, access to inputs (such as raw materials and APIs) and sunk capital cost. |
| **Influence on the direction of search** | No country or region strategy for the development of the sector<br>Lack of coordination between ministries of health, trade and industry and foreign affairs. |
| **Entrepreneurial experimentation** | Limited entrepreneurial activity in the sector in most countries on value-added portions of the value chain. Entrepreneurial activity is focused on imports, packaging and distribution. |
| **Formation of social capital** | Lack of national or regional industry bodies.<br>Few cases of industry cluster formation.<br>Weak regional integration. |
| **Legitimation** | Varying levels of regulatory ability across SADC.<br>Some progress towards regional regulatory harmonisation. |
| **Knowledge development and diffusion** | Pockets of excellence in richer countries but very low capability levels in poorer countries.<br>Low levels of industrialisation in most SADC countries |

The above has left the SADC region with very few manufacturers in the ARV value chain, with some larger players exiting this market for more lucrative alternatives, and instead, we see an increase of local traders/distributors importing final packaged ARV FDFs from the main ARV API producers.

## Next Steps

The 2020 pre-feasibility study[30] found several avenues to explore potential local manufacture in the SADC region, for this study, the following avenue is of particular significance:

[29] Markard, J. and Truffer, B., 2008. Technological innovation systems and the multi-level perspective: Towards an integrated framework. Research policy, 37(4), pp.596-615.

[30] Bertoldi, A., Walwyn, D., Marais, S., Cloete, L, van Lieshout, B., Dean, G.N., & Stanco, R. (2020). SADC pharma pre-feasibility study, Prepared for the Southern African Development Community (SADC).

- *Introduce incentives or subsidies: Various governments in other parts of the continent (e.g. Ethiopia) are attracting pharmaceutical manufacturing development, by offering incentive schemes such as tax breaks, duty-free capital goods, grants and interest-free loans. Subsidies either in the form of a production subsidy (input), or price subsidy (premium), can also help spur local manufacture or the loss of it. An example of this is the story of Varichem Pharmaceuticals from Zimbabwe. They used to produce ARVs as FDFs but have stopped manufacture due to competition from Indian suppliers. The introduction of incentives or subsidies might have made it possible to keep this production local.* [31]

The companies that do partake in ARV manufacturing identified the following as potential incentives to encourage a possible increase in manufacturing of ARVs in the region:

- **Guaranteed Take-off Agreements**: Installation of manufacturing capacity requires substantial capital investment. Currently, such an investment is very high risk and coupled with long time frames to obtain cGMP and/or WHO PQ, which means new entrants must have "deep pockets" to support the company before any take-off or tenders are secured.
- **Adjusting payment terms**: tenders have very stringent payment policies. The payments are made after the fact. A potential suggestion is for an up-front payment to be made to ensure that the company can set-up and procure what is needed or in the very least for payment to be made under normal terms – some public agencies take up to 6 months to pay suppliers after taking delivery of stock. Often after a tender is awarded, governments do not place orders immediately sometimes delaying by years resulting in capacity that was purpose-built or reserved for ARV production lying idle.
- **Increased government support**: Changes in the policy environment that incentivises local procurement of ARVs may additionally incentivise new entrants or may encourage those who have decided to leave the ARV game to reconsider.

[31] Ibid

# 5. HUMAN RESOURCES IN THE PHARMACEUTICAL SECTOR

In Chapter 4, a detailed analysis of the countries in SADC with promising opportunities in ARV manufacturing was discussed. This chapter explains the training opportunities for pharmaceutical production processes in the SADC region. The region's readiness for intra-regional trade in services for human resources for health (HRH) - including pharmaceutical personnel in this context - and mutual recognition of professional health qualifications achieved within SADC member states is also discussed.

## Academic & TVET contributions to pharmaceutical manufacturing

For locally produced ARVs to meet international standards, certified production facilities and highly qualified personnel are required. Pharmacists, pharmaceutical assistances, pharmaceutical technicians, and related occupations are all classified as skilled pharmaceutical personnel. Skilled pharmaceutical personnel are essential for developing the pharmaceutical value chain, as a result, the availability and ease of movement for these skilled personnel within the region are essential.[32]
The following academic programmes were identified as relevant to the manufacturing process:

Table 8: Academic programmes required by SADC ARV Manufacturing companies.

| Manufacturing Process | Desired Skills Requirements |
|---|---|
| API Production | Chemical Engineers, M. Chem, M. Pharm |
| Formulation / Granulation (Liquids & Solids) | Chemical Engineers, M. Chem, M. Pharm |
| Tabletting / Capsulating / Filling | B. Pharm (Production Pharmacist)[a], B. Eng (Technical Operators)[a], Post-basic Pharmacist Assistant[b] |
| Packaging | B. Pharm (Production Pharmacist)[a], B. Eng (Technical Operators)[a], Post-basic Pharmacist Assistant[b] |
| In-Process Controls / Release (Quality Control) | B. Sc Microbiology[a], M. Sc Microbiology, B. Sc Biotechnology[a], M. Sc Biotechnology, B. Sc Chemistry[a], M. Sc Chemistry |
| Final Release (Quality Control) | B. Sc Microbiology[a], M. Sc Microbiology, B. Sc Biotechnology[a], M. Sc Biotechnology, B. Sc Chemistry[a], M. Sc Chemistry |
| Regulatory Affairs: Pharmacovigilance, Product Dossier Composition, Stringent Regulatory Agencies, Drug-Safety Reporting | B. Pharm[a], M. Pharm |

[a]Must have completed a four-year honours degree with in-service training/internship.
[b]Must have experience in a pharmaceutical manufacturing environment (Usually only a supporting role)

[32] See Azariah, Simon; Kiplangat-Ronoh, Wesley; Mckinnon, Malcom and Viola Sawere: "A Study on Member State's Regulatory Regimes in Health & Related Social Services for the SADC Trade in Services Negotiations. 2021.

Table 8 shows the different types of academic qualifications relevant to pharmaceutical manufacturing. To attain the required level of skills, the manufacturing personnel must have the prerequisite tertiary education at bachelor's and master's degree level with a speciality in pharmacy, chemistry or biotechnology. Vocational courses mainly play a supporting role in the manufacturing process and the main qualification under this section is the Pharmacist Assistant.

The National Qualifications Framework (NQF) has been used to compare the vocational qualifications and university degrees from different countries based on learning outcomes, knowledge, skill and competence. Using the framework, the various certificates and degrees that exist in a country are assigned to internationally comparable levels. The NQF is referenced in SADC countries and serves as a guideline for the classification and comparison of the various qualifications. It is valid worldwide and is also actively used in Southern Africa, especially in South Africa[33].

The degrees and certificates identified in Table 9 that are relevant for education and training for the pharmaceutical manufacturing process can be assigned to the following NQF levels[34]:

Table 9:NQF-Levels

| Qualification | NQF-Level | Institution |
|---|---|---|
| National Certificate / Professional Qualification | 4 | TVET-College |
| Higher Certificate | 5 | TVET-College |
| Diploma & Advanced Certificate | 6 | TVET-College, also University in some countries |
| Bachelor's Degree & Advanced Diploma | 7 | University |
| Bachelor Honours Degree & Postgraduate Diploma | 8 | University |
| Master's Degree | 9 | University |

## Study and training programmes in SADC region[35]

All SADC countries have established universities that offer a variety of study programmes that are relevant to the pharmaceutical manufacturing process[36]. However, pharmacy training is quite recent at universities and was only introduced at the beginning of this century, even at long-established institutions such as the University of Dar es Salaam, Tanzania. Although the university was founded in 1970, the pharmaceutical course is currently only being launched. This gives a reflection of the infancy of pharmaceutical training in the SADC region. Pharmaceutical academic programmes at universities were introduced to counteract the existing shortage of qualified pharmaceutical personnel in the

[33] See https://www.saqa.org.za/.
[34] See https://www.saqa.org.za/; for an easy-to-understand overview table, see also: https://www.fundi.co.za/fundiconnect/nqf-levels-whats-that-stuff-about/.
[35] See appendix for details.
[36] See Table 8.

healthcare sector relative to the population. This explains the predominant orientation of these programmes towards hospital pharmacy and community health.

In the SADC countries, TVET programmes at NQF-level 4 to 6 are offered mainly at TVET- colleges. Training at NQF-level 4-to become a pharmacist assistant not available in all SADC countries. In some countries, pharmacist technologists (NQF levels 5 and 6) are trained at the diploma level at TVET-colleges or, in some cases, universities.

**Academic and Vocational Education and Training at a Country Level**

The following analysis focuses on the countries identified in Chapter 4 as being potential ARV manufacturers within the SADC region. The information is limited to those countries where verified data by trusted sources were available.

**Botswana**

In Botswana, programmes relevant to pharmaceutical manufacturing are offered at the following institutions:

Table 10: Study and training programmes in Botswana[37]

| Institution | Degree |
|---|---|
| University of Botswana, Gaborone[a] | B Pharm<br>BSc Chemistry<br>BSc in Mechanical Engineering<br>MSc Chemistry<br>MSc Applied Microbiology<br>MPhil in Biomedical Sciences<br>MSc in Mechanical Engineering |
| Institute of Health Sciences[b], (affiliated with the University of Botswana), Gaborone | Higher National Diploma in Pharmacy Technology |
| Boitekanelo College[b] (private) | Pharmacy Technician |

a: University programmes; b: TVET programmes

As Table 10 shows, the University of Botswana offers the relevant university programmes except for Pharmacy at MSc level, Biotechnology and Microbiology at BSc level and Chemical Engineering. The focus of pharmacy training is the Bachelor of Pharmacy which has four years of full-time study and a training capacity of 33 students/year. The BSc Chemistry and the BSc in Mechanical Engineering also have large student capacities (52/year and 75/year respectively).

The Institute of Health Sciences and the Boitekanelo College both offer pharmacy training at diploma level with a training capacity of 30 students/year for the Institute of Health Sciences and 35-40 students/year for the Boitekanelo College. According to the Institute of Health Sciences, there is no training for Pharmacist Assistants in Botswana.

**Namibia**

In Namibia, programmes relevant to pharmaceutical manufacturing are offered at the following institutions:

[37] For details see appendix E.

Table 11: Study and training programmes in Namibia[38]

| Institution | Degree |
|---|---|
| University of Namibia (UNAM)[a], Windhoek | B Pharm Hons<br>B Hons Medicinal Chemistry<br>BSc Hons Microbiology<br>BSc Hons Mechanical Engineering<br>MPharm Clinical Pharmacy<br>MPharm Pharmaceutical Chemistry<br>MPharm Industrial Pharmacy (planned)<br>MSc Chemistry<br>MSc Microbiology |
| UNAM Faculty of Health Sciences – School of Pharmacy[b] (for NQF level 6) | Pharmacist Technologist |
| Welwitcha Health Training Center[b], Windhoek | Pharmacist Assistant |
| The International University of Management[b] (in cooperation with the Pharmaceutical Society of Namibia), Windhoek | Pharmacist Assistant |

a: University programmes; b: TVET programmes

At the TVET level, the School of Pharmacy at the University of Namibia offers training for Pharmacist Technologists at diploma level with a training capacity of 30 students/year. The two TVET colleges mentioned above offer Pharmacist Assistant training.

**Tanzania**

**Study and training programmes**

In Tanzania, programmes relevant to pharmaceutical manufacturing are offered at the following institutions:

Table 12:Study and training programmes in Tanzania[38]

| Institution | Degree |
|---|---|
| Muhimbili University of Health and Allied Sciences, (MUHAS)[a], Dar es Salaam | BSc of Pharmacy<br>BSc of Biomedical Engineering<br>BSc of Clinical Chemistry<br>BSc of Medical Laboratory Sciences<br>MPharm Industrial Pharmacy<br>MPharm Pharmaceutical Microbiology<br>MPharm Quality Assurance / Quality Control<br>Master of Medicine Microbiology and Immunology<br>MSc Biochemistry |
| University of Dar es Saalam, Dar es Saalam[a] | BSc Mechanical Engineering<br>BSc of Chemistry<br>BSc of Applied Microbiology and Chemistry<br>BSc in Microbiology<br>BSc in Molecular Biology and Biotechnology<br>MSc in Chemistry<br>MSc in Biochemistry |
| Kilimanjaro School of Pharmacy (KSP), Moshi[b] | Basic Technician Certificate in Pharmaceutical Sciences<br>Technician Certificate in Pharmaceutical Sciences<br>Ordinary Diploma in Pharmaceutical Sciences |

a: University programmes; b: TVET programmes

[38] For details see appendix E.

According to the data, the Muhimbili University offers degree programmes in Pharmacy, Clinical Chemistry and Medicine Microbiology and the University of Dar es Salaam offers programmes in Mechanical Engineering, Chemistry and Microbiology. The study capacities are 60-80 students/year at the Bachelor's level in Pharmacy with a study duration of four years, and 5-10 students/year at the Master's level in Pharmacy. The following specialisations offered at the Master's level could be of interest to the pharmaceutical industry: Industrial Pharmacy, Pharmaceutical Microbiology and Quality Assurance. The training capacities at the University of Dar es Salaam in Chemistry and Microbiology study programmes are also considerable, with 60 students/year each at Bachelor's level and 20 at Master's level. Chemical Engineering and Biotechnology, as well as Mechanical Engineering at Master's level, are not offered at all.

At the TVET level, the Kilimanjaro School of Pharmacy (KSP) offers three different courses, which are designed to build on each other, the courses have a one-year duration. The lowest level is the Basic Technician Certificate, followed by the Technician Certificate and the Diploma level. A total of 100 – 150 students/year are trained across all three courses. It should be noted that the KSP has an industrial pharmacy teaching unit which has a pilot plant that is used only for training purposes.

**Zambia**

**Study and training programmes**

In Zambia, programmes relevant to pharmaceutical manufacturing are offered at the following institutions:

Table 13: Study and training programmes in Zambia[39]

| Institution | Degree |
|---|---|
| University of Zambia, Lusaka[a] | BSc of Pharmacy<br>BSc of Biomedical Sciences<br>BSc in Chemistry<br>BSc in Microbiology<br>BSc of Mechanical Engineering<br>MSc of Clinical Pharmacy<br>MSc in Clinical Pharmacology & Nutrition<br>MSc in Pharmaceutics (Pharmaceutical Technology)<br>MSc in Pharmacognosy<br>MSc in Pharmacy Practice<br>MSc in Pharmaceutical Chemistry<br>MSc in Industrial Pharmacy<br>MSc in Medical Microbiology<br>MSc in Pharmacology<br>MSC in Biochemistry<br>MSc in Medical Microbiology<br>MSc in Applied Microbiology<br>MSc in Chemistry<br>MSc in Electrical Power Systems |
| Copperbelt University, Kitwe[a] | BSc In Biotechnology<br>B.Eng. in Chemical Engineering<br>MSc in Biotechnology<br>MSc in Chemical Engineering |
| Evelyn Hone College, Lusaka[b] | Pharmacist Technologist |

a: University programmes; b: TVET programmes

[39] For details see appendix E.

Table 13 shows that all relevant university courses are offered at the University of Zambia, except for Chemical Engineering and Biotechnology, which are offered at the Copperbelt University. With regards to pharmacy training, a five-year bachelor's degree with an annual enrolment of 65-90 students is offered as well as various specialised master's degrees with about 5 students per programme per year. A new Master's in Industrial Pharmacy will be offered from September 2021 with a capacity of 20 students, in line with the plans to expand teaching more in the direction of industrial pharmacy. The Department of Pharmacy is part of the School of Health Sciences and there are plans to develop it to a School of Pharmacy.

The capacity of other relevant courses at the bachelor's level is considerable, with 50 students/year for Biomedical Sciences, 90 – 100 students/year for Mechanical Engineering and 40 students/year each for Biotechnology and Chemical Engineering. At the master's level, the study capacity for the relevant specialised programmes is five students per programme per year.

At the TVET level, the Evelyn Hone College offers diploma-level training in Pharmacist Technologist with a training capacity of 120 students/year. Pharmacist Assistant training could not be identified in Zambia.

**Zimbabwe**

**Study and training programmes**

In Zimbabwe, degree programmes relevant to pharmaceutical manufacturing are offered by the following institutions[40]:

Table 14: Study and training programmes in Zimbabwe

| Institution | Degree |
|---|---|
| University of Zimbabwe, Harare[a] | BSc Honours Pharmacy<br>BSc Honours Drug Discovery and Therapeutics<br>BSc Honours Biomedical Sciences<br>BSC Honours Biomedical Engineering<br>BSc Honours in Chemistry<br>BSc Honours in Industrial Chemistry<br>BSc Honours Biotechnology and Biochemistry<br>BSc Honours Chemical Engineering<br>BSc Honours Mechanical Engineering<br>MSc Biomedical Engineering<br>MSc Medical Microbiology<br>MSc in Analytical Chemistry<br>MSc Industrial and Environmental Biotechnology<br>MSc in Biotechnology |
| Harare Institute of Technology, Harare[a] | B. Tech (Hons) Pharmaceutical Technology |

a: University programmes; b: TVET programmes

Table 14 shows that all the required degree level study programmes are offered at the University of Zimbabwe. The Harare Institute of Technology was originally established in the 1980s as a National Vocational Training Centre, but now offers undergraduate degree programme, i.e. a B. Tech (Hons) in Pharmaceutical Technology.

[40] For details see appendix E

## Private Sector Associations

In many countries and especially in those where Technical and Vocational Education and Training are organised in the apprenticeship system, the private sector plays an important role in TVET, on the one hand by providing apprenticeship-places for vocational training and internships for university graduates. In addition, many professional associations offer training or are active in the development of guidelines, for example. More clarity is needed in the role played by the private sector in SADC-countries in strengthening the training of qualified personnel at all levels for the manufacturing process and how best it can be maximized.

