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Feasibility study on Regional Manufacturing of Medicines and Health Commodities

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List of Abbreviations and Acronyms

AfDB	African Development Bank (http://www.afdb.org/en/)
ACT	Artemisinin Combination Therapy
AMFm	Affordable Medicines Facility - Malaria
AMRH	African Medicines Regulatory Harmonisation (http://amrh.org/)
API	Active Pharmaceutical Ingredient
ART	Antiretroviral Therapy
ARV	Antiretroviral
AS/AQ	Artesunate-amodiaquine
AU	African Union (http://www.au.int/)
BRICS	Brazil, Russia, India, China and South Africa
BMZ	Federal Ministry for Economic Cooperation and Development (www.bmz.de)
CD4 S/P	cluster of differentiation 4 single positive
CL	Compulsory License
CoS	Centres of Specialization
CTD	Common Technical Document (SADC version)
CoE	Centre of Excellence
COMESA	Common Market for Eastern and Southern Africa (www.comesa.int)
CoPP	Certificate of Pharmaceutical Product (WHO format)
DDT	Dichlorodiphenyltrichloroethane
DHA	Dihydroartemisinin
DHA-PPQ	Dihydroartemisinin-Piperaquine
DNDi	Drugs for Neglected Diseases Initiative (www.dndi.org)
DRC	Democratic Republic of Congo
DUI	Doing Using and Interacting
E8	Malaria Elimination 8
EAC	East African Community (http://www.eac.int/)
EPZ	Export Processing Zone
EU	European Union (http://europa.eu/index_en.htm)
FAPMA	Federation of African Pharmaceutical Manufactures Associations
FDC	Fixed Dose Combinations
FDF	Finished Dosage Form
FDI	Foreign Direct Investment
FPP	Finished Pharmaceutical Product
GCP	Good Clinical Practices
GDP	Good Distribution Practices
GF	Global Fund (www.theglobalfund.org)
GIZ	Deutsche Gesellschaft für Internationale Zusammenarbeit (www.giz.de)
GMP	Good Manufacturing Practices
GPCL	Good Practices for National Pharmaceutical Control Laboratories
GU	Government use
GWP	Good Warehousing Practices (included in GDP)
HBsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotrophin

HRD	Human Resource Development
HPLC	High Pressure Liquid Chromatography
IAF	International Accreditation Forum
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (www.ich.org)
ICT	Information and Communication Technology
IDPF	Industrial Development Policy Framework (SADC, 2012)
IGPA	International Generic Pharmaceutical Alliance
ILAC	International Laboratory Accreditation Cooperation (www.ilac.org)
IP	Intellectual Property
IRS	Indoor residual spraying
ITN	Insecticide Treated Nets
IPTp	Intermittent Preventive Treatment
IV	Intra Vascular
IVD	In Vitro Diagnostic
JCRC	Joint Clinical Research Centre, Uganda (http://www.jcrc.org.ug/)
KEMRI	Kenya Medical Research Institute (http://www.kemri.org/)
KfW	German Development Bank (www.kfw-entwicklungsbank.de)
KSP	Kilimanjaro School of Pharmacy (Moshi, Tanzania)
LDC	Least Developed Country
LLINs	Long Lasting Insecticide Treated Nets
LMICs	Low and Middle Income counties
LPC	Lesotho Pharmaceutical Corporation (defunct)
LPP	Local Pharmaceutical Production
MACASA	Medicines and Allied Substances Control Act
MCAZ	Medicines Control Authority of Zimbabwe (http://www.mcaz.co.zw/)
MCC	Medicines Control Council
MDR	Multi-Drug Resistant
MDR-TB	Multi-Drug Resistant Tuberculosis
MPP	Medicines Patent Pool (http://www.medicinespatentpool.org/)
MT	Metric Tons
MUHAS	Muhimbili University of Health and Allied Sciences (http://www.muhas.ac.tz/)
NDSO	National Drug Service Organisation, Lesotho (http://ndso.co.ls/)
NEPAD	New Economic Partnership for Africa's Development (http://www.nepad.org/)
NIPF	National Industrial Policy Framework (South African)
NMRA	National Medicines Regulatory Authority (or Agency)
NNRTI	Non-Nucleoside Reverse-Transcriptase Inhibitors
NQCL	National Quality Control Laboratories
OSD	Oral Solid Dose (facility, Aspen Pharmacare)
PBP	Pharmaceutical Business Plan
PCR	Polymerase chain reaction
PDP	Product Development Partnership
PEPFAR	President's Emergency Plan for AIDS Relief (http://www.pepfar.gov/)
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (http://www.picscheme.org/)
PMI	President's Malaria Initiative (http://www.pmi.gov/)

PMPA	(African Union) Pharmaceutical Manufacturing Plan for Africa
PMTCT	Prevention of Mother to Child Transmission
PP	Pooled Procurement
PPN	Pooled Procurement Network
PPP	Public-Private Partnerships
PPTT	Pooled Procurement Task Team
PQR	Price and Quality Reporting
PSI	Population Services International (http://www.psi.org/)
QA	Quality assurance
QC	Quality Control
QCL	Quality Control Laboratory
R&D	Research and Development
RCORE	Regional Centres of Regulatory Excellence
RDT	Rapid Diagnostic Tests
RIIP	Research Institute for Industrial Pharmacy (http://www.nwu.ac.za/about-us-riip-incorporating-cenqam-0)
RISDP	Regional Indicative Strategic Development Plan
SADC	Southern African Development Community (www.sadc.int)
SADCAS	SADC Accreditation Service (www.sadcas.org)
SAGMA	Southern African Generic Medicines Association
SANAS	South African National Accreditation System (http://home.sanas.co.za/)
SAPMAP	SADC Pharmaceutical Manufacturing Action Plan
SARN	Southern Africa Roll Back Malaria Network (https://tis.sadc.int/english/sarn/)
SARPAM	Southern Africa Regional Programme on Access to Medicines and Diagnostics
SEAMRAC	Southern and Eastern African Medicines Regulatory Affairs Conference
SHD	Social and Human Development
SLD	Second Line Drugs
SNRL	Supra-national reference laboratories
SP	Sulphadoxine Pyrimethamine
SQAM MOU	SADC Memorandum of Understanding on Standardization, Quality assurance, Accreditation and Metrology
SRA	Stringent Regulatory Authority
SSA	Semi-synthetic artemisinin
SSFFC	Substandard/spurious/falsely-labelled/falsified/counterfeit (medicines)
SPPS	SADC Pharmaceutical Procurement Services
STIs	Sexually transmissible infections
STISA	Science, Technology and Innovation Strategy for Africa
TAF	Tenofovir alafenamide fumarate
TB	Tuberculosis
TDR	Tropical Disease Research (http://www.who.int/tdr/en/)
TEN	Techno-Economic Network
TFDA	Tanzania Food and Drugs Authority (http://www.tfda.or.tz/)
TFTA	Tripartite Free Trade Area
TOR	Terms of Reference
TRIPS	Trade Related Aspects of Intellectual Property Rights
UHC	Universal Health Coverage

UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS (www.unaids.org)
UNDP	United Nations Development Programme (www.undp.int)
UNIDO	United Nations Industrial Development Organization (www.unido.org)
WHO	World Health Organization (www.who.int)
WHOPES	WHO Pesticide Evaluation Scheme
WHO PQ	WHO prequalification
WTO	World Trade Organization (www.wto.int)
XDR-TB	Extensively Drug Resistant Tuberculosis
ZRDCL	Zimbabwe Regional Drug Control Laboratory

EXECUTIVE SUMMARY

This report covers the results of a feasibility study on 'Regional Manufacturing of Medicines and Health Commodities' in the Southern African Development Community (SADC) with a focus on Human Immunodeficiency Virus (HIV) related diseases, Tuberculosis (TB) and Malaria. The study followed the Terms of Reference as defined by the SADC Secretariat and was financed by the African Development Bank (AfDB).

The objectives were to (1) **assess the feasibility** of regional production of generic essential medicines, especially those related to the three major communicable diseases (HIV and AIDS, TB and Malaria) and related health commodities such as condoms, Rapid Diagnostic Tests (RDT), dichlorodiphenyltrichloroethane (DDT) and long-lasting insecticide-treated nets (LLITN); and (2) **develop a strategy** or modality for operationalizing regional production of medicines and health commodities for these communicable diseases.

The HIV and AIDS, TB and (less so) malaria epidemics have led to a **serious public health crisis** in SADC. To address this crisis, SADC has developed several strategies, and their implementation requires access to affordable, good quality medicines and commodities. There is still a big treatment gap in SADC: only 50% of eligible patients receive Anti-Retroviral (ARV) treatment. Increasing resistance against affordable first-line treatments will require access to more second and third line treatments in the future. To effectively address the public health crisis, SADC also needs access to new point of care diagnostics, condoms, bed nets and insecticides.

hera proposes the following **vision** for regional production: *"A sustainable pharmaceutical manufacturing industry in SADC that supports public health programmes and universal health coverage"*

As per Terms of Reference, this feasibility study is focusing on medicines and health commodities **for the three pandemic diseases**, which implies specific limitations. The limitations are related to how these three markets are financed, and the quality standards and procurement rules set by those funders. However, most of the situational analysis, the gap analysis, recommendations for improving the enabling environment for local production of pharmaceuticals and commodities, and the overall proposed strategy, will also apply to the regional production of **all other essential medicines and health commodities**.

A successful implementation of a regional production strategy will need **close collaboration between Trade, Industry, Agriculture, Finance and Health** sectors to achieve three main goals: (1) direct and indirect economic benefits; (2) (improved) public health outcomes; and (3) industrial and economic growth.

From an economic perspective, the study assumes the applicability of **innovation theory** to the stimulation of local manufacturing, including the introduction of products, processes or forms of organisation that are new to the firm, or new to the industry, or new to the country and perhaps even

new in a global sense. The resulting development is construed as the consequence of learning and innovation.

Based on documented experiences and relevant literature, the study assumed the following principles for informing the situational/gap analyses and developing the recommendations: (1) access to knowledge is a critical resource, and needs appropriate Information and Communication Technologies (ICT) infrastructure; (2) learning centres play a fundamental role in developing local manufacturing; (3) pharmaceutical industry needs strong interaction with universities and knowledge centres of excellence; (4) governments need to incentivize an innovation strategy based on "doing, using and interacting"; (5) existing techno-economic networks of suppliers and manufacturers might resist efforts to build local manufacturing, and will not always act in the national interest; (6) technology transfer is driven by foreign investment and by early adopters within firms; for regional innovation in SADC, incentives for early adopters are critical, as the pharmaceutical industry is still underdeveloped; (7) manufacturing needs to meet international quality standards in order to be able to supply international markets and donors; (8) the region needs to make use of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) flexibilities and focus on more affordable generic versions of products patented elsewhere; (9) governments and SADC as a whole need to create a level playing field with harmonised regulatory standards and effective access to the regional market; (10) initial incentives, regional preference and tariff/duty reforms will kick-start a strong pharmaceutical manufacturing industry. Over time, governments can then transfer leadership to the pharmaceutical companies, which will lead technology development and take on the commercial risks.

The study applied the **methodology** as approved by SADC Technical Review Committee (TRC) in the revised Inception Report: the Situational Analysis was based on extensive literature review and interviews with a range of stakeholders in all 15 Member States: 35 manufacturers; medicines regulators; laboratories; and centres of excellence. All data were validated and summarized by 2 **hera** partners. Based on this database, the **hera** core team developed a gap analysis, which was validated by the **hera** review team consisting of pharmaceutical entrepreneurs, academics and consultants from 6 SADC Member States. Together, the review team then outlined a strategy for regional production. After internal quality assurance, the draft report was reviewed by the SADC Technical Review Committee, whose comments were subsequently included in the final draft report.

The Existing Policy Context for Regional Manufacturing

The **Situational Analysis** covered all 15 SADC Member States, but the general discussion focuses on the region as a whole. It noted that there are specific challenges or good practice examples for the different countries, including: access to finance; availability of skilled human resources and manufacturing technology; local Research and Development (R&D), especially experimental development leading to product or process technology; supporting industries; regulatory capacity; and the (non-)availability of government incentives.

The **SADC Treaty** provides the overall structure and mandate for working towards regional integration and has inspired the Protocols on Trade and Health. The Regional Indicative Strategic Development Plan (RISDP) and the 2012 SADC Industrial Development Policy Framework (IDPF) provide the framework for the trade and industrialization aspects. The pharmaceutical policy framework is defined

in the 'SADC Pharmaceutical Business Plan (2007-2013)', which has been updated into the Pharmaceutical Business Plan 2015-2019. Both have a specific chapter on stimulating regional production, where the specific strategy is: *"Rationalizing and maximizing the research and production capacity of local and regional pharmaceutical industry of generic essential medicines and African Traditional Medicines".*

The **SADC regional policies and frameworks** are in line with the African Union (AU) 'Pharmaceutical Manufacturing Plan for Africa' (PMPA), its 2012 business plan, the 2015 update report, the AU 'Accelerated Industrial Development of Africa', and the 'Agenda 2063'. These all provide evidence for a broad continental level consensus on prioritising industrialization and pharmaceutical manufacturing. The PMPA also provides for regional and national strategies.

The existing SADC policies and frameworks provide a good basis for regional Pharmaceutical Manufacturing. It is clear, however, that successful implementation of local and regional production requires **more coherence** and **closer collaboration** between Trade/ Industry, Education, Procurement/Finance, Agriculture and Health officials, both at Member State and regional levels.

Implementation of the SADC policies will need to overcome some specific **challenges** identified in the 2015 implementation assessment of the RISDP: (1) inadequate capacities at both the Member State and Secretariat levels; (2) non-alignment of Member State national development plans with the priorities of the RISDP; (3) low levels of Member State ratification and domestication of protocols; (4) low levels of Member State compliance with community obligations; (5) undeveloped community enforcement mechanisms, including low level of utilization of the provisions of the Treaty; (6) insufficient coordination of the implementation of the RISDP; (7) undeveloped monitoring, analysis, reporting, and review systems, and finally (8) overreliance on donor funding for implementation of the RISDP programmes.

Positive lessons for the promotion of local pharmaceutical industry can be learned from countries such as Ethiopia, Kenya, South Africa and Tanzania.

Health policies in SADC aim to treat all patients for the 3 big diseases:

The 'SADC's **HIV and AIDS** Strategic Framework 2010-2015' includes several strategies that require medicines and/or commodities: condom distribution, HIV Testing, Prevention of Mother to Child Transmission (PMTCT), treatment with antiretrovirals and home-based care. Together with the 'Maseru Declaration on the Combating of HIV and AIDS in the SADC Region' these documents provide a clear policy direction and political commitment in combating the AIDS pandemic in the region. SADC has an estimated 14.7 million people living with HIV: 11.7 million of them currently need Anti-Retroviral Therapy (ART), but only 6 million (52%) were actually on ART in 2013. The WHO-recommended policy shift of treating at CD4<350 via CD4<500 to "Test & Treat" and the UNAIDS "90-90-90" strategy will increase the number of HIV+ people to be treated with ART from the existing 6 million to 15 million people by 2020. This tripling of the market is a clear opportunity for regional production, but also requires substantial increases in financing.

The 'Strategic Framework for Control of **Tuberculosis** in the SADC Region (2007-2015)' provides the framework for TB control in SADC. SADC Member States harmonised their treatment guidelines in 2010. SADC's TB policy aims to diagnose, treat and cure the estimated yearly 1.3 million new TB patients in SADC. The TB epidemic is also fuelled by the incomplete treatment of the ongoing HIV epidemic. First-line TB treatment is affordable and locally produced, but the harmonised TB treatment regimens can be better implemented across SADC Member States. Multiple drug resistant (MDR) TB is a serious problem: the existing MDR-TB medicines are quite toxic, expensive, not always effective, and need to be taken for 18-20 months. Three new TB medicines are currently being tested to establish whether they can cure MDR-TB in 6 months; another phase 3 trial is assessing effectiveness of the new medicines for curing Extensively Drug Resistant (XDR)-TB.

SADC **malaria** strategies are well documented in the 'SADC Malaria Strategic Framework (2007-2015)', the 'SADC Malaria Elimination Framework', and the 'SADC minimum standards for malaria control (2010)'. Collaboration among stakeholders is coordinated in SADC by the Southern Africa Roll Back Malaria Network (SARN). Thirty-seven million "presumed and confirmed" malaria cases occurred in SADC in 2013. Malaria is diminishing thanks to the elimination strategy in eight SADC Member States (E8) based on (1) Use of Long Lasting Insecticide Treated Nets (LLINs); (2) Case management with Artemisinin Combination Therapy (ACT) based on objectively diagnosed malaria using rapid diagnostic test kits; (3) Indoor residual spraying (with DDT), and for high transmission areas, (4) Intermittent preventive treatment (IPTp) during pregnancy.

In line with existing SADC health policies and strategies, the SADC pharmaceutical manufacturing strategy should thus aim to contribute to **Universal Health Coverage (UHC)** and Universal Access to Treatment.

SADC Member States have not yet reached full **harmonization of treatment protocols**; this might hinder achieving economies of scale in procurement, cross-border treatments and a well-defined product market. The SADC Treaty, specifically articles 21 and 22, has provisions for regional cooperation, and article 29 of the 1999 SADC Health Protocol provides for harmonization of procedures of pharmaceuticals, quality assurance and registration.

The current SADC pharmaceutical market is **unevenly regulated**: some Member States have better controls than others. Regional production and distribution needs a well-regulated market and level playing field across all SADC Member States. Procurement of HIV and AIDS, TB or malaria products using funds from Global Fund, PEPFAR or other international donors requires adherence to strict quality assurance criteria: the plant must comply with WHO Good Manufacturing Practices (GMP), and the products must be either WHO prequalified or approved by a Stringent Regulatory Authority (SRA).

SADC has been aiming to **harmonize medicines regulation** since 2000, and a set of SADC harmonised guidelines has been available since 2004. However, SADC Member States are still at different stages of development of their National Medicines Regulatory Authorities (NMRA), and implementation of guidelines is inconsistent. There is opportunity for the more experienced NMRAs to assist and build capacity in Member States with less developed regulatory structures. Four Member States are actively practising information exchange, work sharing, and joint assessment of regulatory dossiers and GMP

inspections. A 'Common Technical Document' (CTD) standard for medicines' regulatory dossiers has been agreed upon by all SADC Member States.

South Africa, the biggest market in SADC for ARVs and TB medicines, is **self-financing** and not donor dependent. South Africa based manufacturers can supply the national market provided their products are licensed by the NMRA, and do not need to achieve WHO prequalification. South Africa has successfully insisted on more "local value added" in its tenders for HIV and TB medicines. There are a few more self-financing countries in SADC that could benefit if they had access to the very low priced products in the South African tender, and if their NMRAs recognized the regulatory decisions of the South African Medicines Control Council (MCC).

All new ARVs and TB medicines are **patent protected** by originator companies from USA and Europe. The World Trade Organization (WTO) TRIPS agreement forces all Member States (except Least Developed Countries) to recognize product and process patents, often making such products unaffordable, and preventing local production unless under voluntary or compulsory license. SADC has been relying on affordable generic ARVs from India, but products patented after 2005 can no longer be easily produced in India. A lost 2001 court case and heavy lobbying by AIDS activists in South Africa forced originator companies to grant voluntary licences for their ARVs in sub-Saharan Africa. The Medicines Patent Pool has since regularized access to licenses for generic copies of some existing and new ARVs. Recently, the Medicines Patent Pool agreed to also accept TB and Hepatitis-C medicines: this opens opportunities for regional manufacturers but also allows Indian competitors to enter the new TB medicines market.

Not all SADC Member States have enabled the full **TRIPS flexibilities** in their national Intellectual Property (IP)/patent laws. Zimbabwe has successfully produced quality assured (WHO prequalified) generic ARVs under a government use license since 2001. The majority of SADC countries are least developed countries (LDCs) which are exempt from protecting pharmaceutical patents until 2033: LDCs are allowed to market generic medicines produced under the exemption provision within their economic bloc (in this case SADC). Products can also reach other economic blocs in Africa through overlapping countries. Importing countries with valid patents can override any patents in the interest of public health based on the 2001 Doha Declaration. Legal solutions exist for all possible patent barriers that SADC Member States might experience when importing or producing new generic ARVs or TB medicines. Member States are not obliged to give higher IP protection than the minimum required by TRIPS.

Coherence between Trade, Industry, Agriculture, Finance and Health sectors at national and regional levels tends to be insufficient due to different interests in policies on regional production and procurement. In some Member States imported finished dosage forms are exempted from taxes/duties, whereas Active Pharmaceutical Ingredients (API), excipients and packaging materials are taxed. Regional production of new generics can only be achieved by working together using one balanced regional strategy.

A few Member States promote local production through **incentives**, tax and duty exemption, education grants, exemption of withholding tax, and duty free zones. In Zambia the Multi-Facility Economic Zone has attracted the interest of 3 pharmaceutical companies.

Despite anticipated advantages, **Pooled Procurement** has not yet been operationalised in the SADC region. SADC Health Ministers approved the 'SADC Strategy for Pooled Procurement of Essential Medicines and Health Commodities (2013 – 2017)' in 2012. The strategy was informed by a 'SADC Situational Analysis and Feasibility Study', discussed and agreed in September 2012 by representatives of all SADC Member States. In November 2013, SADC Ministers of Health adopted the electronic platforms for information and work sharing, the 'SADC Medicines Database' and 'Pooled Procurement Network' (PPN), and the setting up of a pooled procurement coordinating mechanism, i.e. the 'SADC Pharmaceutical Procurement Services' (SPPS). In September 2014, SADC Member States adopted the SPPS Charter and tasked the Pooled Procurement Task Team (PPTT) to implement the SADC Pooled Procurement Strategy. The PPTT met in December 2014 and finalised the 'SPPS Business Case' and prepared the 'PPTT Action Plan and Budget 2015'. A 'group contracting' report is being developed. Implementation of SPPS, PPTT and group contracting are critical to enable an organised market for regional production.

Current **domestic preference** schemes applied during financial evaluation of public tenders benefit domestically produced products over regionally produced products or those imported from outside SADC. SADC does not yet have a **regional preference** system. A few SADC Member States buying their own ARVs and TB medicines are using increased "regionally added value" percentages as evaluation criteria in their tender procedures.

While a shortage of pharmacists and other technical staff with pharmaceutical skills is often mentioned as a key challenge in sub-Saharan African countries, respondents in the SADC Member States stated that there are sufficient **human resources** to run at least one GMP compliant manufacturing plant per country, or play a significant role in the process of establishing a GMP compliant plant. However, a recent study commissioned by the Southern Africa Generic Medicines Association (SAGMA) concluded that there is a lack of synchronisation between the training needs of industry and what is currently on offer. Pharmaceutical industry-related training in SADC is largely focused on regulatory affairs and quality matters, neglecting other operational issues such as formulation development, plant engineering and supply chain management. Very little training is directed specifically at wholesalers and distributors. There is broad coverage of good quality executive education in the region, particularly from South African business schools, although these courses are not specific to the pharmaceutical industry. Short courses presently being offered are concentrated in South Africa and Tanzania.

Manufacturers reported that **financing** is a challenge due to the high cost of local commercial capital and the limited access to investments, low interest loans and other financing solutions. Funding for the three diseases is likely to shift over the coming years from international donors to regular national budgets ("graduation"). Finally, it will be a challenge for the region to finance Universal Health Coverage.

The Product Market for the Three Diseases

Medicines for HIV treatment currently represent 86% of the total medicines expenditure for the 3 diseases in the SADC region. The joint annual ARV expenditure in SADC by Global Fund, PEPFAR and the South African government amounts to USD 686 million. The total SADC **ARV market** is estimated

at USD 900 million (6 million people on ART at USD 150 average). Of this, the South African government finances 44%, the Global Fund 20.6%, and PEPFAR 11.1%. The balance is paid by other countries not having access to Global Fund or PEPFAR grants, insurance funds and the private sector. The potential market of ARVs is likely to double from USD 900 million to USD 1.8 billion/year by 2020, assuming a 'test & treat' policy, and a reduced cost of the first-line therapy of USD 100pp/year.

The total SADC male **condom market** is approaching 4 billion units worth USD 105 million. UNFPA supplied 16.7 million female condoms on average per year, worth USD 10 million. SADC has 4 factories in Botswana, Namibia and South Africa that produce condoms according to standards set by the South African Bureau of Standards (SABS). Their total current capacity is 400 million condoms (10% of the SADC demand of 4 billion) and all are sold in South Africa, Botswana or Namibia. Condoms produced in the region cannot be bought with UNFPA or Global Fund funds because they are not UNFPA prequalified.

The total SADC **TB medicines market** is estimated at USD 40-50 million per year. First-line TB treatment is affordable (USD 10-20 per treatment) and sufficient adult fixed-dose combinations are produced in the region, although none are as yet WHO prequalified. Between 2 - 6% of new TB patients suffer from drug resistant TB, requiring expensive MDR-TB medicines. Three of these (cycloserine, capreomycin and teridizone) are made in SADC. Drug-resistant TB comprises only 6.1% of South African cases, but its treatment consumes 32% of the country's total TB budget.

The number of TB patients needing medication will drop in the future, after a temporary increase due to better diagnostics and more HIV+ people being started on ARVs. The potential market for the new TB medicines for MDR and XDR-TB cannot be predicted as they are still being tested. Cost will depend on whether patent holders are willing to issue voluntary licenses, apply differential or access pricing, or whether SADC manages to produce them as generics in LDC Member States (not bound to honour patents until 2033).

Estimating the SADC **malaria market** for ACTs is difficult due to absence of reliable data. Applying the Global Fund ratio of 14% for ACTs of overall malaria programme cost, USD 83 million is currently being spent by public sector malaria programmes on ACTs in SADC. In addition, a substantial amount of medicines needed to treat the 58 million suspected malaria cases may be purchased in the private sector. This means that the estimated market of ACTs could probably reach USD 100 million per year in SADC. Overall the number of malaria cases is expected to drop, due to increased coverage of LLITNs, effective ACTs and indoor spraying with DDT.

