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A Private Sector Perspective

Medicines Registration Harmonisation In the Southern African Development Community

Study commissioned by the Southern African Generic Medicines Association

January 2013

SAGMA
Southern African Generic Medicines Association
Access to affordable quality medicines

Supported by

UNIDO
UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Medicines Registration Harmonization in the Southern African Development Community (SADC)

A Private Sector Perspective

Final Report

January 2013

Study commissioned by the Southern African Generic Medicines Association (SAGMA) and supported by the United Nations Industrial Development Organization (UNIDO)

UNITED NATIONS
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Prepared by Richard Rukwata with the guidance of Chris Chitemerere, SAGMA Chairperson for the Regulatory Harmonization Committee

Table of Contents

Figures

Tables

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Acronyms

ACCSQ	ASEAN Consultative Committee for Standards and Quality
ACTD	ASEAN Common Technical Dossier
ACTR	ASEAN Common Technical Requirement
AFTA	Asian Free Trade Area
AIDS	Acquired Immunodeficiency Syndrome
AMRHI	African Medicines Regulatory Harmonization Initiative
APC	Asian Pharmaceutical Club
APRIA	ASEAN Pharmaceutical Research Industry Association
ART	Antiretroviral Therapy
ARV	Antiretroviral
ASEAN	Association of South East Asian Nations
ASEC	ASEAN Secretariat
AU	African Union
AUC	African Union Commission
AWGTCP	ASEAN Working Group on Technical Co-operation in Pharmaceuticals
BA	Bioavailability
BE	Bioequivalence
BMGF	Bill and Melinda Gates Foundation
CEPT	Common Effective Preferential Tariff
CLMV	Cambodia, Laos, Myanmar, Vietnam
CMT	Committee of Minsters responsible for Trade matters
DFID	Department for International Development
EAC	East African Community
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FTA	Free Trade Area
GCC	Gulf Co-operation Council
GCC-DR	Gulf Central Committee for Drug Registrations
GMPs	Good Manufacturing Practices
HIV	Human Immunodeficiency Virus
HS	Harmonized System
ICH	International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use
IWG	Implementing Working Group

MDR-TB	Multiple Drug Resistance Tuberculosis
MRA	Medicines Regulatory Authorities
MRA	Mutual Recognition Agreement
NEPAD	New Economic Partnership for Africa's Development
NMRAs	National Medicines Regulatory Authorities
NTB	Non-tariff Barrier
NTBs	Non-Tariff Barriers
PANDRH	Pan American Network for Drug Regulatory Harmonization
PAP	Pan-African Parliament
PIC/S	Pharmaceutical Inspection Convention & Pharmaceutical Inspection Co-operation Scheme
PPWG	Pharmaceutical Product Working Group
REC	Regional Economic Community
RISDP	Regional Indicative Strategic Development Plan
SADC	Southern African Development Community
SAGMA	Southern African Generic Medicines Association
SEOM	Senior Economic Officials Meeting
SIPO	Strategic Indicative Development Plan for the Organ
SWOT	Strengths, Weaknesses, Opportunities and Threats
TB	Tuberculosis
TRIPs	Trade Related Aspects of Intellectual Property Rights
UAE	United Arab Emirates
UNIDO	United Nations Industrial Development Organization
WHO AFRO	World Health Organization Regional Office for Africa
WHO EMRO	World Health Organization Regional Office for the Eastern Mediterranean
WHO HQ	World Health Organization Headquarters
WTO	World Trade Organization

Executive Summary

The Southern African Generic Medicines Association report "Medicines Registration Harmonization in the Southern African Development Community – A Private Sector Perspective" was commissioned with the assistance of the United Nations Industrial Development Organization with the intent of harnessing the pharmaceutical private sector's views on pharmaceutical harmonization in the region.

Trade and Health Protocols of the Southern African Development Community make provisions for pharmaceutical regulatory harmonization through various articles. In view of these provisions, the SADC Secretariat developed and implemented a Pharmaceutical Programme which has a number of elements including the medicines registration harmonization initiative. In order to implement this element of the SADC Pharmaceutical Programme, the SADC Secretariat developed a pharmaceutical harmonization project proposal which was submitted to the African Medicines Regulatory Harmonization Initiative, a project conceived to spearhead regulatory harmonization in the African continent. The AMRHI has as one of its focal activities, the mobilization of financial, technical and political support. The SADC Harmonization of Medicines Registration proposal was submitted to the AMRHI in July 2011 and is now awaiting funding.

The SADC pharmaceutical sector is highly polarised towards imports of finished pharmaceutical products with local production only accounting for some 24% of the total regional pharmaceutical market. Given the high burden of the three pandemics namely HIV/AIDS, malaria and tuberculosis in the SADC region, high dependency on imports is a major risk on the ability of the region to safeguard the health needs of its people. The purpose of the SADC Medicines Registration Harmonization project is "to improve public health by achieving rapid and sustainable access to safe, affordable essential medicines of acceptable quality." Access can be attained through two different mechanisms namely local production and importation. Access through importation poses a huge risk to the region as aforementioned. There is thus a need to balance this through access emanating from local pharmaceutical production.

Local production in the SADC pharmaceutical sector is inordinately overshadowed by imports and thus pharmaceutical harmonization will improve access mainly through imports of finished pharmaceutical products. Whilst access is a common goal for all private sector pharmaceutical stakeholders, access largely driven through importation has negative economic and industrial

consequences. The weak local pharmaceutical production in the SADC region has been mainly attributed to the gross lack of adequate human capital and financial resources. This imbalance in resources weakens R&D, the lifeblood of the generic pharmaceutical industry as a constant flow of new products is required to feed and sustain manufacturing capacity. With inadequate financial resources and the ever increasing cost of compliance, the majority of pharmaceutical facilities in the region are in a dilapidated state and equipped with obsolete machinery. This situation does not position the industry well for global competition and access to donor funded markets especially for the three key pandemics. An aggressive regional pharmaceutical sector development strategy should be put in place in order to strengthen local pharmaceutical production.

Whilst there seems to be some conflicting interest between various pharmaceuticals sector players in the private sector with respect to the way in which access can be improved, there is a general agreement on the benefits of medicines registration harmonization in the SADC region. Private sector stakeholders recognize the harmonization of medicines registration in the Southern African Development Community as an important agenda with immensurable benefits to all stakeholders. Several threats and challenges arising from the harmonization of medicines registration in the region have been identified by stakeholders. Suggested solutions to overcome threats and challenges have been put forward by stakeholders.

Pharmaceutical regulatory harmonization is a process which does not happen overnight and there is a need to have a clearly thought out roadmap to implement the initiative. Although three case studies on pharmaceutical harmonization in the European Union, ASEAN region and the GCC region were presented in this paper, they are not a panacea to the Southern African Development Community's need for a well thought out pharma harmonization road map. Stakeholders in the private sector have indicated that a progressive approach which builds on tackling the fundamental requirements for pharmaceutical harmonization is ideal. There still remains however a need for private sector stakeholders to identify a hybrid of pharmaceutical harmonization models which are suitable for the region.