Manufacturers in the African pharmaceutical industry are represented by the Federation of African Pharmaceutical Manufacturers Associations (FAPMA), which in turn is divided into regional groups, such as the Southern African Generic Medicines Association (SAGMA) for most of the SADC countries. However, these supranational associations are not represented at the national level, which means that associations of the pharmaceutical industry at the country level hardly exist. With the exception of Zambia's Association of Manufacturers, (ZAM) which includes a pharmaceutical subsector[41], associations of pharmaceutical manufacturers at the country level could not be identified in SADC countries. SAGMA members consist of individual pharmaceutical companies and, depending on the country, of Professional Associations, i.e., the pharmaceutical societies which represent the pharmacists from all fields of practice.[42] These pharmaceutical societies can only be partially considered as genuine representatives of the pharmaceutical industry as most pharmaceutical societies focus on community and health pharmacy, with less emphasis on other aspects of pharmacy such as academia and industry. The Pharmaceutical Society of Namibia is an exception in that it is active in the field of training at the TVET level by offering a Pharmacist Assistant training course together with the International University of Management.

## Key findings

The research has identified the various training programmes relevant to pharmaceutical manufacturing or ARV production in the SADC region. With such knowledge, appropriate interventions towards increasing the skills and expertise required for ARV production will be designed and implemented. The training capacities at bachelor's level for all the pharmaceutical training in all the countries studied are substantial and vary between 30 and 90 students per year per programme. The same applies to the other bachelor's programmes identified as relevant, where the numbers range between 30 and 100 students per year per programme based on available data.

For more specialised training at the master's level, only a few students are usually trained per year and per programme in contrast to the bachelor's level. This applies to both pharmacy including its various specialisations, with 2 to 10 students per year per programme (except for one programme in Industrial Pharmacy planned for 20 students), and to other master's programmes, with 5 to 20 students per year per programme. However, the master's level is indispensable for certain sub-steps of pharmaceutical production, therefore corresponding training capacities would have to be created.

[41] See http://zam.co.zm/, based on mail from ZAM-secretariat.

[42] Based on interview with SAGMA secretariat.

The conditions under which these capacities could be increased would have to be investigated in more detail.

Larger training capacities are also provided at the TVET level, with 30 to 150 students per year per programme. Just like the university level, the focus of these TVET programmes is on community health training. It would therefore have to be evaluated in more detail the extent to which the existing training programmes for Pharmacist Assistants or Pharmacist Technologists meet the needs of pharmaceutical production and if adaptation is necessary.

The previous focus of the pharmaceutical departments of almost all universities mentioned above on Hospital Pharmacy and Community Health Pharmacy is currently being expanded at some universities to include a programme in Industrial Pharmacy. This offers great potential for the qualification of local personnel for the pharmaceutical sector and can be seen as promising for the planned strengthening of ARV production in the SADC countries.

In summary, the prerequisites for qualified training for the pharmaceutical industry are present in all the countries studied, although not to the same extent. However, the focus is mainly on community and hospital pharmacy practice. In addition to the existing programme for Industrial Pharmacy in Tanzania, the launch of the new master's programmes for Industrial Pharmacy in Zambia and Pharmaceutical Chemistry in Namibia offer the opportunity to tailor the training programmes to the needs of the pharmaceutical industry, specifically the ARV manufacturing process. This builds a good foundation for strengthening SADC's pharmaceutical industry.

## SADC Intra-Regional Trade in Services of Skilled Health Care Workers

In addition to having the necessary training, access to personnel with the required skillset may be realised through intra-regional trade in services of healthcare workers including pharmaceutical personnel. The following sections delve into the policies around regional skills trade and offer a pharmaceutical industry perspective for pharmaceutical personnel.

### Policies and National Plans

In August 2012, the SADC Heads of States and Governments signed the Protocol on Trade in Services (PTIS), which aims to promote the transformation and sustainability of Member State (MS) economies, as well as to assist in the creation of employment opportunities. The PTIS provides opportunities for the MSs to collaborate in agreement to facilitate international trade in services by mutual recognition of professional health qualifications obtained or achieved in one country for practice in another country. As a result of this PTIS initiative, the SADC Pharmaceutical Business Plan 2015-2019 has identified the need to support and retain human resources as critical for the sector (the plan is currently under review).

After the 2015-2019 SADC Pharmaceutical Business Plan, the SADC Health Workforce Strategic Plan 2020-2030 identified a chronic shortage of skilled health workers across the region. In addition to this, healthcare sector is burdened by poor utilisation of the existing workforce and a combination of these factors pose challenges to equitable access to healthcare in SADC MSs.

Substantial improvements are still needed to enable these health systems to adequately meet the health needs of their populations as these health systems are generally, with a few exceptions, well below international standards.

Thus, the noteworthy initiatives in the pursuit of developing the SADC health workforce are;

- the Protocol on Trade in Services (PTIS),
- the SADC Pharmaceutical Business Plan 2015-2019, and
- the SADC Health Workforce Strategic Plan 2020-2030.

The supply of human resources for health (HRH) remains continually deficient in both the numbers and types of health personnel needed. Countries like Namibia and Zambia send students abroad to receive medical education, where up to 85% of the students are funded through the respective governments. Certain MSs have reported that training facilities are growing with the support of the private sector, mission and donor organisations.

The current state of development in SADC MSs can be explained using the Human Development Index (HDI), which is represented in Table 15 below. In addition, the current state of submission of instruments of ratification for PTIS by the MSs is also presented.

Table 15: SADC MSs with respect to status PTIS ratification and HDI[43]

| SADC Member States | PTIS Instruments of Ratification | | Ranking in HDI (2019)[2] |
|---|---|---|---|
| | Submitted | Not submitted | |
| 1. Angola | | X | 0.581 |
| 2. Botswana | X | | 0.735 |
| 3. Comoros | | X | 0.554 |
| 4. Dem Rep of Congo | | X | 0.480 |
| 5. Eswatini | X | | 0.611 |
| 6. Lesotho | X | | 0.527 |
| 7. Madagascar | | X | 0.528 |
| 8. Malawi | | X | 0.483 |
| 9. Mauritius | X | | 0.804 |
| 10. Mozambique | X | | 0.456 |
| 11. Namibia | X | | 0.646 |
| 12. Seychelles | X | | 0.796 |
| 13. South Africa | X | | 0.709 |
| 14. United Republic of Tanzania | | X | 0.529 |
| 15. Zambia | X | | 0.584 |
| 16. Zimbabwe | | X | 0.571 |

Colour coding in HDI column reflects ranking: Red – low; Yellow – medium; Light Green – high; Dark Green – very high

As a result of MSs not depositing instruments of ratification, PTIS is yet to enter into force. PTIS requires at least two-thirds of SADC MSs to deposit instruments of ratification to become enforceable.

[43] See Azariah, Simon; Kiplangat-Ronoh, Wesley; Mckinnon, Malcom and Viola Sawere: "A Study on Member State's Regulatory Regimes in Health & Related Social Services for the SADC Trade in Services Negotiations. 2021.

Currently, the submitted instruments of ratification are from SACU member states and Mauritius, Mozambique, Seychelles, Tanzania and Zambia.

### Regulatory requirements

Compared to public sectors in certain MSs, the private sectors employ more HRH than the public sectors, even though the public sector is the major provider of healthcare services. The private sector accounts for a fraction of the total healthcare workforce. Most SADC MSs have existing legal and regulatory frameworks for HRH, although certain MS have more stringent frameworks. These regulatory frameworks are compulsory to both public and private sectors and are implemented by the following categories of health sector regulators:

- Health Professional Councils
  - (i) Medical and Dental Councils
  - (ii) Nurses and Midwives Councils
- Allied Health Professional Councils
- Pharmacy Boards

SADC MSs have specific requirements for licensing of health professionals, but the following constitute the basic minimum in all countries;

- The authenticity of the qualification/certificates
- The training institution must be recognized by the regulatory authority
- Proficiency in language example English, French or Portuguese as applicable.
- Certificate of Good Conduct

Although MSs claim to welcome incoming health professionals from other member states, they also oppose health professionals leaving their country to live and work in another country. However, MSs seem to agree that if government-to-government agreements exist for the exchange or supply of health professionals from one county to another, no bottlenecks should be faced by the foreign health professionals.[44]

Table 16 below highlights the key drivers and barriers for intra-regional trade of HRH. National policies and cohesive regulatory environments are essential in bridging the gap in the sharing of HRH and technical expertise between SADC MSs.

Table 16: The key drivers and barriers for the movement of health professionals in SADC.

| Drivers | Barriers |
|---|---|
| 1. To address the HRH skills gaps in the country. | 1. Temporary nature of work permits and long lead times in the processing of the same. |
| 2. Skills transfer to and training local personnel. | 2. Language and cultural barriers in recipient countries. |
| 3. Better terms of service e.g., compensation package benefits | 3. Process and delays in recognition of professional qualification. |
| 4. Peace and stability, improved quality of life. | 4. Disruption of Social life of migrant families. |

[44] See Azariah, Simon; Kiplangat-Ronoh, Wesley; Mckinnon, Malcom and Viola Sawere: "A Study on Member State's Regulatory Regimes in Health & Related Social Services for the SADC Trade in Services Negotiations. 2021.

**Movement of Pharmaceutical personnel in the region – Pharmaceutical Industry perspective**

In interviews with some pharmaceutical industry players in the region to determine movement of personnel between the SADC countries, none of the companies indicated having sourced from SADC countries. It was noted that, despite the existence of SADC Common Market Protocol, the pharmaceutical industry was not aware of any preferences given to nationals from SADC countries on employment. They were also not conversant on the opportunities provided by the CMP with regards to movement of people and trade in services. Further findings were:

- Preference by local companies to source experts from India citing better skills, experience and cheaper when compared to sourcing from SA.
- Higher salaries requested by foreign professionals were a deterrent to recruiting them even when local talent was unavailable
- Service and preventative maintenance engineers were not available in country in most of the SADC countries. Instead, the manufacturers had equipment supplier agreements that included servicing and repair as necessary. Most companies, source equipment from India and therefore the service engineers predominantly come from India. They indicated that the service engineers based in South Africa tend to support equipment providers from Europe and they will tend to charge higher fees.

SADC and member states should promote movement of pharmaceutical personnel as part of the wider strategy to address skills gap shortages, optimal use of human resources and grow the local industry. Pharmacists and other licensable pharmaceutical personnel should be prioritized among the list of professionals for consideration in negotiations in Trade in Services. In addition, a mutual recognition mechanism to be used by the MS among these professionals should be established.

# 6. POLICIES FOSTERING ARV PRODUCTION BY THE PRIVATE SECTOR

The following topics are important to consider, when examining factors either conducive to, or which are otherwise important to consider, regarding pharmaceutical industry drivers and challenges.

## National and Regional Policies, and Medicines Regulation

The establishment and maintenance of a strong pharmaceutical manufacturing sector, and related value chain components, is heavily influenced by Government policies affecting the industry, as well as the involvement of the relevant National Regulatory Authorities (NRA). Long term, demonstrable Government support and prioritisation of the sector is a vital step towards the growth and strengthening of pharmaceutical manufacturing.

Several different strategic components, which are either central to or supportive of the pharmaceutical sector, relate directly to the Government. When considering the sector on a regional basis, the actions of the regional governing body and regional policies also come into play.

Key government, regulatory and related stakeholders, influencing the development of the pharmaceutical industry and its ongoing activities, include the following:

- Ministries of Industry/Trade
- Ministries of Health
- Ministries of Finance/Treasury
- Ministries of Foreign Affairs
- National Medicines Regulatory Authorities
- Standards Bureau/equivalent bodies
- Central Medical Stores/equivalent bodies
- Trade associations

Considering both the challenges faced by manufacturers in the SADC region (as identified by the companies operating there), as well as lessons learned from other Sub-Saharan African countries outside the region, the following areas are important to consider. These are areas where government and policymakers either define, or have a significant influence on, factors that are either conducive to or create barriers for companies operating in the region.

**Government and stakeholder coordination.** Industry often indicates a lack of coordination across relevant Ministries and other government entities as being counterproductive to the sector. To address this, it is often valuable to set up a functional working group or committee comprising the relevant ministries, industry and the NRA. This allows important policy and related matters to be raised and addressed, ensuring effective communication between industry and Government.

**Policy coherence.** Policy coherence is considered important in ensuring a supportive business environment is created to enable a strong and viable pharmaceutical manufacturing sector and related value chain components. Equally, the lack of policy coherence creates a situation where companies may struggle to operate sustainably and profitably. The establishment and maintenance of an effective working group, as discussed above, is generally the most useful starting point to addressing the policy coherence questions as this offers a suitable forum to assess and analyse the policies affecting the pharmaceutical sector.

**Incentives.** Incentives are a key tool to stimulate and support any industry. In the case of pharmaceutical manufacturing, they are widely used both across SADC and the wider Sub Saharan African region. There is no single 'one size fits all' package that meets the needs of every territory, given that the existing manufacturing base, its requirements, and the country environment in which it operates all vary across countries. However, there are several typical incentive structures that are utilised.

The incentives must be both correctly designed, and properly implemented. To design a suitable package, dialogue between government, industry and other key stakeholders is important to ensure that the measures will be effective. Again, the government and stakeholder coordination function - the working group or other committee, is most likely the right medium to address the incentives area. Equally important is that, once incentives are developed, they are communicated to the relevant parties and then properly enacted. This can also be monitored via the working group/steering committee structure.

The most common direct financial incentive that is applied is a price preference on tenders, meaning that the purchaser is willing to pay a premium versus imported products. This is typically in the range of 10-20% but may be as high as 25% in some cases. Other financial incentives include VAT exemption on raw materials, other consumables, equipment, and machinery, as well as reductions in income tax.

Industry can also be promoted through the creation of special export-focused company classifications. Whilst broader in nature than a single incentive tool, such approaches also serve to boost exports, by definition, and therefore improve the balance of payments.

It is important to highlight that not all incentives have a financial cost, and the use of, for instance, expedited product registration by the NRA also serves to support local companies.

**Regulatory aspects, including regional harmonisation.** The presence of strong, well-resourced and effective National Regulatory Authorities is also a key factor in promoting local pharmaceutical manufacturing. Regulatory strengthening may be required to achieve this.

At a regional level, regulatory harmonisation is being pursued, in common with other regions in Africa. Whilst often complex, and not something that is generally achieved in a short time frame, this offers the potential to significantly open up the regional market to companies operating in SADC, thereby providing clear commercial opportunities as well as streamlining the product approvals process. Decisions on regulatory harmonisation require good coordination between individual NRAs across the SADC countries as well as effective leadership and decision making from the SADC Secretariat.

## Donor Policies and Influence on the Market

In the HIV field in particular, donors have a highly significant impact on the market and therefore on the manufacturing of ARVs. Although the amount of ARV medicines procured by donors varies dramatically across the SADC region, and although some territories are moving towards greater self-procurement and less donor funding, the role that donors play remains a key one. Donors require international GMP standards, as discussed already and considered in more detail, with specific regard to WHO PQ, later in this chapter. This remains a key requirement, on the basic premise that quality is non-negotiable, and patients must receive safe and efficacious medicines.

What has changed, however, when considering overall donor policies and their approach to the pharmaceutical market, is that in recent years there has been increasing realisation of the wider value of local pharmaceutical production. Previously, the drive to maximise the amount of pharmaceutical product purchased per dollar spent (always at high quality, however) meant that donors allocated tenders with price as a key factor. The extremely tight profit margins, caused by this focus on price, meant that the donor markets became difficult to work in. Typically, this favoured the larger manufacturers in particular, those in India, meaning that local manufacturers in Africa, by and large, missed out.

However, in recent years there has been a shift in thinking amongst donors and greater recognition of the direct and indirect value of local manufacturing. This has led to moves to seek, where possible, greater diversity amongst suppliers and, in some cases, recognition that a local price preference may in fact be desirable as this encourages greater participation from local manufacturers in tenders. There are various arguments in favour of donors moving to this revised strategy, including the following:

- Ensuring greater inflow of donor funds into the recipient countries with associated economic benefits
- Ensuring a robust, strong, and diverse supplier market
- Security of supply for African countries through the promotion of local manufacturing (less overall reliance on imports)

Whilst this shift in policy has taken time to impact on local manufacturing, it indicates the potential for manufacturers in SADC and Africa as a whole to feed into potentially more lucrative markets, with the associated economic benefits as the industry captures more of the ARV market value.

## Good Manufacturing Practice and Quality Standards

Good Manufacturing Practice (GMP) is a requirement for all pharmaceutical manufacturers. GMP defines the requirements for both the company facility as well as its Quality Management Systems (QMS). The specifics of these requirements vary according to the regulatory body setting the standards. Common internationally recognised GMP standards include those set by the US FDA, EMEA and WHO. Within a particular country, the relevant National Regulatory Authority sets, monitors and enforces the requirements, which apply to publicly procured medicines and those available for purchase within the country privately. Donor-financed and purchased medicines typically require an international GMP standard to be demonstrated by the selected manufacturer. ARV medicines purchased by the Global Fund, also require WHO Prequalification (WHO PQ) or registration with an appropriate stringent regulatory authority, whilst PEPFAR only accepts US FDA approval.

The variety of standards means that companies operate within a complex regulatory environment. Depending on whether they meet their national requirements, national requirements within a variety of SADC countries, or global international standards such as WHO PQ, companies may be licensed to manufacture and sell medicines for public and private markets in their own country only, in several SADC countries, or they can apply for donor tenders.

Importantly, different manufacturers pursue different regulatory and commercial strategies. A key factor in this, and the decision as to whether to seek WHO PQ to access the lucrative donor market, is whether the company can invest sufficiently in its facility and QMS to reach the standards required. Even if a company determines that it has access to sufficient expertise and financial resources to do so, the decision is still a complex one.

Within the SADC region, only one company, Aspen Pharmacare, in South Africa, has reached the WHO PQ standards and still has a prequalified product. Aspen, however in 2019, indicated their complete exit out of the Public ARV market through a deal signed with Laurus India. Another company, Varichem in Zimbabwe, previously had one product with WHO PQ but the approval has since lapsed, and the company has not pursued requalification. It, therefore, appears, that for a period of a few years at least, no SADC manufacturer has won significant donor tenders requiring WHO prequalification. This means that the donor money spent on ARVs for use in SADC is not significantly contributing to the economy of the region as the products are imported fully finished. CPT Pharma in South Africa has been awarded SAHPRA accreditation for its new API facility. No ARV APIs are planned for the short term, but there are some in the pipeline.