The Price & Quality Reporting (PQR) database of the Global Fund reports an average annual turnover of USD54 million for **bed nets** in SADC. Two of the 11 LLITN products approved by the WHO Pesticides Evaluation Scheme (WHOPES) are manufactured in SADC (A to Z Mills Ltd, Tanzania). The company has an annual production of 30 million nets valued at USD42 million, of which 80% is supplied to Tanzania and other SADC Member States. The bed nets market is heavily influenced by donors, which buy 140 million bed nets globally per year.

The total SADC pharmaceutical market for all medicines and medical supplies is estimated at USD 4.7 billion. Assuming that SADC expenditure on medicines and medical supplies grows at the same pace as in the whole of Africa, the total pharmaceutical market in SADC could reach USD 6.5 billion in 2020.

The Business Case for Regional Manufacture

Currently, 14 manufacturers based in 7 countries produce 65 products for the 3 diseases. All have national registration, but only one manufacturer (Aspen Pharmacare, South Africa) manufactures WHO prequalified medicines (9 products, some under contract for originator companies).

Five companies in 3 countries manufacture **antiretrovirals**: together they cover only 15% of the SADC generic ARV market. The 3 South Africa-based manufacturers focus mainly on the national ARV tender. Prices are very competitive, causing Aspen Pharmacare, the only company with WHO prequalified products, to consider shifting towards other disease areas (Non-communicable diseases (NCDs)). TPI (Tanzania) has 2 nationally approved ARVs but production has been suspended by the NMRA for the last 2 years. This company is now focusing on other areas. Varichem (Zimbabwe) had 2 WHO prequalified products for several years, but these products have largely been replaced by newer (tenofovir based) regimens. Companies in Zambia, Mozambique and Botswana are planning ARV production, but have not yet started production.

Most manufacturers stated that the strong competition from India, the need to purchase APIs from Indian suppliers, and the lack of an enabling environment make the current ARV market not very interesting. However, the future production of ARVs in SADC might be feasible if it is carefully planned, with adequate investments, supported by an improved enabling environment and some regional protection from Indian competition. As SADC will probably be home to 18 million HIV+ patients in 2020 of which 16 million should be put on ARVs to achieve the '90-90-90' target, an API plant for tenofovir (TDF) could be studied, as the region would need 2.2 million kilograms of tenofovir API. SADC should also look into possible regional production of dolutegravir, which looks a good candidate for 2nd line therapy in the near future.

The four SADC **condom manufacturers** currently only supply 10% of the 4 billion SADC demand for condoms. As the technology is not too difficult, there is an opportunity for expansion of existing or building of new factories. Latex trees grow in DRC, but plantations have fallen into disuse, probably due to more cost-effective production of latex in Asia. The next steps in the value chain (Processing – Dipping – Foiling / packaging / branding) could take place in the SADC region.

Only 4 companies (3 of them in South Africa) manufacture **TB medicines**. The first-line TB drugs are affordable and already made in SADC. Sanofi (which is supplying all public sector TB medicines in South Africa) is in discussions with the South African Department of Trade and Industry (DTI) to start an API plant. Three MDR-TB drugs are made in South Africa, but they might in future be partially replaced by newer TB drugs that can hopefully treat MDR-TB in only 6 instead of 20 months. These new TB medicines are all patent protected, costly and from different companies. A fixed-dose combination (FDC) would be needed from a public health perspective to enhance patient adherence and simplify procurement and supply management but needs first development and testing.

The only manufacturer of WHOPES approved **bed nets** in SADC (A to Z Mills, Tanzania), has a turnover of USD42 million, and operates at 80% capacity, so there is some spare capacity. It obtains resin and chemicals from South Africa, and enters the pyrethroid insecticides into the filaments. The market is competitive and heavily influenced by international donors. The company supplies 80% of its bed nets to Tanzania and the rest of SADC. It could provide insecticide-treated netting in rolls to other knitting factories elsewhere in SADC, where the final bed nets are made.

Companies are in general **willing to upgrade and modernize** provided there is a sizeable and easily accessible regional market. However, some are not in a position to upgrade their plants as these are old and not upgradable. All of them point out that governments and SADC should address the lack of coherence (tariffs on APIs and supporting materials, but no tariffs on finished dosage forms; domestic preference rather than regional preference), the poor enabling environment, and the lack of incentives or specific support. WHO prequalification uses similar GMP standards as SADC NMRAs, but local NMRAs are sometimes less strict in the interpretation of the GMP standard, and do not always insist on bioequivalence studies (South Africa, Zambia, Zimbabwe, Botswana, Namibia and to some extent Tanzania do insist on performing bioequivalence studies as part of their registration procedures). Upgrading to WHO prequalification levels is only interesting if the local/regional NMRAs refuse marketing authorisation to companies with lower than WHO prequalification standards.

For a successful business case implementation, many conditions need to be fulfilled. The **region** needs to provide: (1) a strong enabling environment; (2) financial incentives and tax benefits; (3) a harmonised, strictly regulated market with clear technical guidelines; (4) strong industry platforms; (5) selection of public health relevant products, and (6) maximum use of TRIPS flexibilities.

A strong business case also needs **favourable technical conditions**: (1) access to clean and reliable water, electricity, air and waste disposal; (2) favourable logistics, infrastructure, security and supportive industries; (3) technical and human resources with access to knowledge; (4) technology transfer, and (5) innovative research and development capacity.

The successful **company** should also (1) have good market intelligence; (2) be able to produce with good quality; (3) produce good quality regulatory dossiers (in CTD format); (4) have export capabilities; (5) have access to good quality and affordable APIs; (6) have access to low-interest loans and capital, and (7) have access to a regional market.

In addition, there are a number of external factors which should be addressed, including demand-side support, reduction of tariffs on APIs and raw materials and incentives for API manufacture.

Is there a **'willingness to buy'** from manufacturers based in other SADC Member States? A number of Member States already import medicines from within the SADC region, the majority from South Africa. Most of the Member States reported that there are no barriers for importing generic essential medicines and/or health commodities manufactured in other SADC Member States. For the three diseases, however, Member States rely to a large extent on funding from development partners, which limits possible suppliers to those with WHO prequalification and/or SRA approval. Member States also reported some '**non-tariff barriers**' in trying to export medicines to South Africa, which only accepts clearing medicines at major airports or harbours, thus preventing cheaper transport by road.

Price/revenue behaviour in the pharmaceutical industry varies from Member State to Member State. Taxes and duties on raw materials, API and finished dosage forms (FDF) are important determinants for the final price for the customer/patient. In some Member States imported medicines are generally cheaper to the patient than locally produced medicines, while in other Member States the locally produced medicines are more affordable.

Raw materials (APIs) represent up to 80% of the value of generic ARVs, and therefore an affordable quality source is essential. SADC only has one small API manufacturer (Fine Chemicals in Cape Town) and all APIs are normally sourced from India or China. Economies of scale are important, and the feasibility of API production of tenofovir should be studied (estimated treatment of 16 million people by 2020 would need 2.2 million kilograms of API per year). Another promising development is the production of TB-related APIs, which is being planned by Sanofi with support of DTI South Africa.

hera also recommends to study the feasibility of using a new technology for making APIs: continuous flow chemistry. This technology could be more efficient and less costly than the traditional production in batches.

Potential benefits of regional manufacturing of pharmaceutical products for SADC Member States include employment generation; strengthening of educational basis of Centres of Excellence, universities, business schools; lowering risk of being dependent on imports; development of specific dosage forms (i.e. paediatric – which are of less need in non-African countries); attraction of foreign investments; industrialization in non-pharmaceutical sector; etc.

While the majority of the pharmaceutical companies are willing to expand, upgrade and/or modernize their production, only a **few of them are interested to go for a WHO Prequalification** or SRA approval, as the return on investment is currently too low. For all Member States in SADC, the South African market is the first and most important market for export (or local market in the case of South African pharmaceutical companies themselves).

Regional pharmaceutical manufacturing does not need to be limited to the **3 pandemic diseases**, but the increasing number of patients in need, and the subsequently required high volumes of medicines and commodities makes them a logical target.

Production of **other essential medicines** will benefit from improvements in the enabling environment. For example, production capacity for quality assured **non-communicable disease** medicines **will** benefit from an improved enabling environment including human resources, finance, technology pools and infrastructure (road, industrial building, water supply and electricity).

Regional Strategy

Based on the Situational Analysis, **hera** has produced a **Gap Analysis**. For all major policy and technical areas, the existing situation was compared to the desired situation, and the gaps identified. Actions were suggested to bridge the gaps.

The gaps and proposed actions led to the following recommendations to SADC for the overall **Regional Strategy:**

1. Develop a 5-year **SADC Pharmaceutical Manufacturing Action Plan (SAPMAP)** as part of the Regional Strategy. It should include appropriate coordination, implementation and monitoring of common development goals.
2. Ensure **policy alignment** and **coherence** between finance, trade, industry, agriculture and health sectors.
3. Operationalize the approved **SADC Pooled Procurement Strategy** and its operational arm, the **SADC Pharmaceutical Procurement Services** (SPPS).
4. Use the **TRIPS flexibilities effectively** to manufacture or import more affordable good quality generic medicines.
5. Develop a **Regional Pharmaceutical Human Resources Development Plan**, linking required skills (GMP, GLP, GCP, regulatory, GDP, MBA, pharmaceutical business) to the 5 Centres of Pharmaceutical and Regulatory Excellence.
6. Update and harmonize **regulatory standards** to create **one regional market** and mutual recognition. This should include r**egional GMP certification** and a **regional GMP roadmap**.
7. Harmonize the **standard treatment guidelines** for the three diseases at regional level (in close collaboration with national experts).
8. Develop capacity and business plans for the production of **Active Pharmaceutical Ingredients**. Alternative technologies such as continuous flow chemistry should be investigated.
9. Discuss with Member States to remove **non-tariff barriers** to intra-regional trade.
10. Promote the phased introduction of a **Regional Preference** to replace Domestic Preference.
11. Facilitate **Technology transfer** within and towards the region.
12. Lobby **donors** to shift more procurement funds towards regional products, and mobilise **financial resources** for the implementation of the strategy.

Recommendations for the **Member States:**

13. Adopt a **National strategy for local manufacturing** in line with the Regional Policies.
14. Develop a **National Roadmap** for implementation of the SADC Pharmaceutical Manufacturing action plan; each country to indicate their **areas of specialisation** as part of the regional plan, and to specify **targets**.
15. Create a conducive **enabling environment** for viable and profitable pharmaceutical manufacturing (if applicable). This could include targeted, relevant government incentives, domestic/regional preference, tax holidays, and should also cover raw materials, packaging materials and support industries.
16. Ensure **policy alignment** and **implementation** (health, finance, trade, industry, agriculture).
17. Ensure **coherence** of all laws and policies to promote pharmaceutical manufacturing.
18. **Align laws, policies and tariffs** structures to promote import and export of locally produced medicines and health commodities at regional level.
19. Remove **non-tariff barriers** to trade.
20. Develop an **appropriate mix of industry incentives and instruments.**
21. Promote **transparency, accountability and monitoring** of agreed strategies by multi-stakeholder groups.

22. Align **standard treatment guidelines**, regulatory and registration guidelines to regional templates.
23. Consider a **designation** system for regionally produced medicines and commodities (demand side).
24. Introduce a **regional preference** in procurement legislation to replace domestic preference in a phased approach.
25. Incorporate full **TRIPS flexibilities** in national legislation and utilise them in pharmaceutical manufacturing and import/export.
26. Push for **Curriculum development** to align skills needs and develop/strengthen Centres of Excellence (CoE).
27. Where possible and feasible each country to have access to a national or regional **Human Resources Development facility**.
28. All **National Medicines Regulatory Authorities** to exchange information about efficacy, safety and quality with other NMRAs in the context of regional **regulatory harmonisation**
29. Develop (if applicable) a **national GMP roadmap** to create a level playing field for manufacturers. This may need GMP training and technical support.
30. **Develop a National Pharmaceutical Human Resource Strategic Plan**, which should include industry or focus on industry sector. Implement harmonised curricula especially for industry sectors.
31. Mobilise **financial and technical resources.**

Recommendations for the **Private sector**:

32. Join (if not yet a member) a regional trade association, and participate in the regional debates on the Strategy and Action Plan for Regional Production.

Recommendations for **Civil Society**:

33. Join (if not yet a member) a regional association, and participate in the regional debates on the Strategy and Action Plan for Regional Production

All strategic recommendations have been used to develop a draft **'Strategy on Regional Manufacturing of Medicines and Health Commodities'**, which is published as a separate document.

Data collected during country interviews were summarized in tables in Volume 2. Country summaries and SADC infographics are found in volume 2A. Volume 3 contains the Terms of Reference, the lists of people met, companies interviewed, medicines for the 3 diseases produced or used in SADC, literature consulted, and all data collection tools.

Achieving regional production of current and new medicines for HIV, TB and malaria will require a sustained effort by all stakeholders. But the millions of patients depending on progress in this area for improved access to life-saving pharmaceutical and associated products will make the effort worthwhile.

1. INTRODUCTION

1.1 This Study

This study into the Feasibility of Regional Manufacturing of essential medicines and commodities for the prevention, treatment and control of the three pandemic diseases (HIV, Tuberculosis and Malaria) has been planned for some time.

A request for Expression of Interest was launched in June 2013, and a Request for Proposal on 8 December 2014. After a competitive tender, SADC Secretariat contracted the Consultant on 29 April 2015.

Consultants started the work end May 2015 with a literature study and desk review, and presented an Inception Report with methodology on 16 July 2015. After comments by the SADC Technical Review Committee (TRC) on the methodology, consultants submitted a revised inception report on 11 August 2015.

During the situational analysis (mid-August – end September 2015), consultants visited all 15 Member States and 35 manufacturers, drug regulators, laboratories and universities or Centres of Excellence.

A first draft Feasibility report was submitted 5 October and discussed 12 October 2015 with the TRC. SADC invited consultants to present a progress report at a SADC Industrial Development Forum (IDF) meeting on 12 November 2015. A 2nd draft Feasibility report and outline for the strategy were presented to a Member States validation and consensus meeting on 8-9 December 2015, and to a TRC meeting 10-11 December 2015.

The final draft strategy was submitted 16 December 2015, and the final draft report on 18 December 2015.

1.2 The Audience

This Feasibility Study, including a Situational and Gap Analysis, and the related Strategy are aimed at all stakeholders who are interested in increasing the production of essential medicines or health commodities in SADC or SADC Member States.

The consultancy seeks to assess the feasibility of the production of essential medicines especially those related to the three communicable diseases, namely HIV and AIDS, TB and Malaria as well as the production of health commodities for the three diseases.

1.3 Scope and Organisation of the Report

The scope of the report is defined in the Terms of Reference (TOR) (see Volume 3, sections 1 and 2). The report needs to address all 41 points of these TORs, but must also remain a readable document that tells a story. **hera** has therefore chosen to summarize the story at the beginning of each chapter,

and to provide highlights of the situational analysis in subsections. All details, tables and further country data are presented in Volume 2 (country data).

hera added a gap analysis to this report, which presents the desired outcomes; what the current situation (analysis) is; how big the gap is; and how that gap can be bridged. The gap analysis outcomes have been incorporated in the overall strategy for achieving increased regional production of HIV and AIDS, TB and malaria related medicines and commodities, and included recommendations for health and industry policies, regulatory landscape, coherence between ministries, support to the pharmaceutical sector, human resources and financing.

Volumes 1, 2, 2A and 3

The main report (that you are reading now) is Volume 1. It contains the Situational analysis, feasibility, business case, operational issues and the gap analysis.

Country information and data tables for all TORs are provided in Volume 2. For logistics reasons this will be split in 2 files for emailing: Volume 2 (tables) and 2A (country infographics).

The Terms of References, lists of people/organisations met, bibliography, and copies of all tools (questionnaires) are provided in volume 3.

During the Member States' consensus meeting, a printed document was provided with a 10-page Executive Summary and the Country Infographics. An updated executive summary is now included in Volume 1, and updated Country Infographics in volume 2(A).

2. BACKGROUND

2.1 Industrialization Agenda

The SADC Treaty[1] provides the overall structure and mandate for working towards regional integration, and has inspired the Protocol on Trade[2]. The Regional Indicative Strategic Development Plan (RISDP)[3] and the 2012 SADC Industrial Development Policy Framework (IDPF)[4] provide the framework for the trade and industrialization agenda.

The 'SADC Industrialization Strategy and Roadmap 2015-2063' is anchored on three pillars, i.e. industrialization, competitiveness and regional integration. It prioritizes the regional value chain approach to industrialization in the region, with pharmaceuticals as one of its top priorities in action area 6.[5]

The 'Roadmap for the Industrialization Strategy', approved 29 April 2015 by the SADC Summit, identifies three constraints: infrastructure, human resources/skills, and finance. Improving the value chain in the pharmaceutical sector was one of the three top priorities, along with agro processing and minerals beneficiation. The roadmap has three phases, of which the first phase coincides with the revised RISDP (2015-2020).

The SADC Industrial Development Policy Framework focuses on the promotion of regional value chains in SADC as a key industrial policy priority based on the following approaches:

1. Upgrading of existing manufacturing industries towards more competitiveness (industrial upgrading and modernization);
2. Fostering backward- and forward linkages and complementarities between sectors and industries, and across the region (industrial deepening) ; and
3. Diversifying the region's industrial base through new productive activities (industrial diversification).

2.2 Pharmaceutical Business Agenda

Work in the health sector is based on the SADC Protocol on Health[6] and disease-oriented policies.

Costs for medicines are a major obstacle in most SADC Member States. While medicines represent less than 20% of total public and private health spending in most developed countries, in developing countries (including most SADC Member States) it ranges from 25% to 66%. Medicines constitute the largest public expenditure on health after personnel costs; they are also the largest household health

[1] Southern African Development Community. Website http://www.sadc.int/documents-publications/sadc-treaty/
[2] Southern African Development Community. Website http://www.sadc.int/index.php?cID=190
[3] Southern African Development Community. Website http://www.sadc.int/index.php?cID=201 a new draft 2015-2020 RISDP is being discussed, and was made available to the study team.
[4] Southern African Development Community. Website http://sadc.int/files/2013/8969/0505/Final_SADC_Industrial_Develeopment_Policy_Framework.pdf
[5] SADC/MTF-REI/15/2015/3.
[6] Southern African Development Community. Website http://www.sadc.int/documents-publications/show/804

expenditure. Access and affordability to medicines are therefore important determinants for the state of health and poverty for the region and the households.

The SADC region like the rest of Africa depends heavily on imported medicines, both patented and generics. As an example, in Africa 37% of HIV medicines are patented products, whereas 63% are generics. About 85% of the generic ARV medicines used in the region are imported and only 15% are manufactured within the SADC region. The continuity of supply of affordable medicines is increasingly becoming a concern.

The scope for development of pharmaceutical products is very large in SADC. Of the total pharmaceutical market in the SADC region only 24% are being locally produced.

The specific pharmaceutical policy framework is defined in the 'SADC Pharmaceutical Business Plan (PBP)'. The PBP includes a specific chapter on stimulating regional production[7] with a specific strategy:

> *"Rationalizing and maximizing the research and production capacity of local and regional pharmaceutical industry of generic essential medicines and African Traditional Medicines"*

The 2007-2013 PBP[8] has recently been superseded by the new 2015-2019 PBP[9], which has a specific strategic objective:

> *"Create an enabling environment that will maximize the research into production capacity of local and regional pharmaceutical industry in terms of generic essential medicines"*

It also has a defined target to be reached by 2019:

> *"50 % increase in local production and availability of essential Medicines"*

Several published literature reviews[10] show that up to now it has been challenging to cost-effectively produce quality assured essential medicines in SADC, due to the fierce competition from India and China, who produce both the active pharmaceutical ingredients (APIs) and the finished dosage forms. However, the 2005 changes in the Indian Patent law required by the TRIPS agreement offer a possible niche for SADC, as India cannot easily make copies anymore of medicines patented since 2005.

2.3 Public Health Challenges / Protocol on Health

The SADC region has some of the highest rates of morbidity and mortality due to HIV and AIDS, TB and Malaria. Furthermore, these diseases are both the cause and consequence of poverty in the region. To this end, the disease burden in the SADC region is undermining the efforts to eradicate poverty, which is the overarching priority for the regional integration agenda.

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[7] Southern African Development Community. Website http://www.sadc.int/themes/health/pharmaceuticals/

[8] World Health Organisation. Website http://apps.who.int/medicinedocs/en/d/Js19282en/ (formally approved by SADC Health Ministers in 2007)

[9] Personal communication, Mr Joseph Mthetwa, 9 December 2015.

[10] Kaplan 2011, Equinet 2013, WHO 2011, AMASA 2012, Buizert 2007, Consoli (undated). All studies have been collected in a SADC Regional Production Dropbox: see https://www.dropbox.com/sh/vwlgxy892j75qtp/AAAqNyTPPR0WhzVTaq41-RRva?dl=0

The HIV and AIDS, TB and (less so) malaria epidemics have led to a serious public health crisis in SADC. SADC has developed several strategies to address this crisis, and their successful implementation requires access to affordable medicines and commodities.

SADC Member States have developed different strategies for the control of the three diseases with varying degrees of effectiveness. At the regional level, SADC has also outlined strategies and activities for the control of the diseases through the Protocol on Health. These are based on the principle that a coordinated regional effort is necessary to complement national strategies.

One of the obstacles affecting the response to the three pandemic disease is limited access to medicines and related commodities for prevention and treatment, which has resulted in millions of deaths in the region. There are several reasons for this limited access to medicines and related commodities: unaffordable prices, inefficient procurement and supply chain systems, weak regulatory and quality assurance mechanisms, lack of regional production capacity for medicines, and poor or inadequate payment systems.

There is still a big treatment gap in SADC: only 6 million (51%) of the 11.7 million currently eligible patients receive ARV treatment. Resistance against affordable first-line treatments will need more second and third line treatments in the future. To effectively address the public health crisis, SADC also needs new point of care diagnostics, condoms, bed nets and insecticides.

2.4 Regional, Continental and Global Commitments

The SADC region has made several regional commitments in the Treaty, Protocols, Policies and Frameworks. In trade and industry sectors, SADC is committed to an industrialization program. In health, SADC is committed to controlling the three diseases, and to implementing the Pharmaceutical Business Plan.

In April 2001, Heads of State of African Union countries met and pledged to allocate at least 15% of their annual budget to the health sector. In 2010 only one African country had reached that target, and while 26 had increased health expenditures, 11 had reduced it. Nine others had not had a noticeable negative or positive trend.

At continental level, SADC is collaborating with the Common Market for Eastern and Southern Africa (COMESA) and the East African Community (EAC) in the Tripartite Free Trade Area (TFTA). SADC is also participating in the African Medicines Regulatory Harmonization Initiative (AMRH), and the Pharmaceutical Manufacturing Plan for Africa (PMPA).

SADC is further party to the global Sustainable Development Goals, substituting the Millennium Development Goals agenda in 2015.

The non-LDC countries in SADC are subject to the TRIPS Agreement, which forces them to provide 20 years of patent protection if the patent application is deemed valid. LDC countries are exempted until

2021 from the obligations of the TRIPS Agreement, and until 2033 from honouring pharmaceutical patents.

2.5 Problem Statement and Rationale

SADC is still a global hotspot for the three pandemic diseases. Medicines and commodities are available to prevent, cure or control the diseases. Only 15% of the generic ARVs, and 24% of all other essential medicines are currently produced in SADC.

SADC would like to increase the percentage of medicines produced in the region. This will help both the health agenda (universal health coverage) and the industrialization agenda (building a sustainable pharmaceutical manufacturing capacity).

Benefits of regional production will also include less dependence on far-away suppliers; more supply security; savings on foreign exchange[11]; more industrialization; more knowledge among companies; and more employment.

[11] E.g., by regionally producing the active pharmaceutical ingredients (API)

3. GOALS AND OBJECTIVES

3.1 Goals and Objectives

Given that any set of normative principles will vary according to the objectives of an intervention designed to promote regional manufacturing, in this document the following high level goals are assumed:[12]

1. Direct and indirect economic benefits (measured by increase in Gross Domestic Product, employment, education, retention of highly skilled people, increase in industrialization, per capita income and quality of life) .
2. Improved (public) health outcomes, and in particular health related Sustainable Development Goals, which includes Universal Health Coverage (UHC) and access to essential medicines[13], and human right to health.

A number of possible objectives for such a programme could be adopted, including the following:

1. Increase in employment
2. Growth in high/medium technology products manufacturing and related services
3. Enhanced exports and higher foreign exchange earnings
4. Improved security of supply for the public health sector
5. More robust regulatory oversight
6. Availability of locally produced products for local needs and diseases
7. More laboratories for testing and quality assurance
8. Expanded number/capacity of academic institutions offering master's degree courses in pharmaceutical sciences
9. Development of institutions providing clinical trial services / bioequivalence studies
10. Contribution to provision of a sustainable, comprehensive health package
    a. Motivation is that both the business and public health objectives should be served
11. Fair distribution of resources and equity among SADC Member States.
    a. Motivation is that manufacturing locations will have to be distributed fairly across the region rather than be based on economical / technically best location considerations only.

3.2 Objectives of the Feasibility Study

The objectives of this feasibility study are to:[14]

1. Assess the feasibility of regional production of generic essential medicines, especially those related to the three major communicable diseases (HIV and AIDS, Tuberculosis (TB) and Malaria) and accompanying/related health commodities such as condoms (HIV and AIDS),

[12] Based on the Pharmaceutical Manufacturing Plan for Africa, business plan, SADC Pharmaceutical Business Plan, SADC Industrialization Framework and recent SADC and WHO policies.

[13] UN Resolution, September 2015

[14] SADC Secretariat. 'Terms of Reference for the Feasibility Study on Regional Manufacturing of Medicines and Health Commodities'. SADC-SHD&SP/CD/C39/2014.