Recommendations and action plans to assist the Southern African Generic Medicines Association in taking the pharmaceutical harmonization project forward have been identified. Although it was the intention of SAGMA to take the project forward with minimal resources, it was noted that this approach could be futile as it would yield minimal results. It was therefore recommended that this paper acts as a selling tool in order to mobilize financial resource from

the donor community and other stakeholders. This funding will then drive the recommendations and associated action plans through a reference group to be set up by the SAGMA Board of Directors.

Chapter 1: Introduction and Background

The Southern African Generic Medicines Association (SAGMA) was officially launched on the 4th of April 2011 as a regional body representing the interests of the private pharmaceutical sector in the Southern African Development Community (SADC). The association is a not for profit organization whose main objective is to represent and support the common business, scientific and technical interests of its members. Membership of the association is open to all who are committed to the production and promotion of generic medicines.

The vision of the association is to create a vibrant and self-sustaining generic medicines pharmaceutical industry in the SADC. The mission of the association is to achieve self-sufficiency and reliability in the local production and promotion of affordable, efficacious, quality generic medicines in the Southern African Development Community. (1)

In July 2011, the SADC Secretariat finalized the "*Harmonization of Medicines Registration in the SADC Region*" project proposal. The proposal states that the overall purpose of the project is to improve public health through rapid and sustainable access to safe, affordable essential medicines of acceptable quality. (2) The overall purpose of the SADC medicines registration harmonization project resonates well with SAGMA's mission stated above. Whilst the SADC project will go a long way in contributing to the realization of SAGMA's mission, the involvement of the private pharmaceutical sector in the project has been very minimal or non-existent. It is with this in mind that SAGMA, with the assistance of the United Nations Industrial Development Organization (UNIDO), has commissioned a study "*Medicines Registration Harmonization in the Southern African Development Community – A Private Sector Perspective*".

With the commissioning of this project, SAGMA wishes to engage the private pharmaceutical sector in order to gather and crystalize its views and opinion on the medicines registration harmonization initiative in the SADC Region.

1.1 Project Scope and Objectives

The Southern African Generic Medicines Association with the assistance of UNIDO, have commissioned an independent consultant to conduct a study on "Medicines Registration Harmonization in the Southern African Development Community – A Private Sector Perspective." The objectives of the study were: (3)

- To give an overview and status of the SADC Medicines Registration Harmonization Project
- To describe the current pharmaceutical market in the SADC region
- To review past experience with regulatory harmonization in other geographies
- To sketch out the likely effects of registration harmonization on regional medicines manufacturers and wholesalers
- To collect the concerns and opportunities from private sector namely the manufacturers and wholesalers/distributors
- To distil recommendations to address concerns raised and identify ways to translate these into activities.

1.2 THE SOUTHERN AFRICAN DEVELOPMENT COMMUNITY

The Southern African Development Community (SADC) has been in existence since the year 1980, when it was formed as a loose alliance of nine majority-ruled States in Southern Africa known as the Southern African Development Coordination Conference (SADCC). SADCC was formed in Lusaka, Zambia on April 1 1980, following the adoption of the Lusaka Declaration – "*Southern Africa: Towards Economic Liberation*." The aim of the grouping was to coordinate development projects in order to lesson economic dependence of Member States on the then apartheid South Africa. The founding Member States of the SADCC consist of Angola, Botswana, Lesotho, Malawi, Mozambique, Swaziland, United Republic of Tanzania, Zambia and Zimbabwe.

The transformation of the organization from a Coordinating Conference into a Development Community took place on August 17, 1992 in Windhoek Namibia when a declaration and treaty to form SADC was signed at the Summit of Heads of State and Government to spearhead economic integration of Southern Africa. The SADC vision is one of a common future, with a regional community that will ensure economic well-being, improvement of standards of living and quality of life, freedom and social justice; peace and security for the peoples of Southern Africa.

Current Member States are Angola, Botswana, the Democratic Republic of Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Swaziland, United Republic of Tanzania, Zambia and Zimbabwe. Madagascar was suspended from the regional grouping in 2009. The SADC has a population size of 257.7 million inhabitants and a Gross Domestic Product of 471.1 billion United States Dollars and its headquarters are located in Gaborone, Botswana. In order to overcome its myriad of challenges SADC designed a

Regional Indicative Strategic Development Plan (RISDP) in 2003. Alongside with the Strategic Indicative Plan for the Organ (SIPO), the RISDP epitomizes the path SADC will take for a fifteen year period. In line with the RISDP, the SADC Free Trade Area (FTA) was launched on August 17, 2008 at Sandton, South Africa. As outlined in the RISDP, SADC hopes to become a customs union in 2012. A common market and an economic union are also envisaged. (4)

Below we discuss two important SADC protocols relevant to this project namely the SADC Protocol on Health and the SADC Trade Protocol. Whilst these two protocols are in the spirit of medicines regulatory harmonization, they remain legally unbinding to Member States unless they are enacted into law.

1.2.1 SADC Protocol on Health

In recognizing that close co-operation in the area of health is essential for the effective control of communicable diseases, non-communicable diseases and for addressing common health concerns in the SADC Region, Member States signed a Protocol on Health on the 18th of August 1999 in Maputo, Mozambique. ***Madagascar was not a party to the signing of this protocol and to date has not acceded to and/or ratified the protocol. As at 23 June 2010, Angola and the Democratic Republic of Congo had not ratified the protoco*l**. (5)

The objectives of the protocol are enshrined in Article 3. Article 3 states that member state parties shall co-operate in addressing health problems and challenges facing them through effective regional collaboration and mutual support under the protocol for the purposes of achieving the following objectives: (6)

- To identify, promote, co-ordinate and support those activities that have the potential to improve the health of the population within the Region;
- To co-ordinate regional efforts on epidemic preparedness, mapping, prevention, control and where possible the eradication of communicable and non-communicable diseases;
- To promote and co-ordinate the development, education, training and effective utilization of health personnel and facilities;
- To foster co-operation and co-ordination in the area of health with international organizations and co-operating partners;
- To promote and co-ordinate laboratory services in the area of health;
- To develop common strategies to address the health needs of women, children and other vulnerable groups;
- ***To progressively achieve equivalence, harmonization and standardization in the provision of health services in the Region***; and

- To collaborate and co-operate with other relevant SADC Sectors.

Article 29 of the SADC Health Protocol specifically deals with pharmaceuticals and states that States Parties shall co-operate and assist one another in the:

- ***Harmonization procedures of pharmaceuticals, quality assurance and registration***;
- Production, procurement and distribution of affordable essential drugs;
- Development and strengthening of an Essential Drugs Programme and the promotion of the rational use of drugs;
- Development of mechanisms for quality assurance in the supply and conveyance of vaccines, blood and blood products;
- Research and documentation on traditional medicine and its utilization; and
- Establishing a regional data bank of traditional medicine, medicinal plants and procedures in order to ensure their protection in accordance with regimes and related intellectual property rights governing genetic resources, plant varieties and biotechnology.