There are two basic challenges for any company seeking to attain WHO PQ. Firstly, the finance required to upgrade facilities and QMS, or build a new facility and set up QMS, at the required quality levels. The second is the technical challenge of compiling a product dossier and formulation which will pass the WHO PQ requirements. Beyond this, another key consideration is that, once the investment is made to manufacture a product with WHO PQ there is an inherently higher cost of production for all of a company's products compared to competitors that do not manufacture at WHO PQ standards. Whilst this is not an issue regarding donor tenders requiring PQ, it means that such companies are generally non-competitive on a price basis in the local public markets which do not require WHO prequalification.

Amongst the companies currently operating in SADC working on multiple therapeutic areas (ie a typical local generic manufacturer), the majority do not appear to be targeting WHO PQ in their development strategy. This is most likely due to the rigorous, expensive and technically challenging process of attaining WHO PQ, which then outweighs the benefits of being pre-qualified. In addition, the high cost of goods when competing in the 'non-donor' markets once WHO PQ has been achieved, as depicted above in the Challenges portion of Chapter 4 lowers profit margins. Having said this, it is important to note that amongst the ARV manufacturers in SADC, a number of these companies do indicate an interest or actual plan to pursue WHO PQ.

Currently, most SADC's manufacturers are producing ARVs without WHO PQ. Although – as indicated immediately above – some are working towards WHO PQ for their ARV products, the fact is that the

current pharmaceutical industry in SADC operates outside of WHO PQ and competes in the public and private markets rather than the donor-driven market. Although companies, on the whole, are not seeking upgrading to WHO PQ and GMP, maintenance of standards and achieving the level of the national standard required to expand into neighbouring territories require an ongoing process of identifying issues within either a facility or quality management system and addressing them. Manufacturers use a CAPA (Corrective and Preventive Action) plan to address deviations, defects or otherwise undesirable situations affecting their ability to produce medicines under GMP conditions. The CAPA is typically generated following an inspection and audit, which details the issues found and the action(s)that the company will take to address each one. It serves as both a planning tool for the manufacturer and a monitoring tool for both the manufacturer and the regulatory authority on its next review or inspection of the facility. CAPAs are therefore a key tool in the maintenance of GMP standards of any level and may also be used by partners, for instance, manufacturers supplying bulk products for packaging in another company, to ensure that their quality standards are met.

## The Importance of Market Information

The ARV market, as common with pharmaceuticals in general, both within SADC and the wider Sub Saharan African region suffers from a lack of comprehensive, consistent market information. This is exemplified by the fact that even obtaining a set of clear and comparable information relating to the size of the ARV market across the SADC member states is less than straightforward. Although there is more information on ARV usage and supply compared to medicines for other infectious diseases and therapeutic areas (due to the impact of HIV and the importance placed on combating this), a detailed analysis, as seen in Appendix A, shows that there is minimal consistency and significant gaps exist. Although individual donors, in particular, publish their tender data, when compiling a comprehensive data set including donor, public and private medicines purchases and supply it becomes evident that the required level of detail is not readily available for the majority of SADC countries. There are a variety of reasons for this, including the following:

- The data is often not centrally stored and compiled comprehensively by individual member states, apart from (potentially, in some cases at least) that held by National Aids Offices or similar bodies. It typically is held amongst a mix of stakeholders including the NRA, Ministry of Health, local manufacturers, importers and customs and immigration departments.
- Many of the sources are not obliged to disclose data such that it can be collated and effectively utilised. Self-reported data - as collated and in some cases published, for instance by UNAIDS - may not be fully up to date and accurate and generally requires authentication (by the collating body), where resources allow for this.
- Data is not widely shared amongst member states, meaning that on a regional level there is a lack of comprehensive, comparable data

Solutions to the data issue have been sought elsewhere on the African continent and, generally, it has proved challenging to deliver the desired output. Despite this fact, there are strong arguments to pursue greater transparency within SADC on ARV supply and usage and the generation of a more comprehensive data set. This would bring benefits including, in particular:

- Greater ability to plan and manage ARV supply by public procurement entities, including Ministries of Health and central medical stores
- Greater ability of local manufacturers to effectively plan their production strategies, and increased knowledge of regional market opportunities

- Greater ability for governments to plan and implement effective incentives to promote local ARV production and stimulate the wider value chains, monitor and understand the financial implications of the incentives and assess the impact that they make
- Potential for increased partnerships between local manufacturers and technology/product suppliers through the definition of clear market opportunities

Taking these points into account, there is a strong case for efforts to clarify the ARV market in SADC to be made, given the advantages that this would bring to both local ARV manufacturers, donors and member states.

## Pooled Procurement

APIs, as discussed above in Chapter 3, represent by far the largest cost driver in the production of ARVs. Therefore, when looking to reduce the cost of production and consequently increase profit margins and/or improve competitiveness, APIs represent a clear target. However, for reasons outlined above, the API market and the dynamics of production, along with regulatory constraints, mean that it is very difficult for an individual manufacturer to drive down its costs of API purchase.

With these factors and constraints in mind, how can API costs be reduced and what influence can be brought to achieve this? Pooled procurement is one approach to the API cost challenge. Given that API price is linked to the purchase volume, pooled procurement provides the ability for a group of manufacturers with, individually, small order requirements, to collectively source in sufficient volume to drive the price down. In doing so, these companies can achieve API purchase prices more in line with their main competitors in India and consequently manufacture ARVs with a final ex-factory price closer to these companies, but which still affords them a reasonable profit margin.

Pooled procurement is, of course, only relevant for fully integrated manufacturers with a complete production line starting with raw materials, rather than those which receive either bulk granulated product or bulk tablets and only perform tabletting or primary packaging onwards respectively. Given a number of manufacturers in SADC still fulfil these criteria, there is the potential to work with companies and evaluate the possibility of developing a pooled procurement strategy to support them.

In practice, there are several challenges to overcome. These obstacles are the reason why pooled procurement is not widely utilised by companies. They include the following:

- In a highly competitive industry, manufacturers may be hesitant to work with each other
- Manufacturers may be reluctant to change suppliers
- Regulatory requirements related to API supply can complicate the process. For instance, if pooled API must be stored, and subsequently divided up and distributed to the individual end recipients, all in a GMP compliant manner
- In practice, would pooled requirements work best if conducted by a third party that then distributes API to each manufacturer, or would one manufacturer become the primary recipient?

Despite these issues, which have led to a generally low level of pooled procurement not just in SADC but across Eastern and Western Africa as well, there is an opportunity to investigate the benefits of developing a system to facilitate this approach to API supply. Such a system may be possible at the regional level, with appropriate country and regional support, or may be easier to develop within an individual country if there is a sufficient manufacturing base to make it feasible.

# 7. RECOMMENDED INTERVENTIONS AND CONCLUSION

The primary objective of this Inception Report was to profile and map out the ARV value chain by identifying the major players in ARV pharmaceutical manufacturing and the conditions which they operate under. This included a holistic approach to linking economic, environmental, social and institutional aspects in the SADC region. The report offers a detailed value chain analysis to allow (i) to make well-informed decisions, and (ii) to find innovative solutions and approaches for this regional value chain development programme. This approach will enable the design and implementation of key interventions, most of which are proposed below.

The SIPS joint action has undertaken the following activities in alignment with the intervention strategy to enable the project to initiate the profiling and mapping stages and produce this inception report.

A. Interviews and database creation of ARV manufacturers in SADC:
   SIPS has made contact and engaged with pharmaceutical manufacturers operating in SADC who are already, are planning to, or have the capacity to take part in the ARV manufacturing value chain. This will allow the project in the future to better understand the individual companies' production and regulatory capacities, GMP status, constraints and challenges.

B. Interviews and database creation of Central / National Medical Stores (CMS/NMS) in SADC:
   Engagement was and is still being made with relevant health ministries and public procurement units (CMS/NMS). This was done to better understand 1) procurement processes and requirements of individual member states, 2) government spending versus donor-funded spending for ARVs in the respective member states and 3) availability of reliable procurement information to the private sector.

C. Interviews of Academic Institutions and Technical and Vocational Education and Training (TVET) institutions relevant for the ARV/ pharmaceutical value chain to better understand the linkage between mentioned institutions and the private sector.

D. Hosting a regional stakeholder workshop in which the private pharmaceutical manufacturing sector and relevant ARV Value Chain stakeholders such as CMS/NMS had the opportunity to interact with each other as well as the SIPS project team. The aim of the workshop was to discuss, analyse and expand on the findings and proposed interventions in the draft Inception Report. Stakeholders had the opportunity to give feedback during the workshop or online through a feedback tool and the inputs were incorporated into this report.

## RECOMMENDED INTERVENTIONS

Based on stakeholder engagement and analysis of the ARV wider value chain presented in this report, including the current market, procurement dynamics, the current state of the industry and the opportunities and challenges that exist, the interventions described in this chapter are recommended. Given the very different parameters that govern and drive the identified market segments, the interventions are structured to take account of these individual market segments, which are:

1. **The public market.** This is the highest priority and main focal area due to its relative size and accessibility by local manufacturers.
2. **The donor market.** This represents the largest market by size, excluding South Africa, however, it is largely 'locked' to most local manufacturers since they need to attain WHO PQ or stringent regulatory authority quality standard to access it and as competitive prices for larger donor procurements depend on economies of scale of manufacturers outside SADC.
3. **The private market.** The only large private market in the region is South Africa. From a value perspective, it is attractive however the presence of non-tariff barriers, multinational competition, and the presence of a sizable South African pharmaceutical manufacturing base, makes it challenging to compete in for companies of other SADC members states.
4. **Interventions relevant for all markets.** Certain prerequisites must be met when manufacturers wish to participate in ARV production which include; cGMP standards that satisfy international regulations, business operations and production efficiency, skilled workforces and access to flexible and sound financial solutions.

These points are addressed more in detail below.

## Public markets

Public sector purchasing of ARVs represents the main sales opportunity for local manufacturers, therefore the value of the public market is an important factor to take into account when considering the viability of pharmaceutical manufacturing. Whilst the presence or absence of a sizable local market does not in itself mean that manufacturing would be commercially feasible, it represents a clear and accessible opportunity for producers to sell into.

This situation exists because of two overall factors:

(a) there is, in total, a substantial public market in SADC; and

(b) the donor markets are somewhat closed to local manufacturers under the current donor procurement framework.

There is a substantial ARV manufacturing base in the SADC region, spread amongst several countries, and the following are all relevant when considering the current manufacturing dynamic and opportunities to enhance the sector and capture greater value:

- The vast majority of ARV products sold by the SADC manufacturers are non-WHO PQ (except for a small amount made by Aspen (as seen in appendix D). As indicated above, the majority of this is sold via public tenders (government purchased) although there are small private markets in most SADC countries and a sizeable one in South Africa.
- Outside of SA, a significant proportion of ARV products are manufactured through a technology transfer relationship, via a license, primarily from multinational/ Indian pharmaceutical manufacturing companies. Of these products, most are supplied as bulk tablets which then undergo packaging in SADC-based facilities.

- The dominant ARV manufacturer participating in local SADC manufacture is Mylan[45]. They have business relationships with several companies in separate SADC countries. In most of these cases, Mylan is supplying bulk tablets for packaging although in one instance, in Mozambique, it has planned to supply ready-to-compress granules which will be tableted and packaged locally. Mylan also has a local packaging facility for ARVs in Zambia.
- South Africa represents by far the largest portion of ARV manufacture in the region, with a diverse base of around half a dozen local companies producing ARVs. They primarily serve the local South African market which is, correspondingly, the largest single ARV market in the region.

When considering where on the value chain to act, the areas with the highest probability for successful value capture are (listed in priority order):

Table 17: Potential value capture for the value chain steps

| Value Chain Step | Consideration |
|---|---|
| **API production** | High potential value capture but high-risk long-term investment. Essential for long-term sustainable establishment of ARV manufacturing in the region. |
| **Full Manufacturing Operations and Packaging-only Operations** | Relatively high value capture from an existing base of regional manufacturers. |
| **Packaging Materials Manufacturing** | Relatively high probability of success but low value that can be captured (e.g. jars). |
| **Local Agency, Distribution and Logistics** | Low incremental value capture, since this is already localised in the SADC region. |
| **R&D** | Royalties on new products are not likely to be withheld in SADC region and very low probability of success per project. Relatively low value capture for R&D centres of excellence which operate on service-based model and are likely to be subsidiaries of a multinational R&D organisation. |

Taking into account the market situation and value capture summary analysis immediately above, the following conclusions can be drawn amongst the public market opportunities**:**

**The Joint Action will primarily focus on countries with:**

- **(a) existing manufacturing and packaging operations; and**
- **(b) a local public tender, i.e. Botswana, Mozambique, Namibia, South Africa, Zambia, Eswatini and Zimbabwe.**
- **(c) identified functional (possibly experimental) API manufacturing plants**

Given the aforementioned focus, the <u>main target markets for intervention</u> will be the following:

- In **Mozambique,** there are two manufacturers of FDF products and according to local firms, there will be a public tender of approximately $5-10M in the near future. One firm was started as an ARV focused manufacturer and has an interest in restarting

[45] Mylan is a global generic pharmaceuticals manufacturer domiciled in the Netherlands and with main executive offices in the UK and US. The majority of the company's manufacturing activities are currently conducted in India, therefore, for the purposes of this analysis, it is described as an Indian pharmaceutical manufacturer.

ARV production and the other has begun a technology transfer with a multinational for the production of TLD.

- **Zambia** has an existing government ARV tender (approximately $15-20M/yr) which has been won over the past few years by the local subsidiary of a multinational firm with local packaging operations. There have been reports of late payments by the government for these tenders, but this still appears to be a potentially attractive business for local manufacturers. This attractiveness is very likely to wane if these late payments persist.
- **Eswatini** has a large pharmaceutical development plan in the pipeline, where a fully-fledged ARV production facility will be established by 2024. Manufacturing activities are set to cover from formulation to packaging and release.
- **South Africa** is currently the only member state that appears to have the capacity to manufacture ARV APIs at the required standards necessary for WHO-PQ. There is a local company that is currently venturing into manufacturing APIs for first- and second-line ART. They are at the development stages of their product development plans.
- **Botswana** has three local packaging manufacturers who have all won portions of the recent government ARV tenders (approximately $30-35M/yr). However, initial discussions and analysis indicate that there is inadequate national-level ARV business to sustain all three companies in the long term without some sort of intervention, product diversification by the manufacturers, or increased exports to the region.
- **Namibia** has a sizable public ARV market (approximately $13M/yr) but it appears that its two local packaging manufacturers are not receiving significant portions of this business. Presumably there is not significant local packaging of ARVs although one company and its subsidiary has started a (secondary) packaging facility for ARVs. Unfortunately, one company was forced to shut down after 20 years of operations due to a significant decrease in public market business.
- **Zimbabwe** has several local pharmaceutical manufacturers, some with previous expertise in ARV manufacturing despite this, local ARV manufacturing has ceased. However, before the COVID-19 pandemic, one company had planned on building a new facility along with international technology transfer partners to produce ARVs. These plans are currently on-hold but might be picked up again if the size of the national tender economically allows. Whilst there have been challenges related to government funding of their national ARV tender (according to recent industry feedback), there is an expectation that the tender might be approximately $19-22M/yr in the future.

<u>As a secondary focus</u>:

- Anywhere where there is either a public ARV tender or local manufacturing operations, but not both. This includes:
    - **Malawi** and **Tanzania** both have a manufacturing base, but no local ARV production. Tanzania is said to have a public tender and Malawi has been reported not to have a public tender.

- **Lesotho** has a sizable public tender (~$17M/yr) but no active manufacturers. Lesotho used to have a manufacturer, but it is likely that they are no longer manufacturing.
- It is reported that **Angola and DRC** have no ARV manufacturers or a sizable public market.

The **next steps** take into account the above conclusions on where the most promising project intervention opportunities lie, and the challenges faced by the industry in those countries (as discussed above in Chapter 6. They also consider the additional objective of avoiding industry contraction due to company failures[46].

**Next steps: Public market-related interventions**

1. **Market and tender data.** As discussed in Chapter 6 above, and highlighted in Appendix A, there is an overall lack of transparent and reliable procurement data for ARVs in SADC. This includes not only donor data (e.g. for PEPFAR) but also in terms of national tender awards (i.e. winners, volumes and prices) and supplier performance in fulfilling the tenders which often are not publicly available. Having this data along with reliable demand forecasts for future years will better enable companies to gauge business opportunities and plan operations. For example, some operators in Mozambique were not aware of the pending new tender to be floated by the government and it still is not clear what the size of the ARV tender will be.

   A workable recommendation to address this issue is to establish a common portal for SADC member states where tender information is publicly available via a website. The portal can also serve to act as a database for local qualified manufacturers within SADC, who are timeously notified of impending public tenders to better plan production cycles. Like an approved vendors list, preference could be given to these local manufacturers when taking part in public tenders within the SADC region.

   Another benefit from having a common portal is the ability to build and grow market data in the SADC region, which will map out demand and procurement trends. A system like that could very likely be a useful tool when SADC wishes to perform accurate forecasting in pooled-procurement plans.

2. **Government purchase and payment commitments**. As detailed in Chapter 6, there are a number of issues with payments for public tender awards including delayed payment or never ordering the full amount which was tendered for. This not only creates cash flow issues for companies but can result in too much production capacity being built. The problem of overcapacity seems to be one of the most prevalent issues in the region. Companies have often built facilities based on government purchase commitments that do not fully materialize. Some companies can pivot to private markets or to areas where government purchases have grown, but others are simply forced to close or sell out to competitors which

[46] Pharmaceutical company failure is an ongoing industry risk. In countries with a wider industry base (e.g. 10-20+ companies, as is the case in various countries in the wider SSA region, it is not unusual that there is a turnover of companies and one or two failures or mergers/consolidations in a typical 1-2-year period. During the inception phase of this project one company based in SADC, Dore (Namibia) ceased operations and a few are operating with a skeleton staff. This illustrates the risks present within both the pharmaceutical sector and in SADC.

was for example, observed in Zambia. According to participants of the stakeholder workshop, it is key to engage governments on reliable and long-term commercial commitments with suppliers to ensure sustainability in the sector.