Rapid Diagnostic Tests (RDT), Dichlorodiphenyltrichloroethane (DDT) and long-lasting insecticide-treated nets (LLITN) (malaria).

2. Develop a strategy or modality for operationalizing regional production of medicines and health commodities for these communicable diseases.

4. METHODOLOGY

The Terms of Reference provided a detailed list of 41 tasks that the consultant had to perform.

In the inception phase, consultants reviewed the literature and performed a desk analysis of the many reports on the SADC pharmaceutical sector. A conceptual framework was generated for how the sector could be analysed. Tools were developed, and a detailed methodology was written for the feasibility phase.

4.1 Vision

Consultants propose the following vision for regional production of medicines for the three diseases:

"A sustainable pharmaceutical manufacturing industry in SADC
that supports public health programmes and universal health coverage"

This vision points to the interrelation between industrialization and health objectives, both of which have to be achieved. SADC has embraced this vision by putting the focus for the regional production feasibility study on three diseases with considerable public health relevance (HIV and AIDS, TB, and malaria).

4.2 Design and Conceptual Framework

The study design of this feasibility study is a descriptive, observational study.

Figure 1 provides an overview of the factors impacting on regional production, as found in the literature and desk review. Together they form the (enabling / not enabling) environment for the development of more extensive local manufacturing of pharmaceuticals, medical devices and commodities in the SADC region. These factors were further investigated using the various semi-open-ended questionnaires.

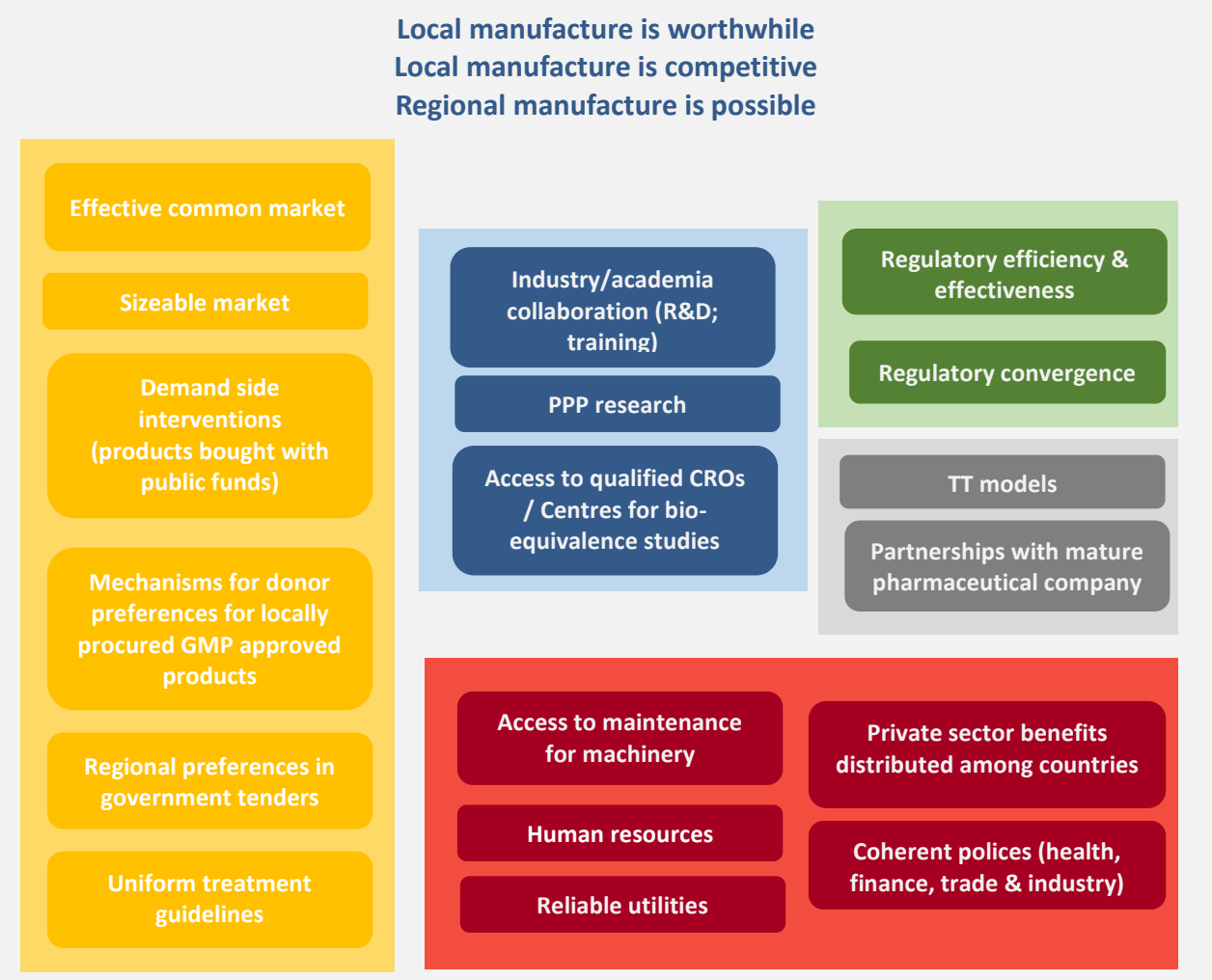
The feasibility study report was written after all data had been collected and analysed.

In the gap analysis consultants identified the targets as the desired state in 2020. The gap with the current situation was used to make suggestions on how the gap could be bridged.

For the Strategy, consultants used the Logical Framework Approach. A "problem tree" was generated from the Situational and Gap Analysis. Then the tree was "turned" into strategic objectives to achieve the high-level goal of a sustainable pharmaceutical industry.

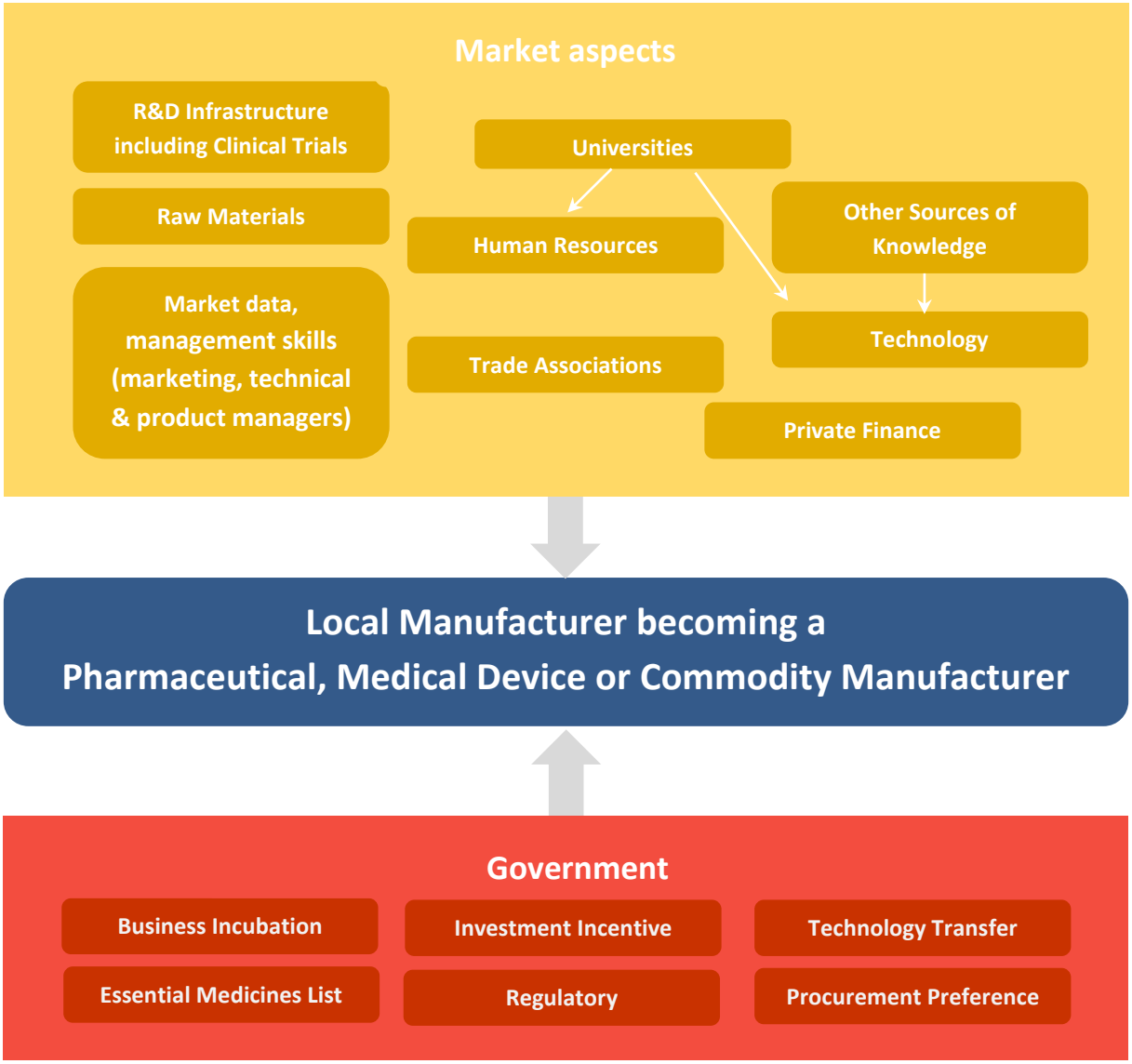
A results framework with outcomes and outputs was developed. This can be the basis for an Action Plan to achieve the high-level goal.

Figure 1 - Factors impacting on sustainable manufacture of new generics in SADC



There are many factors that impact on the manufacture of new generic essential medicines in SADC. Figure 2 below shows the different aspects of the production environment that could facilitate and incentivise local manufacturing for the SADC region (and beyond). This framework is used in the remainder of this report to present the findings related to the current status of this environment and resulting strategic considerations.

Figure 2 - Market aspects and government influence on Regional Manufacturing



Successful implementation of a regional pharmaceutical manufacturing program requires the integration of trade, industrial and health policies. This is well illustrated in WHO's recommended framework for local production (see Figure 3).

Figure 3 - WHO framework for local production and access to essential medical products, 2012

4.3 Scope and Focus

The Scope and Focus of the study are as per the Terms of Reference (see Volume 3, Section 1).

4.4 Data Collection Methods and Tools

Standardised questionnaires were developed for countries, manufacturers, regulators and Centres of Excellence (see volume 3), and approved in the revised Inception Report. Data were collected by local and visiting consultants in all 15 Member States. Results were tabulated per TOR (see volume 2 for details).

4.5 Sampling

No sampling was done in the study. The Terms of Reference stated that stakeholders in all 15 SADC Member States had to be interviewed. Also, all manufacturers were interviewed that were known to make at least one product for the treatment or prevention of the three pandemic diseases. The TORs also specified which regulatory authorities, laboratories and Centres of Excellence had to be visited. Consultants slightly adapted this list with motivations in the inception report.

4.6 Data Analysis

The results of the questionnaires were collected from country consultants, and the findings subsequently validated and analysed by two **hera** partners. The results have been inserted in the relevant sections as a table or text.

The core team then wrote a draft report with a gap analysis, and discussed it with the **hera** internal review team, which met 28-29 September 2015 in Johannesburg. The meeting discussed and validated the situation and gap analysis, and drafted the Strategy. A summary of the final draft report was also discussed with a meeting of the SADC Industrial Development Forum (IDF) on 12 November 2015.

4.7 Ethical Considerations

AfDB and SADC had approved the Terms of Reference for the study. No ethical review was performed as no personal or privacy sensitive data were sought. Potential conflicts of interests of **hera** consultants (such as having to assess the situation in their own country or a company owned by relatives/friends) were identified before the situational analysis, and were avoided by using another consultant. If no alternative consultant was available, the potential conflict of interest was noted in the report.

4.8 Limitations of the Study

This study TORs focus on the feasibility of products **for the three pandemic diseases**, and thus has specific limitations mostly related to how these three markets are financed, and the quality standards and procurement rules set by those funders. However, most of the situational analysis, the gap analysis, recommendations for improving the enabling environment for local production of pharmaceuticals and commodities, and the overall proposed strategy will also apply to the regional production of most essential medicines and commodities.

There may be merit for SADC to also look into the wider market of **other essential medicines**, and follow the recommendations of the African Union (AU) Pharmaceutical Manufacturing Plan for Africa (PMPA) for a regional situational analysis, strategy design and regional implementation of an overall pharmaceutical development plan.

The study TORs have a geographical focus on the SADC region, but the literature review and country examples also include experiences from other countries and economic blocks in Africa and Asia.

5. FINDINGS

All findings are based on a literature review and on interviews with 35 manufacturers, drug regulators, laboratories and universities or Centres of Excellence, which took place in all 15 Member States.[15]

5.1 Enabling Environment

5.1.1 Introduction

The situational analysis looked at all 15 SADC Member States, but the general discussion focuses on the region as a whole. It is noted that there will be specific challenges or good practice examples for the different countries and sub-sectors (pharmaceuticals, etc.), including some of the following:

1. Access to finance
2. Availability of skilled human resources
3. Availability of manufacturing technology
4. Local Research & Development (R&D), especially experimental development leading to product or process technology
5. Supporting industries
6. Regulatory capacity in government
7. Availability of government incentives

Where feasible, these specific challenges have been mentioned in the tables as illustration of lessons learned or good practices.

5.1.2 Industrialization Policy

The Summit of SADC Heads of State and Government held in Harare, Zimbabwe in April 2015 approved the Revised Regional Indicative Strategic Development Plan (RISDP) 2015-2020 and the SADC Industrialization Strategy and Roadmap 2015-2063 and directed the Secretariat to develop an Action Plan for implementation of the Strategy and Roadmap.

The Revised RISDP, which places industrialization at the centre of the regional integration agenda, has "Regional Production of Essential Medicines and Health Commodities established and functional" as a targeted output for 2020.

The 'SADC Industrialization Strategy and Roadmap 2015-2063' is anchored on three pillars – industrialization, competitiveness and regional integration. It adopts the regional value chain approach to industrialization in the region, with improving the value chain in the pharmaceutical sector as one of its top priorities, along with agro-processing and minerals beneficiation (see The Industrialization Strategy Roadmap, Action area 6).[16]

[15] The relevant questionnaires can be found in Volume 3.

[16] SADC/MTF-REI/15/2015/3.

The SADC Industrialization Strategy and Roadmap 2015-2063 identifies three phases of development, of which the first phase coincides with the Revised RISDP (2015-2020). It also identifies three binding constraints: infrastructure, human resources/skills, and finance.

All SADC Member States are expected to align their national industrialization strategies and action plans with the SADC Industrialization Strategy and Roadmap 2015-2063. Tanzania drafted a 'Strategy for promotion of domestic pharmaceutical Production 2013-2023'[17], however not as part of the SADC industrialization Roadmap.

5.1.3 Government Support for the Pharmaceutical Sector

The SADC Treaty[18] provides the overall structure and mandate for working towards regional integration, and has inspired the Protocols on Trade[19] and Health[20]. The Regional Indicative Strategic Development Plan (RISDP)[21] and the 2012 SADC Industrial Development Policy Framework (IDPF)[22] provide the framework for the trade and industrialization aspects; the pharmaceutical policy framework is defined in the 'SADC Pharmaceutical Business Plan (2007-2013)'[23], which has been updated into the Pharmaceutical Business Plan 2015-2019[24]. Both have a specific chapter on stimulating regional production[25]. The specific strategy for regional production is:

> *"Rationalizing and maximizing the research and production capacity of local and regional pharmaceutical industry of generic essential medicines and African Traditional Medicines"*

SADC regional policies and frameworks are in line with wider African policies, such as the 'African Union Pharmaceutical Manufacturing Plan for Africa' (PMPA), its 2012 business plan, the 2015 update report, the AU Accelerated Industrial Development of Africa, and the 'Agenda 2063'. These all provide evidence for a broad continental level consensus on prioritising industrialization and pharmaceutical manufacturing.

Countries are also increasingly defining their national frameworks: Tanzania developed a 'Strategy for promotion of domestic pharmaceutical production'[26]; Kenya developed a 'Roadmap for Local Manufacturers' to achieve WHO GMP standards using a stepwise approach;[27] and Ethiopia launched its 'National Pharmaceutical Manufacturing Plan July 2015'[28]. This study concludes that only countries

[17] Personal communication, Marianne Schürmann.
[18] Southern African Development Community. Website http://www.sadc.int/documents-publications/sadc-treaty/
[19] Southern African Development Community. Website http://www.sadc.int/index.php?cID=190
[20] Southern African Development Community. Website http://www.sadc.int/documents-publications/show/804
[21] Southern African Development Community. Website http://www.sadc.int/index.php?cID=201 a new draft 2015-2020 RISDP is being discussed, and was made available to the study team.
[22] Southern African Development Community. Website http://sadc.int/files/2013/8969/0505/Final_SADC_Industrial_Develeopment_Policy_Framework.pdf
[23] World Health Organisation. Website http://apps.who.int/medicinedocs/en/d/Js19282en/ (formally approved by SADC Health Ministers in 2007)
[24] Personal communication, Dr Joseph Mthetwa, 9 December 2015
[25] Southern African Development Community. Website http://www.sadc.int/themes/health/pharmaceuticals/
[26] Strategy for promotion of domestic pharmaceutical production in Tanzania 2013 – 2023. Tanzanian government, 2012.
[27] Kenya GMP Roadmap: A Stepwise Approach for the Pharmaceutical Industry to Attain WHO GMP Standards. UNIDO, Kenya, 2014.
[28] World Health Organisation. Website http://whoethiopia-whoafroccmaster.newsweaver.com/19qa3yal7221cr9r2ai8pj?email=true&a=1&p=48882328&t=22361785

with strong, coherent government support and access to external technical & financial support are making progress.

The SADC pharmaceutical industrialization agenda is likely to get the interest and support of international development partners (e.g. Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ), German Federal Ministry for Economic Cooperation and Development (BMZ), development banks (African Development Bank (AfDB), World Bank and the German Development Bank KfW) and UN agencies (United Nations Industrial Development Organization (UNIDO), United Nations Development Programme (UNDP) and the World Health Organization (WHO)).

Challenges

SADC policies are relying on Member States and other stakeholders for implementation. The implementation of the overall RISDP was assessed in April 2015, and the following challenges found may also be relevant for the implementation of SADC's industrialization and the regional pharmaceutical production ambitions:[29]

1. Inadequate capacities at both the Member State and Secretariat levels.
2. Non-alignment of Member State national development plans with the priorities of the RISDP.
3. Low levels of Member State ratification and domestication of protocols.
4. Low levels of Member State compliance with community obligations.
5. Undeveloped community enforcement mechanisms (including low level of utilization of the provisions of the Treaty).
6. Insufficient coordination of the implementation of the RISDP.
7. Undeveloped monitoring, analysis, reporting, and review systems.
8. Overreliance on donor funding for implementation of the RISDP programmes.

It is possible that the implementation of a SADC Pharmaceutical Manufacturing Action Plan (SAPMAP) would face similar challenges, especially if the work was to be done by SADC Secretariat and Governments only.

Consultants strongly recommend to bring the private sector, civil society and academics or independent experts on board in the discussion, decision making, coordination and implementation of SAPMAP.

Strategic Considerations

1. The existing SADC policies and frameworks are a good basis for regional pharmaceutical manufacturing.
2. Successful implementation of local production requires, however, **more coherence** between trade/ industry, agriculture, education, procurement/finance and health officials, both at country and regional level, and
3. **Closer collaboration** between SADC, governments, private sector, civil society and academics/independent experts.

[29] Draft revised regional indicative strategic development plan 2015-2020, SADC Secretariat, April 2015. SADC/EOC/1/2015/3.1B

5.1.4 Pooled Procurement

Pooled procurement by several/all Member States of SADC provides the necessary economies of scale to ensure the economic feasibility of local production.

1. SADC Health Ministers agreed in November 2012 in Maputo to the 'SADC Strategy for Pooled Procurement of Essential Medicines and Health Commodities (2013 – 2017)' [30]. This was informed by a 'SADC Situational Analysis and Feasibility Study'[31], discussed and agreed in September 2012 by representatives of all SADC Member States.
2. In November 2013 SADC Ministers of Health adopted the electronic platforms for information and work sharing, the 'SADC Medicines Database'[32] and 'Pooled Procurement Network' (PPN), and the setting up of a Pooled Procurement Coordinating Mechanism, i.e. 'SADC Pharmaceutical Procurement Services' (SPPS).
3. In September 2014 SADC Member States adopted the SPPS Charter and tasked the Pooled Procurement Task Team (PPTT)[33] to implement the SADC Pooled Procurement Strategy. The PPTT met in December 2014 and finalised the 'SPPS Business Case'[34] and prepared the 'PPTT Action Plan and Budget 2015'. By September 2015, the SPPS and PPTT action plan have not yet been implemented.
4. A SADC consultant presented a draft report on group contracting to SADC TRC and Member States in 2015.[35]
5. Most SADC Member States have a procurement policy or Act that allows for **domestic preference** in national tenders. Differences in the public procurement legislation and regulations do exist, but are not expected to have a major impact on the SADC Pooled Procurement Strategy, possibly with the exception of domestic preferences.
6. Interviews conducted for the SADC Pharmaceutical Market Analysis revealed that 8 of the 13 study Member States had provided for a **domestic preference** for locally manufactured products in their tenders. In most cases, the preference is applied as a percentage deduction from the quoted price during financial evaluation. The study interviews also revealed that 6 Member States apply preferences for products that are offered by local wholesalers (even though the products are actually manufactured abroad – this does not help regional production). The range of preferences given was between 5% and 30%, and is set out in Member State legislation and regulations.[36]
7. There is currently no **regional preference** – this should be considered as key component of a regional strategy for regional production. The current domestic preference percentages

[30] Southern African Development Community. Document available at http://www.sadc.int/files/7614/1898/8449/SADC___Strategy_for_Pooled_Procurement_of_Essential_Medicines_and_Health_Commodities.pdf

[31] Southern African Development Community. Document available at http://www.sadc.int/files/6614/1890/8516/SADC___SADC_POOLED_PROCUREMENT_OF_ESSENTIAL_MEDICINES_AND_MEDICAL_SUPPLI...pdf

[32] Southern African Development Community. Medicines Procurement Information and Work Sharing Manual. Version 3.0 10 December; available at http://med-db.medicines.sadc.int

[33] Southern African Development Community. 2014. Terms of Reference Pooled Procurement Task Team

[34] Southern African Development Community. 2014. SPPS Business Case including the Draft SPPS Charter;

[35] Lloyd Matowe. An Overview of Procurement and Supply Management Systems in the Southern Africa Development Community Member States. SADC, September 2015.

[36] Southern African Development Community. Document (page 24) available at http://www.sadc.int/files/6614/1890/8516/SADC___SADC_POOLED_PROCUREMENT_OF_ESSENTIAL_MEDICINES_AND_MEDICAL_SUPPLI...pdf

promote domestic production rather than regional production. Such a regional preference scheme should apply only to manufacturers, and not be applied to wholesalers in other SADC Member States who only import finished products, as this does not add any value for SADC.

Strategic Considerations

1. SADC Secretariat and Member States should establish the **SADC Pharmaceutical Procurement Services** to coordinate the buying power of SADC Member States and thereby provide a predictable and sizeable market for regional production.
2. SADC Member States' governments should agree on a **regional preference** system provided to regionally manufactured products in national tenders, and remove domestic preference schemes. Initially, the regional preference could be piloted for medicines for the three diseases.
3. SADC Member States buying their own ARVs and TB medicines should consider including **increased "local added value" percentages** as award criteria in their tender procedures.

5.1.5 Government Incentives for Pharmaceutical Manufacturing

Member States have different levels of support to the pharmaceutical sector. A number of Member States do not separate the pharmaceutical sector from other sectors and have general preference schemes to support local procurement. Member States give up to 30% domestic preference during public sector tenders. South Africa uses 'designation' in government tenders: a certain percentage of the tender (depending on the product and local capacities) has to be filled by local manufacturers. In practice, however, in many Member States local companies have difficulties in competing with products from India and China, especially as finished dosage forms often do not attract import taxes/tariffs, but raw materials, excipients and packaging materials do. See Volume 2.

Among the SADC Member States, the most common incentives include:

1. **Sectoral Incentives**, with minimum investment stipulated (on average about USD 100,000 for local companies and USD 300,000 for foreign investors). This includes support for rural development, building industrial centres away from major cities and reducing environmental hazards, over-urbanization and concentration of population. Most Member States offer this incentive. [37]
2. **Tax incentives**, the most common being tax holidays, ranging from 2 to 10-year tax holiday according to level of minimum investment required (USD 5-10 million respectively).[38]
3. A **customs tax exemption** for imported equipment, goods, raw materials and packaging materials used by an industrial company; offered in most Member States. Some offer consumption tax exemption to companies that export more than 59% of their production.[39]
4. **Export incentives** and **free trade zones**: Incentives for establishing export manufacturing operations include an export tax allowance from 12%-25%. Most Member States offer this.[40] Export processing zones (EPZs): The objectives and purposes of EPZs are to attract, promote or increase the manufacture of goods for export; to create or increase industrial employment,

[37] http://www.sadc.int/themes/health/pharmaceuticals/
[38] ibidem
[39] ibidem
[40] ibidem

export earnings, and industrial investments; and to encourage technology transfer and the development of management and labour skills. Customs Duty Drawback Facility: for companies that export outside the Southern African Customs Union (SACU).[41, 42, 43]

5. **Infant Industry Support**, example being South Africa where government provided financial support through the Department of Trade and Industry (DTI) to the Ketlaphela project (ARV API manufacturer) via incentives like the Critical Infrastructure Fund and the 121 Tax Incentive.[44]
6. **Education Grants**: Namibia[45] offers an allowance of 25 per cent related to employment and approved training costs for employees directly engaged in manufacturing operations.[46] Botswana gives access to 200% tax training rebate; [47] in Swaziland, 100% of training costs is permitted to be written off against tax liabilities.[48]
7. **Loss Carry Forward**: in Malawi, manufacturing companies can deduct operating expenses incurred up to 24 months before the start of operations. Indefinite losses carry forward for tax allowances. Losses are carried up to 7 years.[49]
8. **Duty exemptions** on raw materials including machinery and equipment: for Member States in general, and duty free imports for SACU members in particular. Raw materials imported into the country to manufacture products to be exported outside SACU are exempt from import duties.[50]
9. **Exemption on withholding tax**: ranges from 0% - 12% among the Member States.[51]

In the majority of the Member States, **R&D** is very limited. Generally, the R&D that is taking place is done in a few bigger countries, and financed within pharmaceutical companies, mostly linked to large international pharmaceutical companies. The European Union (EU) has funded clinical research programmes, and also the WHO Tropical Disease Research (TDR) programme. There is hardly any government support for R&D throughout the region.