Following its ratification by two thirds of Member States, the instrument came into force in August 2004. In order to facilitate the operationalization of the protocol, an implementation plan which provides an overall framework for effecting the provisions of the SADC Protocol on Health was developed. Although the Protocol on Health identifies twenty-three (23) areas of co-operation, the implementation plan prioritizes four areas namely Disease Control, Family Health, Health Promotion and Education and Health Systems. (7) Within the Health Systems priority area, pharmaceuticals are listed as an area of co-operation in the protocol within the implementation plan. The implementation plan outlines milestones and expected results for each of the six areas identified in Article 29 of the SADC Protocol on Health.

The SADC identified the need to develop and implement a Pharmaceutical Programme in line with the SADC Protocol on Health and the SADC Health Policy. (8) The purpose of the programme is to enhance the capacities of Member States to effectively prevent and treat diseases that are of major concern to public health in the Region. The programme addresses issues that are concerned access to quality of medicines in all Member States. In order to operationalize the Pharmaceutical Programme, a business plan was developed in June 2007. Whilst the Implementation Plan for the SADC Protocol on Health clearly articulates the objective of promoting the harmonization of pharmaceuticals, quality assurance and registration, the SADC Pharmaceutical Business Plan does not clearly detail the objective of harmonization procedures of pharmaceuticals, quality assurance and registration as outlined in Article 29 of the SADC Protocol on Health other than by

implication when it states the requirement of facilitation of trade in pharmaceuticals in the SADC neither does the SADC Pharmaceutical Matrix – Log frame. The detailed SADC Pharmaceutical Matrix – Log frame (an appendix to the SADC Pharmaceutical Business Plan) which details the hierarchy of objects, activities, expected outcomes, responsibility, performance indicators, indicative targets etc., does not cover the regulatory and/or registration harmonization aspect as outlined in Article 29 of the SADC Health Protocol.

1.2.2 SADC Trade Protocol

Having recognized that trade in goods and services and the enhancement of cross-border investment are major areas of co-operation among SADC Member States; Heads of State signed a SADC Trade Protocol in August 1996 in Maseru, Lesotho. Angola, the DRC, Madagascar and Seychelles were not signatories of the Protocol when it came into existence. As at 23 June 2010, Angola and Madagascar had acceded to the Protocol and all the original signatories to the Protocol had ratified it. (5) The objectives of the Protocol are: (9)

- To further liberate intra-regional trade in goods and services on the basis of fair; mutually equitable and beneficial trade arrangements, complemented by Protocols in other areas;
- To ensure efficient production within SADC reflecting the current and dynamic comparative advantage of its Members;
- To contribute towards the improvement of the climate for domestic, cross-border and foreign investment;
- To enhance the economic development , diversification and industrialization of the Region; and
- To establish a Free Trade Area in the SADC Region.

Within the context of this project, the following articles of the SADC Trade Protocol are of major relevance:

- Article 3 – Elimination of barriers to intra-SADC trade
- Article 6 – Non-Tariff Barriers
- Article 14 – Trade Facilitation
- Article 20 – Safeguard Measures
- Article 21 – Protection of Infant Industries

Article 3 states that the process and modalities for the phased elimination of tariffs and non-tariff barriers shall be determined by the Committee of Ministers responsible for trade matters (CMT). Medicines registration requirements by SADC Member States before one can export and/or import medicines are considered a non-tariff barrier to trade. Thus the

SADC protocols on Health and Trade are complementary to each other in that the SADC Protocol on Trade lays out the fundamental requirement for trade facilitation by the elimination of barriers to intra-SADC trade with the SADC Health Protocol complementing this through Article 29 and specifically when the protocol mentions the need for the promotion of the harmonization of pharmaceuticals, quality assurance and registration. The complementary position stated in relation to Article 3 also applies in relation to Article 6 which states that "Except as provided for in this Protocol, Member States shall, in relation to intra-SADC trade:

- Adopt policies and implement measures to eliminate all existing forms of Non-Tariff Barriers (NTBs); and
- Refrain from imposing any new NTBs."

Article 14 of the SADC Trade Protocol states that:

"Member States shall, as provided for in Annex III of this Protocol, take such measures as are necessary to facilitate the simplification and harmonization of trade documentation and procedures." Medicines registration requirements and other regulatory requirements on imports and exports of medicines indeed are so cumbersome (although necessary) that they hinder intra-SADC trade in pharmaceuticals.

Whilst Articles 3, 6 and 14 of the SADC Trade Protocol are in the same spirit with Article 29 (a) of the SADC Protocol on Health, Articles 20 and 21 of the SADC Trade Protocol work against the harmonization of medicines registration in that they promote some level of protectionism in certain circumstances. Specifically, amongst other clauses within Article 20, Article 20 (1) states that:

"A Member State may apply a safeguard measure to a product only if that Member State has determined that such product is being imported to its territory in such increased quantities, absolute or relative to domestic production, and under such conditions as to cause or threaten to cause serious injury to the domestic industry that produces like and directly competitive products."

Within Article 20, there are however checks and balances to guard against excessive or abusive use of safeguard measures and specifically, Articles 20 (5) and 20 (6) respectively state that:

"A Member State shall apply safeguard measures only to the extent and for such a period of time necessary to prevent or remedy serious injury and to facilitate adjustment. …."

"Notwithstanding the provision of paragraph 5 of this Article, the total period of application of a safeguard measure shall not exceed eight (8) years."

Article 21 (1) states that:

"Notwithstanding the provisions of article 4 of this Protocol, upon application by a Member State, the CMT may as a temporary measure in order to promote an infant industry, and subject to WTO provisions, authorise a Member State to suspend certain obligations of this Protocol in respect of like goods imported from the other Member States."

Given the large disparities in the level of development of the pharmaceutical industry amongst SADC Member States, countries with concerns over medicines registration harmonization have a fall-back position to take to address any such concerns, in harmony with the SADC Trade Protocol as enshrined in Articles 20 and 21 of the protocol. Chapter 3 of this paper on stakeholders' analysis will deal with the opportunities, threats and challenges of medicines registration harmonization in the SADC region from a private sector perspective.

1.3 Regional Medicines Regulatory Harmonization Initiatives

Harmonization of various elements of medicines regulatory activities has taken place in the last decade and has involved regional and global organizations. The driving force behind the harmonization effort is the need to improve availability of pharmaceutical products and respond to the forces of international trade with adequate standardized technical regulations of safety, quality and efficacy. (10)

Marketing of pharmaceutical products is highly regulated because it involves several ethical and human health and safety implications. Pharmaceuticals are regulated by governments via specialized medicine regulatory authorities (MRAs) that have the responsibility to ensure the quality, safety, and efficacy of medicines before approving their marketing by granting marketing authorizations to qualified medicines, which allows their availability to the public. One of the main obstacles to international approval of pharmaceutical products is that different models for regulation of medicines exist in countries across the world. The diversity of the regulatory requirements in different countries makes pharmaceuticals marketing a very complex and costly process that often delays access of the public to essential and often life-saving medicines. (11)

Historically, drug regulation was virtually synonymous with national sovereignty. Over the last decade, this has begun to change: national regulatory agencies are more closely cooperating with one another. (12)