3. **Policy advocacy at the national and regional level**. This includes, in particular, effective and coherent procurement and trade policies as well as consideration of local production incentives and size/ availability of public tenders. To support this process, it is valuable to engage with the key stakeholders in the correct environment and in an effective manner. An initial step involves working with industry, so that the challenges and opportunities are understood, prioritised, and then can be effectively brought to the attention of policymakers. Whilst this overall process entails coordination between the two implementing parties of the overall SIPS project (with SADC having responsibility for the policy and regulatory aspects of the project), a starting point can be the industry engagement process. Policy issues of specific relevance, which could be addressed to improve the environment for pharmaceutical manufacturers, include the lowering of international trade barriers for raw materials and other production inputs, and the lowering of regional trade barriers (tariff and non-tariff-related) to promote intra-regional trade since at present, there are various challenges facing companies looking to export more products within the region. In addition to these areas, there are advantages to having a regionally coherent price preference policy. Another example of a specific policy-related issue relates to the manufacturers in Botswana, who had previously been unable to collectively meet with and consequently better coordinate local production demand with the national pharmaceuticals procurement manager. This is an important issue in a country where most pharmaceuticals are bought by the government and given all local companies are operating at less than 30% utilization and face closure if this persists.

   A possible intervention is to involve regional and national business networks relevant in the ARV regional value chains by engaging public-private dialogues to better understand industry needs.

## Donor market

It is important to understand the historical dynamics driving donor markets. In simple terms, the focus was on maximising the volume of products, at internationally recognized quality levels, delivered to recipient countries. This delivers the most impact per dollar spent while providing their funders with the transparency and comfort on quality that was required. The donor markets were not driven by a focus on stimulating and growing the local pharmaceutical manufacturing base.

Having said this, in recent years there has been increasing recognition of the fact that the billions of dollars spent on medicines for Africa are not spent in Africa. Consequently, there has been increasing debate as to how to capture this value locally, thereby increasing the overall impact of the donor money that is spent through stimulating the local economy as well as delivering improved healthcare. Furthermore, there is a desire to reduce countries' dependence on donations as they become richer and move towards self-sufficiency in terms of medicines purchase.

Despite the shifting sentiment and increased dialogue regarding local procurement, in effect, the donor market remains 'locked away' from the majority of SADC manufacturers due to the requirement

for WHO PQ or comparable stringent regulatory authority approval. The other key challenge relating to donor tenders is that pursuit of WHO PQ or another stringent regulatory authority approval results in companies increasing their COGS such that they often become uncompetitive in the national public tender field, where companies require less investment to meet the regulatory requirements. This commercial strategy issue, combined with the technical and financial challenges in attaining WHO PQ, and the changing ARV regimen, makes the donor market unavailable or unviable for, in effect, all current SADC manufacturers.

Although donors have indicated a desire to source a greater proportion of medicines from Africa, particularly ARVs from SADC countries given the especially high burden of HIV in the region, the market data indicates this has not translated into additional actual local sales. The opposite is true when considering the value of ARV purchases from African companies over the past few years, including Varichem and Aspen Pharmacare. Varichem achieved PQ only to decide a few years later not to maintain their prequalification status and is no longer eligible to compete for donor tenders whilst Aspen Pharmacare has recently recorded much lower sales values to Global Fund and has much fewer PQ products compared to the levels achieved 5-10 years ago (See Appendix D for further details and data).

In summary, it can reasonably be concluded that, despite its size, the pursuit of the donor market by a SADC-based manufacturer is in most cases not the most attractive strategy available. This also considers the technical and financial challenges associated with achieving and maintaining WHO PQ or similar internal level quality requirements and recent experience of manufacturers with WHO PQ.

Given this conclusion, the donor market falls behind the public market when considering near-midterm opportunities for the SADC ARV manufacturing value chain, and a key requirement to unlocking this market would be movement from donors to address the aforementioned challenges.

**Next steps: Donor market-related interventions**

1. **Dialogue with donors**. Engage in a dialogue with key donors, notably the Global Fund, to better understand its current position regarding local pharmaceutical manufacturing of ARVs within SADC. This is a key first step given that the position and direction that donors, and their funders take, determines whether the market could be more attractive and achievable for local manufacturers. There are three potential policy shifts that could be considered. Firstly, giving a bigger weight to local production in the tender award process. Another would be to consider alternate means of ensuring product quality other than having PQ for the entire production process (i.e. local packaging plant not requiring WHO Audit or relying on 3$^{rd}$ party audit or technology transfer partner audit). Lastly, there could be regional certification of products to meet donor specifications and enable participation in the value chain by producers in the region.

2. **Support local manufacturer WHO PQ strategies where/ if applicable (partly contingent on success in above step)**. If there is success in "unlocking" greater access to the donor market as described above, a next or simultaneous step would be to consider and evaluate manufacturers regarding WHO prequalification, to understand the position of SADC manufacturers in more detail. This would involve dialogues with manufacturers demonstrating the most credible intent regarding WHO PQ, and consideration of the viability

of their strategies given the technical, financial, and commercial considerations. If there is no further unlocking of donor market access for local firms, WHO PQ might not be regarded as advantageous by regional manufacturers because of the additional costs.

## Private market

As discussed previously, outside of South Africa, the private markets in SADC countries are very small and do not represent significant business opportunities that will drive industrial growth within the ARV segment and related value chains.

The South African market is, in practical terms, somewhat 'locked away' from non-South African SADC manufacturers due to the strong competition from its national pharmaceutical manufacturing base and imported multinational products, plus the existence of non-tariff barriers including the requirement that imported pharmaceuticals cannot enter the country by road and must be flown in. This requirement makes it commercially non-viable since the increase in COGS due to the air freight charge, at the volumes that SADC producers would supply, makes it uncompetitive compared to either South African-based suppliers or Indian importers that work at high volumes.

Furthermore, within the limited private markets that do exist, the key driver determining a company's success is its ability to successfully compete on a marketing basis against companies with higher brand equity. Given these factors, the private market does not represent a major area of focus for the project. Consequently, there are no recommended actions or next steps to be taken for this market sector.

## Interventions relevant for all markets

This section outlines possible recommendations for intervention strategies to mitigate the challenges currently faced by SADC manufacturers in all markets. As the findings in this report suggests, key areas of focus include, (1) input materials, (2) operational efficiency, (3) GMP, (4) academia, and (5) funding.

1. **Evaluation and possible promotion of inputs production.**

    a) **API.** A company in South Africa is at its early-stage plans to produce APIs, including at least three for ARVs. As reported, APIs account for approximately 70% of the cost for FDFs. This is the major challenge for developing the ARV value chain in SADC, as the vast majority of manufacturers only enter the value chain at the formulation/ granulation stages at best and most of them currently do packaging operations only. A manufacturer able to spearhead API production in the SADC region is a thus a key requirement for the further development of the ARV value chain.

    b) **Packaging materials.** During the inception phase, only a few packaging materials projects were identified, and the majority of packaging ARV manufacturers are contractually bound to import packaging materials from India. A company in Zambia is aiming to set up a pharmaceutical grade plastic jar production unit in the country. For this under-subscribed sector to proliferate, the following recommendations need to be considered, (i) new intra-regional market connections must be established to activate export opportunities within the SADC region, and (ii) promotion of public-

private dialogues to overcome non-trade barriers (NTBs) to effectively allow for the supply of packaging materials and other input materials across the region.

For such key manufacturing projects, especially in the API sector, possible interventions to consider is to facilitate information sharing and technical transfers of innovative and resource-sustainable manufacturing equipment and techniques. This can be made possible by introducing technical and subject-matter experts into existing companies to efficiently learn and transition to acceptable international standards.

2. **Improving manufacturing production and business operations efficiency**. To ensure manufacturers are operating efficiently, there are benefits to assessing weaknesses that exist and then designing interventions to address the problems identified. This could include training on approaches such as Lean Six Sigma, which can be performed at a company level as well as through group training. Applications of strategies such as this, will help manufacturers reduce cost, improve productivity and competitiveness and be highly effective in pilot projects in the pharmaceutical sector within Sub Saharan Africa[47]. This could also be an opportunity for collaborations with local Universities to develop more efficient production and business operations. The fact that manufacturers in some cases reported lack of a relatively simple decision-making model such as purchasing materials based on the total landed cost of the goods rather than the ex-factory cost points to a fundamental weakness that is prevalent in the region.

3. **GMP** Acceptable good manufacturing practice (GMP) standards remains an area of substantial improvement in the SADC region. Firstly, for companies to legally manufacture and market pharmaceutical products in their territories of incorporation, their facilities have to be validated for GMP certification. Secondly, in some cases, a company's GMP status may not be recognised in another SADC member state due to the differences in regulatory stringency and/or regulatory capacity of the issuing member state. In those cases, most of the member states rely on WHO GMP standards as their benchmark for accepting pharmaceutical products from manufacturers that have achieved that certification.

   As described in this report, ARV procurement sourced with donor funds requires WHO prequalification (PQ), which is a very stringent and costly endeavour. That is why it is of utmost importance for local manufacturers within the SADC region to firstly, improve their GMP standards, and secondly, aim to achieve WHO-PQ to enable them to market their locally produced ARVs within the region.

   Although this undertaking may appear arduous, proper GMP training and preparedness will allow manufacturers to achieve this goal. The Joint Action SIPS will identify opportunities to overcome these gaps by promoting access to technical and subject-matter experts and promote exchange of information between manufacturing companies and regulatory

[47] For more information, go to www.unido.org. UNIDO's local pharmaceutical project conducted a pilot activity in Kenya to train and assist manufacturers in the application of LSS (Lean Six Sigma).

agencies. Thus, interventions to consider are (i) GMP gap-analysis programmes, and (ii) resulting GMP and/ or total quality management (TQM) trainings.

4. **Academic and TVET considerations.** An important component of the SADC SIPS project is to bridge the gaps identified in academic and TVET integration in pharmaceutical manufacturing within SADC. The aim of this intervention is to link the private pharmaceutical manufacturing sector to academic institutions to promote dialogue in the pursuit of developing academic programmes (Honours, Masters, PhD) to suit the pharmaceutical manufacturing sector. A strong focus on tertiary education and vocational training must be emphasized with respect to pharmaceutical manufacturing. Currently, to a greater extent, the academic sector within the region mainly focuses on retail and hospital pharmacy disciplines. Thus, it is highly recommended that there should be an increase in academic programmes which cover chemical and pharmaceutical engineering, biotechnology, medical microbiology and other programmes identified as relevant for the pharmaceutical industry. The recommended intervention is to support the pharmaceutical manufacturing sector and academia to jointly develop and implement a training program relevant for the pharmaceutical manufacturing, i.e. ARV manufacturing, sector. To harmonize and coordinate efforts for the development of the training programmes amongst the various stakeholders, the Southern Africa Regional University Association (SARUA), which works closely with the SADC secretariat on the education programme will also be engaged. A possible approach is to coordinate with subject matter experts in pharmaceutical production and regulatory such as USP, WHO in the setting up of a regional training programme. This will contribute to bridge the gap of the region having a lack of skilled and competent workforces in the pharmaceutical sector.

5. **Facilitating access to affordable, flexible and innovative financing arrangements for spearheading ARV manufacturing projects.** It is of importance to understand that most (if not all) pharmaceutical manufacturers in the region manufacture a variety of medicines and are not dedicated ARV manufacturers. As described in this report, the current pharmaceutical landscape unfortunately does not allow these manufacturers to solely manufacture ARVs and in many cases, allow these manufacturers to take on the risk of ARV manufacturing. Because of these reasons, access to affordable and sustainable financial arrangements together with financial and investment advice would be vital to jumpstart and sustain this sector. The inclusion of improved financing arrangements or reduction of costs for non-technical activities such as Environmental Impact Assessment studies is one way of creating an enabling environment for commercialising technology while ensuring availability of high-quality data to assist with feasibility decisions.

   With local government cooperation in making the market more attractive, i.e. protecting local pharmaceutical and ARV markets, manufacturers will have easier access to investment opportunities in the form of investment banks, development banks, equity and venture capitalists. These financial institutions find more incentive in funding manufacturing companies who have long-standing government supply contracts as outlined in Chapter 6.

Access to funding and government support also allows for growth and upscaling in capacity building.

## Conclusion

With the inception phase nearing completion, the in-depth assessment undertaken by the SIPS joint action suggests a reasonable probability of success for the ARV manufacturing value chain to get off the ground when all the measures previously mentioned are met. SIPS component 1 (Policy Development) and SIPS component 2 (Private Sector Development) of the project were intentionally constructed separately as to allow complete attention and oversight of the requirements needed to establish a sustainable ARV manufacturing value chain within SADC.

Market analysis of the ARV value chain clearly highlights that 70-80% of the cost of ARV final dosage forms (FDFs) accounts for APIs. As India and China have captured this generic API market, the value chain will remain heavily skewed away from the SADC region if API manufacturing is not emphasized and shifted to the region. Industry players in the region have suggested that local governments in the region should procure APIs on a tender basis, as opposed to FDFs. The result of this would give local manufacturers access to competitive API pricing and thus balance the API playing field. The passive (secondary) outcomes from this approach would include long-term agreements between local API manufacturers and local governments, thereby retaining and expanding domestic formulation capacity.

The potential for value capture in the manufacturing operations within the ARV value chain is not limited to API manufacture alone but also extends to full formulation, FDF packaging, excipient and packaging material production. If the identified pilot API manufacturing projects and the manufacturers in the other segments of the value chain receive the necessary support, sustainable value chain development may be realised. Proposed areas for support are not only limited to establishing ARV manufacturing operations but to attaining GMP certification, improving manufacturing and business efficiency together with facilitation of access to affordable, flexible and innovative financing arrangements. Attaining GMP certification has a spill-over to other pharmaceutical manufacturing activities on non-ARVs, thereby increasing sustainability and competitiveness of manufacturers in the region.

Processing and increasing accessibility to national and, better, regional public tender data, e.g. by developing a national or regional tender portal(s), will be instrumental in building reliable regional ARV market data that will allow all players in the ARV value chain, particularly the local manufacturers and procurement agencies to forecast and plan accordingly for any future tenders. The portal may also be extended to include all ARV manufacturers in the region and could be modelled into a local manufacturer vendor list where local preference for tenders by national public procuring agencies could be applied.

Support for the academic and TVET institutions to foster dialogue with the industry in order to develop curricula relevant to pharmaceutical manufacturing is recommended. The development of a database for these institutions is a first step to allow better cooperation of industry and these institutions and develop more industry-need-based curricula. The success of these interventions will go a long way in bridging gaps that have been identified in the availability of skilled pharmaceutical personnel. This will complement policies that support intra-regional skills trade in the SADC region.

Technical preparedness is a key component but the efforts from and targeting the private sector would be moot if the public sector does not complement these development plans for ARV value chain promotion. It is clear to industry and market leaders that governmental commitment is vital for the pharmaceutical and ARV manufacturing markets to grow and remain sustainable. This includes commitments to procure from local producers and removing regulatory constraints that prevent pharmaceutical products to reach the market. This report recommends that regulatory agencies in the region be upscaled to meet the necessary capacity to ensure efficiency and improved timelines for product approvals. This would require intensive investment and training, but the outcomes would greatly outweigh the efforts. With regulatory activities in each member state vastly improving and reaching a level of comparable stringency, regulatory harmonisation would become a far more attainable task. The ability to register a product in multiple member states within the region with a single submission is a key driving factor to realise ARV value chain promotion in SADC. The aim is to remove any bureaucracy, while retaining the core principles of quality, safety and efficacy of medicines registered in the region.

With governmental commitment to local procurement and regulatory harmonisation achieved and working in tandem, seemingly difficult endeavours such as pooled procurement will have a much higher probability of success. If there is comparable medicine regulation with regulatory harmonisation, procurement specifications would also be similar for all member states. This will most likely create a fertile environment for a pooled-procurement system in SADC, which should opt to preferentially support local manufacturers, and which would drastically reduce the costs of FDFs when taking economies of scale into consideration.

With policy and industry preparedness aligning in unison, the joint SIPS project will allow for the proliferation of industrialisation, inter-regional trade of goods, services and experts, job creation, fair equity in value chain promotion, and academic and skills development.

# Appendix A: ARV Market Size by Funder for each SADC country

As no single source of ARV market data exists for all 16 SADC countries, various sources of procurement data and funding needed to be analysed to create a fuller picture of the overall market. Unfortunately, these various data sources often contained conflicting or incongruous data which needed to be rectified before Figure 5 above could be deemed accurate enough to use for this report. This Appendix explains that process.

The main sources of ARV market data were:

UNAIDS[48]

The UNAIDS HIV Financial Dashboard page allows a user to download an excel file with data on 85 key indicators. According to the website: "The indicators included in the dashboard are an extension of the data reported through Global AIDS Monitoring and also triangulates information reported on HIV and Health financial resources from other agencies." The main strength of this data set is that the spending report is broken down into various Public, Donor and Private funding sources and often disaggregated into actual ARV purchase cost vs other HIV/AIDS program costs. While this is overall a useful source of information, due to its reliance on various primary sources of funding data, which is often self-reported by countries, there are a few drawbacks to solely using this dataset:

- There is no data for Tanzania or Eswatini
- Data for some SADC countries is as old as 2014
- Some values represent multiple-year spends which can be misleading since the assumption is that all totals are single year amounts
- Data directly from PEPFAR and Global Fund don't always align with the number shown in this dataset

Global Fund[49]

The Global Fund Price and Quality Report (PQR) shows exact quantities, prices and delivery dates for all ARVs procured through the fund. This transparent database has proven to be very useful. From this data, it is possible to see that there is often a highly variable amount of ARVs provided by the fund to select countries from year to year.

PEPFAR[50]

On the "Financial Management" cover page of the PEPFAR dashboard, it is possible to download an excel of the PEPFAR program expenditures from 2015-2019. While this excel is extremely detailed, it doesn't provide the same level of transparency as the Global Fund PQR reports. A PEPFAR database like the PQR report used to be available before 2015 but has been made non-public because "its

[48] See http://hivfinancial.unaids.org/hivfinancialdashboards.html.

[49] See https://insights.theglobalfund.org/t/Public/views/PriceQualityReportingTransactionSummary/TransactionSummary?iframeSizedToWindow=true&:embed=y&:showAppBanner=false&:display_count=no&:showVizHome=no

[50] See https://data.pepfar.gov/dashboards

release would pose a risk to ongoing operations" according to the data administrator responsible for its publication. Like the Global Fund PQR data, the PEPFAR expenditures excel show a highly variable amount of ARV spending from year to year in each country.