Public-Private Partnerships (PPP) may need to be considered. South Africa has experience with PPPs in API manufacture (Ketlaphela), Vaccines (Biovac) and a new project on TB APIs (Sanofi-DTI).

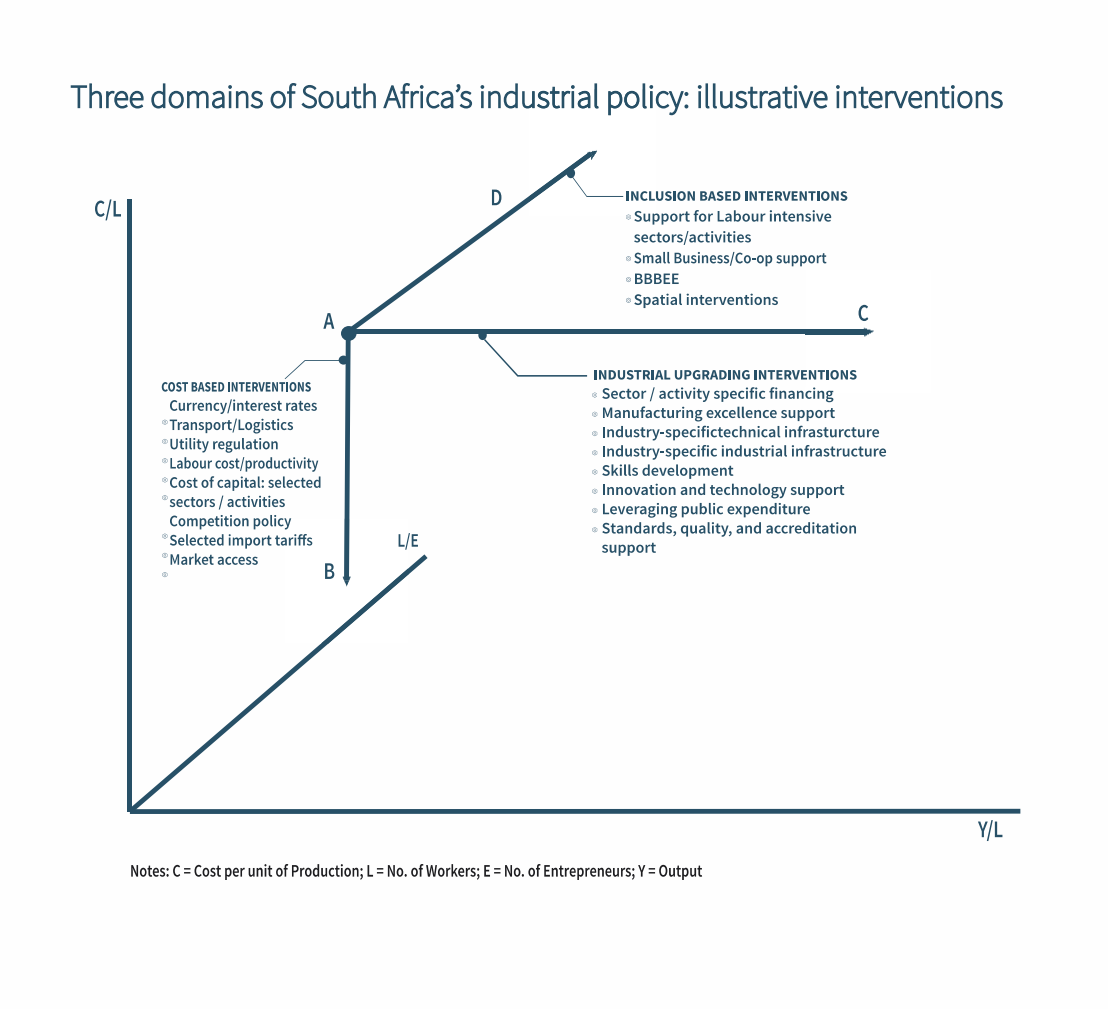
The South African National Industrial Policy Framework (NIPF) vision, especially the strategic programme 'SP2: Industrial financing', sets the structure for such a collaboration. The Government has a number of instruments at its disposal including: regulatory changes, skills development, provision of infrastructure, funding for research, trade policy and industrial financing. All these instruments are important for the private partner, who in return will have to achieve measurable benchmarks.

An overview of possible interventions are summarized in Figure 4 below:

[41] http://www.namibiahc.org.uk/resources/content/manufacturers_exporters_incentives.pdf
[42] http://www.malawi-invest.net
[43] WTO (2010) Trade Policy Review Malawi, Report by the Secretariat, http://www.wto.org/english/tratop_e/tpr_e/tp331_e.htm
[44] www.thedti.gov.za/news2013/ipap_2013-2016.pdf
[45] AUC – UNIDO. Pharmaceutical Manufacturing Plan for Africa. Addis Ababa. November 2012.
[46] http://www.namibiahc.org.uk/resources/content/manufacturers_exporters_incentives.pdf
[47] Botswana Investors Handbook page 26, available from http://www.bitc.co.bw/bitc-investors-handbook
[48] http://www.satradehub.org/assets/_files/Reports/Swaziland_Investment_Policy_Issues_Paper.pdf
[49] http://www.malawi-invest.net

[50] http://www.finance.gov.bw/index.php?option=com_content1&parent_id=334&id=338
[51] ibidem

Figure 4 - A National Industrial Policy Framework [52]



This kind of policy could be mirrored by other SADC Member States to construct public-private partnerships in order to guarantee production of essential medicines within the region. In this way, the sharing of technology and know-how from the private sector can be preserved within SADC. Market access on a regional basis would also help the economic feasibility of such projects.

Strategic Considerations

1. Not all Member States consider all listed possible support structures and incentives from governments to the pharmaceutical sector. Maximising these will create a more favourable enabling environment for companies to expand or establish pharmaceutical production in the region.
2. Public-Private Partnerships are needed to expand the R&D infrastructure.

5.1.6 Coherence between Ministries of Health and Trade/Industry

The conflicting interests between trade agreements (specifically the issues of patent protection), industrial policy (including efforts to promote local production) and public health (particularly the

[52] DTI South Africa, 2014. Adapted from Amsden (2001)

imperative to ensure widespread and affordable access to quality assured essential medicines) have been the subject of intense debate for a number of years.[53; 54]

A successful regional strategy to promote local production and achieve access to essential medicines will need intensive collaboration (and compromises) between Health and Trade/Industry Ministries[55]. The WHO framework for local production and access to essential medical products describes the issues very well, and proposes a possible joint framework – see Figure 3.

The SADC region is not very homogenous in industrial development – the pharmaceutical industry is strong in a few countries but weak in many. This poses extra challenges in developing a regional coherence policy. SADC Member States will have to accept that distribution of medicines across SADC is more efficient than manufacturing them in each country. The SADC region will therefore need to agree where the required medicines for all the patients in SADC can be made. This will require compromises between efficiency and equitable distribution of manufacturing sites.

There is a lesson to be learned from EAC: Kenya, Tanzania and Uganda all tried to produce the same ARV in a national company for their own population. As a result, all three companies struggled as they could not have economies of scale. Countries will have to think in terms of regional markets rather than just national markets.

Examples of policy (in-) coherence can be found in volume 2, section 16.

Strategic Considerations

1. It is essential that coherence is improved between trade/industry and health sectors at national and regional levels. Only by working together in one balanced strategy, the region can achieve regional production of new generics.

5.1.7 SADC Member States Utilization of TRIPS Flexibilities

Until 2005 India could make affordable generics of products patented elsewhere. Generic competition drove down prices, and was an important factor for the roll-out of ARVs in sub-Saharan Africa after the originator companies gave up their court case against President Nelson Mandela in 2001, and allowed generic ARVs to enter the market. All pre-2005 patented products can still be produced as generics in India and supplied to SADC at very competitive prices.

However, for post-2005 patented products Indian companies cannot automatically make generics anymore. This opened a possible niche for companies in Least Developed Countries in SADC who can produce generics until at least 2033, while Indian manufacturers will not be able to produce them in India as long as valid patents exist. They can, however, produce generics if a voluntary license is

[53] Chen, W., Tang, S., Sun, J., Ross-Degnan, D. & Wagner, A. K. 2010. Availability and use of essential medicines in China: manufacturing, supply, and prescribing in Shandong and Gansu provinces. BMC Health Services Research, 10(1), pp 211.
[54] Kaplan, W. 2011. Local production and access to medicines in low-and middle-income countries: a literature review and critical analysis. World Health Organisation (Geneva).
[55] WHO. Local Production for Access to Medical Products - Developing a Framework to Improve Public Health. Policy brief and background documents, Geneva 2011.

obtained, a patent has been refused or declared invalid (e.g., Gleevec, imatinib) or a compulsory license was issued in India (several cancer medicines).

The Doha Declaration of 2001 confirmed that countries can put health considerations above trade rules if pharmaceutical patents are inhibiting access to needed products. For this, TRIPS flexibilities need to be enabled in national laws.

The status of TRIPS flexibilities in IP/patent laws in SADC (see Volume 2) was assessed by the SARPAM project in 2012 checking the following criteria: (1) Does the country have Least-Developed-Country status? If so, this means that there is no obligation to honour pharmaceutical patents until 2033. (2) Does the country allow parallel import, or does it apply an exhaustion regime? International exhaustion is the most flexible. (3) Does the country allow generic copies of patented originator medicines to be tested and apply for registration before patent expiry (Bolar)? and (4) Does the country allow compulsory licensing (CL) or does the government have "government use licencing" powers in the national IP/Patent Act?[56] The status of TRIPS flexibilities per country can be found in Volume 2.

The eight Least Developed Countries in SADC have no obligation to honour TRIPS until 2021, or pharmaceutical patents until 2033. Other countries can use TRIPS flexibilities, provided they have been included in national IP/patent legislation.

Between 2012 and 2014 amendments to the IP/patent laws of seven SADC Member States were discussed in national workshops to generate awareness and consensus on how to maximize TRIPS flexibilities and minimize/mitigate "TRIPS plus" features. Results are documented in a SARPAM legacy website.[57]

Eight other SADC Member States still need to review their IP/patent legislation and maximize the TRIPS flexibilities, so that they can import or produce more affordable generic medicines.

Until now, three SADC countries have issued compulsory or government use licenses for generic ARVs but in only one country (Zimbabwe) has this resulted in good quality ARVs being produced at affordable prices.

Licenses for almost all important ARVs are available from the 'Medicines Patent Pool' for generic production in specified countries (needs a product specific analysis, but nearly always includes India and sometimes also Africa. Strict criteria for GMP and quality are limiting the choices in Africa). TB and Hepatitis-C medicines have recently been included in the Medicines Patent Pool.

Strategic Considerations

1. SADC can benefit from the fact that the majority of its Member States are Least Developed Countries, which have no obligation to implement TRIPS until 2021 or honour pharmaceutical patents until at least 2033. This is an opportunity to make new generics that India can no longer make for products patented in India since 2005.

[56] Musungu. Pharmaceutical Patents, TRIPS Flexibilities and Access to Medicines in Southern Africa Development Community (SADC). SARPAM 18 September 2012. Available in 3 languages from http://ttatm.sarpam.net/overview/

[57] SARPAM Trade, TRIPS and Access to Medicines project, 2012-2014. See http://ttatm.sarpam.net

2. SADC countries with valid patents on important medicines or commodities should enable all TRIPS flexibilities in their national patent law, and be prepared to use them to get more affordable access to patented products.
3. Legal solutions exist for all possible patent barriers that SADC Member States might experience when importing or producing new generic ARVs or TB medicines.

5.1.8 Medicines Regulation and Quality Control

1. The SADC Treaty, specifically Article 21 and 22, has provisions for regional cooperation[58]. Following this provision, Article 29 of the SADC Health Protocol provides for harmonisation of procedures of pharmaceuticals, quality assurance, and registration.[59]
2. Eleven of the 15 SADC Member States have a functional National Medicines Regulatory Authority (NMRA) or equivalent, with GMP standards and inspectors.
3. Ten of the 15 SADC Member States have a Quality Control (QC) Laboratory for Medicines. Two Member States have outsourced this function to another country or a private sector QC laboratory. Mandates and capabilities of these institutions vary across the region.
4. Countries are at different stages of development of their NMRAs; this adds a complication to the regional harmonisation. Information exchange, work sharing, joint assessment of regulatory dossiers and GMP inspections can help to build capacity in new NMRAs. Full regional harmonisation is needed if a regional market with harmonized quality standards and regulation is wanted.
5. Regulatory harmonisation efforts have taken place in SADC since 2000. SADC technical guidelines have been agreed since 2004 but are only partially implemented. The New Economic Partnership for Africa's Development (NEPAD) has been supporting regional harmonisation since 2010.[60]
6. GMP standards are more or less similar across SADC Member States, but capacities to enforce and inspect differ greatly. Only one NMRA (South Africa) is a member of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation scheme (PIC/s). Many local companies are GMP approved by their national NMRAs, but the interpretation of standards is sometimes less strict than by WHO prequalification or SRA inspectors.
7. In the majority of the SADC Member States, GMP certification of premises, licensing of products and assessing Good Practice standards is the responsibility of the NMRA. Licensing of professionals is often done by Professional Associations or Councils.
8. For a successful regional production of HIV , TB or malaria products and sale to Global Fund or international donors, the plant must be international level GMP (WHO, PIC/S) certified, and the product WHO prequalified or 'Stringent Regulatory Authority' (SRA) approved, as otherwise Global Fund recipients cannot purchase the product.
9. Only one SADC manufacturer currently has WHO prequalified products (Aspen Pharmacare, South Africa). Varichem Zimbabwe had WHO prequalified ARVs for some years, but their listing lapsed.

[58] SADC Treaty

[59] SADC Health Protocol 1999

[60] M Ndomondo-Sigonda and A Ambali. The African Medicines Regulatory Harmonisation Initiative: Rationale and Benefits. Clinical Pharmacology & Therapeutics Volume 89, Issue 2, February 2011, Pages: 176–178.

10. The Common Technical Document standard was accepted by SADC Health Ministers, and should enable manufacturers to apply using one standard dossier format.
11. Four SADC NMRAs (Zambia, Zimbabwe, Botswana and Namibia) have been collaborating since 2013 in fast-track registration, work sharing in joint dossier analysis and joint GMP inspections of manufacturing facilities. The SADC Ministers of Health endorsed this work-sharing initiative in January 2015.
12. Ten SADC Member States have an official medicines regulatory quality control laboratory. They can be public or private sector organisations (contracted by the NMRA). All pharmaceutical manufacturers should have at least a small laboratory for in-process quality control. Final tests can be outsourced to an independent QC laboratory. The WHO Good Laboratory Practices are broadly accepted as the technical standard in SADC.
13. Four QC laboratories have achieved WHO prequalification status (2 in South Africa, 1 in Tanzania and 1 in Zimbabwe): this allows them to do official tests for Global Fund recipients. ISO-17025 is an equivalent international standard.
14. Condoms are seen as medical devices, except in Zimbabwe where they are defined and controlled as medicines. Condom testing can be done by Bureaus of Standards (e.g., the SABS in South Africa) or in QC laboratories with special condom testing equipment (e.g., MCAZ, Zimbabwe). The condoms produced in Botswana and Namibia use SABS certification.

Strategic Considerations

1. A fully capacitated NMRA is needed to credibly certify GMP compliance of manufacturers and to ensure that non quality assured products will be withdrawn from the market. GMP certificates issued by NMRAs recognised as working according to acceptable standards will facilitate export of locally manufactured products into the SADC region and beyond.
2. Access of locally produced medicines to the SADC regional market will be facilitated by regional harmonisation of regulatory standards, implementation of the SADC Common Technical Document, exchange of regulatory information, fast track procedures and regional collaboration in regulatory training.
3. Regulatory capacities in SADC Member States are not homogenous. Apart from training, capacity building, mutual exchange programmes and South-South cooperation (e.g. through joint inspections) there is need for the more experienced NMRAs in the region to proactively involve their colleague regulators in the regional regulatory assessment of the manufacturing plants where these critical products are being manufactured.
4. South Africa based manufacturers already have a big national market based on their national (MCC) regulatory approval. MCC approval is probably also helpful in exporting and supplying private sector markets and government tenders in other SADC countries. As a result, there is little interest on the part of South African manufacturers in achieving the “higher” WHO prequalification status in order to supply Global Fund recipients in the SADC region, as there is strong competition and price pressure by Indian manufacturers which already have WHO prequalification status.

5.1.9 Availability of Quality Medicines in Public, Private and Non-profit Private Sectors

SADC Member States have developed treatment guidelines for the three pandemic diseases. All medicines included in the treatment guidelines were included in the National Essential Medicines Lists

(unless the list had not yet been updated), and products were registered by National Medicines Regulatory Authorities.

The country questionnaire did ask for percentages of essential medicines that were available in health facilities (there is a standard indicator for this in the WHO/HAI Pricing and Availability survey method). Unfortunately very few countries could provide such availability figures to the country consultant.

5.1.10 Health Policies on HIV, TB and Malaria

Health policies in SADC are all aiming at controlling the three diseases by, among others, treating all patients using standardised treatment guidelines, especially in the context of Universal Health Coverage[61].

HIV

1. The 'SADC's HIV and AIDS Strategic Framework 2010-2015'[62] includes several strategies that require medicines and/or commodities: condom distribution, HIV Testing, Prevention of Mother to Child Transmission (PMTCT), treatment with antiretrovirals and home-based care. Together with the Maseru 'Declaration on the Combating of HIV and AIDS in the SADC Region'[63] these documents provide a clear policy direction and political commitment in combating the AIDS pandemic in the region.
2. For HIV, there is **policy drift** from initiating treatment at CD4<350 via CD4<500 to "test and treat" as part of the UN "90-90-90" strategy.[64] This means that in future all HIV+ people should receive ARV treatment, implying an increase of the number of HIV+ people to be treated from currently 6 million to 15 million in 2020.
3. This tripling of the number of people on ARVs will put serious financial pressure on GFATM, other donors and SADC Governments.

TB

1. The SADC Protocol on Health Article 12 states that *"Member States shall cooperate and assist each other to (a) develop strategies for the sustained control of TB, including efficient supply and delivery of drugs; and (b) to ensure, where appropriate, the harmonisation of TB control activities and HIV/AIDS programmes."*

[61] http://www.who.int/universal_health_coverage/un_resolution/en/

[62] Southern African Development Community. Website http://www.sadc.int/documents-publications/show/SADCHIVandAIDSStrategyFramework2010-2015.pdf

[63] Southern African Development Community. Website http://www.sadc.int/documents-publications/show/Maseru_Declaration_on_the_fight_against_HIVand_AIDS2003.pdf

[64] This 2014 UNAIDS strategy proposes that 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. See http://www.unaids.org/en/resources/documents/2014/90-90-90

2. SADC developed a 'Strategic Framework for Control of Tuberculosis in the SADC Region (2007-2015)'. The region harmonized TB treatment guidelines in 2010[65], and has developed specific standards for prevention[66] and treatment of TB in the military[67], prisons[68], and the mines[69].
3. The SADC annual TB reports (2009-2012) provide information on the state of the epidemic and its control activities[70].

Malaria

1. Articles 9 and 11 of the 'SADC Protocol on Health' call upon Member States to harmonize and standardize policies pertaining to malaria control and urges Member States to efficiently utilize resources, harmonize goals, policies, guidelines, protocols and interventions and coordinate operational research for the effective control of malaria.
2. SADC malaria strategies are well documented in the 'SADC Malaria Strategic Framework (2007-2015)', 'SADC Malaria Elimination Framework'[71], and the 'SADC minimum standards for malaria control (2010)'. Collaboration in SADC among stakeholders is coordinated by the Southern Africa Roll Back Malaria Network (SARN)[72].
3. Malaria treatment guidelines are however not yet fully harmonized across countries. Private sector treatments are often not compatible with WHO recommendations.

Strategic Considerations for the three Diseases

1. Respecting principles of existing SADC health policies and strategies, the SADC pharmaceutical manufacturing strategy should aim to contribute to Universal Health Coverage and Universal Access to Treatment.
2. Harmonisation of treatment protocols among SADC Member States is critical, as that allows better economies of scale in procurement, cross-border treatments, and a well-defined product market.
3. New, more effective and easier to take ARVs (like Tenofovir alafenamide fumarate (TAF) and Dolutegravir) might gradually replace current ARVs. Planning the production of their raw materials, finished dosage forms (FDF) and possibly new fixed-dose combinations should start now, so that their products are available in the next 5-7 years.
4. The increasing resistance of TB to current treatments, and the long, expensive treatment using the current MDR-TB medicines with many side-effects, requires that SADC gives high priority to further test and (if found effective) develop the production of the API and FDF of the new TB medicines (bedaquiline, delamanid, linezolid, and pretomanid (PA-824)), if possible, in fixed-dose combinations. This will also require clinical trials and post-marketing surveillance and pharmacovigilance of the new medicines.

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[65] SADC. Harmonized Minimum Standards for the Prevention, Treatment and Management of Tuberculosis in the SADC Region, 2010.
[66] SADC. Harmonised Minimum Standards for the Prevention Treatment and Management of TB in SADC. 2012
[67] SADC. Regional Minimum Standards for the Harmonized Control of HIV and AIDS, Tuberculosis and Malaria in Militaries in the SADC Region, 2010.
[68] SADC. Minimum Standards for HIV and AIDS, TB, Hepatitis B and C, and Sexually Transmitted Infections Prevention, Treatment, Care and Support in Prisons in the SADC Region, 2011
[69] Framework for the harmonized management of tuberculosis in the mining sector, 2014. http://www.health-e.org.za/wp-content/uploads/2014/04/Hamonization-report.pdf
[70] SADC Annual TB report 2012. http://www.sadc.int/files/5114/1898/8224/000_13SADC_Tuberculosis_Report_2009.pdf
[71] Southern African Development Community. Website https://tis.sadc.int/english/sarn/elimination-eight-e8/
[72] Southern African Development Community. Website https://tis.sadc.int/english/sarn/about-sarn/

5. The weather and farmer dependent growing of Artemisia Annua in Vietnam and China, and related global price fluctuations of artemisinin for ACTs pose a concern for supply security. SADC should make itself less dependent of ACT imports, and take advantage of a local production of artemisinin in Madagascar, and of ACT in Tanzania. Specialized dosage forms (e.g., rectal artesunate for unconscious children with serious malaria in rural areas) and the longer term prospects of making semi-synthetic artemisinin (Sanofi, Italy) possibly also need consideration.

Table 1 – Product focus in situational analysis

Disease focus	Products covered in the situational analysis
HIV	Anti-retrovirals, condoms
Malaria	Anti-malaria medicines, bed nets, insecticide sprays, rapid diagnostic tests
TB	Anti-TB medicines, rapid diagnostic tests, BCG vaccine

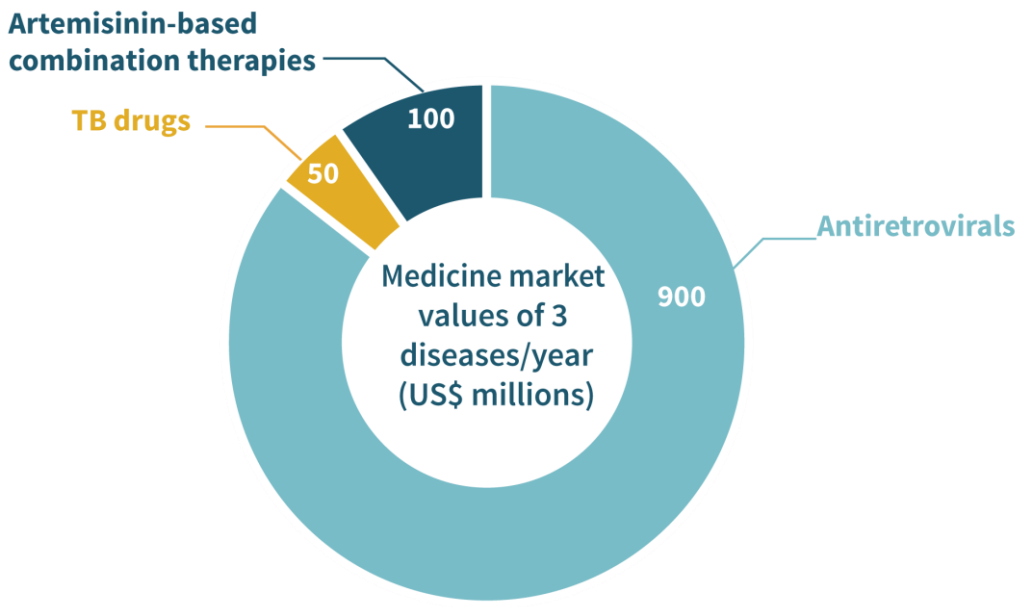
The list of all specific products used in SADC for the three diseases is based on the Global Fund Price and Quality Reporting (PQR) database, and can be found in Volume 2.