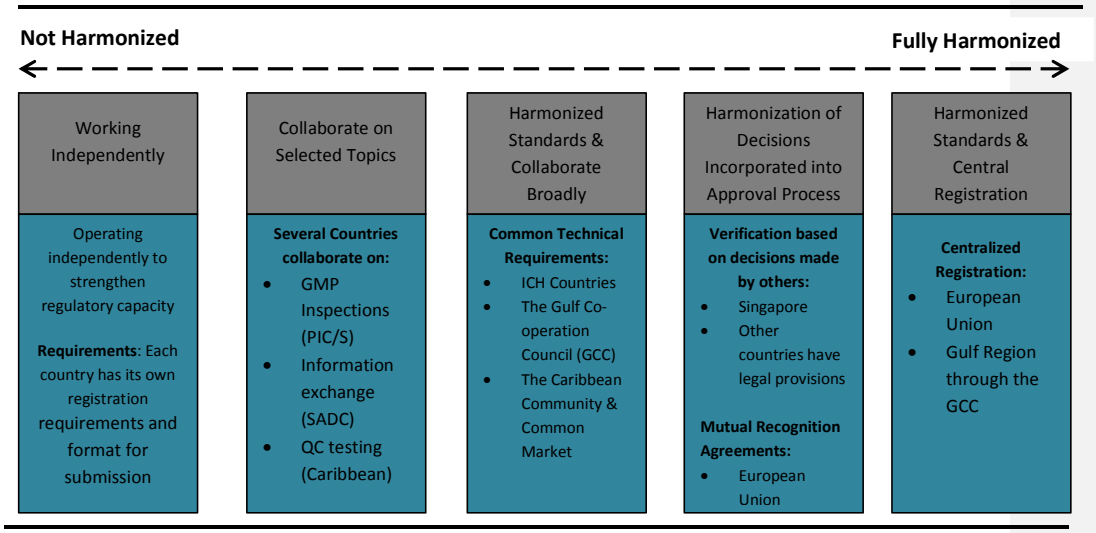
Medicines regulatory harmonization is a process consisting of the following non-exhaustive co-operation elements:

- establishment of common technical requirements (guidelines) for the regulation of medicinal products;
- mere co-operation in sharing information on Good Manufacturing Practices (GMPs) inspections, safety, quality and efficacy of medicines, strengthening of GMP inspectorate and regulatory standards;
- medicines registration co-operation through an approved procedure such as a centralized one or through mutual recognition;
- Joint evaluation of application dossiers and inspection of manufacturing sites.

It is important at this juncture to differentiate between **regulatory** and **registration** harmonization. Regulatory harmonization is a broader all-encompassing co-operation process whereas registration harmonization is a narrower aspect of regulatory harmonization which does not include all the co-operation elements listed above. However, for registration harmonization to be feasible, some elements of regulatory harmonization have to be undertaken. It should however be noted that one can achieve some form of regulatory harmonization (harmonization of technical requirements) without necessarily achieving registration harmonization.

The following figure illustrates this distinction: (13)

Figure 1: Continuum of Medicines Regulatory Harmonization and Examples



The above figure has been adopted from the above reference, with a minor adjustment of the caption. The original document uses the words “Registration” and “Drug” which we have changed to “Regulation” and “Medicines” respectively. It our opinion that the continuum from the left to the right does not necessarily refer to medicines registration harmonization as put by the originators of figure. For example, collaboration on selected topics and harmonized standards and collaboration broadly can be termed “regulatory” harmonization or more specifically, harmonization of technical requirements for registration, but not necessarily “registration” harmonization. However if one were to refer to the “Harmonization of the Technical Requirements for the Registration of Medicines” as per the ICH convention, this would have a totally different meaning to “Medicines Registration Harmonization.”

Harmonization of medicines regulation is a desirable goal for many reasons: (14)

- Companies have to generate only one data set for all regions, and consequently the amount of human and animal experimentation is reduced;
- The cost of development of new drugs and their regulatory documentation is reduced, which would logically lead to lower prices;
- Common regulatory standards for evaluation and inspection facilitate regulatory communication and information sharing;
- Local products are more likely to be acceptable for export to other countries;
- Faster access to medicines of high public health value; and
- Increased competitiveness resulting from newly developed common markets.

Co-operation at the regional level in regulatory harmonization has proved more effective in many cases in strengthening regulatory capacity at the national level. (14) Regional initiatives involved in medicines regulatory harmonization include the Association of South East Asian Nations (ASEAN), the Andean Community, the African Medicines Regulatory Harmonization, the European Union (EU), the Gulf Co-operation Council (GCC), Mercosur and the Southern African Development Community (SADC).

1.3.1 African Medicines Regulatory Harmonization Initiative

The overall objective of the African Medicines Regulatory Harmonization Initiative (AMRHI is to improve health in the African Region by increasing access to safer and effective medicines of good quality for the treatment of priority diseases. The AMRH initiative seeks to support African Regional Economic Communities and countries to harmonize medicines registration using existing political structures and building on existing plans and commitments. The project was initiated at a New Partnership for Africa’s Development (NEPAD) and Pan-African Parliament (PAP) consultation meeting in February 2009. Specifically, the project objectives include: (14)

- To create a collaborative network through partnership between regulatory authorities of participating countries and/or selected sub-regional economic blocks;
- To harmonize technical requirements for the regulation of medical products and build confidence so that agreed harmonized standards are respected by participating authorities.
- To establish a framework for joint evaluations of application dossiers and inspections of medicine manufacturing sites;
- To strengthen the capacity for regulatory oversight; and
- To develop information management systems and promote the exchange of regulatory information.

The major focal activities for the AMRHI include the following:

- Information gathering and analysis for building a better understanding of on-going efforts, barriers and potential socio-economic benefits of harmonizing medicine regulations particularly essential medicines in Africa;
- Support the development of regional project proposals to expedite and strengthen medicines registration through regional collaboration and harmonization; and
- Mobilize financial, technical and political support

The following are the participating Organizations and Regional Economic Communities (RECs) in the African Medicines Regulatory Harmonization Initiative: (15)

Table 1: AMRHI Participating RECs & Organizations

Organization/REC Name	Abbreviation
Arab Maghreb Union	AMU
Monetary Community of Central Africa	CEMAC
The Community of Sahel-Saharan States	CEN-SAD
Common Market for Eastern and Southern Africa	COMESA
East African Community	EAC
Economic Community of Central African States	ECCAS
Economic Community of West African States	ECOWAS
East, Central and Southern African Health Community	ECSA
The Intergovernmental Authority on Development	IGAD

Southern African Development Community	SADC
The Economic and Monetary Union of West Africa	UEMOA
The West African Health Organization	WAHO

The African Medicines Regulatory Harmonization Initiative is made up of a project consortium. The Consortium brings together political, technical and donor organizations, in response to RECs' technical and financial support needs, with respect to harmonization of medicines registration. Beyond working to mobilize financial and technical resources for project implementation, the Consortium is promoting and facilitating inter-REC communication, co-ordination and shared learning. It is also working to develop linkages and build an institutional structure around the AMRHI to ensure the broad representation and active participation of all stakeholder groups, thereby enhancing sustainability. (15)

Table 2: AMRHI Project Consortium (15)

Existing Consortium Partners	**Political/Technical/Organizational:** • World Health Organization (WHO HQ, AFRO, EMRO) • New Partnership for Africa's Development (NEPAD) • Pan-African Parliament (PAP) • African Union Commission (AUC)	**Donors:** • Bill & Melinda Gates Foundation (BMGF) • United Kingdom Department for International Development (DFID) **NGOs:** • William J. Clinton Foundation
Consortium Objectives	1. Mobilize political & high level support, financial & technical resources for AMRH 2. Promote & facilitate inter-REC communication, co-ordination, technical consistency & shared learning with respect to AMRH. Build a continental initiative 3. Provide technical support to assist with: priority setting & plans for regulatory harmonization; a common format for registration documentation & common technical requirements for assessing the quality, safety & efficacy of medicines; good regulatory practices; regulatory capacity building (for assessment & inspections); and regulatory decision making and communication.	
Communications	• NEPAD manages AMRH initiative communications & is responsible for liaising with RECs and NMRA partner institutions on behalf of the Consortium and in line with its steering and co-ordinating role.	