SADC Estimates

Data for ARV expenditure was also obtained from the office of the Senior Program Officer, Health and Nutrition at the Directorate of Social and Human Development (SHD). This data was obtained from member states and is derived from overall HIV/AIDS program spending. However, there appear to be significant discrepancies between this data and the data received from other sources (where there was generally a greater degree of consistency).

South Africa Tender Data[51]

The South African Department of Health regularly publishes the results of its medicines tenders in an excel sheet. This is a transparent source of detailed information similar to the PQR about all the ARV purchases made by the South African government. As one of the largest purchasers of ARVs in the world, this has proven to be a very useful source of data not only on market size but also on ARV utilization in SADC in general.

Primary Market Intelligence

Discussions with various SADC pharmaceutical firms in the ARV market also yielded market size estimates, particularly for the local national tenders. This source of data proved to be very important because outside of South Africa, few countries publicly announce the details of their ARV tender awards. Furthermore, challenges such as those depicted in Chapter 4D above can make information on national tender sizes less than transparent. Where possible, all data here was cross-checked with at least one other source.

Cost of Annual ART per person

Using data published by CHAI in their 2018 Annual HIV Market report along with data from a presentation given at Global Fund's annual procurement meeting in 2019, a cost of $90 per person per year was calculated for ARVs in LMIC. Since this price is based on donor prices for ARVs (known to be the lowest) and are Ex-Factory, this can be assumed to be the absolute lowest price point for annual ART per person. Using South African 2020 tender data, combined with the UNAIDS estimate for the total number of ART patients in South Africa, a cost of $115 per person per year was calculated. Since this price is inclusive of VAT and is based on DDP Incoterms, this can be assumed to be a reasonable top price point for ARVs purchased through public tenders in Africa.

[51] See http://www.health.gov.za/index.php/medicine?download=3675:master-procurement-catalogue-1-november-2019.

Table A 1: Breakdown of Donor Funding from various sources: Global Fund PQR Database, PEPFAR Program Expenditures Report, UNAIDS Financial Dashboard and SADC Directorate of Social and Human Development.

| Country | Donor Funds | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Direct from Donor Database | | | | | | UNAIDS Funding Reports | | | | SADC Data |
| | Global Fund (Based on Purchase Order date) | | | PEPFAR | | | | | | | |
| | 2017 | 2018 | 2019 | 2017 | 2018 | 2019 | GF | PEPFAR | Other Donor | Year | All Donors 2017 |
| ANGOLA | $1,360,185 | $1,246,757 | $0 | $197,736 | $0 | $0 | $1,820,269 | $4,447,779 | $0 | 2017 | $9,255,266 |
| BOTSWANA | $0 | $0 | $0 | $11,124,974 | $5,585,701 | $4,334,326 | $0 | $2,023,939 | $0 | 2017 | $32,120,528 |
| COMOROS | $17,839 | $1,705 | $3,361 | | $0 | $0 | $0 | $0 | $0 | 2017 | $1,171,652 |
| DR CONGO | $3,121,250 | $18,925,798 | $6,086,591 | $9,505,779 | $6,665,331 | $10,200,986 | $14,140,061 | $8,445,398 | $8,013,894 | 2014 | N/A |
| ESWATINI | $4,543,320 | $0 | $0 | $4,699,695 | $3,787,046 | $4,488,855 | N/A | N/A | N/A | N/A | N/A |
| LESOTHO | $5,938,715 | $0 | $6,030,873 | $3,288,470 | $0 | $0 | $5,968,901 | $501,937 | $207,510 | 2017 | $51,569,537 |
| MADAGASCAR | $181,022 | $270,330 | $46,344 | N/A | N/A | N/A | $0 | $29,026 | $0 | 2017 | $2,722,404 |
| MALAWI | $41,129,548 | $70,065,190 | $50,237,602 | $752,141 | $4,723,390 | | $0 | $0 | $46,231,461 | 2017 | $117,066,056 |
| MAURITIUS | $62,285 | $0 | $0 | N/A | N/A | N/A | $0 | $0 | $0 | 2018 | N/A |
| MOZAMBIQUE | $5,855,600 | $72,533,192 | $28,251,032 | $32,939,398 | $16,963,420 | $20,936,114 | $56,059,133 | $16,897,102 | $772,597 | 2016 | N/A |
| NAMIBIA | $8,721,354 | $5,344,698 | $610,946 | $0 | $41,105 | $597,886 | $9,834,590 | $23,543,990 | $0 | 2017 | $45,875,506 |
| SEYCHELLES | $0 | $0 | $0 | N/A | N/A | N/A | 0 | 0 | 0 | 2016 | N/A |
| SOUTH AFRICA | $10,341,489 | $14,614,966 | $20,299,035 | $696 | | $0 | $7,974,387 | $173,672,554 | $0 | 2017 | $298,464,788 |
| TANZANIA | $43,124,254 | $17,800,997 | N/A | $59,222,299 | $26,997,415 | $82,423,018 | N/A | N/A | N/A | N/A | N/A |
| ZAMBIA | $15,899,893 | $53,593,893 | $8,691,990 | $33,275,173 | $43,893,678 | $59,110,418 | $20,281,200 | $152,470,731 | $0 | 2017 | $221,056,417 |
| ZIMBABWE | $190,556 | $58,050,866 | $4,630,569 | $26,595,906 | $16,067,070 | $22,856,556 | $34,587,962 | $4,382,364 | $67,285,256 | 2017 | $159,596,989 |

Table A 2: Breakdown of National Public and Private Funding from various sources: Primary Market Intelligence, UNAIDS Financial Dashboard and SADC Directorate of Social and Human Development.

| Country | Government Market | | | | Private Market | | | |
|---|---|---|---|---|---|---|---|---|
| | Primary Intelligence | UNAIDS Funding report | | SADC Data | Primary Intelligence | UNAIDS Funding report | | SADC Data |
| | 2020 | Total Public | Year | All Local Funds 2017 | 2020 | Total Private | Year | All Private Funds 2017 |
| **ANGOLA** | | $2,730,403 | 2017 | $1,810,934 | | $0 | 2017 | $0 |
| **BOTSWANA** | $32,500,000 | $60,193,570 | 2017 | $55,324,948 | | $0 | 2017 | $0 |
| **COMOROS** | | $0 | 2017 | $81,936 | | $0 | 2017 | $25,265 |
| **DR CONGO** | | $24,793,740 | 2014 | N/A | | $47,530 | 2014 | N/A |
| **ESWATINI** | $13,500,000 | N/A | N/A | N/A | | N/A | N/A | N/A |
| **LESOTHO** | | $17,108,861 | 2017 | $11,466,269 | | $0 | 2017 | $0 |
| **MADAGASCAR** | | $0 | 2017 | $159,430 | | $0 | 2017 | $1,596 |
| **MALAWI** | $0 | $0 | 2017 | $3,076,795 | | $0 | 2017 | $0 |
| **MAURITIUS** | $0 | $3,372,711 | 2018 | N/A | | $0 | 2018 | N/A |
| **MOZAMBIQUE** | $10,000,000 | $0 | 2016 | N/A | | $0 | 2016 | N/A |
| **NAMIBIA** | $13,000,000 | $71,583,800 | 2017 | $68,473,796 | $150,000 | $9,763,430 | 2017 | $41,206,066 |
| **SEYCHELLES** | 0 | $160,927 | 2017 | N/A | | $0 | 2017 | N/A |
| **SOUTH AFRICA** | $583,568,758 | $1,028,430,792 | 2017 | $1,039,154,490 | | $0 | 2017 | $0 |
| **TANZANIA** | N/A | N/A | N/A | N/A | | N/A | N/A | N/A |
| **ZAMBIA** | $17,500,000 | $31,095,097 | 2017 | $20,179,417 | | $0 | 2017 | $648,634 |
| **ZIMBABWE** | $20,500,000 | $30,059,529 | 2017 | $27,297,634 | | $6,785,438 | 2017 | $42,989,758 |

Table A3: Estimates of total market spend based on CHAI and South Africa's average cost of ART per person per year of $90 and $115 respectively along with estimated size of each procurement channel.

| Country | Estimated Total ARV Spend 2018 | | | Breakdown of Procurement Channels | | | Total |
|---|---|---|---|---|---|---|---|
| | 2018 ARV Patients | $90/yr | $115/yr | Donor | Public | Private | |
| **Angola** | 88,734 | $7,986,060 | $10,204,410 | $6,268,048 | $2,730,403 | $0[f] | $8,998,451 |
| **Botswana** | 307,377 | $27,663,930 | $35,348,355 | $4,960,014 | $30,096,785 | $0[f] | $35,056,798 |
| **Comoros** | 96 | $8,640 | $11,040 | $7,635 | $0 | $0[f] | $7,635 |
| **Dr congo** | 256,486 | $23,083,740 | $29,495,890 | $18,168,578 | $0[a] | $0[f] | $26,289,815 |
| **Eswatini** | 177,156 | $15,944,040 | $20,372,940 | $8,681,270 | $13,500,000[c] | $0[f] | $22,181,270 |
| **Lesotho** | 206,298 | $18,566,820 | $23,724,270 | $6,678,348 | $17,108,861 | $0[f] | $23,787,209 |
| **Madagascar** | 3,510 | $315,900 | $403,650 | $165,899 | $174,489 | $19,388 | $359,775 |
| **Malawi** | 814,275 | $73,284,750 | $93,641,625 | $58,534,170[a] | $0 | $0[f] | $83,463,188[a] |
| **Mauritius** | 2,756 | $248,040 | $316,940 | $0 | $282,490 | $0[f] | $282,490 |
| **Mozambique** | 1,212,562 | $109,130,580 | $139,444,630 | $73,728,832[a] | $0[e] | $0[f] | $124,287,605[a] |
| **Namibia** | 184,245 | $16,582,050 | $21,188,175 | $5,105,329 | $13,000,000[c] | $0[f] | $18,885,113[a] |
| **Seychelles** | 554 | $49,860 | $63,710 | $0 | $160,927 | $0[f] | $160,927 |
| **South africa** | 4,788,139 | $430,932,510 | $550,635,985 | $15,085,163 | $583,568,758 | $90,000,000 | $688,653,921 |
| **Tanzania** | 1,108,728 | $99,785,520 | $127,503,720 | $86,676,870 | $26,967,750[a] | $0[f] | $113,644,620 |
| **Zambia** | 964,689 | $86,822,010 | $110,939,235 | $71,488,348 | $17,500,000[c] | $0[f] | $88,988,348 |
| **Zimbabwe** | 1,150,543 | $103,548,870 | $132,312,445 | $110,082,431[a] | $20,500,000[b] | $0[f] | $130,582,431 |
| **Total** | | **$1,013,953,320** | **$1,295,607,020** | **$465,630,934** | **$733,711,699** | **$90,019,388** | **$1,365,629,595** |

**Notes to Table A3**

a: Denotes values that need more due diligence to verify (See bullet points below),
b: Whilst there are issues related to government funding of their national ARV tender (according to recent industry feedback), there is an expectation that the tender will be roughly $19-22M/yr in the near future,
c: Estimates based on interviews with local SADC producers.
d: Given the uncertainties regarding the accuracy of the data constituting the donor and private market channels, in particular, the total figures should be regarded as 'best estimates.
e: According to local firms, there will be a public tender of approximately $5-10M in the near future.
f: The private markets are not truly $0 but are small in each case other than South Africa. Consequently, since there is not reliable data for each private market, they have been recorded as $0.

The "Breakdown of Procurement Channels" section of Table A3 (the same data depicted in Figure 5), was derived by comparing the various sources of donor, public and private ARV spending detailed in Figures A1 and A2. A final check of this was done by comparing the "Estimated Total ARV Spend 2018" data in Figure A3 with the total spend estimated for a country. By doing this, most gaps in funding were spotted and rectified except for:

- A shortfall of $36-66M between what ART is estimated to cost in Mozambique and the donor funding which has been identified from PEPFAR and Global Fund.
- A shortfall of $15-35M of a similar nature in Malawi and $5-11M in DRC are also observed.
- The UNAIDS report stated that there was $67M in donor funding for ARVs in Zimbabwe which came from sources other than PEPFAR and Global Fund, however no one that has been contacted can identify who these donors are to verify the amounts they have donated.
- The donor market in Tanzania doesn't seem to be sufficient to cover the needs there and it has been reported that the government does have an ARV procurement budget but the amount hasn't been verified yet

# Appendix B: Local value capture and employment model for ARV manufacture

Final Dosage Formulation (FDF) manufacturing facilities formulate products from API and excipients, form tablets or capsules and package. Most ARV products are FDF (i.e. tablets or capsules) and most government and donor tender products are packed into plastic jars rather than blister packs.

This model is based on insight provided by the CEO of a company that has built multiple FDF facilities in Africa. It has also been verified in its final form by this same CEO. It assumes a hypothetical facility that produces 1 billion tablets or capsules each year, a capital expense between $12-15M and a design consistent with WHO GMP specifications. It would take roughly 110 to 125 people to run it on two shifts, of which 10-15 are expats. It assumes ARV gross margins between 20-25% (NB this figure includes a local price preference - without which it would be in the region of only 5-8%), with a cost of goods breakdown for the products of 80% APIs/Excipients, 5% plastic jars, 15% other packaging material (PM).

Table B1: Local content breakdown of FDF ARV full manufacturing based on annual operation of ARV only facility.

| | 20% Margin | 25% Margin | 20% Margin | 25% Margin | |
|---|---|---|---|---|---|
| **ARV Sales** | $10,000,000 | $10,000,000 | $20,000,000 | $20,000,000 | |
| **Opex** | $2,400,000 | $2,520,000 | $2,400,000 | $2,520,000 | Local |
| | | | | | |
| **COGs** | $8,000,000 | $7,500,000 | $16,000,000 | $15,000,000 | |
| APIS/Excipients | $6,400,000 | $6,000,000 | $12,800,000 | $12,000,000 | Not Local |
| Jars | $400,000 | $375,000 | $800,000 | $750,000 | Not Local |
| Local PM | $1,200,000 | $1,125,000 | $2,400,000 | $2,250,000 | Local |
| | | | | | |
| **GM** | $2,000,000 | $2,500,000 | $4,000,000 | $5,000,000 | |
| as % of Total Sales | 20.0% | 25.0% | 20.0% | 25.0% | |
| | | | | | |
| **EBIDTA** | -$400,000 | -$20,000 | $1,600,000 | $2,480,000 | Mostly Local |
| | | | | | |
| **Total Local Value** | $3,200,000 | $3,625,000 | $6,400,000 | $7,250,000 | |
| Local (Local PM, Opex) | $3,600,000 | $3,645,000 | $4,800,000 | $4,770,000 | |
| Mostly Local (EBIDTA) | -$400,000 | -$20,000 | $1,600,000 | $2,480,000 | |
| as % of Total Sales | 32% | 36% | 32% | 36% | |

Please note the following:

- This example assumes the entire production capacity is devoted to ARV production throughout the year, which as discussed above is not representative of how most facilities would operate. However, it does enable the determination of the rough value of local value capture from the full manufacturing of ARVs.

- Given the assumption stated above, roughly $10M in annual sales is the breakeven point for a facility like this.
- OPEX is slightly higher for 125 employees than for 110. Thus, the higher OPEX cost in the 25% Gross Margin column represents the higher 125 employee value.
- It is assumed Jars are not procured from a local SADC manufacturer as is the case throughout most of the region now.
- OPEX should be mostly retained locally in the form of wages, utility payments, third-party services, etc.
- Expenses paid from Earning Before Interest, Depreciation, Tax and Amortization (EBIDTA) would also mostly stay local unless a disproportionate amount of the financing or ownership structure resides outside of the country.

While employment costs are captured above in the OPEX, it is also possible to estimate the total number of employees that could be employed from the ARV industry in the SADC region using the model in Figure B1. Using the South Africa tender data for 2019-22 combined with UNAIDS' estimate of the total number of people receiving ART in South Africa, it is estimated that each person on ART will require approximately 542 ARV tablets or tablets per year. This can then be used to extrapolate the total number of ARV tablets or capsules currently being used in each SADC country annually, and thus how many people the production of ARVs could employ if all ARVs were made locally.