5.1.11 Current Use and Supply

Total SADC annual turnover for medicines and medical supplies for ALL diseases is estimated as USD 4.7 billion. Assuming that SADC expenditure on medicines and medical supplies grows at the same pace as in the whole of Africa, the total pharmaceutical market in SADC could reach USD 6.5 billion in 2020.

Among the three diseases, **HIV** treatment currently accounts for 66% of Global Fund funding. In terms of ARV procurement, ARVs account for 85% of the medicines costs of the three diseases. See Figure 5.

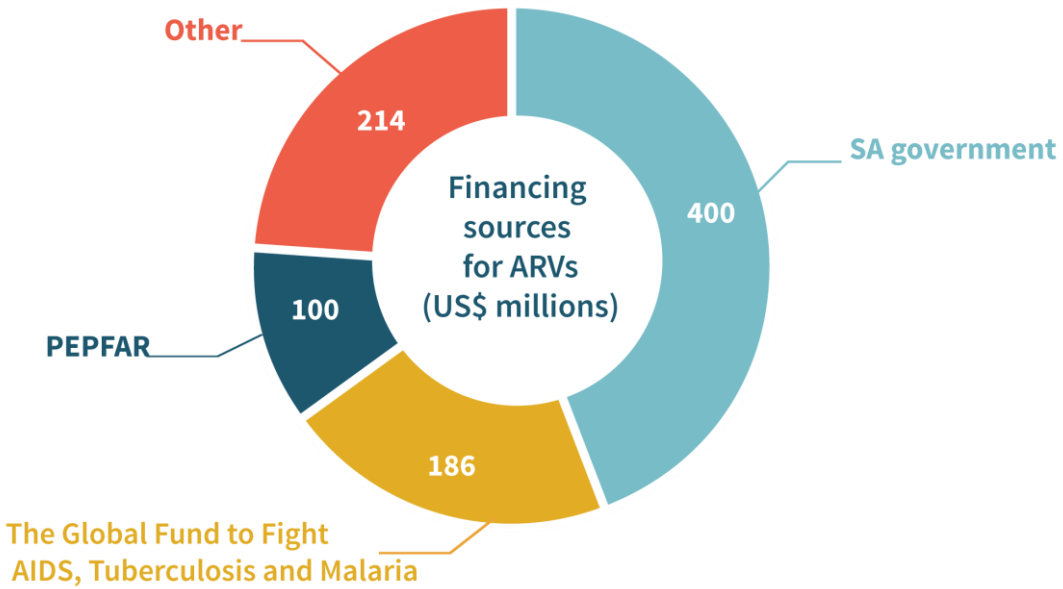
Figure 5 - Relative market value of medicines for three diseases in SADC



HIV

1. SADC is home to an estimated 14.7 million people living with HIV; according to current treatment policies 11.7 million of them need Anti-Retroviral Therapy (ART), but only 6 million (52%) were actually on ART in 2013.
2. 95% of people on treatment use a tenofovir-based first-line protocol, which is costing less than USD 150 per year; 5% use 2nd line, and only very few patients are on the expensive, patented 3rd line ARVs.
3. A large portion of regional HIV funding goes into financing tenofovir based products. The SADC region produces tenofovir based ARVs for 1 million people: 16% of the currently treated 6 million HIV+ patients. The balance of generic ARVs are imported, mainly from India. None of the originator ARV products are produced in SADC; all are imported from Europe and USA.
4. Treatment protocols could be better harmonized among SADC Member States: this would facilitate pooled procurement of ARVs.
5. Joint annual ARV expenditures of Global Fund, PEPFAR and the South African government are USD 686 million. The total SADC ARV market is estimated at USD 900 million (6 million people on ART at USD 150 average).
6. Eight HIV products manufactured in SADC are WHO prequalified: all are made by Aspen Pharmacare in Port Elizabeth, South Africa.

Figure 6 - Sources of financing for ARVs in SADC



Condoms

1. South Africa under the 2012-2014 tender contracted 8 suppliers to supply 1.3 billion male condoms worth ZAR 364 million. This translates into an annual quantity of 650 million male condoms worth USD 17.8 million (2.7 US cents each)

2. For the South African tender July 2015-June 2018 contracts were awarded to 13 companies for a total amount of ZAR 3,459,448,841 (about USD 252 million, or USD84 million/year). The number of condoms to be supplied was not (yet) published, but at the 2012-2014 price this would mean 3 billion condoms annually.
3. UNFPA's Reproductive Health Interchange database reports supplying 2.8 billion condoms worth USD 97.6 million to SADC countries over 4.5 years (2010-2015), or an average annual sales of 623 million condoms worth USD 21.7 million.
4. The total SADC male condom market is thus approaching at least 4 billion male condoms worth USD 105 million, as private sector purchases and direct procurement from other governments is not included in the above figures.
5. UNFPA supplied 16.7 million female condoms on average per year, worth USD 10 million.
6. UNFPA has a list of 27 prequalified male condom and 2 prequalified female condom manufacturers; none of these are located in Africa.
7. SADC has 4 condom factories in Botswana, Namibia and South Africa. Their total current capacity is 400 million SABS approved condoms, only 10% of the SADC demand. All of these are sold to South Africa, Botswana and Namibia.
8. The DRC has good climatological environment for rubber trees, the base material for the production of condoms.

TB

1. The number of annually reported TB patients has been decreasing from almost 800,000 in 2010 to just over 735,000 in 2014[73]. Officially reported mortality rates are 5% for smear-positive cases, and 7% for all forms of TB.
2. However, the number of new TB cases is estimated to be much higher at 1.3 million TB cases, and about 128,000 people are estimated to have died from TB in 2013.
3. Global Fund PQR database reports a spent of USD 6 million/year on TB medicines in SADC; this looks low, given that the South African Government alone purchases USD 28 million worth of TB medicines per year. Reliable market data are not available, but we estimate the total SADC TB market at USD 40-50 million per year.
4. First-line TB treatment is affordable (USD 10-20 per treatment) and the fixed-dose combinations are sufficiently produced in the region, although none are WHO prequalified as yet.
5. Two to six percent of new TB patients suffer from drug resistant TB, for which there were until recently only expensive and not easy to handle or unsafe medicines available, requiring treatment for up to 18-20 months. Drug-resistant TB comprises 6.1% of South African cases[74], but its treatment consumes 32% of the country's total TB budget[75].
6. Cycloserine is the only WHO prequalified TB product manufactured in SADC (Aspen Pharmacare, Port Elizabeth, South Africa). Capreomycin and teridizone are produced in SADC but not WHO prequalified.

[73] WHO Global TB database, 9th November 2015.

[74] 2014: 306166 incidence TB patients, 18734 MDR diagnosed = 6.1%

[75] TB Alliance. NIXTB factsheet. http://www.tballiance.org/downloads/NixTB/NixTB_factsheet.pdf

7. Bedaquiline, delamanid, linezolid, and pretomanid (PA-824) are new TB medicines that are currently being tested in at least 5 clinical trials to establish whether they can reduce the treatment time to 6 months.[76]
8. Prices of the new TB medicines are very high (>USD 30,000 per patient for a 6-month treatment for one product). All are produced in high income countries, although several clinical trials take place or are planned in South Africa. It would be important for SADC to evaluate the possibility of locally producing the new TB medicines using TRIPS flexibilities. The Medicines Patent Pool has recently opened for TB medicines, but there are no voluntary licences yet available for the new TB medicines. The new TB medicines could legally be made in a LDC, and in a non-LDC where the patents are not valid, or where the authorities have issued a government use license.
9. If the ongoing trials are successful, regional production of the new oral TB medicines could become a priority, as the SADC region has the highest disease rates. SADC also has the capacity and patients to run the required clinical trials for regulatory approval of the products.
10. SADC will, in such a scenario, also have to make the APIs. As this will probably not be supported through technology transfer by the originator, the region could consider whether new API production processes (e.g., continuous flow chemistry) would be an option, or whether it could work with a strong API experienced partner (e.g. from India or China) in a joint venture.
11. A fixed-dose combination would be desirable from an adherence and logistics perspective, but the formulation would still need to be developed and tested while the individual API and/or generics are being produced. SADC also has the patients, health workers and infrastructure to do the required clinical trials for FDCs.
12. Paediatric TB drugs are neglected essential medicines. The problem of paediatric TB is difficult to assess in terms of numbers because of under-diagnosis and under–reporting. There is a global lack of adequate paediatric formulations.
13. BCG Vaccine was produced in SADC by the Biovac Institute in South Africa, the only vaccine manufacturer in sub-Saharan Africa.

Malaria

1. The 2014 WHO Global Malaria report lists 58 million suspected and 37 million “presumed and confirmed” malaria cases for SADC in 2013.
2. The SADC Malaria strategy is based on: (1) Use of Long Lasting Insecticide Treated Nets (LLINs); (2) Case management with Artemisinin Combination Therapy (ACT) based on objectively diagnosed malaria using rapid diagnostic test kits; (3) Indoor residual spraying (using DDT), and for high transmission areas, and (4) Intermittent preventive treatment (IPTp) during pregnancy.
3. SADC region malaria programmes are financed with USD 595 million/year.[77] Of the USD 158 million annual Global Fund malaria funds, 56% is spent on procuring goods (USD 89.6 million per year). Of this, Global Fund spent 60% on bed nets, 24.7% on various ACT medicines (USD 22,186,912 per year), 13.6% on diagnostics, and 1.4% on Insecticide Residual Spraying (incl. DDT).

[76] NIXTB, STREAM I and II, NEXT, STAND.

[77] WHO Global Malaria report 2014. Annex 3 analysed for SADC MS only.

Artemisinin Combination Therapy (ACT) Products

1. Estimating the overall ACT market for SADC is difficult due to absence of reliable data. If we apply the Global Fund ratio of 14% ACTs over all malaria programme cost, this would mean a financing of USD 83 million for ACTs in SADC. In addition, a substantial amount of medicines needed to treat the 58 million suspected malaria cases are expected to be purchased in the private sector. This means we could probably increase the estimated SADC ACT market to at least USD 100 million per year.
2. There are no WHO prequalified anti-malaria products made in SADC. Zenufa (Tanzania) is expected to submit one ACT (AS/AQ) for WHO prequalification with the help of DNDi.
3. *Artemisia Annua* plants (source of artemisinin) are currently grown and extracted in Madagascar. The Madagascar production and extraction capacity can be expanded. Artemisia Annua could also grow in Tanzania or DRC, but extraction there is less efficient, and farmers are less interested to plant because global prices of artemisinin are fluctuating, and production is currently below their cost price.
4. The conversion from extracted artemisinin to the APIs artesunate or artemether is currently done outside SADC. It might be worthwhile to consider whether this conversion could be done in SADC itself. This would then also facilitate producing appropriate dosage forms (e.g., paediatric rectal artesunate).

Bed Nets

1. The Global Fund PQR database lists an average turnover of USD54 million/year for SADC.
2. Two of the 11 "WHO Pesticide Evaluation Scheme" (WHOPES) approved long-lasting insecticide-treated nets (LLITN) are manufactured in SADC (A to Z Mills Ltd, Tanzania).
3. It could be worthwhile to assess whether an increase of production capacity is possible; the potential impact of a 'Buy SADC nets' campaign could also be investigated.
4. The value chain should be further investigated: production already takes place in Tanzania, but the resizing, knitting, forming and stitching activities could also be performed in other countries in the SADC region. Impregnation could be done in a specialized facility at a different location. Pyrethroid insecticides are produced from Pyrethrum plants that can grow in SADC.

Rapid Diagnostic Tests

1. Africa does not (yet) have WHO pre-qualified factories for malaria Rapid Diagnostic Tests (RDT), but research is being done in South Africa based universities and companies. No information could be identified whether production of tests is planned in SADC.

Indoor Residual Spraying

1. There is only one manufacturer of DDT left in the world (Hindustan Insecticides Inc., India), after Ethiopia and China halted production. This poses a supply security risk for SADC, because there is decreasing need for DDT for the local Indian market due to the almost complete eradication of malaria. There are unconfirmed reports of a Cuban company planning production in Tanzania.

5.1.12 Need and Demand until 2022

HIV

1. The number of HIV+ patients eligible for treatment will increase by 0.5 million/year from 12 million in 2013 to about 15.5 million in 2020. If the new "Test and Treat" policy is implemented as part of the UNAIDS "90-90-90" strategy, the number to be treated will reach 18 million (all HIV+ patients). The feasibility study proposes a target of 15 million HIV+ people on ARVs for 2020 (90% diagnosed and 90% treated of 18 million HIV+). This is 2.5 times the number of people treated today in SADC (6 million).
2. The potential market of ARVs will increase from USD 900 million to USD 1.8 billion assuming a 20% reduced cost of the first-line therapy currently at USD 120pp/year.

TB

1. The number of reported new TB patients in SADC has been slowly decreasing (from 792,362 in 2010 to 736,727 in 2014). However, the total estimated number of TB patients in SADC is at least 1.3 million[78]. So there is still a reservoir of at least 500,000 TB patients that remain undiagnosed and probably untreated. With better diagnostics and screening under Universal Health Coverage, the number of TB patients to be treated could therefore go up. For 2020, the region could expect between 750,000 and 1 million people needing treatment for TB. The first-line TB market value can be estimated at USD 15-20 million, assuming a USD 20 drug cost per first-line treatment course.
2. In 2013, 12,825 (69%) of the 18,720 diagnosed MDR-TB cases in SADC were put on treatment. In 2014, 16,611 MDR-TB patients were diagnosed. With the introduction of rapid molecular tests in many countries, more information becomes available on the existence of DR-TB also in countries where no recent drug resistance surveys had been done. Though there is no evidence yet that rates of DR-TB are increasing, this development will lead to (temporary) increased numbers of diagnosed patients that need DR-TB treatment regimens. At least 2% of TB patients in SADC (18,720 in 2013) suffer from resistant TB, and need MDR-TB medication. Using current MDR-TB medicines and prices, the MDR-TB market could be worth USD 30 million. As the future medicines and prices are not yet known it is impossible to predict the size of this market. Cost will depend on whether originator companies are willing to issue voluntary licenses and/or whether SADC manages to produce such generics.
3. The number of paediatric TB patients is unknown, and adequate dosage forms are missing.

Malaria

1. The number of malaria cases is expected to drop, due to increased coverage of LLIN bed nets, effective ACTs and indoor spraying of DDT.
2. The future market of ACTs is likely to be less than the current USD100 million; the bed net market will also be less than the current USD 100 million.

[78] WHO. Global TB report 2014. See also volume 2 with a table of TB patients per SADC country.

5.1.13 Human Resources

While a shortage of pharmacists and other technical staff with pharmaceutical skills is often mentioned as a key challenge in sub-Saharan African countries, respondents in the SADC Member States stated that there are sufficient human resources to run at least one GMP compliant manufacturing plant per country.

However, a recent study commissioned by the Southern Africa Generic Medicines Association (SAGMA) concluded that there is a lack of synchronisation between the training needs of industry and what is currently on offer:[79]

"The majority of companies indicated a willingness to pay for their employees to attend short courses and workshops. However, their training budgets were very modest in comparison with international standards. The preferred format for course delivery was short workshops (of less than three days duration) and part-time modular courses with two to four contact sessions. The most popular delivery modes were workshops (75%) and DVD-packaged self-learning material (63%). Most trainers and institutions were already offering contact learning although they expressed willingness to develop self-learning material.

Pharmaceutical industry-related training available in Southern Africa is largely focused on regulatory affairs and quality matters, neglecting other operational issues such as formulation development, plant engineering and supply chain management. Very little training is directed specifically at wholesalers and distributors. There is broad coverage of good quality executive education in the region, particularly from South African business schools, although these courses are not specific to the pharmaceutical industry. Mapping of short courses in the region showed them to be concentrated in South Africa and Tanzania. Intellectual Property (IP) protection, international patent law and Trade and Related Aspects of Intellectual Property Rights (TRIPS) flexibilities, as well as pharmaceutical engineering and plant operations, are underserved priority areas and yet they are at the heart of LPP policies and strategies."

The study made several recommendations on the steps SAGMA should take in order to meet the training needs of its members and to bridge training/skills gaps. It is suggested to incorporate these into the SADC Pharmaceutical Manufacturing Action plan (SAPMAP).

Another SADC study done in 2015 to determine **training and research needs of pharmaceutical regulators and managers**, and to facilitate the establishment of Centres of Specialization (CoS) and Centres of Excellence (CoE) in the region, concluded:[80]

"The findings of the assessment confirmed that there are major gaps in the capacity of pharmaceutical managers and regulators to carry out their required tasks in regulation, research/research oversight and management in the SADC region. There were reported institutions carrying out pharmaceutical training and research in the region but they may not necessarily be up to par with expected

[79] SAGMA. Analysis of Training Needs in the Generic Medicines Sector in SADC. UNIDO, 2014.
[80] Prof Henry Fomundam. Identifying Training and Research Needs and Facilitating the Selection of Centres of Excellence and Centres of Specialisation in Pharmaceutical Training. SADC, August 2015.

international norms. They however provide a potential starting point in strengthening regional pharmaceutical training and research programmes."

A total of eight thematic areas for the **Centres of Specialisation** were proposed: pharmaceutical manufacturing; medicines regulation and quality assurance; pharmacy practice; clinical trials monitoring; pharmaceutical training; patient safety and pharmacovigilance; pharmaceutical management and pharmaceutical policy and operations research.

The study also recommended two **Centres of Excellence**: clinical trials design, and general research skills with special preference to pharmaceutical and health systems research.

As to **pharmaceutical industry-academia linkages**: most of the pharmaceutical staff is trained in country, although in the majority of the Member States training only covers a basic degree. In some Member States universities and Schools of Pharmacy have started to offer specific courses on pharmaceutical manufacturing. The majority of the staff, however, has to undergo training on the job or training abroad.

Strategic Considerations

1. SADC needs to build more capacity in dedicated post-graduate and technical programmes that provide skills for pharmaceutical manufacturing.
2. Regional production of new generics will require that skilled professionals are able to work in any SADC country where the manufacturing plant is being established.
3. University graduates are inadequately equipped to work in industry and the existing science, engineering and technology, and pharmaceutical curricula are not an adequate response to industry needs[81]. The Pharmaceutical Manufacturing Plan for Africa (PMPA) also cited this problem as being continent-wide and a likely barrier to development of the pharmaceutical industry if not urgently addressed.[82]

5.1.14 Financing for Pharmaceutical Production

1. The main historical sources for financing have been commercial loans.[83] However, these cover mainly short term needs as there is a general reluctance by banks and financial institutions to provide multi-year loans. This is also confirmed by a WHO study that identifies the high cost of local commercial capital and the limited access to it as constraints.
2. Possible sources and examples for financing are found in volume 2 sections 22 and 27.
3. Specific experiences with financing show mixed results:
    a. UNDP supported Varichem, Zimbabwe, with an upgrade program (USD 2.1 million).[84] This resulted in Varichem supplying good quality (WHO prequalified) and affordable ARVs. More recently, UNIDO started a support program to strengthen the Zimbabwean pharmaceutical sector.[85]

[81] Department of Trade and Industry (DTI).Human Capital Outlook Implications for Skills Development in the Pharmaceutical Sector: The Adequacy of Higher Education and Training Provision for API and Biotechnology Manufacturing Skills Requirements.
[82] AUC – UNIDO. Pharmaceutical Manufacturing Plan for Africa. Addis Ababa. November 2012.
[83] International Conference on Local Pharmaceutical Production in Africa, April 2011, Cape Town. Dr Martin Nicholson, consultant UNIDO.
[84] http://www.researchandmarkets.com/reports/613668/zimbabwe_pharmaceuticals_and_healthcare_report_q2
[85] SADC Feasibility study for local production, Zimbabwe country report. 2015

b. European Union supported TPI Arusha, Tanzania (€5 million, through Action Medeor). A GMP-compliant Greenfield plant was built. Unfortunately the company was suspended for 2 years during an investigation by the NMRA, and only produced test batches of ARVs.
c. Zenufa in Tanzania received an HPLC and blister packaging machine from DNDi as well as all the raw materials, the formulation technology and the manufacturing process know-how for the production of AS/AQ. It also received reagents and standards. An application for WHO prequalification is expected in 2016.
d. Mozambique: Brazil supported Mozambique with technology transfer, capacity building and financing for the construction and operation of an ARV factory. The support was based on Brazil's own experience with the production of ARVs. In total, USD 23 million was spent by Brazil. The factory is, however, not yet producing ARVs.

Strategic Considerations

1. The anticipated SADC regional manufacturing plan will need substantial amounts of financing: investments, low interest loans and other financing solutions.
2. The financing risk will be less if the market for the new generics is ensured through effective joint procurement systems (e.g., SADC Pharmaceutical Procurement Services)
3. Funding for the three diseases is likely to shift over the coming years from international donors to regular national budgets ("graduation"). It will be a challenge for the region to finance Universal Health Coverage.

5.2 Business Case for Regional Production of Pharmaceuticals

5.2.1 Introduction

At a high-level, the business case should demonstrate the following:

1. What we know from the situational analysis about the existing environment;
2. Whether companies are interested, in what products they are interested and how they plan to achieve that production;
3. Whether governments, consumers and donors support regional production, in which instances, and under what conditions

It is emphasised again that this study is limited to feasibility of regional production of products **for the three pandemic diseases**, and thus has specific limitations, mostly related to how these three markets are financed, and the quality standards and procurement rules set by the funders.

As the majority of financing for these diseases is donor dependent with strict quality and procurement conditions attached (Global Fund, PEPFAR), some of the more developmental approaches towards non-GMP manufacturing plants suggested in the AU's PMPA would not be advisable for this market. South Africa-based companies can enter the national tender market with national regulatory approval by MCC, which is at PIC/S level.

5.2.2 Willingness of Pharmaceutical Companies Currently Operating in the SADC Region to Expand, Upgrade and/or Modernize

Interviews with manufacturers gave a mixed pattern. Companies are in general **willing to upgrade and modernize** provided there is a sizeable and easily accessible regional market, and if they can get support/investments. All of them point out that governments and SADC should address the lack of coherence (tariffs on APIs and supporting materials, but no tariffs on finished dosages forms; domestic preference rather than regional preference), the poor enabling environment, and the lack of incentives or specific support.

Manufacturers are studying the market for HIV, TB and malaria, but in general have problems achieving the GMP standards and quality, efficacy and safety documentation (dossiers) and bio-equivalence requirements of WHO prequalification

Manufacturers in South Africa can supply the substantial South African market with national MCC registration. They do not see much benefit in upgrading to WHO prequalification as they have higher costs and cannot compete with Indian prequalified manufacturers in other SADC markets. One reason is that the same Indian manufacturers are making the API, which they will sell to South African companies at higher prices if they become competitors for finished dosage forms.

Factories which did upgrade their facilities, are still experiencing barriers for production at competitive cost of the current ARVs:

1. The only manufacturer in South Africa with WHO prequalified products (Aspen Pharmacare) is considering leaving the three diseases market, as they cannot compete with Indian generics in other SADC markets.
2. Tanzanian TPI obtained €5 million support from EU to build a new ARV plant, but decided after 2 years of suspension by the NMRA, to use the plant for production of other essential medicines.
3. Despite support from Brazil worth USD 23 million, the Sociedade Moçambicana de Medicamentos is not yet manufacturing ARVs.

5.2.3 Willingness of Key Players to Buy/Consume

A number of Member States import medicines from the SADC region, the majority from South Africa. Most of the Member States state that there are no barrier(s) for importing generic essential medicines and/or commodities manufactured in other SADC Member States.

For the three diseases, however, the less developed Member States rely to a large extent on funding from development partners, who require WHO prequalification and/or who purchase through their own mechanisms.

Ability and willingness to buy medicines differ by level, and often depend on the procurement conditions of the funder:

1. Governments: Ministries of Health are mostly buying on price + quality (from cheapest source), but Trade/Industry Ministries promote buying locally or regionally (even if more expensive or

non-quality assured). Domestic preference schemes are in place in all SADC countries. A slightly higher price is justified by the secondary benefits from buying locally produced products (employment, spin-off industries, education, increase in Gross Domestic Product, etc.).

2. Wholesalers and retail pharmacies generally buy what their clients want.

5.2.4 Market Size and Product Availability (Locally Produced – Imported) for HIV, TB and Malaria

1. The potential market size is based on the number of patients who need treatment for the 3 diseases. Those numbers, with break-down to the country level for each disease, can be found in Volume 2.
2. Of the 11,764,677 patients with HIV who would need ART based treatment based on WHO 2013 guidelines, only 52% are being treated.
3. For first line TB, all 1,337,424 patients are treated with medicines which are readily available within the SADC region, and which are also produced within the region.
4. Of the 18,697 patients within SADC which have MDR-TB, only 69% are treated.
5. There are 37,214,806 presumed and confirmed annual cases of malaria within the SADC region (twelve Member States have endemic malaria).
6. A comprehensive list of medicines and commodities produced in SADC for the three diseases, can be found in Volume 2. This list contains 91 different products. They are grouped by disease, and provide information concerning the SADC Member State where they are produced, and by whom. WHO prequalified medicines in SADC are also listed.
7. A list of medicines (locally produced or imported) which are used in SADC for the three diseases can be found in Volume 2 of this report.
8. An inventory of the expenditure for the three diseases can be found in Volume 2.

5.2.5 Current Manufacturers

Currently, 14 manufacturers based in 7 SADC countries make 65 products for the three diseases. All have national registration, but only one pharmaceutical manufacturer (Aspen Pharmacare, South Africa) manufactures WHO prequalified or SRA approved products (9 products, some under contract for originator companies).