	• Other members of the Consortium also utilize their networks and institutional relationships to publicise and promote the AMRH initiative. • An AMRH newsletter is published as needed and an AMRH website is in place.
Funding	Initial funds were committed, more resources required to fully operationalize the project

Some of the key contributions of the Consortium partners are outlined below. In practice, however, the Consortium has adopted a collaborative and consensus-driven approach in all aspects of its work – meaning a high level of participation from each of the partners across the full range of Consortium activities. (15)

WHO Role in implementing AMRHI (14)

There may be many ways of introducing medicines harmonization to Africa, however, the WHO has proposed focussing on two scenarios that seem the most feasible.

In the first scenario, the WHO's involvement could be limited to assisting foundations, funding agencies, or any other partner in developing and finalizing the proposal for medicines regulatory harmonization and then hand over the project to an appropriate party such as a professional international organization, or regional or sub regional agency for implementation.

The implementation agency, in this case, would take full responsibility for selection of the partners, for performance of the planned activities and for reporting outcomes of the project to the donors. The WHO would provide technical expertise in the preparatory phase of the project but involvement would not go beyond this point.

In the second scenario, the WHO would take the lead in the project, from both a managerial and organization point of view would develop and finalize the project proposal and select partners for the implementation phase in collaboration with Member States.

Historically, WHO has actively supported several harmonization initiatives such as ASEAN and the SADC. In the case of Pan American Network for Drug Regulatory Harmonization (PANDRH), the secretariat is provided by the WHO Regional Office for the Americas.

Implementation of AMRHI (14)

In implementing AMRHI, the WHO identified the following steps:

1. Mapping exercise
2. Brainstorming kick-off meeting
3. Regional stakeholders' meeting
4. Roadmap
5. Establishment of the AMRHI secretariat and Steering Committee
6. Common technical requirements (guidelines) for regulation of medicinal products and starting joint activities
7. Development of a training and confidence building plan for regulators
8. Joint evaluation of application dossiers and inspection of manufacturing sites
9. Information management and exchange system

The above steps are generic and can be used by any Regional Economic Community (REC) wishing to embark on medicines regulatory harmonization. As noted above, the WHO has supported the ASEAN, PANDRH and SADC medicines regulatory harmonization initiatives. Section 4 of this study gives some cases studies of successfully implemented regional medicines regulatory harmonization initiatives. The East African Community (EAC) project proposal was finalized submitted to donors and received commitment for funding. Implementation of the project will commence in March 2012. The SADC project proposal has been finalized and is now awaiting funding commitment.

NEPAD Role

NEPAD is responsible for political advocacy, administrative and planning support to the Consortium, mobilizing, co-ordinating and share between various RECs, political link to the African Union, Pan-African Parliament and African Union Commission, identifying and mobilizing donors for the Consortium. NEPAD is also responsible for assisting RECs in developing their project plans and monitor project progress at REC and national level.

World Bank's Role

Pending approval of a proposal by BMGF, the World Bank will become the fund holder for the pooled funds that go into AMRH, starting with a grant from BMGF. World Bank will manage project implementation in partnership with NEPAD, WHO and RECs, who will become sub-grantees under the AMRH Trust Fund.

AMRHI status and Future Plans (15)

The following events have been lined up by the AMRHI:

- AMRH Programme Stakeholders Plenary Meeting, 29 March 2012, Arusha, Tanzania. The aim of the plenary is to generate discussion and input into developing the way forward for medicines regulatory harmonization in Africa.
- Launch of the East African Community (EAC) Medicines Registration Harmonization Project, 30 March 2012, Arusha, Tanzania.
- Inaugural meeting of the AMRH Advisory Committee, 30 March 2012, Tanzania. The Advisory Committee is intended to function as an advisory body on the AMRH Programme implementation and is composed of representatives from global stakeholders, African Union organs, regional economic communities and NMRAs from respective regions.
- Roundtable meeting of experts and stakeholders, 31 March 2012, Arusha, Tanzania. The aim of the roundtable meeting is to generate discussion and get expert advice on the role of NMRAs and Academic Institutions in the institutionalization of Regulatory Training Programmes in Africa using existing Regional structures.

1.3.2 Southern African Development Community Medicines Registration Harmonization Initiative

One of the elements of the SADC Implementation Plan for the SADC Protocol on Health and the SADC Pharmaceutical Programme with its corresponding business plan as outlined in section 1.2.1 above is the medicines registration harmonization initiative. The SADC medicines registration harmonization initiative falls under the ambit of the AMRHI. Cognisant of the importance of the AMRHI, the New Economic Partnership for Africa's Development (NEPAD) commissioned a consultancy to conduct a situational analysis of medicines regulation harmonization in the SADC. The study was aimed at establishing the status of medicines regulation capacity, harmonization efforts and challenges in REC and Member States with a view to enhancing a better understanding of the situation in Africa learn from the past experiences and develop appropriate interventions to facilitate AMRH. (16)

The situational analysis revealed that there is enthusiasm and commitment from the SADC, MRAs and pharmaceutical industry towards implementation of a harmonized medicine regulatory system. The study however uncovered several challenges in pushing the medicines harmonization agenda and these include: (16)

1. Lack of a medicines regulatory authority in a Member State, Seychelles;

2. The human capital resources (both skills and numbers) as the Secretariat and in respective Member States are limited;
3. Physical facilities vary in member states and require expansion to cater for full functions of medicines regulation;
4. There is a shortage of quality control laboratories in most MRAs with a few of the pre-qualified by the WHO;
5. Inadequate financial support especially for small medicines regulatory authorities; and
6. Regional decisions remain undomesticated by Member States and hence decisions made by individual members are rarely recognized by others.

At a meeting convened by the SADC Secretariat with the support of the African Medicines Regulatory Harmonization Consortium held in Malawi in May 2011, National Medicines Regulatory Authorities (NMRAs), Pharmaceutical Industry and Civil Society representatives to review the findings of the NEPAD Agency's situational analysis study of medicines regulation and harmonization in the SADC, agreed to prepare a project proposal for the Harmonization of Medicines Registration. In July 2011, the SADC Secretariat submitted a project proposal to the AMRH Consortium on Harmonization of Medicines Registration in the SADC Region.