Table B2: Estimate of total ARV tablets/capsules used in each SADC country annually, regardless of source, along with estimated number of Full Time Equivalents (FTEs) dedicated to running facilities for ARV manufacture.

| Country | ARV Patients 2018 | ARV tablets 2018 | ARV FTEs Form/Pkg | ARV FTEs PKG only |
|---|---|---|---|---|
| ANGOLA | 88,734 | 48,057,283 | 6 | 4 |
| BOTSWANA | 307,377 | 166,471,740 | 21 | 14 |
| COMOROS | 96 | 51,992 | 0 | 0 |
| DRC | 256,486 | 138,909,778 | 17 | 12 |
| ESWATINI | 177,156 | 95,945,590 | 12 | 8 |
| LESOTHO | 206,298 | 111,728,552 | 14 | 9 |
| MADAGASCAR | 3,510 | 1,900,974 | 0 | 0 |
| MALAWI | 814,275 | 441,001,690 | 55 | 37 |
| MAURITIUS | 2,756 | 1,492,617 | 0 | 0 |
| MOZAMBIQUE | 1,212,562 | 656,709,209 | 82 | 55 |
| NAMIBIA | 184,245 | 99,784,908 | 12 | 8 |
| SEYCHELLES | 554 | 300,040 | 0 | 0 |
| SOUTH AFRICA | 4,788,139 | 2,593,199,336 | 324 | 216 |
| TANZANIA | 1,108,728 | 600,473,945 | 75 | 50 |
| ZAMBIA | 964,689 | 522,464,129 | 65 | 44 |
| ZIMBABWE | 1,150,543 | 623,120,453 | 78 | 52 |
| **Total** | | | **763** | **508** |

A few things to note:

- A direct means of calculating the actual number of people employed making ARVs requires good sources of primary data which is lacking. For example:
    - Estimating this directly from manufacturers themselves is difficult because identifying each company is rather difficult let alone getting a meeting set with them. Furthermore, since each company usually makes more than just ARVs (often one line will make ARVs one week and another product the next), estimations of the % of their workforce who are devoted to making ARVs will vary considerably from company to company. Asking them for the sensitive head count, sales and production data to complete the analysis for this report would also not be possible to do for all of the companies.
    - Labour statistics from ILO, SADC and the countries themselves are often quite a few years old and aren't specific enough to determine how many people work in the pharmaceutical manufacturing industry, let alone make ARVs. See below for more on this.
- Table B2 represents the total estimated number of people who would be employed making ARVs if all of the country's ARVs were produced locally. It is known this is not the case for each country including South Africa. Therefore, it is reasonable to assume the total number of people directly employed in the production of ARVs in SADC is probably between 125-175, with most of them being in South Africa.
- These numbers are based on Full Time Equivalents (FTEs) which are the number of hours worked by an employee on a full-time basis. This is because most employees will not be devoted to the production of ARVs for the full year and thus their time must be prorated accordingly.
- The number for those needed to work in a packaging only facility would be roughly ⅔ of those needed in a full manufacturing facility of equal size. Most of the ancillary and support staff would still be needed in places like the warehouse, offices (HR, accounts, procurement, management, etc.), quality labs, quality assurance and facilities management. Furthermore, packaging operations tend to be more manpower-intensive than formulation and tabletting which must all be automated.
- This estimate of 125 employees represents only one company's operating model for newly constructed facilities operating at WHO GMP levels. There are multiple competing factors that may shift this number. Older facilities or state-owned ones may have higher overall staff numbers as they tend to be run less efficiently. Higher automation can greatly reduce the number of employees, especially in a place like packaging where one machine run by 1-2 operators can replace 5-10 manual packers. By contrast, higher quality levels will typically increase the number of employees. According to one report, 22%[52] of staff at Sanofi's South African facility works on quality management. This is a much higher proportion of quality staff than most Sub-Saharan African pharma manufacturers. Lastly, there are several labour intensive functions (such as canteen, cleaning, calibrations and maintenance, security and landscaping) which could be done in house by employees or contracted out to third parties, further varying the onsite headcount. It is also important to note that capacity utilization and the size of the facility also play a big role in determining final headcount. For example, a

[52] Hera Consulting group's "Feasibility study on Regional Manufacturing of Medicines and Health Commodities"

facility that runs 1 shift, 5 days a week will have a much higher ratio of indirect to direct labour than the same sized one that runs 3 shifts 7 days a week. This is in part why the CEO who provided the financing estimate in Figure B1 also assumed roughly 250 indirect jobs could also be created from a facility with 125 direct employees producing 1B FDF units per year.

- Women typically account for the minority of employees in most Sub-Saharan African pharmaceutical manufacturing facilities. The percentage of female employees typically ranges from 20-40%[53] of the workforce. In general terms women are more likely to be:
    - Preferentially employed compared to men in functions such as: cleaning, manual packaging, office administration and canteen roles.
    - Employed in roughly equal numbers compared to men in functions such as: quality assurance, laboratory and office roles
    - Employed less often in functions such as: equipment operator, production supervisor, maintenance or engineering.

Three sources of employment data were reviewed but none provided the level of granularity needed to estimate the number of pharmaceutical manufacturing jobs let alone the number of ARVs jobs.

1) SADC[54]: SADC used to issue a yearbook that had detailed economic data for each country, but this has not been published since 2014. SADC's Selected Indicators report[55] was last published in 2018 and provides an estimate of the total workforce in each country. However, there is no indication of the size of the workforce in the manufacturing sector let alone the employment in different manufacturing industries.
2) National Reports: Two country-level labour reports were reviewed: South Africa[56] (published quarterly) and Namibia[57] (last published in 2018). Both countries' reports give an employment number for the Manufacturing sector, but neither break this down further into different manufacturing industries.
3) International Labour Organization (ILO): The ILO is the focal point to the United Nations on labour statistics. As such, they work to create reports with standard labour statistical categories using various sources to aid the compatibility of these statistics across multiple countries. Therefore, rather than searching for each country's labour reports, it was deemed easier and more accurate to use ILO generated reports here. However, these reports are still limited by what is published in the national reports from which they are derived. For this reason, ILO reports still didn't provide pharmaceutical manufacturing specific employment data for all SADC countries (see Table B3 below).

[53] Based on Authors' experience working in various pharma manufacturing facilities throughout Africa

[54] See https://www.sadc.int/information-services/sadc-statistics#Indicators.

[55] See https://www.sadc.int/files/6215/6630/2592/SADC_Selected_Indicators_2018.pdf.

[56] See http://www.statssa.gov.za/?page_id=737&id=1.

[57] See https://d3rp5jatom3eyn.cloudfront.net/cms/assets/documents/Labour_Force_Survey_final_-_2018.pdf.

Table B3: ILO "Employment by sex and economic activity - ISIC level 2 (thousands)" report depicting total thousands employed in the Manufacture of pharmaceuticals, medicinal chemical and botanical products.

| Country | Sex | Source Date | 1000's Employed | Label from ILO Report |
|---|---|---|---|---|
| **Comoros** | Total | 2014 | 0.1454 | Unreliable |
| **Comoros** | Male | 2014 | 0.0666 | Unreliable |
| **Comoros** | Female | 2014 | | Unreliable |
| **Tanzania, United Republic of** | Total | 2014 | 1.5897 | Break in series* |
| **Tanzania, United Republic of** | Male | 2014 | 0.929 | Break in series* |
| **Tanzania, United Republic of** | Female | 2014 | 0.6607 | Break in series* |
| **Zambia** | Total | 2018 | 2.2694 | Unreliable |
| **Zambia** | Male | 2018 | 2.2694 | Unreliable |

*the more often there are breaks in regular data collected

Most ILO reports show data down to the manufacturing sector only and not all SADC countries are included, presumably due to the lack of a national employment report in that country. Figure B3 is the only ILO report which included data depicting total numbers employed in the Manufacture of pharmaceuticals, medicinal chemical and botanical products. However, a few issues still exist even with this data:

- Most of it is from 2014 and deemed unreliable or as a "break-in series"[58], a specific term for why the data is unreliable
- Only three countries in SADC had data broken down to the ISIC[59] Level 2 which in part includes pharmaceutical manufacturing
- This category also includes the production of other medicinal chemicals and botanical products which can be sizable operations on their own. Well, known examples of these include the production of traditional herbal medicines, cosmetic botanicals and botanical products like Artemisinin which is used in the production of the antimalarial drug Artemether. Thus, even this data can't be meant to reflect the total pharmaceutical manufacturing jobs in the country let alone ARV production jobs.

[58] According to https://ilostat.ilo.org/topics/covid-19/covid-19-impact-on-labour-market-statistics/, the more often there are breaks in regular data collection, the less reliable that data will be

[59] International Standard Industrial Classification (ISIC) of All Economic Activities

# Appendix C: API Production Case Study

The question of whether large scale API production in Africa makes sense has been an ongoing debate. The drivers to do so are very clear as it would increase industrialization, shorten supply lines, lessen imports, and increase the security of supply for life-saving medicines. However, the fact remains that there is almost no API production occurring on the continent apart from Fine Chemicals in Cape Town, South Africa (a subsidiary of Aspen) and one other in Egypt. The often-quoted company in Ghana, LaGray, closed down around 2018 after running into financial trouble. The brief case study below offers a perspective on the challenges of setting up an ARV API facility.

The HERA consulting group's "Feasibility study on Regional Manufacturing of Medicines and Health Commodities" study that was commissioned by the SADC Secretariat and financed by the African Development bank in 2015 laid out a plan for API production of Tenofovir as a viable option. It estimated that the facility would take roughly 5 years to plan, build and commission and cost between $5-10M depending on whether it was a traditional batch operation or continuous flow operation. The target capacity was stated to be 2,200 metric tonnes which the report estimated would constitute the entirety of the Tenofovir required to treat the 15M patients it expected would be on ARVs in SADC by 2020. There was no detailed financial feasibility published but, it did state that the expectation was that Tenofovir would no longer need to be imported from China or India from which one can draw two conclusions: 1) a capacity of roughly 2,200 metric tonnes would yield a financially viable enterprise and 2) the cost would be competitive enough with Chinese and Indian sources that companies would willingly buy it.

Since the readers of this report are likely aware of the HERA study, it seemed appropriate to use it as a basis to discuss some of the biggest barriers to entry for ARV API production in Africa. With the advantage of hindsight, it is also possible to look back and see just how certain project assumptions would have played out over the planned facility construction period.

Uncertain Volumes of Tenofovir

According to the 2019 Clinton Health Access Initiative (CHAI) annual HIV market report[60], the total need for Tenofovir for the roughly 19M people receiving ARVs in all Lower Middle-Income Countries (LMICs) where generic ARVs are widely accessible, would peak at roughly 2,000 metric tonnes in 2021. The 2015 CHAI HIV market report[61] estimated that by 2019, the global Tenofovir market would be roughly 1,600 metric tonnes, a similar number to what it reported in 2019. This suggests that the SADC region (which has roughly 60% of all people on ART in LMICs) would never have 2,200 metric tonnes of Tenofovir being used in 2020. In fact, according to these estimates, SADC will only need roughly half of these 2,200 metric tonnes in 2021 when the demand for Tenofovir is expected to peak.

Data from the South Africa ARV tender seems to support this view as well. Over the 2019-22 tender period, South Africa will purchase 532 tonnes of tenofovir annually in various products to treat its

[60] See https://www.clintonhealthaccess.org/the-state-of-the-hiv-market-in-low-and-middle-income-countries-2/

[61] See https://www.clintonhealthaccess.org/arv_market_report_2015/

roughly 4.8 million HIV positive citizens receiving ARVs. Granted, this is the total estimated number of those in South Africa receiving ARV treatment according to UNAIDS and some may not be receiving their ARVs from the government as there is a sizeable private market there. However, if that data is extrapolated to what would be required for the original target market of 16M patients, that would result in only 1670 tonnes of tenofovir being needed. Furthermore, since UNAIDS estimates that only 11.3M people in SADC are taking ARVs as of 2018, the region may be somewhat closer to needing only 1200 or 1300 tonnes of Tenofovir today.

The HERA report was also written at a time where there were fewer WHO Prequalified manufacturers of Tenofovir API (and presumably fewer Tenofovir API without PQ). Thus, it may have been possible for a single additional manufacturer could be expected to gain a significant market share. In 2014, there was only one API manufacturer with WHO PQ with three more being added in 2015, and five more in 2018. Today there is a total of 9 total, making it highly unlikely one coming online now would find the same market conditions which existed when the hera report analysis was done.

Additionally, one of the most stated barriers to entry for ARV producers everywhere on the value chain is that the ART regimens change so often that it is hard for anyone but the big global innovators to keep pace. By the time a smaller company independently develops the capability to produce a given product, the treatment protocol has most likely moved on and the forecasted demand and price falls accordingly. However, lower than expected volumes does not seem to be the case here according to the CHAI reports which have shown consistent data projections over the past 4 years. Instead, this would have been deemed more a failure of market intelligence than of a sudden lack of demand due to a shifting regimen.

If the facility would have been built based on the assumptions listed in the original report, it most likely would have found itself in an untenable situation running at approximately 60% of its capacity in a market with such tight margins. However, even if the facility had been built to produce the 12-1300 metric tonnes of Tenofovir that SADC uses today, it would have found it very difficult to capture the entire SADC market.

<u>Single Source of Tenofovir for SADC</u>

It is highly unlikely that all Tenofovir for the entire SADC region would come from a single facility for a few reasons:

1. There are now 9 different WHO Prequalified sources of Tenofovir
2. Less than 0.2% of all Tenofovir that was purchased in the recent South Africa tender was for Tenofovir as an active ingredient on its own. The vast majority of Tenofovir was purchased as fixed dose combinations (FDCs) with Emtricitabine, Efavirenz, Lamivudine and/or Dolutegravir. Therefore, the other APIs that are needed to make these FDCs would have to come from another supplier. It is unlikely that a Chinese or Indian firm (especially vertical integrated ones competing with local African firms producing the FDCs or ones that also produce Tenofovir) would be willing to sell the other APIs to African firms at a price cheap enough for the African firms to win global tenders. ARVs have notoriously thin margins already.
3. In markets outside of South Africa, the majority of ARVs are provided by donors, these donors would also need to compel their existing suppliers to buy Tenofovir from this facility which is

unlikely to happen for two main reasons: 1) these suppliers already have existing supply agreements for APIs are making them themselves, 2) the new API product would then need to have WHO PQ to sell to Global Fund suppliers and US FDA approval for PEPFAR suppliers. Clearing the additional WHO-PQ and US FDA hurdles alone would increase the timeline for the project and add extra cost pressure to already thin margins.

4. The new API producer would still find it difficult to capture the entirety of the remaining market comprised of the few local independent manufacturers of Tenofovir containing products (mostly in South Africa). This is because many of these are subsidiaries or partners of the same multinational firms who are selling to the donors and thus receive their APIs from those international sources.
5. Lastly, pooled procurement in the pharma industry regionally and domestically in Africa has proven to be very difficult both at the finished goods level and the API/Excipient level.

Thus, this new producer would hardly be able to count on all Tenofovir in the region being bought from them, reducing their overall capacity utilisation even further.

Higher Costs in Africa

Energy, borrowing, equipment maintenance, and skilled labour (often expats) all tend to cost more in Africa than in many other places. One former executive from Strides mentioned that the biggest barrier to API production in Africa was freight costs, generally, 10 tonnes of intermediate materials are needed to produce 0.5 to 1 ton of API. The higher transportation costs of intermediates to sites in Africa, usually from China or India, and finished API throughout Africa, where its often cheaper or faster for cross-continent shipments to travel via Europe, would push costs above international market prices.

**Conclusion**

Due to the barriers above, it seems highly unlikely that the majority of the Tenofovir needed in SADC will be produced locally in SADC. It is possible that Tenofovir or other ARVs could be produced in smaller quantities and sold to various local manufacturers. This will most likely not be using traditional batch processing and existing synthesis pathways due to the lack of the economies of scale required for competitive pricing.

It could be possible for a smaller producer of API that would not have to rely solely on large economies of scale to bring its COGs in line with the rest of the industry. The ability to produce smaller volumes may also further insulate them from shifting treatment protocols since they may still be able to compete with a portfolio of products at these smaller volume levels.

One such project is being evaluated for South Africa but due to strict confidentiality, details on the project are scarce. However, the plan will be to use batch manufacturing combined with novel synthesis routes to produce a portfolio of APIs which would be sold to local manufacturers to combat the ever-changing ARV regimen changes and slim margins, the company plans to produce ARVs along with other generic medicine APIs, such as tuberculosis, which have more stable, long term demand profiles and higher margins.

In the meanwhile, the strengthening of pooled procurement mechanisms and local manufacturing of ARVs in their final form would be great enablers to any future API production on the continent. After all, without local independent full manufacturers, there will be no market for this API manufacturer to sell to.

As an update to the HERA study in 2015, a pre-feasibility study[62] on local manufacturing in the SADC region was carried out in 2020. A SWOT Analysis was carried out and the below was found:

**Strengths**

- **Growing market:** Growing domestic pharmaceutical markets, with existing trade agreements and regional harmonisation protocols within SADC.
- **Low-cost labour:** Relatively low cost of labour.
- **Favourable legislation:** Legislation for delineation of designated industries exists in some countries (demand-side measures to stimulate local production).
- **Existing pharma network:** Existing clusters of pharmaceutical production in RSA, Zimbabwe, Tanzania, Namibia and DRC with well-established downstream companies (formulation, packaging and distribution).
- **Suppliers are far away:** Large distances to major suppliers, hence high transport costs for bulkier products, thus attractive to produce locally.

**Weaknesses**

- **Lack of knowledge, skills:** Limited technical expertise especially in API manufacture, weak regulatory agencies in most SADC countries.
- **Poor financing conditions:** the high cost of capital with limited availability, and inability to attract foreign direct investment from international pharmaceutical companies due to regulatory or legal barriers experienced in the SADC region.
- **Weak industry infrastructure:** limited supporting industries outside clusters, high utility costs and varying reliability.
- **Fragmented procurement:** limited regional cooperation in pharmaceutical procurement, poor governance in many countries, low level of compliance within SADC to previously-agreed policy initiatives and trade dominated health policy (which does not promote local manufacturing)

**Opportunities**

- **Serving high needs in quality and accessibility:** large burden of disease which requires treatment (HIV in RSA and elsewhere, malaria in SADC except RSA) based on local products, opportunity to address the issue of 'pharmaceutical security' (reducing import dependency

[62] Bertoldi, A., Walwyn, D., Marais, S., Cloete, L, van Lieshout, B., Dean, G.N., & Stanco, R. (2020). SADC pharma pre-feasibility study, Prepared for the Southern African Development Community (SADC).

and improving the security of supply), more robust regulatory oversight (especially of API quality).

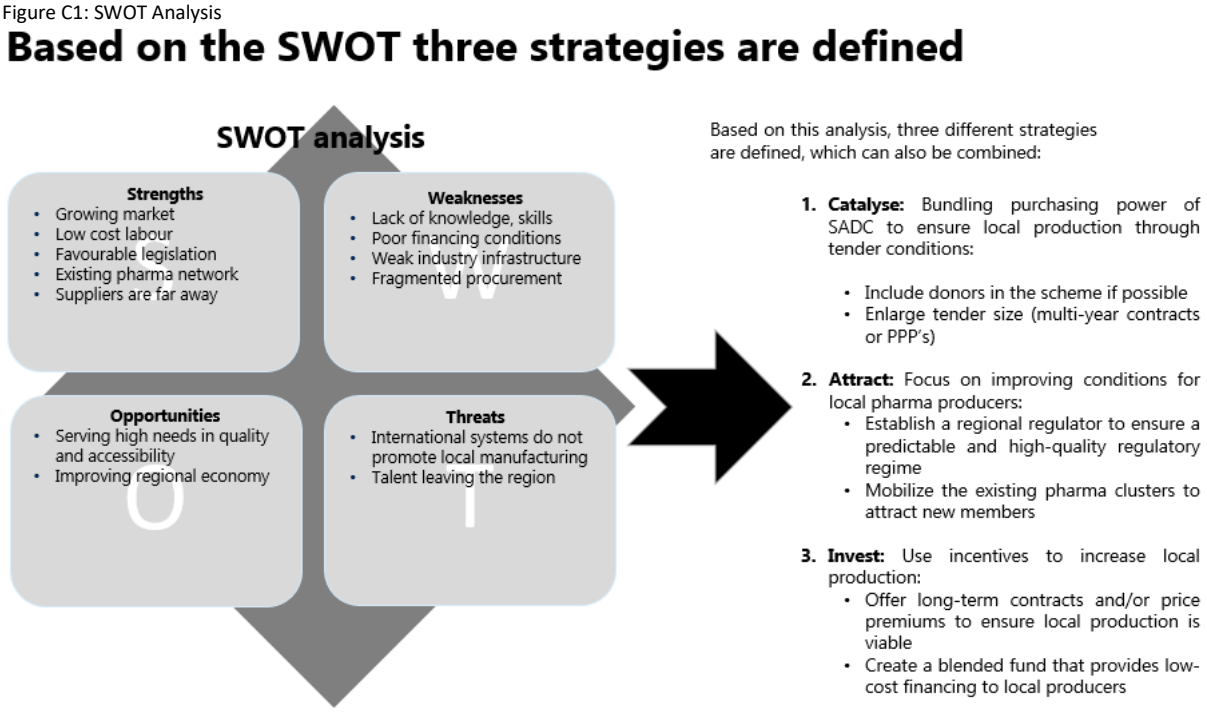
- **Improving regional economy:** Boost the manufacturing of high/medium technology products and services across the region, developing all the associated components of the cluster including laboratories for pharmaceutical testing and equipment manufacturers, increasing local economic value-added and economic activity in general, increasing regional employment, reduce the deficit on the balance of payments as a result of lower imports.