Five companies in three countries manufacture **anti-retrovirals**: together they cover 15% of the SADC generic ARV market. The three South Africa based manufacturers focus mainly on the national ARV tender. Prices are very competitive and profits are low, causing Aspen Pharmacare, the only company with WHO prequalified products, to consider shifting towards other disease areas (NCDs). TPI (Tanzania) has 2 nationally approved ARVs but production has been suspended by the NMRA for the last 2 years. The company is now focusing on other areas. Varichem (Zimbabwe) had 2 WHO prequalified products for several years, but these products have largely been replaced by newer (tenofovir based) regimens. Companies in Zambia, Mozambique and Botswana are planning ARV production, but have not yet started production. Most manufacturers state that the strong competition from India, the need to purchase APIs from Indian suppliers, and the lack of an enabling environment make the current ARV market unattractive. Future production of ARVs in SADC needs to

be carefully planned, with adequate investments, a strongly improved enabling environment and some regional protection from Indian competition. As SADC might be home to about 50% of the world's people on ART, an API plant for the tenofovir based backbone therapy could also be studied.

The 4 SADC **condom manufacturers** (2 in Botswana, 1 in Namibia, and 1 in South Africa) have SABS approval for their condoms (allowing them to sell in South Africa, Botswana and Namibia), but not UNFPA approval. As they supply only 10% of the 4 billion SADC demand for condoms, there is an opportunity for expansion or new factories.

Only 4 companies (3 of them in South Africa) manufacture **TB medicines**. The first-line TB drugs are affordable and already made in SADC. Three MDR-TB drugs are made in South Africa.

Sixteen different**, new TB vaccines** are currently being tested globally[86]; it is however too early to make any predictions about future candidates, let alone production.

SADC has one manufacturer of **bed nets** (A to Z Mills, Tanzania), whose Olyset LLINs are WHOPES approved. The factory has a turnover of USD42 million, and operates at 80% capacity, so there is some spare capacity. The market is competitive and heavily influenced by international donors. The company supplies 80% of its bed nets to Tanzania and the rest of SADC. It would be capable of supporting another knitting factory elsewhere in SADC and provide it with insecticide-treated raw materials.

Nearly all national manufacturers have obtained **national marketing authorisation** for their locally manufactured product(s) and a positive decision on GMP inspection. However, the inspection by foreign, PIC/S or WHO inspectors may lead to a different result, as they are stricter, even though the GMP standards are the same. WHO prequalification also requires bioequivalence studies for generic products, which NMRAs might not always insist on.

Four SADC countries still have **no legally established NMRA**[87] – this makes it difficult for companies to prove their quality/GMP. This was illustrated in Lesotho, where the Lesotho Pharmaceutical Corporation (established 1980 as LDA) produced and exported TB drugs for many years to Botswana and other SADC Member States, but had to close in 2006 after the recipient countries increased their regulatory requirements, and LPC could not show regulatory approvals or GMP inspection results.

5.2.6 Demand and Supply Distortions

Except for issues related to weak forecasting and planning in terms of demand, not a lot of specific issues regarding the control of the supply chain systems for manufacturers were reported. Controlling the supply chain in order to secure sufficient stocks of raw material and API was repeatedly reported as a problem (see 5.2.7).

[86] http://www.who.int/immunization/research/development/tuberculosis/en/

[87] Lesotho, Mauritius, Seychelles and Swaziland.

5.2.7 Inventory Management Issues

Manufacturers reported several issues related to inventory management, which lead to increased costs. Some of the issues highlighted are internal for which the manufacturers could put improved systems in place, but most of the issues are external and not directly under the control of the manufacturers. Examples are lengthy importation procedures for raw material and API, and the need to keep considerable stocks.

It takes a long time to import goods so that companies have to maintain a high security stock, which represents a high value. Insurance has to be paid.

Since almost all the raw materials are imported, a huge working capital is required to run a plant smoothly.

Many of the manufacturers interviewed accept the fact that their inventory management is poor and ineffective at best; they all report the following:

1. Lack of a clear and concise Inventory management system.
2. Inadequate demand forecasting makes it difficult to know how much raw material to keep in stock, and how much finished stock to carry. So, frequent lack of space for storage.
3. Most of the raw material comes from abroad, with delivery times of 4-6 months. Hence, the turn-around times are long.
4. Limited on-shelf availability of finished products, hence, significant loss of sales; at times, it takes about 8 months to deliver, after an order has been placed.
5. Unqualified Staff; poor control and unaccountability of both raw and finished stock stemming from inaccurate checks and balances.
6. Frequent raw material stock-out resulting in disruption of production; loss of productivity.
7. Improper storage facilities leading to spoilage and waste; this can be costly.
8. Significant resources are tied up in inventory - expensive Insurance.

5.2.8 Financing Local or Regional Production

The financing environment for local production is currently not conducive. General financing options are discussed in section 5.1.14 and Volume 2. The majority of financing seems to be provided through company's own funds and commercial banks. On an incidental basis, governments and local and international NGOs provided financing to support production. For specific examples, see Volume 2.

5.2.9 Manufacturing Costs

The responses of manufacturers varied greatly by country and product category, and some respondents chose not to reply. See Volume 2 for country specific examples.

Price/revenue behaviour in the pharmaceutical industry varies from Member State to Member State. It seems that the situation regarding taxes and duties on raw materials, API and FDF is an important determinant in the final price for the customer/patient. In some of the Member States imported medicines are generally cheaper to the patient than locally produced medicines, while in other Member States the locally produced medicines are more affordable.

In general, the following costs were mentioned:

1. APIs have the highest percentage share of FPP production cost: for ordinary essential medicines this could be 50%, but for expensive products like ARVs this can be up to 80%
2. Tariffs on imported APIs, excipients, chemicals are putting manufacturers at a disadvantage if importers have not to pay tariffs on finished products.
3. Human resources: salaries for local staff were not often mentioned, but getting skilled experts from other countries was mentioned as being costly (visa, travel, ex-patriate benefits)
4. SADC NMRAs have been raising standards so manufacturers must spend more resources on documenting the quality, safety and efficacy of their products. Some NMRAs have also raised regulatory application and retention fees. Generics and domestically produced medicines sometimes get discounts, but regionally produced goods might not qualify (yet) in national legislation. The introduction of a standardised CTD format can save companies money as they can in principle use the same basic dossier in all SADC NMRAs.
5. Marketing can be a substantial cost, especially for new products, and if there are competitors in the same market.
6. Distribution is costly if there is no well-organised market or tender mechanism.
7. Higher production and subsequently sales volumes normally mean more profits/higher margins: exportation is therefore vital.
8. Selling to other countries is also costly (transport, importation, local registration, local agent, distribution costs). SPPS could make it easier for regional manufacturers by issuing one tender for the regional SADC market with standardized quality requirements.
9. Financing through commercial banks is costly (high interest rates). Soft loans and investments are possible alternatives.
10. Delayed payments by customers and some governments also means losses.

Pressure on pricing may also be seen as a "cost":

1. South Africa has price controls at manufacturer level.
2. Competition also has an impact on price setting.
3. New methods like Health Technology Assessment (HTA) will affect prices in the context of national / social health insurance schemes that are being planned in a number of countries.

5.2.10 Technical Considerations for Pharmaceutical Production

1. **Basic conditions**: Access to clean water, clean air, stable electricity, and safe waste disposal.
2. **Logistics**: access to (air)port, road infrastructure, housing, security, supportive industries and associated infrastructure.
3. **Technical and human resources**: skilled staff, link with R&D institute and/or university; technical assistance from national science & technology institute, Centres of Excellence (both on QA and HRD); development partners; collaboration with ANDI CoEs, WHO, UNIDO.
4. **Technology transfer**: knowledge, skills in R&D, link to Schools of Pharmacy, preferably pharmaceutics departments, joint venture with a strong business partner, voluntary license agreement with originator.

5. **Research & Development** for new formulations (paediatric ACTs and ARVs; fixed-dose combinations of new ARVs, TB medicines; better stability in tropical climate); pilot production of APIs and FDF in university laboratories and Centres of Excellence.

5.2.11 Company-specific Considerations

1. **Market intelligence**: good knowledge of national policies, incentives, needs, (export) markets.
2. **Quality**: The manufacturing plant must comply with cGMP standards, confirmed by the NMRA. But for export and reputation purposes, the cGMP status should be confirmed by international inspectors of Stringent Regulatory Authority, PIC/S member (e.g., MCC/South Africa), or WHO inspectors. Bio-equivalence studies are already needed for most of the products and are required by half of the NMRAs within the region as per SADC Registration Guidelines; important to have level playing field for all manufacturers (GMP road map).
3. **Product dossier**: should be approved/registered by the NMRA (efficacy, safety, quality, but also the description of the manufacturing process etc.).
4. **Export**: For export to other SADC markets, the product should also be registered in the other SADC Member States and have a WHO-style export certificate[88] from the NMRA in country of manufacture. If the product is to be sold to Global Fund recipients, it has to be WHO prequalified or approved by a Stringent Regulatory Authority (SRA).
5. **Raw material:** source must be reputable, preferably also be a WHO prequalified API. As the API is often 70-85% of the cost of a FPP, the cost of the API must be competitive. This often means larger volumes or long-term contracts. Globally, 95% of APIs now come from India and China.
6. **Finance**: access to low-interest loans and capital; regional pharmaceutical Investment Fund.
7. **Market**: Access to a big enough market; a level playing field in SADC; organised buyers through SADC Pharmaceutical Pooled Procurement Services.

5.2.12 Conclusion

Regional and National Considerations Supporting Pharmaceutical Production

1. **Enabling environment**, strong political will, strong 'pro-manufacturing' policy; implementation of national industrialization plan, based on PBP and PMPA; level playing field, coherence between health and trade policies and practices, at both national and regional level;
2. **Incentives** like low or no taxes, national and regional preference, low interest loans, special economic zone. Time-limited for start-ups or extra for specific important public health products. Ideally an integrated incentives package linked to a national pharmaceutical manufacturing policy. Taxation on imported finished dosage forms must be higher than on imported raw materials/API in order to stimulate local production. Market guarantee schemes which are designed to reduce the default risk for investing in enlarging or establishing pharmaceutical plants, should be organized. They decrease the collateral requirements for a loan and hence increase the access of companies to the loan market.
3. **Regulatory:** Stringent National Medicines Regulatory Authority with an effective pharmaceutical inspectorate, clear legislation and fair implementation (keeping poor quality and falsified products out of the market), access to an ISO-17025 Quality Control laboratory,

[88]http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/modelcertificate/e/

GMP roadmap to support near-GMP manufacturers; a pool of hospitals with WHO prequalification for Good Clinical Practices that can perform clinical and bioequivalence studies so that export of products beyond SADC is feasible.

4. **Regional harmonisation**: collaborate with NEPAD in AMRH; develop harmonised regulatory standards and processes, CTD, joint assessment of priority essential medicines and fast-tracking of products already registered by stringent NMRAs or WHO prequalified; technical assistance to weaker NMRAs; exchange of information and work practices; regional database of registered products.
5. **National, regional and international pharmaceutical industry platforms**: establish national and regional partnership or business linkages platforms; joint lobbying for enabling environment, incentives and level playing field; regional web portal and clearing house; a stronger SAGMA; link with the Federation of African Pharmaceutical Manufactures Associations (FAPMA) and the International Generic Pharmaceutical Alliance (IGPA);
6. **Selection of public health relevant products**: assess WHO Model List of Essential Medicines, national and regional Essential Medicines Lists; assess regulatory status of (potential) competitors; SADC wide policy to prioritize specific products to GMP compliant manufacturers in the SADC region.
7. **Opportunities**: TRIPS flexibilities, India post-2005 patent niche; regional and domestic preference; local language labelling; local specific product needs; special climatic conditions (zone 4)

Overall Conclusion

The current market environment shows a mixed picture for a local production business case. The lack of an enabling environment and the lack of coherence make the business case difficult at present, especially for the production of ARVs. With a well-implemented Strategy, the enabling environment and coherence could however change the situation, and make large-scale production of raw materials and finished products a possibility.

A reasonable case can be made for the production of more condoms and bed nets in SADC.

The potential benefits of regional manufacturing in terms of regional development and public health outcomes are quite substantial: employment; strengthening of Centres of Excellence, Universities, and business schools; lowering the risk of being dependent on imports from overseas; manufacturers' access to donor funding (linked to upgraded quality of production by achieving WHO pre-qualification); development of neglected dosage forms, especially paediatric ARVs and TB medicines; attraction of foreign investments; and industrialization in non-pharmaceutical sector. Specific examples are given in volume 2.

As the SADC region has expressed a strong political will to go for regional production, the task is now to address poor coherence and create the enabling environment for manufacturing of essential medicines. For the three diseases, opportunities have been identified for the near future, such as the huge quantity of tenofovir raw material needed for tripling the number of patients on ART; new ARVs such as TAF and dolutegravir; the new TB medicines for MDR-TB, and an important dosage form for severe malaria in children (rectal artesunate).

5.3 Operational Issues

5.3.1 Profile of the SADC Pharmaceutical Industry

While the majority of the pharmaceutical companies are willing to expand, upgrade and/or modernize their production, 11 out of 20 manufacturers that were interviewed are interested to go for WHO prequalification or SRA approval (see country summaries –volume 2). For all Member States in SADC, the South African market is the first and most important sizable market for their export (or local market in the case of South African pharmaceutical companies themselves). However, with local GMP accreditation and inspection by the respective National Medicines Regulatory Authorities, the regional market for other essential medicines might be worth the investment. WHO prequalification status is not relevant in this market. Provided the SADC region can agree about the minimum quality standards, this could enable the successful competitive production of essential medicines/health commodities within the SADC region, replacing partially the current generic imports from India and China.

Pharmaceutical manufacturing is not limited to the three pandemics, but the mere scale of patients in need, and subsequent need for high-volume medicines/health commodities makes the HIV market a logical choice for expanding the pharmaceutical industry in SADC, while limiting imports of those products from outside the region. Once the basis for pharmaceutical production is laid and economically viable, and the enabling environment has been shaped for the big volume production needs (human resources, finance, technology pools, infrastructure (road, industrial building, water supply, and electricity)), expansion into production for the even greater market of non-communicable diseases has already started, and will only be growing. One important advantage is that this market has not yet been 'captured' by the donors.

5.3.2 Current Manufacturers

A database was made of all companies producing products for any of the 3 diseases. Currently, 14 manufacturers based in 7 countries produce 65 products for the 3 diseases (see Volume 2).

All manufacturers were asked how they experienced the market, and what their future plans were. Nearly all companies pointed out the lack of an enabling environment, and the lack of coherence, especially in taxing APIs, excipients and packaging materials, while finished dosage forms could enter without taxes.

Private organisations are driven by profit. While the majority of the pharmaceutical companies interviewed are willing to expand, upgrade and/or modernize their production, and half of them are interested in achieving WHO prequalification, few companies have gone that route as the return on investment of a WHO Prequalification process under current market conditions seemed to be too low.

Five companies in three countries manufacture **ARVs**: together they cover only 15% of the SADC generic ARV market. The three South Africa-based manufacturers focus mainly on the national ARV tender. The other manufacturers in Tanzania and Zimbabwe have problems (re-)entering the ARV market. WHO prequalification is needed if companies want to supply Global Fund or PEPFAR recipients. Government or SADC incentives could be developed to support local/regional production in tenders,

but the problem remains that for the currently used mass production HIV medicines, margins are so low that investment in WHO prequalified factories is economically not viable, even with pooled procurement of a SADC market with a total of 6 million patients on ART. This is illustrated by the comments of Aspen Pharmacare, the only SADC manufacturer with WHO prequalified ARVs.

The **ARV market could be different in 2020**, when Universal Health Coverage and "Test & Treat" policies will require tripling the number of HIV+ patients on ART from 6 million to 15-18 million. The sheer volume of API needed for the TDF-containing backbone (2.2 million kg) and the purchasing power of the non-Global Fund countries could leverage Indian manufacturers to start production of APIs or FDFs in joint ventures in the SADC region. Another possible niche are the promising new ARVs (i.e. Dolutegravir, TAF), where patents are in place, and the voluntary licenses of the Medicines Patent Pool allow production in Southern Africa. Recent developments in cheaper API production through innovative synthesis technology (continuous flow chemistry), could give the SADC region a leading role for these products, which will be the "block buster" ARVs for the near future (5-10y).

The four SADC **condom manufacturers** currently only supply 10% of the 4 billion SADC demand for condoms. As the technology is not too difficult, there is an opportunity for expansion of existing or building of new factories. Latex trees grow in DRC, but plantations have fallen into disuse, probably due to more cost-effective production of latex in Asia. The next steps in the value chain (Processing – Dipping – Foiling / packaging / branding) could take place in the SADC region.

Four companies (3 of them in South Africa) manufacture **TB medicines** in SADC. The first-line TB drugs are affordable and already made in SADC. Sanofi (which is supplying all public sector TB medicines in South Africa) is in discussions with the South African Department of Trade and Industry (DTI) to start an API plant for TB medicines. Three MDR-TB drugs are currently made in South Africa, but they might in future be partially replaced by newer TB drugs that can hopefully treat MDR-TB in only 6 instead of 20 months. The new TB medicines are all patent protected, costly and from different companies. A fixed-dose combination (FDC) would be ideal from a public health perspective to enhance patient adherence and simplify procurement and supply management but needs first development and testing.

Bionexx in Madagascar is the only company in SADC extracting artemisinin as a starting material for **Malaria** from Artemisia Annua plants. The company has better extraction results than Chinese or Vietnamese companies, and supplies originator manufacturers of ACTs. It can expand its capacity if needed for a new manufacturer in SADC to make APIs or FDFs. The production of quinine by PharmaKina in DRC is expected to reduce, now that WHO has shifted the first-line treatment of severe malaria from IV quinine to IV artesunate.

A to Z Mills (in Tanzania) is the only manufacturer of WHOPES approved **bed nets** in SADC. It has a turnover of USD42 million, and operates at 80% capacity, so there is some spare capacity. It obtains resin and chemicals from South Africa, and enters the pyrethroid insecticides into the filaments. The market is competitive and heavily influenced by international donors. The company supplies 80% of its bed nets to Tanzania and the rest of SADC. It could provide insecticide-treated netting in rolls to other knitting factories elsewhere in SADC, where bed nets could be made.

Consultants could not verify rumours that a Cuban company wants to set up **DDT** production in Tanzania. This could be important for supply security for indoor spraying against malaria as there is only one manufacturer left in the world making DDT (Hindustan Insecticides Inc., India).

5.3.3 Scaling up the Current Manufacturers

From the currently produced medicines/commodities within the SADC region **hera** proposes to further investigate the possibility for expansion of production of the following products:

1. **ARV's**: Tenofovir use in SADC requires the production of 2,200 metric tonnes of API. To produce at this scale could imply the building of a huge API plant in the SADC region, which would reduce the dependency on foreign imports.
2. **Condom** production: currently only 4 manufacturers are present within SADC (Botswana 2, Namibia 1, and South Africa 1) with a production capacity of 400 million condoms. This is only 10% of the regional demand. Expansion at the existing plants is less preferable than production in other SADC Member States (avoiding transport etc.). Technology transfer for building condom factories is readily available from the manufacturers of semi-vulcanised latex from Asia. Exploration of producing latex within SADC, where DRC has the ideal climatological circumstances, is an option.
3. Nearly all **first-line TB medicines** for South Africa are produced by Sanofi in Pretoria. The company is considering starting an API manufacturing plant. If the Sanofi products are SRA approved, they could also supply Global Fund recipients in the rest of SADC.
4. Current **MDR-TB medicines** will slowly be replaced by new patented medicines (preferably also in a fixed dose combination), which could be produced in a Least Developed Country in SADC if the patent holders are not prepared to issue voluntary licenses.
5. **Artemisinin** production in Madagascar by Bionexx, which is planning to increase its production to cover 25% of the needed volume in SADC, could be motivated to further increase its market share, and transfer know-how to other countries with the ideal climatological circumstances to grow *Artemisia Annua,* the basis for artemisinin production (e.g. DRC). To complete the value chain, a new factory is needed to convert artemisinin into dihydroartemisinin (DHA), artesunate and artemether, which are the APIs for ACTs.
6. **LLINs**: the A to Z Mills plant in Tanzania already exports to other SADC Member States. Expansion of their production to cover a larger part of the required LLINs in the region would be a possibility, but transfer of technology into other SADC Member States and involvement into a public-private partnership is another preferable option.
7. Africa does not (yet) have factories with WHO pre-qualified malaria Rapid Diagnostic Tests (RDT), but research is being done in South Africa based universities and companies. Malaria RDT's for instance, detect specific antigens (proteins) produced by malaria parasites that are present in the blood of infected individuals. The production of these tests requires a biotechnology facility, which is expensive to build (production of antigens, sterile manufacturing), and needs highly specialized personnel. The vast number of RDT's needed for the diagnosis of malaria and TB, however, justifies further research to explore the feasibility to produce these tests within the SADC region. A PPP with an international player would be a necessary factor for the production for these high-tech tests.

5.3.4 Technical and Human Resource Capacities of Existing Pharmaceutical Manufacturing Firms for Expansion, Upgrading and/or Modernization

Although a shortage of pharmacists and other technical staff with pharmaceutical skills is often mentioned as a key challenge in sub-Saharan African countries, respondents in the SADC Member States stated that there are sufficient **human resources** to run at least one GMP compliant manufacturing plant per country.

However, a recent study commissioned by the Southern Africa Generic Medicines Association (SAGMA) concluded that there is a lack of synchronisation between the training needs of industry and what is currently on offer. Pharmaceutical industry-related training in SADC is largely focused on regulatory affairs and quality matters, neglecting other operational issues such as formulation development, plant engineering and supply chain management. Very little training is directed specifically at wholesalers and distributors. There is broad coverage of good quality executive education in the region, particularly from South African business schools, although these courses are not specific to the pharmaceutical industry. Short courses presently being offered are concentrated in South Africa and Tanzania.

Obstacles for expansion, upgrading and/or modernization are usually related to lack of financial resources.

5.3.5 Raw Materials

SADC currently only has one API manufacturer: Fine Chemicals, Cape Town, owned by Aspen Pharmacare. Nearly all raw materials and APIs are imported from India and China. Some of the manufacturers even import their packaging from outside the SADC region. Import procedures particularly for raw material and API are usually lengthy and cumbersome processes.

Regional production of pharmaceuticals to treat life-threatening diseases is vital, given the current dependency on imports for those products. If market situations change and commercial margins are not sufficient anymore to continue the production of some products (see Aspen's decision to move from ARV to NCD production), a public health situation can occur which could cost lives of millions of patients. Therefore, the production of essential medicines should not only be exclusively left to private companies, but public-private partnerships should also be considered.

As an example of public-private partnership to create or expand local manufacturing in SADC, the collaboration between the Department of Trade and Industry of the Republic of South Africa and Sanofi to establish an API plant for TB medicines is interesting. Ketlaphela (ARV APIs) and Biovac (vaccines) are other PPP examples in South Africa.

5.3.6 Quality Assurance

The regulatory environment (GMP, GDP and GLP) and WHO prequalification have been discussed in section 5.1.8. There are good reasons for the region to insist on a well-regulated pharmaceutical sector. If the region wants to have a thriving pharmaceutical industry, it will need to export to increase market

size and the international market is becoming more stringent on quality requirements. A “flexible” regulator might be popular in the short-term with local businesses, but SADC as a whole has more to gain in the medium- and long-term from “stringent” regulators that help manufacturers to achieve international level GMP standards and product dossiers. The NMRAs of the region should give guidance to the industry on how they plan to raise the standards over time. National or regional GMP roadmaps are a recommended approach to bring the whole sector to a higher level.

The Quality Management Systems (QMS) and Quality Assurance (QA) processes inside pharmaceutical companies vary throughout the SADC region. It depends to a large extent on the country regulator (NMRA, GMP inspector) whether the manufacturing plants have adequate Drug Master Files and follow their Standard Operating Procedures. Companies are obliged to respect national standards, but should strive to adhere to WHO standards wherever possible.

Nearly all manufacturing plants have in-house in-process QC laboratory capacity, but the capacities to test the final product in their QC laboratory are variable. WHO recommends a medium-sized QC laboratory, but it is generally acceptable to outsource this to a private sector or university QC laboratory. At present only three countries have WHO prequalified QC laboratories. It might be useful to make an inventory of ISO-17025 certified QC laboratories in the region, so that manufacturers and regulators can have easier access to reliable QC laboratories and test results.

The TORs speak about Good Warehousing Practices: as this is normally included in Good Distribution Practices, consultants have not specifically studied “GWP”.

5.3.7 R&D Investments by Local Pharmaceutical Companies and Foreign Direct Investments

In the majority of the Member States, R&D is very limited.

Generally, the R&D that is taking place is done within pharmaceutical companies. For instance, Bionexx (in Madagascar), has in-house researchers to increase the yield of the *Artemisia Annua* plant in order to improve the productivity of their extraction process. (See Volume 2).

5.3.8 Production Requirements

Critical success factors for producing pharmaceuticals are not limited to issues directly related to the production of pharmaceuticals such as human resources, low cost starting materials, unfavourable tax rates between finished dosage forms and API’s, regulatory issues, technology transfer, and a sizable market helped by pooled procurement: infrastructure, especially stable water and electricity supply at reasonable cost, is a crucial basic element for sustainable industrial production.

Water is one of the major commodities used by the pharmaceutical industry. It may be present as an excipient, or used for reconstitution of products, during synthesis (API), during production of the finished dosage form (FDF) or as cleaning agent for rinsing vessels, equipment, primary packaging materials (bottles, vials, ampoules), etc.

Control of the quality of water, in particular, the microbiological quality, is a major concern and the pharmaceutical industry devotes considerable resources to the development and maintenance of water purification systems.

The better the quality of available "public" water, the less purification is needed to attain the grade of water quality which is required depending on the different pharmaceutical uses.

Pharmaceutical production needs reliable and stable electricity supply. The energy requirements in production plants are present in:

1. Process thermal energy: input of heat via high quality fluids in reactors, fermenters and mixers.
2. Process chilling: for product cooling, preservation, cooling production tanks and cleaning stations
3. Compressed air for process controls, pressurization of process tanks etc.
4. Vacuum: for suction intake of materials in the process or packaging.
5. Reliable electricity to supply machines, instrumentation, control systems and measurement equipment.