The purpose, goal and objectives of the project proposal are: (2)

Purpose: To improve public health by achieving rapid and sustainable access to safe, affordable essential medicines of acceptable quality.

Goal: To improve the availability of medicines through the regional harmonization of regulatory systems, guidelines and processes among Member States in the SADC through:

- Harmonizing the system of medicines registration and broadening the scope of products reviewed (new chemical entities, vaccines and biologicals) and regulatory functions undertaken (clinical trial oversight, pharmacovigilance etc.)
- Achieving political, legislative and financial support by communicating the value of the project to all stakeholders
- Building regulatory capacity and capability
- Sharing information to facilitate faster decision making.

The following 5 objectives were identified:

1. To develop and implement harmonized guidelines for the application of registration of medicines in the SADC Region.
2. To develop regional and national capacity to implement medicines regulatory harmonization
3. To develop and implement national and regional management information systems (MIS) to facilitate decision making and sharing of information among Member States and stakeholders.
4. To develop and implement a Quality Management System (QMS).
5. To create a platform for engaging key stakeholders on the harmonized registration system at national and regional level.

The SADC pharma harmonization project is now waiting funding in order to progress forward.

1.4 Respondents

Companies were sampled through a judgemental sampling methodology. Appendix I gives the details of the sample design. Appendix ii shows the companies sampled.

1.5 Data Collection Methods

- **Mailed questionnaire:** A questionnaire was developed and emailed to pharmaceutical companies to complete. Follow-up calls were made to all companies to confirm receipt of the questionnaire. Those who could not be reached by telephone were sent emails. Following several telephone calls and email reminders, 12 completed questionnaires were received, 2 (two) from category 2 countries and 9 (nine) from category 3 countries. The category 1 country questionnaire received was from a SAGMA member.
- **Follow up telephonic calls** were made as follow up to check for non-responses.
- **Secondary Data** were obtained from various documents; *inter alia* sector research reports, international studies, websites and academic publications.

1.6 Report Structure

The rest of the report is structured as follows:

Chapter 2 provides a brief overview of the Southern African Development Community pharmaceutical sector, including its structure, key players, size and value, exports and imports, key health and socio-economic indicators and the disease burden of key pandemics.

Chapter 3 presents the findings of the study and analysis thereto.

Chapter 4 presents case studies of regional communities who have successfully implemented medicines registration harmonization.

Chapter 5 concludes the report with lessons learnt from case studies and gives recommendations and action plans necessary to take the registration harmonization agenda in the SADC Region forward.

Chapter 2: The SADC Pharmaceutical Sector Overview

The purpose of this chapter is to provide a brief overview of the Southern African Development Community (SADC) pharmaceutical sector in terms of its structure, players, value of imports and exports, local production, and policy, legal and regulatory environment. This overview is important in setting up the context within which intra-SADC current and potential pharmaceutical trade can analysed in view of the envisaged regional medicines registration harmonization initiative. One of the most importance elements of a feasible medicines registration harmonization project is market viability. This section of the report will give some insights into the various elements of market viability shaping the SADC pharmaceutical market. Whilst the SADC market is deemed a sizeable one in terms of population, epidemiology of key disease areas, total gross domestic product and other elements, various issues limit intra-SADC trade. A medicine registration requirement before one can market a pharmaceutical product in the intended target market is considered a non-tariff barrier to trade. Various studies have shown that harmonization of medicines registration has a positive impact on pharmaceutical trade. Section 2.2 below gives an overview of non-tariff barriers to market access in the pharmaceutical sector.

It is important that there be a common understanding on the definition of the pharmaceutical sector as this can be interpreted to mean different things to different groups for different purposes. This chapter opens up by giving a sector definition and classification in the context of this study. It is also important to give a background on the regional epidemiology of key diseases affecting the region together with key health and socio-economic indicators as they play a key role in shaping the pharmaceutical sector.

2.1 Pharmaceutical Sector Definition and Classification

The pharmaceutical sector in the region can be broadly classified into two categories, namely manufacturing and wholesale and retail trading. According to the International Standard Industrial Classification (ISIC) Revision 4, class 2100, “Manufacture of pharmaceuticals, medicinal chemical and botanical products” includes the following:

- Manufacture of medicinally active substances
- Processing of blood
- Manufacture of medicaments
  - Antisera and other blood fractions

    - Vaccines
    - Diverse medicaments including homeopathic preparations
- Manufacture of medical diagnostic preparations
- Manufacture of radioactive in-vivo diagnostic substances
- Manufacture of biotech pharmaceuticals

This class however excludes:

- Wholesale of pharmaceuticals (class 4649)
- Retail sale of pharmaceuticals (class 4772)
- Research and development for pharmaceuticals and biotech pharmaceuticals (class 7210)
- Packaging of pharmaceuticals (class 8292)

For the purposes of this study, the ISIC (17) Revision 4 classification of the pharmaceutical sector will be revised and broadened to include all of the four above excluded activities. This classification is ideal in that it is all-inclusive and covers the two broad areas which are the focus of this study namely manufacturing and wholesaling. With all these activities classified under the broad pharmaceutical sector classification as adopted above, the whole pharmaceutical value chain will be covered.

2.2 Non-Tariff (Technical) Barriers To Market Access

With the cost of innovation and the necessity to achieve economies of scale, the pharmaceutical industry is continuously re-organizing on a worldwide scale. Over the past 20 years, there has been an increase in globalization for both innovative and generic medicines. Globalization in this sector has occurred with respect to both distribution of medicines in new markets as well as shifting of R&D and manufacturing to lower cost markets. (18) Globalization and Regionalization of the pharmaceutical sector faces a number of non-tariff or technical barriers to market access.

In the interest of safety, efficacy and affordable medicine to the general population every country in world regulates the pharmaceutical industry in their respective countries. The regulation is all pervasive from price controls to reimbursement of pharmaceutical expenses to the consumer through national health protection/insurance schemes to drug registration (including WHO Pre-qualification), market authorization, quality control, quality standards,

imports and distribution, packaging and labelling, intellectual property, negative import lists and preferences to local companies in public procurement. (19)

While countries are free to impose such regulation in keeping with their sovereign status, some of the regulation is excessive and hinders regional intra-trade. Some of the major technical barriers to trade in major pharmaceutical markets are briefly elaborated below. (19)

2.2.1 Multiple Approvals by Various Drugs Regulatory Authorities

The multiplicity of drug approval agencies in various countries raises drug registration costs and site inspection costs. Country regulatory agencies insist on pharmaceutical standards and quality procedures of their country, which often varies from country to country. The documentation to register drugs is extremely detailed and often it is very expensive to provide such dossiers.

With respect to current Good Manufacturing Practices (cGMPs), most NMRAs in SADC adhere to the WHO Guidelines. Only South Africa is a member of PIC/S (The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation 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 harmonized 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 harmonized 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 organizations.

There are currently 41 Participating Authorities in PIC/S (Convention and Scheme taken together).