**Threats**

- **International systems do not promote local manufacturing:** Powerful socio-technical regimes that resist local manufacturing, much of pharmaceutical procurement driven by international aid agencies which use country-national suppliers or accredited suppliers, international trade agreements which limit technology transfer e.g. for certain drugs. This is compounded by the market power of major incumbents in certain sectors such as glove manufacture.
- **Talent leaving the region:** Emigration of key personnel with the required expertise in pharmaceutical manufacturing.

Based on this SWOT analysis, three different strategies have been defined, which can also be combined. The SWOT analysis is shown in **Figure 5** below.

Figure C1: SWOT Analysis



# Appendix D: Sales of ARVs to Global Fund by African Firms

The one seemingly straightforward way to localize more of the ARV value chain in SADC is for local manufacturers to obtain the required regulatory approval for their ARVs to sell them through the donor procurement channels.

Only four companies in Sub-Saharan Africa have ever achieved WHO-PQ for an ARV product: Quality Chemical Industries Ltd in Uganda, Universal Corporation Ltd in Kenya, Varichem Pharmaceuticals Ltd in Zimbabwe, and Aspen Pharmacare Ltd in South Africa. Furthermore, only Aspen has ever achieved US-FDA approval for an ARV which would enable it to win PEPFAR tenders.

Quality Chemical Industries Ltd (QCIL) - Uganda

- A wholly-owned subsidiary of India's Cipla, a large manufacturer of WHO-PQ ARVs.
- Received technical assistance and technology transfers from CIPLA to achieve WHO PQ.
- Cipla Medpro a South African based, wholly-owned subsidiary of Cipla but has no WHO-PQ approved products nor is it planning to pursue it.

Universal Corporation Ltd - Kenya

- A wholly-owned subsidiary of India's Strides, a large manufacturer of WHO-PQ ARVs.
- Achieved WHO-PQ for its first and only ARV in 2009 on its own before being purchased by Strides in 2016.

Varichem Pharmaceuticals Ltd - Zimbabwe

- Fully owned by private Zimbabwean shareholders.
- Achieved WHO-PQ for their ARV product in 2013 on their own before losing their WHO PQ status in 2016 and subsequently exiting the ARV market altogether.

Aspen Pharmacare Ltd - South Africa

- Publicly traded multinational based in South Africa.
- Currently have WHO-PQ for two ARVs down from nine as reported by the "Feasibility study on Regional Manufacturing of Medicines and Health Commodities" study conducted by the hera consulting group in 2015.
- The only company in Africa with US FDA approval for its ARVs, enabling it to win PEPFAR tenders (currently 1 active and 6 withdrawn approvals)[63].
- Launched their TLD product, the currently recommended first line treatment and the highest grossing ARV globally, in late 2018 but still do not have WHO PQ for it while 8 others do[64].

[63] See https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=pepfar.page
[64] See https://extranet.who.int/prequal/content/prequalified-lists/medicines

Table D1: ARV Sales from African manufacturers to Global Fund from 2011 to 2019 (no sales in 2017)[65].

| Manufacturer | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2018 | 2019 | Grand Total |
|---|---|---|---|---|---|---|---|---|---|
| Aspen Pharmacare | $171,328 | $2,422,511 | $5,722,105 | $75,268 | $4,526 | $44,656 | $103,332 | $108,563 | **$8,652,287** |
| QCIL | | | | | $7,858,717 | | | | **$7,858,717** |
| Universal | | | $126,600 | $57,888 | | | | | **$184,488** |
| Varichem | $110,757 | $19,094 | | | | | | | **$129,851** |

Table D1 depicts the total sales by these four companies to the Global fund since 2011. A similar set of sales figures could not be obtained from PEPFAR as they have ceased publishing this data.

A few observations can be drawn from this data:

- Sales volumes for Varichem and Universal were never very large, despite Universal being a subsidiary of a top global ARV manufacturer since 2016.
- Except for a single year of large sales, QCIL hasn't sold much to Global Fund despite having the backing of a large parent company
- Sales for Pharmacare have dropped significantly starting in 2013, in line with the lapsing of the PQ status of many of its ARVs. This includes no sales in 2017 or thus far in 2020.

These observations are consistent with multiple conversations this team has had with top management at companies throughout Sub-Saharan Africa including QCIL, Varichem and Universal as well as others who have pursued WHO-PQ. Furthermore, the aforementioned "Feasibility study on Regional Manufacturing of Medicines and Health Commodities" study conducted by the HERA consulting group in 2015 echoes a similar theme.

[65] See https://insights.theglobalfund.org/t/Public/views/PriceQualityReportingTransactionSummary/TransactionSummary?iframeSizedToWindow=true&:embed=y&:showAppBanner=false&:display_count=no&:showVizHome=no

# Appendix E: Pharmaceutical manufacturing-related Study programmes in SADC

Details are available for the following countries: Botswana, Namibia, Tanzania, Zambia, Zimbabwe (in alphabetical order).

**Botswana:**

| **University of Botswana UB, Gaborone** https://www.ub.bw/ | | | | | | |
|---|---|---|---|---|---|---|
| **Faculty** | **Study programme** | | | **Study Programme** | | |
| | **BSc (NQF 7) B Hon (NQF 8)** | **Duration of studies** | **Training capacity** | **MSc (NQF 9)** | **Duration of studies** | **Training capacity** |
| Faculty of Health Sciences – School of Pharmacy | B Pharm | 4yft | 33/year | None | | |
| Faculty of Science | BSc Chemistry | N/A | 52/year | MSc Chemistry<br><br>MSc Applied Microbiology (2yft) | 2yft<br><br>2yft | N/A<br><br>N/A |
| Faculty of Medicine | None | | | MPhil in Biomedical Sciences (2yft) | N/A | N/A |
| Faculty of Engineering and Technology | BSc in Mechanical Engineering | 5yft | 75/year | MSc in Mechanical Engineering (2yft or 3ypt) | 2yft | N/A |
| **TVET-Level** | | | | | | |
| | **Certificate level (NQF 4)** | | | **Diploma level (NQF 6)** | | |
| **Boitekanelo College, Gaborone** | None | | | Higher National Diploma in Pharmacy Technology | 3yft | 35-40/year |

**Namibia:**

| **University of Namibia UNAM, Windhoek** https://www.unam.edu.na | | | | | | |
|---|---|---|---|---|---|---|
| **Faculty** | **Study programme** | | | **Study programme** | | |
| | **BSc (NQF 7) B Hons (NQF 8)** | **Duration of studies** | **Training capacity** | **MSc (NQF 9)** | **Duration of studies** | **Training capacity** |
| Faculty of Health Sciences – School of Pharmacy (FIP-Recognition) | BPharm Hons | 4yft | 40/year | MPharm clinical pharmacy<br><br>MPharm pharmaceutical chemistry (start in spring 2021)<br><br>MPharm industrial pharmacy (planned and process started, but uncertain development) | 3yft<br><br>2-3yft | 10/year (capacity for 15)<br><br>2/year |
| Faculty of Science | BSc Hons Medicinal Chemistry<br><br>B Sc Hons Microbiology | 4yft | N/A | MSc Chemistry<br><br>MSc Microbiology | 2yft or 3ypt<br><br>2yft | 5/year<br><br>8/year |
| Faculty of Engineering and Information Technology | BSc Hons Mechanical Engineering | 4yft | N/A | None | | |
| **TVET** | | | | | | |
| | **Certificate level (NQF 4)** | | | **Diploma level (NQF 6)** | | |
| **UNAM Faculty of Health Sciences – School of Pharmac**y | None | | | Pharmacist Technologist (Conditions of admission: Certificate as Pharmacist Assistant) | 2ypt | 30/year |
| **Welwitcha Health Training Center** Windhoek | Pharmacist Assistant | 2yft | N/A | None | | |
| **The International University of Management** with the Pharmaceutical Society of Namibia (joint offer), Windhoek | Pharmacist Assistant | N/A | N/A | None | | |

**Tanzania:**

| **Muhimbili University of Health and Allied Sciences, Dar es Salaam**<br>https://www.muhas.ac.tz/. | | | | | | |
|---|---|---|---|---|---|---|
| **Faculty** | **Study programme** | | | **Study programme** | | |
| | **BSc (NQF 7)**<br>**B Hons (NQF 8)** | **Duration of studies** | **Training capacity** | **MSc (NQF 9)** | **Duration of studies** | **Training capacity** |
| School of Pharmacy<br><br>FIP-Recognition Cooperation with Karolinska Institute for MSc- and PhD-Training | Bachelor of Pharmacy | 4yft | 60 – 80 /year | Mpharm Industrial Pharmacy<br>Mpharm Pharmaceutical Microbiology<br><br>Mpharm Quality Assurance/Quality Control | 2yft | 5-10/year |
| School of Medicine | Bachelor of Biomedical Engineering<br>Bachelor of Clinical Chemistry<br>Bachelor of Medical Laboratory Sciences (BMLS) | N/A | N/A | Master of Medicine Microbiology and Immunology (MMed Micro/ Immuno)<br>MSc Biochemistry | N/A | N/A |
| **University of Dar-es-Salaam, Dar es Salaam** | | | | | | |
| | **BSc (NQF 7)**<br>**B Hons (NQF 8)** | | | **MSc (NQF 9)** | | |
| College of Engineering and Technology COET | BSc Mechanical Engineering | 4yft | N/A | None | - | - |
| College of Natural and Applied Sciences CONAS | BSc of Chemistry | 3yft | 30/year | MSc in Chemistry (Coursework and Dissertation) | 2yft | 20/year |

| | | | | | | |
|---|---|---|---|---|---|---|
| College of Natural and Applied Sciences CONAS | BSc of Applied Microbiology and Chemistry | 3yft | 60/year | None | | |
| | BSc in Microbiology | N/A | 60/year | | | |
| | BSc. in Molecular Biology and Biotechnology | N/A | 60/year | | | |
| College of Natural and Applied Sciences CONAS | None | - | - | MSc in Biochemistry (Coursework and Dissertation) | 2yft | 20/year |
| **TVET-Level**<br><br>**Kilimanjaro School of Pharmacy KSP, Moshi**<br>https://ksp.ac.tz/ | | | | | | |
| **Certificate Level NQF 4** | **Higher Certificate Level NQF 5** | | | **Diploma Level NQF 6** | | |
| Basic Technician Certificate in Pharmaceutical Sciences* | Technician Certificate in Pharmaceutical Sciences* | 1yft each | | Ordinary Diploma in Pharmaceutical Sciences* | 1yft | |
| 3 years full time in total, 100 – 150 students/year over all three levels | | | | | | |

**Zambia:**

| University of Zambia, Lusaka<br>https://www.unza.zm/ | | | | | | |
|---|---|---|---|---|---|---|
| **Faculty** | **Study programme** | | | **Study programme** | | |
| | **BSc (NQF 7)<br>B Hon (NQF 8)** | **Duration of studies** | **Training capacity** | **MSc (NQF 9)** | **Duration of studies** | **Training capacity** |
| School of Health Sciences – Department of Pharmacy (FIP-recognition) | Bachelor of Pharmacy | 5yft | 65 – 90/year | Master of Clinical Pharmacy (MclinPharm)<br><br>Master of Science by Research:<br>MSc in Clinical Pharmacology & Nutrition<br>MSc in Pharmaceutics (Pharmaceutical Technology<br>MSc in Pharmacognosy<br>MSc in Pharmacy Practice<br>MSc in Pharmaceutical Chemistry | 2yft or 3ypt, each plus 6 months for field data collection | 10/year<br><br>5/year/ programme |
| | | | | MSc Industrial Pharmacy<br>(Start September 2021) | 2yft | Planned for 20 students |
| School of Health Sciences – Department of Biomedical Sciences | BSc in Biomedical Sciences | 5yft | 50/year | MSc by Research<br>MSc in Immunology<br>MSc in Parasitology<br>MSc in Medical Microbiology | 2yft | 5/year/ programme |
| School of Medicine | None | | | Master by Research:<br>MSc in Pharmacology<br>MSc in Biochemistry<br>MSc in Medical Microbiology<br>MSc (Medicine Microbiology | 2yft | 5/year/ programme |
| School of Natural Sciences | BSc in Chemistry: various options, but no detailed information available<br>BSc in Microbiology: no detailed information available | N/A | N/A | MSc in Applied Microbiology: no information available<br>MSc in Chemistry: 3 options, Analytical chemistry, medicinal chemistry, natural products chemistry | 2yft | 5/year/ programme |
| School of Engineering | BSc of Mechanical Engineering (5yft) | 5yft | 90-100/year | Master in Electrical Power Systems | 2yft | 5/year |

| | | | | | | |
|---|---|---|---|---|---|---|
| | BSc Electrical & Electronics Engineering | | | | | |
| **Copperbelt University, Kitwe** https://www.cbu.ac.zm/ | | | | | | |
| COPPERBELT UNIVERSITY School of Mathematics & Natural Sciences | BSc in Biotechnology | 5yft | 40/year | MSc in Biotechnology | 2yft | 5/year |
| COPPERBELT UNIVERSITY School of Mines & Mineral Sciences | B.Eng. in Chemical Engineering | 5yft | 40/year | MSc in Chemical Engineering | 2yft | 5/year |
| **TVET** | | | | | | |
| | **Certificate level (NQF 4)** | | | **Diploma level (NQF 6)** | | |
| **Evelyn Hone College, Lusaka** Health and Applied Sciences | None | | | Pharmacist Technologist | 3yft | 120/year |

## Zimbabwe:

| **University of Zimbabwe, Harare**<br>https://www.uz.ac.zw/ | | |
|---|---|---|
| **Faculty** | **Study programme** | |
| | **BSc (NQF 7)**<br>**B Hons (NQF 8)** | **MSc (NQF 9)** |
| Faculty of Medicine and Health Sciences<br>School of Pharmacy<br>(FIP-Recognition) | BSc Honours Pharmacy<br><br>BSc Honours Drug Discovery and Therapeutics | MPhil (no details available) |
| Faculty of Medicine and Health Sciences<br>Department of Biomedical Sciences | **BSc Honours Biomedical Sciences (with pathways to):**<br>Biomedical Engineering;<br>Biomedical Informatics;<br>Medical Laboratory Sciences etc. | MPhil (no details available) |
| Faculty of Medicine and Health Sciences<br>**Department of Biomedical Informatics and Biomedical Engineering** | BSc Honours Biomedical Engineering | MSc Biomedical Engineering |
| Faculty of Medicine and Health Sciences<br>Department of Medical Microbiology | None | MSc Medical Microbiology |
| Faculty of Science Department of Chemistry | BSc Honours in Chemistry (CHH)<br>BSc Honours Industrial Chemistry | MSc in Analytical Chemistry (MACH) |
| Faculty of Science<br>Various Departments, the information about the programs offered, vary within the website | BSc Honours Biotechnology and Biochemistry (with options in):<br>Biotechnology and Molecular Biology<br>Immunology and Microbiology | MSc Industrial and Environmental Biotechnology<br><br>MSc in Biotechnology (MBTC) |
| Faculty of Engineering and the Built Environment | BSc Honours Chemical Engineering<br>BSc Honours Mechanical Engineering | None |
| **Harare Institute of Technology HIT, Harare**<br>https://www.hit.ac.zw/ | | |
| School of Industrial Sciences & Technology - Pharmaceutical Technology | B. Tech (Hons) Pharmaceutical Technology (4yft) | |

# Appendix F: List of ARV Value Chain Stakeholders

| Operations | Company | Country |
|---|---|---|
| **ARV API Manufacturing** | Hetero | International |
| | Aurobindo | International |
| | Laurus | International |
| | Cipla Limited | International |
| | Mylan (now Viatris) | International, Zambia |
| | CPT Pharma | South Africa |
| | Msizi Pharmaceuticals | South Africa |
| **ARV Formulation and/or Packaging** | Mylan | International, Zambia |
| | Africure | Regional |
| | Avacare Health | Regional, Mauritius |
| | Portfolio Pharma | Botswana, South Africa |
| | Sun Pharma | South Africa |
| | SwaziPharm/Avapharm | Eswatini |
| | Strides Pharma Mozambique | Mozambique |
| | Sociedade Moçambicana de Medicamentos (SMM) | Mozambique |
| | Erongomed | Namibia |
| | Aspen | South Africa |
| | Adcock Ingram | South Africa |
| | Cipla Limited | South Africa |
| | Sonke Pharmaceuticals | South Africa |
| | New Avakash | Zimbabwe |
| **Excipients** | SAPPI | International |
| | Illovo Sugar | South Africa, Regional |
| | Tongaat Hulett | South Africa, Regional |
| | Barloworld Ingrain | South Africa |
| | Du Pont | South Africa |
| | AECI Speciality Chemicals | South Africa |
| | Ingredion | South Africa |
| | Tranarc | South Africa |
| **Packaging Materials** | Ensemble Plastics SWD (Pty) Ltd | Eswatini |
| | Avoma | Eswatini, Mozambique |
| | Boxmore Plastics | Mauritius |
| | Mmaauli Associates | Mauritius |
| | Indo Cap Closures | Mauritius, Malawi, Namibia |
| | B&I Polycontainers | South Africa |
| | Blakelin Plastics | South Africa |
| | Bonpak | South Africa |
| | GB Packaging | South Africa |
| | Lendon Packaging | South Africa |
| | Marsing & Co | South Africa |
| | Nurrin Pharmalab | South Africa |
| | Phormpak SA | South Africa |
| | Premier Packaging | South Africa |
| | Polyoak Packaging | South Africa, Regional |

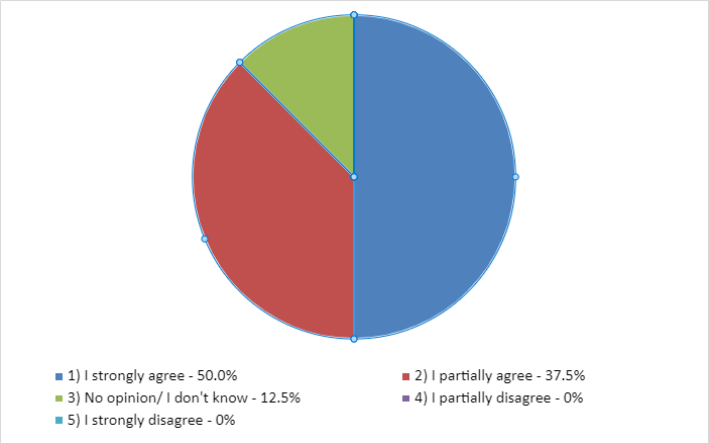
Note: The above list is based on the information available at the time of reporting. More stakeholders will be added as new projects are identified during the implementation phase.