The operational cost of generators as back-up systems depends on the reliability of public electricity network.

Most of the pharmaceutical manufacturers interviewed have an adequate supply of water, but several reported having problems with the electricity supply. The unreliability of public electricity supply forces all of them to have a power generator for back up. The manufacturers complained about the high costs of water treatment and electricity, and the costs incurred for running the power generators.

Safe disposal of waste is done in different ways, but generally in line with NMRA and/or environmental institutions and/or city or municipality guidelines.

5.3.9 Technical and Human Resources

Although a shortage of pharmacists and other technical staff with pharmaceutical skills is often mentioned as a key challenge in sub-Saharan African countries, respondents in the SADC Member States stated that there are sufficient **human resources** to run at least one GMP compliant manufacturing plant per country.

However, a recent study commissioned by the Southern Africa Generic Medicines Association (SAGMA) concluded that there is a lack of synchronisation between the training needs of industry and what is currently on offer. Pharmaceutical industry-related training in SADC is largely focused on regulatory affairs and quality matters, neglecting other operational issues such as formulation development, plant engineering and supply chain management. Very little training is directed specifically at wholesalers and distributors. There is broad coverage of good quality executive education in the region, particularly from South African business schools, although these courses are not specific to the pharmaceutical industry. Short courses presently being offered are concentrated in South Africa and Tanzania.

5.3.10 Technology Transfer and other Collaborations

If the SADC region wants to play a bigger role in pharmaceutical manufacturing, such as becoming less dependent on imports and having direct access to donor funds, greater investments in human capital development, the strengthening of scientific institutions and equipment, as well as significantly higher funding for science and R&D will be needed.

Only two countries within the SADC region (Malawi and South Africa) spend above one per cent of their gross domestic product on R&D, a target endorsed by the African Union (AU) in 2006.

R&D is dominated by academics from major universities and, since the 1990s, there has been a shift in research focus from agricultural science to medicine.

The role of the business enterprise sector in R&D ranks higher in South Africa than in other SADC Member States. Private non-profit institutions play a very modest role in R&D activities, with the notable exception of Malawi.[89]

R&D activities play a major role in the development of pharmaceutical production infrastructure. Investments in human capital development and higher funding for (pharmaceutical) science is the basis for such a development. Since the SADC region already has top-scientists in their ranks, supporting the institutions where they work at and dissemination of their scientific output to other scientific centres within SADC through scholarships and guest-professorships would be a good start.

Increase in R&D investments in every SADC Member State will lead to increased industrialization , self-sustained mass production of essential medicines, and hence, should be considered as an investment opportunity, rather than an expenditure item in national budgets.

Over the last two decades there is an increasing use of product development partnerships (PDPs) financed by donors and government agencies[90]. PDPs are often explicitly established and managed to do experimental development and commercialisation; for example, a recent review of US government support for global health product development lists over 350 projects covering the development of new drugs and vaccines (preclinical to Phase 3), diagnostics and contraceptives, with government involvement including funding, joint R&D, use of infrastructure and secondment of expertise[91].

PDPs are changing the perception that governments should not support pharmaceutical product development and commercialisation. However, the success of PDPs seems to have done little to change the funding patterns of governments in developing countries, which have failed to either increase their overall health R&D budgets, or re-allocate these budgets to product development and incremental innovation. Public health in developing countries can be significantly improved by shifting

[89] African Innovation Outlook 2010, AU-NEPAD, Pretoria

[90] Chatelain and Loset, 2011; Grace, 2010; Moran et al., 2010

[91] Policy Cures and Global Health Technology Coalition, 2012

funding from early to late stage R&D. The benefits of such a change in strategy are now illustrated using the public health programme for TB prevention, treatment and control as a case study. [92]

Supporting industries

Several manufacturers reported importing their packaging from outside the SADC region: this might be an opportunity for a regional feasibility study into packaging materials. For spare parts of highly technical pharmaceutical and laboratory equipment, manufacturers can only source them from outside the SADC region (Europe, India, and China). Maintenance is usually done locally.

5.3.11 Conclusion

What medicines to focus on in SADC?

Only Aspen Pharmacare (South Africa) currently manufactures WHO prequalified products. However, Aspen Pharmacare's management does not see much additional value for prequalification, as the margins on existing products are thin, and the MCC registration already allows access to the big South African market. Aspen is considering focusing on other products such as those required for NCDs.

Varichem Zimbabwe is trying again to be WHO prequalified, however the business case for producing current ARVs is weak (very low margins due to Chinese and Indian imports).

Other manufacturers in the region see little value in going for WHO prequalification; achieving prequalification requires additional (financial and technical) resources, while the expected market is competitive. TPI Arusha has decided to no longer aim for ARVs when the EU supported new factory reopens during autumn 2015.

NRB Pharmaceuticals in Zambia is part of the NRB Group based in India. The group is currently investing USD8 million in this plant, and expects to produce a number of ARV's and anti-malaria medicines within the next couple of years.

New MDR-TB drugs are likely to become available in the coming years and will partly replace the existing ones.

Currently all APIs have to be sourced from India and China, although there are plans to make TB APIs in Pretoria, South Africa.[93] The region should also consider producing tenofovir API (see below).

Production of existing ARVs or MDR-TB drugs in the SADC region for sale to Global Fund recipients or PEPFAR is restricted to one South Africa-based manufacturer, given their strict quality conditions. South Africa-based manufacturers can produce for the South African market under national (MCC) registration. The remaining private and public sector market for the three diseases in non-Global Fund and non-PEPFAR countries is currently too fragmented and suffers from strong Indian competition, making it unattractive for SADC manufacturing. However, in light of the dynamic nature of a number

[92] Walwyn D et al. Renegotiating the role of public health R&D. International Association for Management of Technology – IAMOT 2015 Conference Proceedings.

[93] A joint project of Sanofi and the South African Department of Trade and Industry.

of factors that determine the feasibility of pharmaceutical manufacturing, this conclusion might change in the future. Indeed, most companies who were considering to go through the administrative, technical and financial burden to achieve WHO prequalification for their products, were suffering from lack of demand: if a pooled procurement scheme was implemented throughout the SADC region, economies of scale might make the investment to go for WHO prequalification worthwhile.

Furthermore, the Tripartite Free Trade Area (COMESA-EAC-SADC) offers exciting trade and infrastructure development opportunities which could make market access even larger. Additionally, if tenders were covering a regional demand, then negotiating power would increase towards the Global Fund and PEPFAR to allow for African companies producing WHO prequalified medicines to play a more important role in the bidding. In this way African manufacturers could be given a larger piece of the tender versus international bidders.

The feasibility for regional production will be better with:

1. New post-2005 patented medicines that India can no longer easily produce as generic due to TRIPS (e.g., the new TB medicines bedaquiline, linezolid and delamanid).
2. Production of essential medicines that are not subject to strict quality requirements of donors.
3. Production of API and FDF for high-volume ARVs (backbone TDF, possibly later replaced by TAF).

Technical Requirements for Solid Dosage Form Production

Ideally, finished dosage formulation should be undertaken by the existing local pharmaceutical formulators. Medicines are mainly administered as solid oral dosage forms which are also the relevant dosage forms for the APIs investigated in this study. Production implications for tablets are discussed below.

Tableting of the powdered API and excipients may require granulation, however, direct compression is the speediest technology as it only involves blending and compression, thus requiring fewer unit operations, less machinery, reduced number of personnel and considerably less processing time along with an increased product stability. However, excipients for direct compression are more expensive and many active ingredients are not directly compressible. If feasible though, direct compression would be the preferred manufacturing method for drugs to be produced in Africa as wet-granulation needs to be performed in a controlled air/humidity environment. Moreover, obtaining a GMP certificate for a direct compression plant will be easier than for the granulation method. This will be an important factor for the choice of API candidates that SADC would like to produce in the near future.

A production line capable to produce 50 million tablets/year would typically cost USD 2 million. The QA/QC laboratory cost would be less than USD 750,000.

Total number of personnel for the manufacturing unit (mini-factory size at 50 million tablets/year) would be around five staff, and laboratory personnel would be three.

API Production

Today, the API for the common medicines for HIV and MDR-TB are not produced in the SADC region. If for instance, tenofovir was to be produced within SADC, there would need to be vertical integration

(API and finished dosage form production) in order to be economically feasible. Reactors would have to be made to produce 2,200 metric tonnes of tenofovir API (to treat 15 million patients annually), which then should not be imported anymore from India or China.

Currently, there is only one API-manufacturer operating in the SADC region focusing its business on other APIs than discussed here. It is therefore suggested to invest in a multi-product plant for the production of the respective target APIs (ARV APIs, anti-TB APIs and/ or anti- Malaria APIs). Conventional batch reactors as well as innovative continuous processing technologies can be employed for this purpose depending on the chosen target APIs. Both production modes are discussed in the following paragraphs.

Equipment for a conventional batch reactor plant comprises reactor vessels, process piping, tanks, powder transfer systems, distillate receivers, product isolation devices, and product dryers. The investment costs for multipurpose fine chemical conventional batch-mode plants vary considerably, depending on location, available infrastructure, size and quality of vessels (high end or basic cGMP standard, degree of containment) and the degree of automation. Typically, costs in China would be USD4,400,000 for a 60 m^3 plant (based on 3m^3 reactor vessels) and the annual standard operating costs for production would be USD1,930,000 (comprising depreciation over 5 years, labour, production overhead and energy). Estimates for the SADC region would be at least 30% higher than these costs.[94]

In recent years, continuous flow chemistry has gained momentum in API process development internationally and China and India are at the forefront of implementation. In general, the pharmaceutical industry has been reluctant to commit to respective process innovations due to already existing batch reactor capabilities. Given the context of building a new API production facility, leapfrogging into this new technology provides an option that should be given careful consideration as continuous flow chemistry processes not only provide a much smaller foot print with respect to the production equipment and subsequent plant size, but also better process control as well as a smaller environmental footprint. **hera** developed a proposal on this technique – see Volume 2 Section 8.

Human resources for an API production plant consist of chemical engineers, maintenance engineers, safety officers, technicians and operators.

Apart from the production plant and its dedicated staff, there is also the need for a Quality Assurance (QA) and Quality Control (QC) department. If the API production plant is on the same site as the finished dosage form plant, one laboratory could be shared by the two plants. Typical qualifications for QA and QC staff would be science graduates and post graduates (chemistry, biochemistry, microbiology and pharmacy). Costs for setting up a QA/QC lab (excluding personnel costs) would be USD 3,900,000 (comprising stability cabinets, HPLC systems, clean room, construction cost). In addition, regulatory expertise as well as procurement staff is required.

Feasibility of API and FPP Production

For a product like **tenofovir**, given the massive amount of API (2200 metric tonnes) and FDF's that have to be produced to treat 15 million patients, and the possibility to develop a more efficient, and hence

[94] API Manufacturing: Facts and Fiction, P. Pollak, Contract Pharma, January/February 2012

economically superior manufacturing process (continuous flow chemistry), it would make sense to produce this in the SADC region. This might not be the case for lesser used medicines from the essential medicines list, since production in China and India would still be cheaper than doing this within SADC.

For newer medicines used to treat **HIV,** like TAF or Dolutegravir, and for treating **Multi Drug Resistant TB**, like delamanid, linezolid or bedaquiline, and considering the high cost of those products, it might be economically feasible to produce them within the region.

For example, **hera** recommends to SADC to investigate the feasibility of producing **delamanid** within the SADC region based on the following observations:

1. Demand for MDR-TB treatment is likely to increase due to improved diagnostics (e.g., Xpert).
2. Lack of short, effective, streamlined DR-TB regimens (current regimens are complex and expensive; last 20-24 months, including 8 months of injections, and have severe side-effects).
3. Delamanid is presented as a tablet of low dose (100mg) which has to be taken once or twice daily for 6-8 months.
4. Based on limited data, delamanid seems to be well tolerated. Interactions with other drugs are not yet well known.
5. Delamanid is a nitro-imidazole and is not too complex to synthesize.
6. Delamanid is only available from the originator, and very expensive: USD 33,244 for 2x100mg/d for 6 months.
7. Delamanid has not (yet) been licensed to generic manufacturers or the Medicines Patent Pool. The feasibility study should also review how the product can be produced in the SADC region in a country where the patent is not valid or under government use licence. The study should also make suggestions as to how vital products can be developed without collaboration and Technology Transfer from the originator.
8. This might include alternative, more efficient ways to produce the API/raw material (e.g. using continuous flow chemistry).
9. A joint venture with a strong generic manufacturer/formulator should be investigated as a role model for other patented products.

Making a full feasibility report is however outside of the scope of this report, and has several uncertainties due to limited data available on delamanid at this point in time.

For malaria, the production of more artemisinin (raw material for the production of API) in the region to avoid supply insecurity, and the development of clinically needed products such as Rectal Artesunate (RAS), could be considered in more detailed feasibility studies.

The following observations justifies the consideration for a feasibility study to produce RAS in the SADC region:

1. The risk of death from severe malaria is greatest in the first 24 hours, access to pre-referral treatment is important to “buy time” for patients who are in transit to a facility where they can receive intravenous treatment with artesunate, which replaced quinine as first choice in the May 2015 WHO malaria guidelines.[95]

[95] WHO Guidelines for treatment of malaria, 3rd Edition, 2015.

2. WHO recommends the use of a single dose of RAS for pre-referral treatment.
3. Only two RAS products are available (Cipla, Mepha/Acino) and a third in registration phase (2015). But the available strengths are not ideal: 50mg and 200mg; the WHO recommendation is 400mg.
4. Artemisinin supply (base molecule from which artesunate is synthesised) is predominantly coming from China and Vietnam. Currently only Madagascar grows the *Artemisia Annua* crops in SADC, which are needed for the production of artemisinin.
5. A feasibility study is proposed to evaluate the value chain: expansion of planting *Artemisia Annua* in the SADC region and extracting artemisinin in order to become less dependent on Chinese import. Synthesis of artesunate, and the production of 400mg suppositories for children would be desirable from a public health and trade perspective.

Achieving regional production of current and new medicines for HIV, TB and malaria will require a sustained effort by all stakeholders. But the millions of patients depending on progress in this area for improved access to life-saving pharmaceutical and associated products will make the effort worthwhile

6. GAP ANALYSIS

The Gap Analysis was not included in the TORs. However, consultants found it a useful tool to compare the current situation (as found in the situational analysis) with the desired situation in 2020. The desired situation was formulated based on existing regional policies, global developments and what consultants thought could be achieved over the next 5 years. However, the lifespan of some of the interventions will extend beyond 2020, with other longer-term projects coming on-stream during the 2021-2030 planning period. The desired situation is obviously linked to the strategic objectives in the Strategy.

Finally, actions were suggested to bridge the gap between the current and the desired situation. These actions may be considered in the Action Plan to be developed to implement the Strategy.

Table 2 – Gap analysis

Desired situation	Current situation	Gap	Actions to bridge the gap
REGIONAL POLICY			
Regional policy and strategy for regional production agreed and implemented	Regional policies exist; so is political will. But implementation is yet to begin in most countries. Countries and companies are still competing to produce medicines in their countries for their own populations. Limited technical and some financial support is available from multi- and bilateral donors, and national government agencies.	Implementation of agreed policy and strategy, and bridging the gaps	Develop a 5-year SADC Pharmaceutical Manufacturing Plan to implement the agreed policies and Strategy. Introduce monitoring and evaluation of policy implementation.
At least 10 Member States have an enabling environment in place for regional pharmaceutical manufacturing	Three Member States have successfully used incentives and enabling environment for domestic pharmaceutical production	Seven Member States to create incentives for pharmaceutical production	Action plan for 5 years to implement the (pharmaceutical) manufacturing strategy and the SADC pharmaceutical business plan (combined in the SADC Pharmaceutical Manufacturing Plan). National coordinators meet regularly as SADC working group.
Health, Trade and Finance Ministries collaborate and have	There is very limited coherence between Health, Trade and Finance Ministries.	Coherent policies and implementation	Give priority in the SADC Pharmaceutical Manufacturing Plan and Strategy to making

Desired situation	Current situation	Gap	Actions to bridge the gap
coherent, coordinated policies to promote regional production and access to medicines			policies and actions more coherent among Ministries of Health, Trade, Industry, Agriculture and Finance.
Independent monitoring system within SADC, that is transparent for all stakeholders	There is a limited monitoring system.	Monitoring	Annual reporting by governments and major stakeholders; have an independent multi-stakeholder group to monitor the implementation of policies.
SADC has a regional support and incentive program for pharmaceutical production	SADC has policies but no specific support and incentive programs for regional pharmaceutical production	Regional support/incentive program	SADC to develop mutually agreed support and incentives programs for regional pharmaceutical industry as part of the SADC Pharmaceutical Manufacturing Plan.
COLLABORATION			
80% of the manufacturers are organised in a SADC Pharmaceutical Manufacturers Association (expanded SAGMA) to implement regional generics production	Several national pharmaceutical manufacturing and wholesaling associations and individual generic manufacturing companies are members of SAGMA	More generic manufacturing companies join SAGMA	SAGMA to develop a 3-year plan to bring on board the remaining generic manufacturing companies, and participates in high-level discussions on how to promote more regional production of good quality generics, related capacity building, technology transfer and technical / financial assistance.
Improved multi-stakeholder collaboration in the pharmaceutical production sector at regional and national levels. This can include an annual high level meeting of regional policy makers, Member States, professional organisations and manufacturers.	Very limited collaboration of policy makers, Member States, professional organisations and manufacturers	Collaboration between policy makers, Member States, professional organisations and manufacturers	Regional multi-stakeholder platforms to be included in the monitoring system of the Regional Pharmaceutical Manufacturing Plan. The meeting can also assist to enrich/improve a draft Regional Pharmaceutical Manufacturing Plan.
TREATMENT GUIDELINES			
HIV policy "test and treat" and achieve "90-90-90" plans developed and implemented.	Treatment policy now: CD4<350 or <500 (not all SADC Member States have the same standard)	Member States to upgrade their national	Member States to develop plans and timelines for implementation of “test and treat”, taking into account their local

Desired situation	Current situation	Gap	Actions to bridge the gap
		policies to WHO recommendations.	contexts and resources. HIV policies to be raised to “90-90-90” and "test & treat".
Treatment guidelines for three diseases harmonized, using same dosage forms and similar first-line choices	National treatment guidelines differ and use different dosage forms and different first-line choices	Treatment guidelines to be harmonized	Professional bodies with members of all SADC countries compare the various protocols, and make scientific, evidence-based recommendations for a SADC standard protocol. Civil society and patient groups can lobby and monitor implementation.
SUPPLY SIDE			
Regional agreement which countries / manufacturers shall make what priority products for the SADC market (and beyond)	No agreement; companies struggling to make affordable quality products for the three diseases; they produce mainly for domestic markets.	Shaping the regional production market	Countries / companies can make proposals to produce priority products in a regional Expression of Interest procedure which is supported by regional incentives and backed up by investment funds.
DEMAND SIDE			
SADC Pharmaceutical Procurement Services operational: it has quantified the regional needs and runs regional tenders	SADC Health Ministers have agreed to a SADC pooled Procurement Strategy, and Member States have agreed to a charter for SADC Pharmaceutical Procurement Services. However SPPS is not yet operational, and there is no system (yet) to quantify regional needs. There are no regional tenders yet.	Implementation of the agreed SPPS structure	SADC and Member States to implement the approved SADC Pooled Procurement Strategy, and operationalize the agreed SPPS.
Governments use their leverage for demanding more local added value in their national/regional tenders from non-SADC suppliers	Most SADC Member States offer domestic preference, but only few Member States have managed to convince Indian manufacturers to add some local value in their national ARV and TB tenders.	Use the leverage of Member States paying for their medicines	Implement the pooled procurement Strategy, and ensure that SPPS collates the needed quantities and available budgets for a regional group contracting tender. Use leverage and regional preference to obtain higher % of local value added in regional procurement.

Desired situation	Current situation	Gap	Actions to bridge the gap
SADC operates a Regional Preference system in its regional procurement system (and coverts domestic to regional preference systems in SADC Member States)	About half of SADC Member States operate 15-20% domestic preference schemes which promote local production, but also undermine regional production.	Move gradually from a system of domestic to regional preference	SADC high level decision to gradually move towards a 15-20% regional preference system, while gradually diminishing domestic preference to (for example) 10%. For established and affordably produced products in the region, consider a designation system in local/regional tenders.
LOCAL MANUFACTURE			
3 of the 4 new TB drugs (delamanid, bedaquiline and linezolid) made as generics under (compulsory / voluntary) license in SADC.	None of the 4 new TB drugs are made in SADC. Only 3 MDR-TB drugs are manufactured in SADC (of which one is prequalified).	3 new TB drugs to be researched, developed, registered and produced in SADC	A specific TB chapter in the SADC Regional Manufacturing Action Plan outlines a path for the needed R&D, negotiating of licenses, technology transfer, clinical trials, regulatory approval and manufacturing of the new TB medicines. This is obviously subject to successful outcome of current MDR-TB trials.
Improved supply security for artemisinin due to regional growing of artemisinin or production of semi-synthetic artemisinin	Most artemisinin imported from Vietnam and China; fluctuating prices due to market manipulation, climate, farmer behaviour	More artemisinin produced in SADC (for supply security).	SADC to consider planting more Artemisia, add local value in the conversion to artemisinin and consider the production of paediatric rectal artesunate
Increased capacity in the existing plants or additional plants in the region produce enough SABS approved condoms to satisfy the South African public sector market and the private sectors in other SADC markets	3 SABS approved condom plants in SADC can produce 400 million condoms, but are unable to supply enough for the SADC market (4 billion condoms); none are UNFPA approved.	3.6 billion condoms at SABS quality level to be produced in SADC to meet current and future demand	Existing condom manufacturers increase their capacity and/or assist the establishment of manufacturing plants in other Member States of SADC (Tanzania?) Expansion will need capital investment, and agreement of SADC Member States to accept SABS level quality condoms
SADC to develop some APIs of the new and high-volume existing molecules needed in the treatment	Only one small API factory exists in Cape Town; DRC and Madagascar are growing cinchona trees from which bark quinine	API production in SADC region	CoEs and manufacturing companies to work on collaborative projects to develop new API molecules, with government support (e.g.

Desired situation	Current situation	Gap	Actions to bridge the gap
of the 3 diseases, if possible using new technologies	can be derived, and Artemisia plants. Rubber tree plantations have been operational in DRC but are currently neglected and non-productive. SADC has experts in an alternative API technology (continuous flow chemistry)		financing universities, or non-financial support)
SADC pharmaceutical manufacturing plants operate at regionally certified GMP level. Manufacturers interested to supply Global Fund and/or intl. donors agree to develop new products, upgrade and modernize their plants to WHO prequalification.	Several companies are willing to develop new products, upgrade and modernize their plants. Unfortunately the strong competition by Indian prequalified products for the 3 diseases makes investment in WHO PQ financially not viable. Of the two companies having reached WHO PQ, one has lost its status and the other is contemplating leaving the 3 diseases market.	Roadmap to GMP	A collaboration of SAGMA, Financiers and Regulators to develop a 5-year GMP Roadmap plan to bring all generic companies in SADC to a regionally agreed and inspected GMP level. In addition, identify and support companies to WHO PQ status that want to supply the Global Fund and international donor market.
45% of generic ARVs made in SADC by 2020 (of which 5% in other Member States than South Africa), and 75% by 2030.	15% of generic ARVs made in SADC	Triple the local production of ARVs in SADC (initially mainly in South Africa, for the South African market, but later also in other SADC Member States)	Implement the SADC Regional Pharmaceutical Manufacturing plan
HUMAN RESOURCES			
Regional capacity and skills building programs of CoEs and Pharmacy Schools offer valuable support to human resources and skills needed in regional production of APIs and FDF	A system of CoEs has been set up[96]	Strengthen PPP between CoE/Pharmacy schools and pharmaceutical manufacturers	Expand the system of CoE for capacity and skills building of staff working in regional pharmaceutical production, and start a continuous professional development program for pharmaceutical industry HR.

[96] See SADC CoE report by Prof Henry Fomundam.

Desired situation	Current situation	Gap	Actions to bridge the gap
IP REGULATORY			
SADC Member States include maximum TRIPS flexibilities in their national IP/patent laws, and minimize “TRIPS plus”.	Nearly all SADC Member States have some TRIPS flexibilities such as Compulsory Licensing in their national IP/patent laws. Seven countries so far reviewed their legal texts, maximized TRIPS flexibilities, and minimized “TRIPS plus”.	Eight Member States to review their legal texts to maximize TRIPS flexibilities and minimize TRIPS plus	Action plan for 3 years to review national IP/Patent laws for maximum TRIPS flexibilities and minimal "TRIPS plus"
LDCs make use of their TRIPS exemption for pharmaceutical patents until 2033; other Member States declare government use licences for expensive products	LDCs are not (yet) making use of their TRIPS exemption. Only 1 Member State (Zimbabwe) used the TRIPS flexibilities to enable a national manufacturer to make ARVs.	All LDCs yet to make use of TRIPS flexibilities.	Action plan for 3 years to implement TRIPS flexibilities
MARKET			
15 million of the 18 million HIV+ patients treated by 2020 with affordable, good quality ARVs	6 million HIV+ treated	9 million additional HIV+ people to be treated; additional USD 1.5 billion financing needed	Expand and strengthen the health system. Provide universal testing and treatment. Additional funding required (USD 1.5 billion). Opportunity for local production
Financing for all 15 million patients using ARVs available (USD 1.8 billion per year at USD 120 price level) through increased Government contributions (15% Gross Domestic Product promise), Global Fund and intl. donors	USD 900 million ARV market financed from South African government (USD 400 million), Global Fund (USD 186 million), PEPFAR (USD 100 million), and other sources (USD 214 million)	Gap of USD 900 million, while GF and PEPFAR are increasingly "graduating" Member States to pay more for themselves	High level SADC Summit decision to commit 15% of Gross Domestic Product to realize Universal Health Coverage and the right to treatment, supported by regional solidarity and donor funding
R&D			
90% of MDR-TB patients cured in 8 months using a generic FDC of 3-4 new and/or existing oral TB medicines	60% of MDR-TB patients treated with 18-20 months regimen using quite toxic and expensive MDR-TB medicines[97]	30% more MDR-TB patients cured in 10 months less time	Develop, test, manufacture and get regulatory approval for generic new TB medicines and if possible, also fixed dose combinations of them

[97] South Africa (p. 62, WHO global TB report 2015) notified 18,734 and enrolled in treatment 11,538 (62%).