The following advantages of joining PIC/S are extracted from their website:

- **Training opportunities:** PIC/S provides a forum for the training of GMP inspectors thus allowing the latter to benefit from increased training opportunities by attending PIC/S Seminars and Expert Circles and by participating in the PIC/S Joint Visits Programme. In this respect, PIC/S is unique as there is no other international training forum run jointly by Regulatory Authorities (individually, Regulatory Authorities or organizations such as the WHO or the EMA provide basic training courses, mainly to new inspectors).
- **International GMP harmonization:** By taking part in the meetings of the PIC/S Committee, PIC/S Participating Authorities are involved in the development and harmonization of international GMP guides and guidelines. The PIC/S Committee also actively promotes the uniform interpretation of GMP and Quality Systems for GMP Inspectorates.
- **Networking:** By attending PIC/S activities, participants benefit from personal contacts with other agencies, whether they are part of PIC/S or not. This networking often simplifies contacts and the exchange of GMP related information. In addition, PIC/S is one of the few international GMP fora for networking and confidence building amongst regulatory inspectors where experts (GMP inspectors, specialist GMP inspectors and chief inspectors) can meet, discuss issues of mutual concern and share experiences and information. In other fora, participation is either at the level of Heads of Agencies (e.g. WHO) or at the level of experts in a particular field (ICH).
- **High standards:** PIC/S ensures that all Members comply with PIC/S standards at all times (assessment of new applicants and reassessment of existing member inspectorates). Preparing for the accession to the Scheme (or reassessment) forces improvements in the GMP inspection system and procedures. This results in increased efficiency of the GMP inspectorate. This is particularly true for Quality System requirements, where PIC/S standards are high, and for GMP training, which is essential in PIC/S.
- **Sharing of information:** PIC/S allows for a more effective use of inspection resources through the voluntary sharing of GMP inspections reports. Membership is also a cost-saving measure for the inspection authorities confronted with an increase of inspections, notably in the field of active pharmaceutical ingredients (APIs).
- **Rapid Alert System:** Through PIC/S membership, Regulatory Authorities automatically benefit from being part of the PIC/S Rapid Alert and Recall System arising from quality

defects of batches of medicinal products, which have been distributed on the market. The PIC/S alert and recall system is part of a wider system, which includes the alert and recall system of EU/EEA/MRA partners.

- **Facilitating the conclusion of other Agreements:** Membership in PIC/S may also facilitate the conclusion of other agreements, e.g. Mutual Recognition Agreements, between Members at various levels (e.g. Australia-Canada MRA, EU-Switzerland MRA, etc.). During the recently concluded initial negotiation on ASEAN MRA on GMP Inspection, PIC/S membership accession was accepted as one of the essential criteria for MRA.

As mentioned earlier, most NMRAs in SADC use the WHO cGMPs Guidelines, which have significant similarities to the PIC/S cGMPs Guide with respect to content. However, that is where the similarity ends. Whilst WHO will occasionally provide training for inspectorates of member countries' NMRAs on cGMPs, it by no means offers the advantages that come with membership to PIC/S. This means that NMRAs that follow the WHO Guidelines often have to fend for themselves with respect to developing the capacities of their inspectorates. This leads to varying levels of expertise amongst NMRAs and it is not surprising for a manufacturer to be approved by one NMRA's inspectorate and failed by another. This lack of consistency makes it difficult to establish Mutual Recognition Agreements between Member States. In fact, just browsing the advantages of joining PIC/S one can see that it is in fact an advanced forum for the harmonization of cGMPs amongst Participating Authorities, replete with quality assurance mechanisms to ensure that Participating Authorities maintain the high standards expected of them. All this is lacking on the WHO cGMPs side. This leads to the conclusion that if harmonization is to take place within the SADC region, South Africa is unlikely to lower its standard to accommodate the other NMRAs that are not members of PIC/S. The others would, instead, have to improve and upgrade their processes up to the PIC/S standard.

2.2.2 Bioequivalence Studies for Generics in Local Populations – An Emerging Technical Barrier

Japan, Mexico and Thailand want bioequivalence studies to be carried out in their local populations in their countries. As each additional BE study costs more for each additional country, this new NTB can adversely affect market access.

2.2.3 Drug Registration Fees

Countries charge various levels of fees for granting drug registration and approvals. A fee has to be paid for each strength and variation. A variation is a change in the contents of a dossier. In some cases, some of these fees are considered exorbitant. In the African Region, further fees known as retention fees are required annually to maintain product registration. The Medicines Control Authority of Zimbabwe charges the following fees for the following various activities:

Category	Fee (USD)
Application for registration of a medicine locally manufactured	900
Application for registration of a medicine imported into Zimbabwe as a finished product	2250
Registration fee for a medicine imported into Zimbabwe as a finished product	100
Retention of a registered medicine annually in the case of a medicine imported into Zimbabwe and which is relabelled and repackaged before being sold.	300
Retention of a registered medicine annually in case of an imported finished product	500
Retention of a registered medicine annually in the case of a locally manufactured product	200

2.2.4 Reference Product

When conducting bioequivalence studies, a generic needs a comparator product also known as the reference product. This is normally the innovator product. Many countries insist on innovator products of their countries. This is to say that Japan for example, will accept a reference product registered in Japan, Brazil accepts a reference product registered in Brazil and so on. Often, this places difficulties on exporters to obtain reference products of different

countries. In Zimbabwe and South Africa, the reference product source has to be registered with the MCAZ and MCC respectively, one therefore has to look for the specific source and this causes a lot of logistical problems in trying to source a reference product. Further, there is the tacit implication that a bioequivalence study undertaken for a particular jurisdiction might not be acceptable in another, thereby increasing the costs or registration for manufacturers.

2.2.5 Requirement for Local Presence

South Africa requires a tie-up with a local manufacturer or distributor, so called an applicant, for the registration of products in that country. This invariably raises compliance costs for the exporter.

2.2.6 Government Procurement

Local suppliers are normally awarded a local preference when evaluating government tenders for various goods including pharmaceuticals.

Processes of removing multiple approvals by various drug regulatory authorities in different SADC countries, is the subject of this paper. The diversity of the regulatory requirements in different countries makes pharmaceutical drugs' application approvals and marketing a very complex and costly process that often delays access of the public to essential and often life-saving drugs. Regulatory harmonization in the SADC region will entail removal of multiple approvals by different regulatory authorities and this is likely to result in some cost savings especially in the area of dossier compilation as a standardised dossier will remove the need to prepare a specific dossier for each individual national regulatory authority. With respect to fees like application fees etc., the actual outcome is not predictable as it will depend on the regulatory harmonization model and agreements by national regulatory authorities.

2.3 KEY HEALTH AND SOCIO-ECONOMIC INDICATORS

The SADC Free Trade area is a home some 270 million people with a Gross Domestic Product (GDP) of US$575 billion at 2010 nominal prices. Table 3 below shows some key socio-economic and health indicators for the SADC Region. The table shows varying disparities in terms of the key socio-economic and health indicators amongst SADC Member States. The limiting nature of some of these statistics might reduce the attractiveness of some countries as candidates for registration harmonization. The country population and 2010 nominal GDP of SADC Member States varies from a modest 1.3 million people in Mauritius and USD2.1 billion for Lesotho to a high of 66 million people in the DRC and a nominal GDP of USD364 billion in

2010 figures for South Africa respectively. These statistics indirectly shape the size of the pharmaceutical market. It is not surprising that South Africa with its high population and nominal GDP figures is the largest and most lucrative pharmaceutical market in the SADC Region.