# Appendix G: Findings from Stakeholder Feedback

**Explanatory note**: The stakeholder consultation workshop took place virtually on 21.09.2021. Stakeholders from the ARV Value Chain were invited to provide comments and feedback on the results of the inception report and the proposed interventions. Therefore, a survey tool was shared along with the invitation to the workshop and feedback from the participants was provided until the 10th of October 2021. Out of 19 questions, 14 were answered by the participants. The overall survey result shows that participants widely approved the inception report and its findings. These findings were also reflected in the comments and questions during the stakeholder engagement workshop. Comments by the SIPS Team are included in *italics*.

Following are the results:

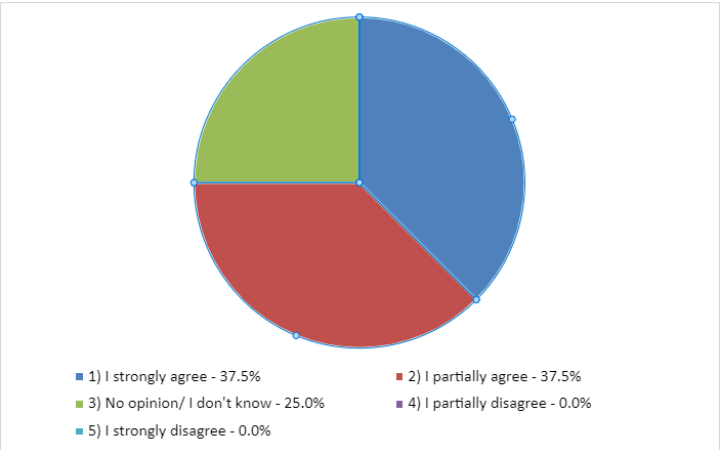
**Question 1: The Inception Report correctly describes the current situation of the ARV Value Chain in the SADC region as a whole.**




**Question 2: The Inception Report correctly describes the current situation of the ARV Value Chain in the SADC region as a whole. Can you please indicate what fundamental content was missing, inaccurate or not represented at all?**

No responses were given to this question.

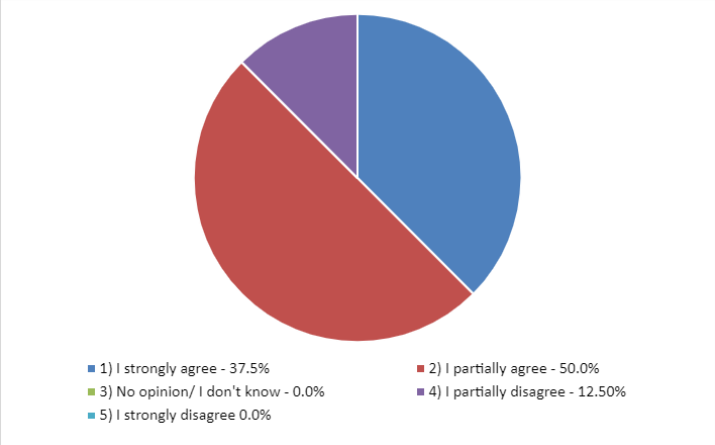
**Question 3: Specific country and regional information on HIV statistics are accurately reflected (compare Chapter 2).**



**Question 4: "Specific country and regional information on HIV statistics are accurately reflected (compare Chapter 2)."Please name the country and corresponding information that was missing or inaccurately represented and provide a source if possible.**

No responses were given to this question.

**Question 5: The challenges for ARV manufacturing in the SADC region are fully described (compare Chapter 4 to 6).**

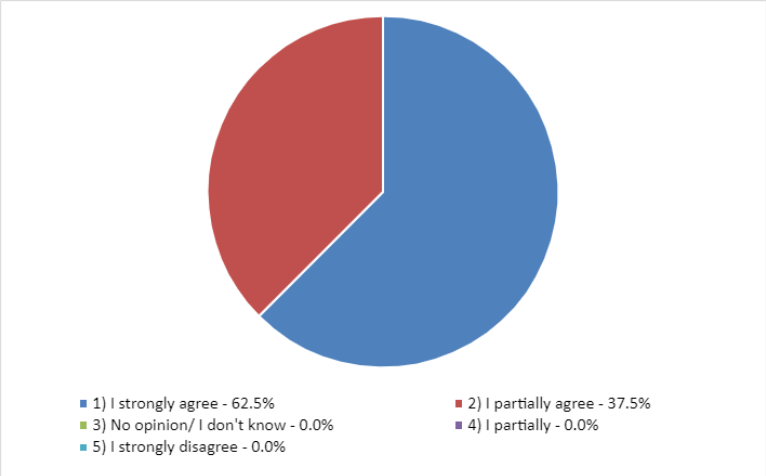



**Question 6: "The challenges for ARV manufacturing in the SADC region are fully described (compare Chapter 4 to 6)."Please indicate additional manufacturing, political or human resources-related challenges that were not covered in the Inception Report.**

"Manufacturing technologies not mentioned."
*Mozambique and Eswatini are looking into technology transfer as mentioned on page 32 and 33.*

"Very silent on the funding requirements which is the most important missing element."
*The report mentions that the pharmaceutical industry needs more funding like other sectors. See page 45 and 75.*

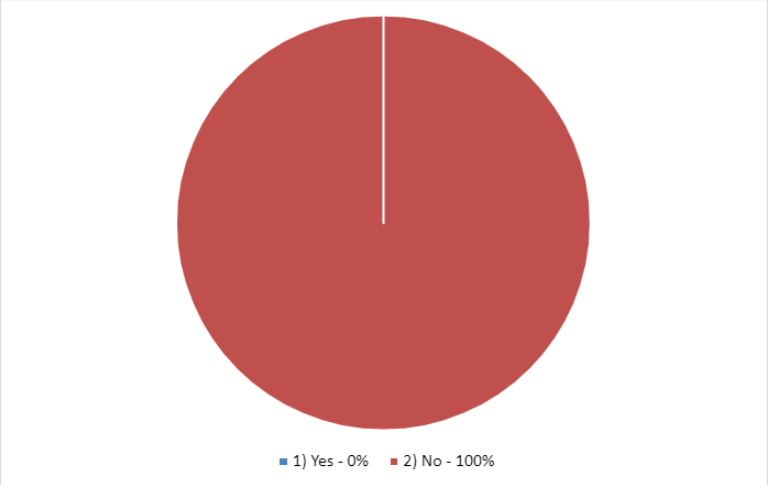
**Question 7: The Human Resources in the Pharmaceutical Sector section describes the situation in the presented countries correctly (compare Chapter 5).**



**Question 8: "The Human Resources in the Pharmaceutical Sector section describes the situation in the presented countries correctly (compare Chapter 5)"What is missing or inaccurately represented in your opinion?**

No responses were given to this question.

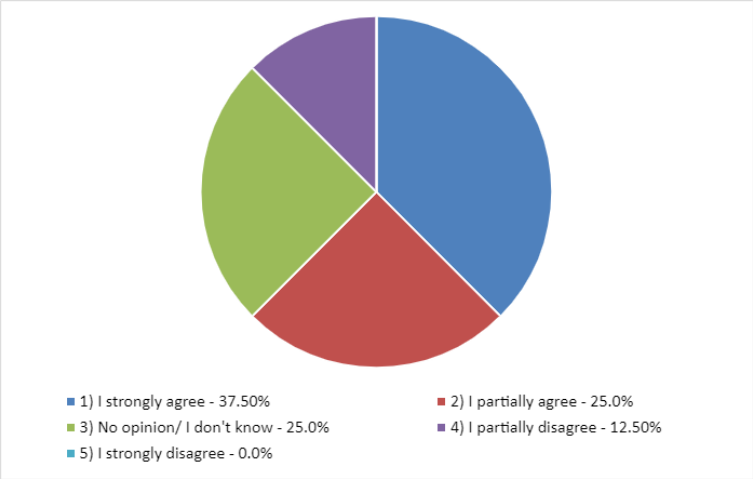
**Question 9: Do you know of other TVET/ academic institutions offering relevant programs for the pharmaceutical sector in the SADC region?**




**Question 10: "Do you know of other TVET/ academic institutions offering relevant programs for the pharmaceutical sector in the SADC region? "If so, please list them here.**

No responses were given to this question.

**Question 11: The presented interventions are relevant and realistic (compare Chapter 7).**




**Question 12: " The presented interventions are relevant and realistic (compare Chapter 7)."Please indicate which intervention you do not find relevant and/ or realistic and indicate why.**

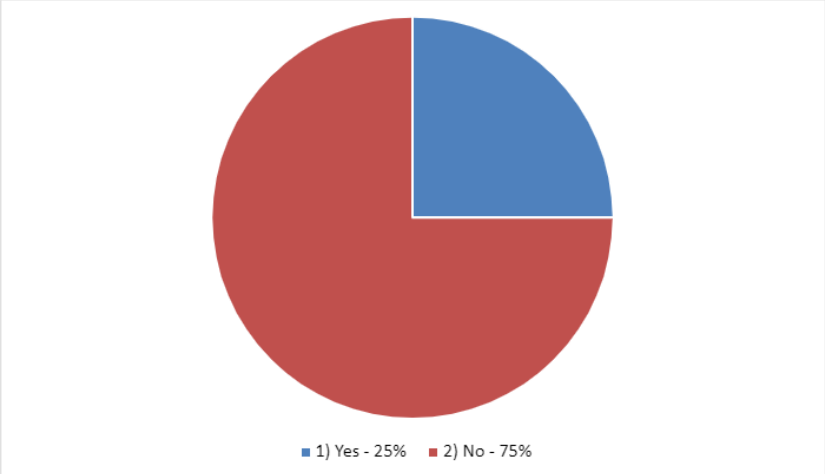
“The proposed interventions revolve around engaging with the established platforms for supply of ARVs. We find that an important barrier to the indigenous production of ARVs in Mozambique (and

the region) is the parallel QMS requirements that exacerbate the cost and risk of attempting it. GF looks for WHOPQ, PEPFAR specifically USFDA, and each SADC member state, despite Zazibona, have their own discrepancies."
*These are policy issues which are being addressed by SIPS component 1 which is implemented by the SADC secretariat*.

"We continue to find ourselves in a chicken and egg situation where we want the principal beneficiaries or donors to commit to creating a commercial opportunity but are each individually stuck focusing on a particular piece of the pie, mostly limited to our markets. This we have determined is because ARV manufacture is significantly more costly than general products which find competition from India and China. So, we have to contemplate dedicated ARV plants, at least in Mozambique, to avoid making our others products non-competitive in the local market. I don't see adequate intervention proposed to mitigate this. "
*One key intervention is to engage donors as mentioned on page 66.*

"In the absence of a legitimate solution, all proposed interventions still seem entirely reliant on subsidy to compensate for the inefficiency/barriers to local manufacture which short the political will to budget will continue to delay action and implementation."
*SIPS Component 1 focusing on regulatory aspects and SIPS Component 2 focusing on development of the private sector propose multiple interventions towards ensuring sustainability of local pharmaceutical manufacturers.*

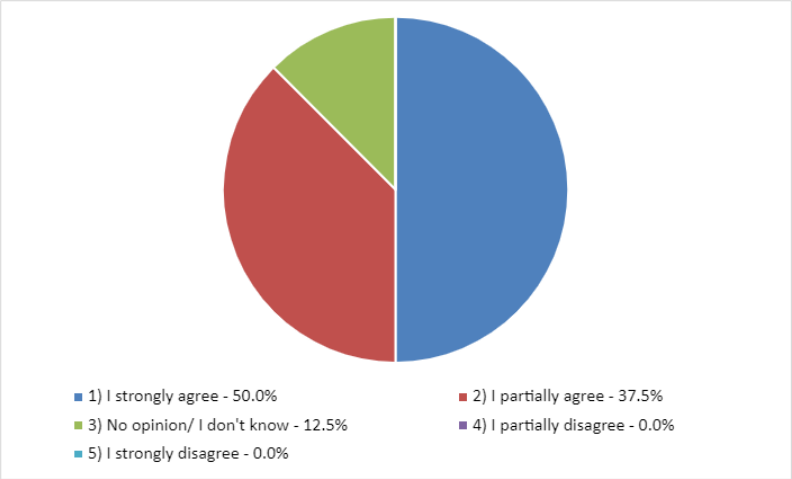
**Question 13: Would you like to provide additional recommendations for interventions?**




**Question 14: Please provide additional recommendations for interventions.**

"Need more focus on supporting projects, particularly with regards to government providing off-take agreements. Getting 2-3 projects active and assessing their effectiveness is what is required now."
*One major intervention of the project is supporting essential technology for the value chain such as API production and assessing its impact and value addition to the regional pharmaceutical market.*

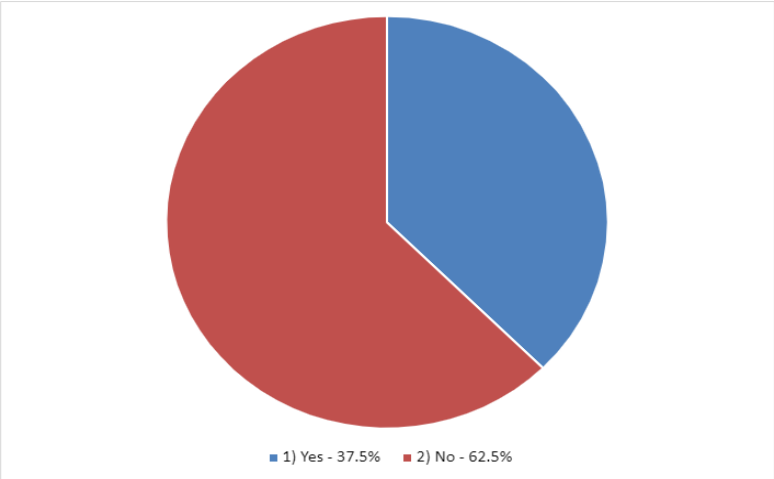
**Question 15: The key stakeholders in the ARV manufacturing value chain in the SADC region have been correctly identified in the Inception Report (compare Appendix F).**




**Question 16: "The key stakeholders in the ARV manufacturing value chain in the SADC region have been correctly identified in the Inception Report (compare Appendix F)."Please list stakeholders that have been incorrectly identified and provide the correct information.**

No responses were given to this question.

**Question 17: Do you know of additional private sector stakeholders active in the ARV pharmaceutical manufacturing value chain in the SADC region (compare Appendix F)?**




**Question 18: "Do you know of additional private sector stakeholders active in the ARV pharmaceutical manufacturing value chain in the SADC region (Compare Appendix F)?"Please indicate company name and country.**

Specpharm Holdings (Pty) Ltd, South Africa
Msizi Pharmaceutical Holdings (Pty) Ltd
Adcock - South Africa

Sun Pharma - South Africa
Cipla - South Africa
Aurobindo - South Africa

*The companies have been included in the list of ARV stakeholders (Appendix F)*

**Question 19: Do you have any additional remarks?**

1. “No”
2. "What is needed from the governments in the region is a framework for supporting the development of API manufacturing capability for specific molecules, coupled with funding and procurement mechanisms. It has been correctly noted by participants in the workshop that this discussion has been underway for at least six years and needs to be taken forward.”
3. “The study needs to look more closely at the process for establishing Ketlaphela in South Africa and why it hasn't worked in the manner originally intended. The origins of the project date back to 2010.”

*Several manufacturers and production initiatives were consulted during the inception phase and more stakeholders will be engaged during implementation with a focus on building capacity where there is manufacturing or research activity. SIPS Component 1 will address the regulatory and policy issues affecting the successes or failures of stakeholders in the ARV VC.*

4. “Also need to consider whether there are perverse incentives in place that restrict locally API manufacturing getting the support that is needed."
*SIPS Component 1 focusing on policy and regulatory issues will explore this aspect.*
5. “Thanks, none.”
6. “Excellent Work!”
7. “We are at the implementation phase. We need funding.”

*Implementing stakeholders are being contacted to explore opportunities for collaboration.*

8. “For the time being no additional comments from my side”
9. “Setting up a regional training program using inputs from subject matter experts (e.g. USP, WHO, etc) will address shortage in skilled manpower.”

*One of the interventions is to engage the Southern Africa Regional University Association (SARUA) and explore this possibility (Page 69).*

10. “Funding for non-technical studies (e.g. EIA, off-take agreements) will reduce pressure on industry when commercialising technology while ensuring high quality data to assist with feasibility decisions"
*See page 69.*