Desired situation	Current situation	Gap	Actions to bridge the gap
REGULATORY			
All 15 SADC Member States have regulatory body / bodies for controlling medicines and commodities	11 SADC Member States have a NMRA	4 Member States still to establish an NMRA	Regional regulatory action plan with increasing levels of work and information sharing, joint assessments, joint GMP inspections and capacity building to enable all Member States to start a NMRA
A regional manufacturer can get its product registered in 10 Member States within 12 months	Regionally harmonized guidelines but not equitably implemented; 4 countries doing joint assessments of new essential medicines.	10 countries to start joint assessments and build trust in other NMRAs	Regional regulatory action plan (see above). Implement the AMRH Initiative project for SADC. 10 NMRAs are practising joint assessment of priority dossiers
CTD accepted and used in all Member States for standardised regional applications	Most existing NMRAs accept CTD format but are not yet actively using it	CTD use actively encouraged	Regional regulatory action plan (see above). 10 NMRAs to accept using CTD for marketing authorisation.
Mutual recognition agreements between 6 NMRAs in place, and information exchange in place between all 15 NMRAs	No mutual recognition (yet) and only limited information exchange. Several others need technical support.	All NMRAs to participate in information exchange, and 6 NMRAs participate in Mutual Recognition	Regional regulatory action plan: all MS agree to start exchanging information; one NMRA runs a common database of all SADC registration data. The increasing trust makes mutual recognition between 6 NMRAs possible
SAHPRA (new South African NMRA) to be a Stringent Regulatory Authority	South African NMRA inspectorate is PIC/S approved	New South African NMRA to achieve ICH level status	South African NMRA to negotiate observer status with ICH, and gain SRA status
50% of the inspectorates of the region apply PIC/s GMP guidelines	Only South Africa uses PIC/S GMP inspection guidelines	7 more NMRAs agree to work using PIC/s GMP guidelines	Regional regulatory action plan: all NMRA with an active GMP inspectorate start doing joint GMP inspections, and training in PIC/s guidelines
The SADC region has higher level GMP illustrated by 3 plants outside South Africa obtaining WHO prequalification for selected products + 3 plants being WHO prequalifiable	One South Africa based company has WHO PQ status, and is producing medicines for the 3 diseases. 0 prequalified plants (1 re-applying, and 1 applying) outside South Africa.	6 plants to upgrade their GMP and registration dossier level to be WHO prequalifiable	Regional Pharmaceutical Manufacturing plan includes a plan to raise GMP to a regional level of GMP equivalent to WHO GMP. Some companies that bid for the regional production fund will receive also

Desired situation	Current situation	Gap	Actions to bridge the gap
			regulatory support to make WHO prequalifiable dossiers for priority products
FINANCING			
Global / regional development Banks have established a Technical and Financial support fund	International donors and development banks are providing some Technical and limited Financial support	Increased technical and financial resources	Develop a 3-year plan to set up a Technical and Financial support fund.
SADC governments, insurance schemes, and donors work out policies, benefit schemes, price negotiation or price controls to ensure that the needed medicines and related commodities are financially accessible in a sustainable manner	Financing available to treat only half of the HIV+ and MDR-TB patients	Finances to treat an additional 9 million patients with ARVs	SADC Member States receive support in developing their health sector financing strategies
National or Regional Development Fund can provide soft loans to SME pharmaceutical industry	Loans are available from commercial banks, but interest rates are high.	Increased access to soft loans	Fill and use the SADC Development Fund, or use a temporary SADC Pharmaceutical Manufacturing Investment facility

The Gap Analysis has been instrumental in developing the Strategy – see separate document.

7. DISCUSSIONS

7.1 Enabling Environment

The situational analysis shows that the current environment is not (yet) sufficiently enabling for the development of a healthy regional pharmaceutical manufacturing industry. The lack of coherence is best illustrated by the tariffs and duties imposed on raw materials (APIs), excipients and packaging materials, whereas finished products enter without tariffs or are zero-rated. Another example is that the current domestic preference in procurement laws of SADC Member States is treating manufacturers of other SADC Member States the same as Indian or Chinese manufacturers.

In theory, the SADC health and industrialization policies are all adequate; the problem is in the implementation. An example is the 2012 Pooled procurement Strategy which is still awaiting regional implementation in 2015; without an organised regional buying scheme with group contracting, it will be difficult for companies to sell, and reach the entire SADC market.

A multi-stakeholder collaboration of government, private sector, civil society and academia will be needed to achieve meaningful implementation, transparency and accountability in the regional pharmaceutical manufacturing action plan.

SADC could also make much better use of the TRIPS flexibilities. LDCs can ignore pharmaceutical patents until 2033, and because of its majority in SADC (8/15) there are no restrictions in export from one Member State to another.

The region has sufficient capacities in terms of basic human resources and quality laboratories. There is however a need for industry specific skills training in pharmaceutics, regulatory affairs and product development.

Financing will need a big boost, as the new global policy means increasing the number of HIV+ patients on ART from the current 6 million to 16 million by 2020. As the Global Fund might not have enough funds, it will probably reduce the number of countries eligible for funding. Therefore the region has to look for more self-financing of its ARV needs. On the other hand, this also allows more leverage to motivate Indian suppliers to set up joint ventures inside SADC.

Finally, SADC can learn lessons from how India has developed its generic pharmaceutical industry though a long-term policy and consistent incentives for its generic manufacturers to produce and export (See Volume 2, section 40). SADC should create an enabling environment for its pharmaceutical industry and make the policies of the various Ministries more coherent. The WHO framework for local production and access to medicines is a good basis to develop coherent national and regional policies for a healthy pharmaceutical industry in SADC.

7.2 Business Case

The current market environment shows a mixed picture for a local production business case. The lack of an enabling environment and the lack of policy coherence make the business case difficult at present, especially for the production of ARVs.

Existing companies are eager to get a larger share of the Global Fund and PEPFAR funded supplies. They will however need to strengthen their quality policies, and strive for WHO prequalification status. National Medicines Regulatory Authorities can help by developing and implementing GMP Roadmaps. The SADC market is big enough for regional production; to speed up the development of the regional pharmaceutical manufacturing capacity, a regional manufacturing investment facility will be needed. Such an investment facility will also facilitate a fair distribution of manufacturing plants across SADC.

With a well-implemented Strategy, the enabling environment and policy coherence could make large-scale production of raw materials and finished products feasible.

The best opportunities are in bulk production of tenofovir API (2,200 tonnes needed per year by 2020), and new 2nd-line ARVs dolutegravir and raltegravir in finished dosage forms.

If the current clinical trials confirm their effectiveness and safety to treat MDR-TB, the new TB medicines bedaquiline, delamanid, linezolid, and pretomanid (PA-824) would be needed in SADC, possibly also in fixed-dose combinations.

A reasonable case can be made for the production of more condoms, bed nets and DDT in SADC. Detailed feasibility studies and business cases are needed to implement all leads.

7.3 Operational Issues

Companies have been struggling to achieve the quality levels required by donors and Global Fund. They can achieve the quality level (in fact 11 of 20 companies interviewed stated they would be eager to achieve WHO prequalification) but under current conditions this does not make economic sense.

The SADC market is still too fragmented, and the long-planned SADC Pharmaceutical Procurement Services with regional group contracting tenders is not yet operational. Market access for regional manufacturers is thus not yet very easy.

Scaling up to a regional market is important, especially for the first-line treatments with ARVs, which are likely to triple in demand and market size due to the expected shifts in health policy towards ‘test & treat’ and ‘universal health coverage’.

The biggest cost factor of a generic medicine is the Active Pharmaceutical Ingredient. Currently, all APIs are made in India and China, often by the same companies that bid for ARV tenders in South Africa or Global Fund. Any factory trying to manufacture finished dosage forms from imported APIs is potentially subject to price manipulation by the Indian API source. It is therefore urgent that SADC investigates

the possibility of building API plants in SADC. For a new API factory, new techniques such as continuous flow chemistry might prove to be cheaper than the traditional batch processing.

The SADC pharmaceutical industry will ultimately benefit from having a strict regulatory environment, as this will remove the low-quality producers and limit availability of cheap counterfeits on the market. Export will only be possible if the medicines regulators of the producing country have a reputation of being fair and strict.

8. CONCLUSION AND RECOMMENDATIONS

The SADC region has the political will, the needs and the right technical policies on industrialization, health and pharmaceuticals to achieve greater regional production of medicines and health commodities for the three pandemic diseases.

Regional production can become viable in SADC, provided the necessary enabling environment is created, the government incentives are provided, and policies of health-trade-industry-finance-agriculture are coherently streamlined.

The study has generated a large amount of country and pharmaceutical sector data, which are available in volumes 2, 2A and 3 of this report. All literature is also publicly available in a Dropbox[98]. A strategy paper has been produced, which will soon be complemented by a 5-year action plan.

Consultants present a list of recommendations for the different actors involved in regional manufacturing (which need to be further developed in the regional Action Plan).

Recommendation for **SADC** as a region (represented by the SADC Secretariat):

1. Develop a 5-year **SADC Pharmaceutical Manufacturing Action Plan (SAPMAP)** as part of the Regional Strategy. It should include appropriate coordination, implementation and monitoring of common development goals.
2. Ensure **policy alignment** and **coherence** between finance, trade, industry, health, agriculture and education sectors.
3. Operationalize the approved **SADC Pooled Procurement Strategy** and its operational arm, the **SADC Pharmaceutical Procurement Services** (SPPS).
4. Use the **TRIPS flexibilities effectively** to manufacture or import more affordable good quality generic medicines.
5. Develop a **Regional Pharmaceutical Human Resources Development Plan**, linking required skills (GMP, GLP, GCP, regulatory, GDP, MBA, pharmaceutical business) to the 5 Centres of Pharmaceutical and Regulatory Excellence.
6. Update and harmonize **regulatory standards** to create **one regional market** and mutual recognition. This should include r**egional GMP certification** and a **regional GMP roadmap**.
7. Harmonize the **standard treatment guidelines** for the three diseases at regional level (in close collaboration with national experts).
8. Develop capacity and business plans for the production of **Active Pharmaceutical Ingredients**. Alternative technologies such as continuous flow chemistry should be investigated.
9. Discuss with Member States to remove **non-tariff barriers** to intra-regional trade.
10. Promote the phased introduction of a **Regional Preference** to replace Domestic Preference.
11. Facilitate **Technology transfer** within and towards the region.
12. Lobby **donors** to shift more procurement funds towards regional products, and mobilise **financial resources** for the implementation of the strategy.

[98] https://www.dropbox.com/sh/vwlgxy892j75qtp/AAAqNyTPPR0WhzVTaq41-RRva?dl=0

Recommendations for the **Member States:**

13. Adopt a **National strategy for local manufacturing** in line with the Regional Policies.
14. Develop a **National Roadmap** for implementation of the SADC Pharmaceutical Manufacturing Action Plan; each country to indicate their **areas of specialisation** as part of the regional plan, and to specify **targets**.
15. Create a conducive **enabling environment** for viable and profitable pharmaceutical manufacturing (if applicable). This could include targeted, relevant government incentives, domestic/regional preference, tax holidays, and should also cover raw materials, packaging materials and support industries.
16. Ensure **policy alignment** and **implementation** (health, finance, trade, industry, agriculture).
17. Ensure **coherence** of all laws and policies to promote pharmaceutical manufacturing.
18. **Align laws, policies and tariffs** structures to promote import and export of locally produced medicines and commodities at regional level.
19. Remove **non-tariff barriers** to trade.
20. Develop an **appropriate mix of industry incentives and instruments.**
21. Promote **transparency, accountability and monitoring** of agreed strategies by multi-stakeholder groups.
22. Align **standard treatment guidelines**, regulatory and registration guidelines to regional templates.
23. Consider a **designation** system for regionally produced medicines and commodities (demand side).
24. Introduce a **regional preference** in procurement legislation to replace domestic preference in a phased approach.
25. Incorporate full **TRIPS flexibilities** in national legislation and utilise them in pharmaceutical manufacturing and import/export.
26. Push for **curriculum development** to align skills needs and develop/strengthen Centres of Excellence (CoE).
27. All **National Medicines Regulatory Authorities** to exchange information about efficacy, safety and quality with other NMRAs in the context of regional **regulatory harmonisation**
28. Develop (if applicable) a **national GMP roadmap** to create a level playing field for manufacturers. This may need GMP training and technical support.
29. **Develop a National Pharmaceutical Human Resource Strategic Plan**, which should include industry or focus on industry sector. Implement harmonised curricula especially for industry sectors. Where possible and feasible, each country should have access to a national or regional **Human Resources Development facility**.
30. Mobilise **financial and technical resources.**

Recommendations for the **Private sector**:

31. Join (if not yet a member) a regional trade association, and participate in the regional debates on the Strategy and Action Plan for Regional Production.

Recommendations for **Civil Society**:

32. Join (if not yet a member) a regional association, and participate in the regional debates on the Strategy and Action Plan for Regional Production

GLOSSARY

Term / concept	Description	Source
Active Pharmaceutical Ingredient	Substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient).	QAS Terminology db - List of Terms and related guidelines
Bolar (early working) exception	An exception to patent rights allowing a third party to undertake, without the authorization of the patentee, acts in respect of a patented product necessary for the purpose of obtaining marketing approval for the sale of a product	Extracted from the WHO/CIPIH report on public health, innovation and intellectual property rights 2006, and from the UK Commission on Intellectual Property Rights, 2nd edition, 2002.
Compulsory Licence (CL)	A licence to exploit a patented invention granted by the state upon request to a third party, for instance in order to remedy an abuse of rights by the patentee	Extracted from the WHO/CIPIH report on public health, innovation and intellectual property rights 2006, and from the UK Commission on Intellectual Property Rights, 2nd edition, 2002.
Coordinated informed buying	A type of procurement where Member States undertake joint market research, share suppliers' performance information and monitor prices. Member States conduct procurement separately	PP strategy
Counterfeit medicines	Medicines which are deliberately and fraudulently mislabelled with respect to identity or source. Counterfeiting can apply to both branded and generic products. Counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging	Extracted from the WHO/CIPIH report on public health, innovation and intellectual property rights 2006, and from the UK Commission on Intellectual Property Rights, 2nd edition, 2002.
Cross-licensing	The mutual exchange of licences between patent holders	Extracted from the WHO/CIPIH report on public health, innovation and intellectual property rights 2006, and from the UK Commission on Intellectual Property Rights, 2nd edition, 2002.
Doha Declaration (on TRIPS and Public Health)	Declaration, agreed at the Doha WTO Ministerial Meeting in 2001, which states that to the TRIPS agreement should be interpreted and implemented in a way that supports public health and clarifies some flexibilities allowed by the Agreement for that purpose	Extracted from the WHO/CIPIH report on public health, innovation and intellectual property rights 2006, and from the UK Commission on Intellectual Property Rights, 2nd edition, 2002.

Term / concept	Description	Source
Essential medicine	Those medicines that satisfy the health care needs of the majority of the population. WHO's Expert Committee on the Selection and Use of Essential Medicines updates the WHO Model List of Essential Medicines at two-year intervals. Each country may use this model to generate its own list of essential pharmaceutical products.	Adapted from QAS Terminology db - List of Terms and related guidelines
Exhaustion of rights	Principle whereby the right holders' intellectual property rights in respect of a product are considered exhausted (i.e. he or she can no longer exercise any rights) when that product has been put on the market by the right holder, or by an authorized party	Extracted from the WHO/CIPIH report on public health, innovation and intellectual property rights 2006, and from the UK Commission on Intellectual Property Rights, 2nd edition, 2002.
Fair Use or Fair Dealing	An exception to copyright allowing third parties to use the copyrighted material in certain circumstances. National copyright laws in most countries incorporate exceptions for copying for personal use, research, education, archival copying, library use and news reporting, based on principles of 'fair dealing', or 'fair use' (US)	Extracted from the WHO/CIPIH report on public health, innovation and intellectual property rights 2006, and from the UK Commission on Intellectual Property Rights, 2nd edition, 2002.
Finished Dosage Form	Pharmaceutical drug products in the form in which they are marketed for use, typically involving a mixture of active drug components and non-drug components (excipients), along with other non-reusable material that may not be considered either ingredient or packaging (such as a capsule shell, for example)	Adapted from www.fda.gov
Good Clinical Practice	A standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analysis, reporting and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented.	QAS Terminology db - List of Terms and related guidelines
Good Distribution Practice	That part of quality assurance that ensures that the quality of a pharmaceutical product is maintained by means of adequate control of the numerous activities which occur during the distribution process as well as providing a tool to secure the distribution system from counterfeits, unapproved, illegally imported, stolen, counterfeit, substandard, adulterated, and/or misbranded pharmaceutical products.	QAS Terminology db - List of Terms and related guidelines

Term / concept	Description	Source
Good Manufacturing Practice	That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization	QAS Terminology db - List of Terms and related guidelines
Good Pharmacy Practice	The agreed description of the pharmaceutical organisation, procedures and standards that enable the required quality of service to be delivered, including criteria for organisational structures, personnel, facilities, equipment, materials, all kinds of operations, and quality control	PP strategy
Group contracting	A type of procurement whereby Member States jointly conduct and negotiate tender processes. They establish specifications, quantification, sourcing of suppliers, competitive bidding, technical and financial evaluations and adjudication, and contract awards. Member States agree to purchase from the selected suppliers, but they place purchase orders separately (in other words, the commitment is between the individual Member State and supplier).	PP strategy
Information sharing	Member States share information about products and suppliers (such as prices, quality, source and suppliers' performances).	PP strategy
Informed buying and coordinated informed buying	Countries share details of their procurement transactions including prices, sources and information on the quality of the products through the SADC Medicines Database (SMD).i SMD started in 2013 and analysis of the current more than 1100 procurement transactions made available by 14 countries shows that 9 of these countries managed to achieve savings with their procurement of ARVs, antibiotics and medicines for non-communicable diseases for a total of USD 23.5 million.	SADC
Intellectual property rights	Rights awarded by society to individuals or organizations over inventions, literary and artistic works, symbols, names, images, and designs used in commerce. They give the titleholder the right to prevent others from making unauthorized use of their property for a limited period	Extracted from the WHO/CIPIH report on public health, innovation and intellectual property rights 2006, and from the UK Commission on Intellectual Property Rights, 2nd edition, 2002.

Term / concept	Description	Source
Multisource	Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.[99]	Extracted from the WHO/CIPIH report on public health, innovation and intellectual property rights 2006, and from the UK Commission on Intellectual Property Rights, 2nd edition, 2002.
National Medicines Regulatory Authority	The national agency responsible for the registration of and other regulatory activities concerning pharmaceutical products.	QAS Terminology db - List of Terms and related guidelines
Parallel Imports	The import of a patented product from another country once it has been put on the latter's market by the titleholder, or other authorised party. For instance, in the EU it is legal to buy a product from a wholesaler in Portugal to retail in the UK, although the product is patented in both countries. The legal status of parallel imports is a matter for national decision, and is related to the issue of the Exhaustion of Rights	Extracted from the WHO/CIPIH report on public health, innovation and intellectual property rights 2006, and from the UK Commission on Intellectual Property Rights, 2nd edition, 2002.
Patent	An exclusive right awarded to an inventor to prevent others from making, selling, distributing, importing or using the invention, without licence or authorization, for a fixed period of time. In return, the patentee discloses the invention to the public. There are usually three requirements for patentability: novelty (new characteristics which are not "prior art"); inventive step or non-obviousness (knowledge not obvious to one skilled in the field); and industrial applicability or utility	Extracted from the WHO/CIPIH report on public health, innovation and intellectual property rights 2006, and from the UK Commission on Intellectual Property Rights, 2nd edition, 2002.
Patent pools	An agreement between two or more patent owners to license one or more of their patents to one another or third parties	Extracted from the WHO/CIPIH report on public health, innovation and intellectual property rights 2006, and from the UK Commission on Intellectual Property Rights, 2nd edition, 2002.
Pharmaceutical procurement and supply management system	The pharmaceutical procurement and supply management system is composed of all steps in the procurement and supply system: selection, quantification, shopping, tendering, negotiation, ordering, storing, selling, distributing and dispensing of essential medicines and medical supplies.	PP strategy

[99] WHO prefers the term "multisource" rather than "generic" which can be multi-interpretable.

Term / concept	Description	Source
PIC/S or the Pharmaceutical Inspection Convention Scheme	The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities, which provide together an active and constructive co-operation in the field of GMP. PIC/S' mission is "to lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products." This is to be achieved by developing and promoting harmonised GMP standards and guidance documents; training competent authorities, in particular inspectors; assessing (and reassessing) inspectorates; and facilitating the co-operation and networking for competent authorities and international organisations. There are currently 46 Participating Authorities in PIC/S (Convention and Scheme taken together).	http://www.picscheme.org/
Pooled procurement	Pooled procurement (also known as joint procurement or procurement cooperation) is the overarching term for procurement where part or all of the procurement processes of different procurement entities (agencies or departments of bigger entities) are jointly executed by either one of those procurement entities or by a third party procurement entity.	PP strategy
Prequalification	An initial evaluation of the capabilities of suppliers (technical and financial) and of the quality of their products to allow them to participate in the procurement process.	PP strategy
Protocol	1. The official procedure or system of rules governing affairs of state or diplomatic occasions. The accepted or established code of procedure or behaviour in any group, organization, or situation. 2. The original draft of a diplomatic document, especially of the terms of a treaty agreed to in conference and signed by the parties	PBP 2015-19
Registration	A formal procedure for obtaining an IP right typically requiring an application and examination of that application. Certain IP rights such as copyright are available	Extracted from the WHO/CIPIH report on public health, innovation and intellectual property

Term / concept	Description	Source
	automatically without the need for registration. Patent applications in some countries may simply be registered after a basic check	rights 2006, and from the UK Commission on Intellectual Property Rights, 2nd edition, 2002.
Regulation	Typically refers to the process by which a governmental authority reviews medical interventions for marketing authorization. Although methods vary, this normally involves determination of product safety, quality and efficacy. Regulation also involves ongoing monitoring and evaluation of safety, efficacy and quality of products that have already obtained marketing authorization.	Extracted from the WHO/CIPIH report on public health, innovation and intellectual property rights 2006, and from the UK Commission on Intellectual Property Rights, 2nd edition, 2002.
SADC Protocol on Health	The Protocol on Health was approved by the SADC Heads of State in August 1999 and entered into force in August 2004 Acknowledging that a healthy population is a prerequisite for sustainable human development and increased Productivity, the Protocol on Health promotes cooperation among Member States on key health issues. It recognises that this cooperation is essential for the control of Communicable and Non-communicable Diseases, for addressing common health concerns, including emergency health services, Disaster Management, and bulk purchasing of Essential Drugs	PBP 2015-19
SADC Strategy for Pooled Procurement of Essential Medicines and Health Commodities (PP Strategy)	The SADC Strategy for Pooled Procurement of Essential Medicines and Health Commodities was adopted by the SADC Ministers of Health and HIV and AIDS in 2012 in Maputo. It contains a carefully balanced results framework which makes use of the strengths and opportunities in the region. The following phased approach is based on models developed and described by Management Sciences for Health (MSH) about 10 years ago.	SADC
Stringent Regulatory Authority (SRA)	The medicines regulatory authority in a country which is: (a) a member of the International Conference on Harmonisation (ICH) (European Union (EU) Japan and the United States of America); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by SwjssMedic and Health Canada (as may be updated from time to time);or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time); and — only in relation to good manufacturing practices (GMP) inspections: a medicine regulatory authority that is a member of the	QAS Terminology db - List of Terms and related guidelines

Term / concept	Description	Source
	Pharmaceutical Inspection Co-operation Scheme (PIC/S) as specified at http://www.picscheme.org.	
WHO Prequalification Programme (different from prequalification)	WHO Prequalification aims to ensure that diagnostics, medicines, vaccines and immunization-related equipment and devices for high burden diseases meet global standards of quality, safety and efficacy, in order to optimize use of health resources and improve health outcomes. The prequalification process consists of a transparent, scientifically sound assessment, which includes dossier review, consistency testing or performance evaluation and site visits to manufacturers. This information, in conjunction with other procurement criteria, is used by UN and other procurement agencies to make purchasing decisions regarding diagnostics, medicines and/or vaccines.	(http://www.who.int/topics/prequalification/en/)
Work sharing	Member States adopted SADC Pharmaceutical Procurement and Supply Management (PPSM) Good Practices (SADC Standards)[ii] for all Member States to aim for. It includes a self-assessment tool to establish the strong elements in their PPSM systems and what the weaknesses are. The subsequent country PPSM strengthening programmes can draw upon a pool of SADC PPSM and Quality Assurance experts for exchange of tools and expertise through the Pooled Procurement Network (PPN)[iii]. The first of a series of capacity building workshops was successfully held in November 2014 for pharmacists from the Ministries of Health, National Medicines Procurement Agencies (NMPA) and National Medicines Regulatory Authorities (NMRA) from all 15 SASDC Member States.	SADC

[i] SADC Medicines Database; http://med-db.medicines.sadc.int/
[ii] SADC. 2014. Pharmaceutical Procurement & Supply Management Good Practices. Version 3.0 November; https://www.dropbox.com/sh/m46dhsothsxmc8k/AADd3qX9pdkws4MkYDTgp4cma?dl=0
[iii] SADC Pooled Procurement Network (PPN); http://ecs.sadc.int/_/ay0jxcn2