Table 3 further high lights the large differences amongst SADC Member States in terms of the structure of the different health sectors. Within SADC, there member countries like Angola, Mozambique and Tanzania, with a strong government expenditure on health as a percentage of total health expenditure. This results in a very strong public health care sector but one which is very volatile and prone to the vagaries of economic cycles. There are some countries like the DRC and Namibia with balanced private and government expenditure on health as a percentage of total expenditure on health. At the other extreme are countries like South Africa and Mauritius with relatively strong private health care sectors where private expenditure on health as a percentage of total expenditure on health outstrips public health care expenditure.

The private sector is normally the pillar of the pharmaceutical sector in terms of value and profit margins. The structure of the private sector within SADC Member States can be analysed in terms of the statistics given in Table 3. Out-of-pocket expenditure on health as a percentage of total private expenditure on health is relatively high in Angola, the DRC, Lesotho, Madagascar, Mauritius and Tanzania, ranging from a low of 65% to a high of 100%. This is in direct contrast to Namibia and South Africa which have private pre-paid plans as a percentage of private expenditure on health of 77.3% and 66.2% respectively signalling a stable private health care sector which does not overly depend on out-of-pocket expenses which are volatile.

In summary, within SADC member states, Angola, Botswana, Madagascar, Mozambique and Tanzania, have relatively strong public health care markets as measured by general government expenditure on health as a proportion of total expenditure on health. The population size of Botswana however limits the attractiveness of this market in terms of size. Namibia and South Africa have relatively strong private health care sector when compared to other SADC Member States as measured by the nearly balanced private and public expenditure on health coupled with a high level of pre-paid plans as a percentage of private expenditure on health. As with Botswana, the relatively small population of Namibia limits the attractiveness of this market from a numbers point of view.

In addition to other chronic ailments, the public health care sector mainly caters for diseases represented largely by the three main pandemics of HIV/AIDS, tuberculosis and malaria which

are discussed below. These disease areas are to a large extent funded by international organizations which have stringent requirements to funding access. This then limits the effects of registration harmonization in the SADC Region in this sector. However, countries like South Africa, with their positive economic fundamentals, are able to fund public health programmes using internally generated funds. It is not surprising that the South African ART programme is largely funded by the South African government and thus this market is an exception to the previously stated position on the effect of medicines registration harmonization in the public sector in terms of increased market access. Thus medicines registration harmonization in the SADC Region should be viewed largely from a private health care sector perspective because of the easier access to this segment from a funding view.

While 53 African countries signed the Abuja Declaration pledging to devote 15% of their national budgets to health, in 2009 only four countries in the SADC Region, namely Botswana, the DRC, Tanzania and Zambia, managed to meet this target.

Table 3: Key Socio-economic and Health Indicators in SADC (20)

Statistic	Angola	Botswana	DRC	Lesotho	Madagascar	Malawi	Mauritius	Mozambique	Namibia	South Africa	Swaziland	Tanzania	Zambia	Zimbabwe[1]	Totals/Average
Population (m), 2009	18.489	1.950	66.020	2.067	19.625	15.263	1.288	22.894	2.171	50.110	1.185	43.739	12.935	12.523	270.26
GDP (Bn), 2010	84.39	14.86	13.15	2.13	8.72	5.11	9.73	9.59	12.17	363.70	3.65	23.06	16.19	7.47	573.92
Total Expenditure on Health as a % of GDP	3.3	7.6	7.3	7.6	4.4	9.1	5.5	4.7	6.9	8.2	5.8	4.5	5.9		
General government expenditure on health as a % of total expenditure on health	85.0	78.2	54.2	63.3	70.2	60.6	34.8	75.2	54.6	39.7	60.8	72.3	62.0		
Private expenditure on health as a % of total expenditure on health	15.0	21.8	45.8	36.7	29.8	39.4	65.2	24.8	45.4	60.3	39.2	27.7	38.0		
General government expenditure on health as a % of total government expenditure	6.8	16.6	17.5	8.2	14.6	12.1	8.3	12.6	12.1	10.4	8.5	18.0	15.3		
External resources for health as a % of total expenditure on health	3.0	4.2	18.8	19.3	16.1	88.9	2.0	80.8	21.4	1.2	11.1	59.5	38.4		
Social security expenditure on health as a % of general government expenditure on health	0	0	0	0	0	0	0	0.3	2.6	3.0	0	3.3	0		
Out-of-pocket expenditure on health as a % of private expenditure on health	100	33.1	85.5	68.9	67.6	30.1	88.7	28.2	17.9	29.7	42.3	65.1	74.5		
Private prepaid plans as a % of private expenditure on health	0	6.3	0.2	0	15.0	15.4	6.3	1.9	77.3	66.2	18.9	14.5	4.1		

[1] Zimbabwean figures are being recalculated in view of dollarization of the economy in 2008. All Health indicators are for the year 2009. GDP figures from World Bank, World Development Indicators database, 1 July 2011

2.4 Disease Burden Of Key Pandemics

The three key pandemics namely HIV, Malaria and tuberculosis continue to ravage the African continent more than any other continent. Although these three communicable diseases are at centre of every day discussions (the so called pandemic blind sight), chronic conditions such as obesity and cardiovascular diseases are looming as the greatest threat. Below we discuss these three pandemics in order to put into context the magnitude of the requirement of key essential medicines required in southern Africa. Despite the huge potential of the SADC Region as a 'huge' market for intra-SADC pharmaceutical trade, the region continues to be one characterised by single country markets because of market access barriers, one of which is lack of registration harmonization. Section 2.3 of this paper outlined some of the challenges to market access presented by the three pandemics. The financing of healthcare in Africa remains a patchwork of meagre public spending, heavy reliance on foreign donors and a large dependence on out-of-pocket contributions. (21)

An estimated $15 billion is needed each year to prevent and treat HIV/AIDS, tuberculosis, and malaria around the world. Today, a quarter of all international funding for HIV/AIDS-related programs, over half for tuberculosis, and almost three-quarters for malaria worldwide comes from The Global Fund.[2] The Global Fund to Fight AIDS, Tuberculosis and Malaria (often called The Global Fund or GFATM) is an international financing organization that aims to attract and disburse additional resources to prevent and treat HIV and AIDS, tuberculosis and malaria. Access to these funding for HIV, TB and malaria medicines attracts stringent marketing authorization requirements which can be a further barrier to market access for most pharmaceutical companies within the SADC Region. As noted, in section 2.3 above, except for SADC Member States with their own strong funding for the purchase of medicines used in the management of these three pandemics, medicines registration harmonization in the SADC Region will not necessarily increase market access to member countries in view of the extra barriers to market entry introduced through international funding mechanisms despite the huge magnitude of the three pandemics in the Southern African Development Community.

For the near future, donor funding will remain one of the dominant sources of healthcare financing in Africa. This is problematic for two reasons. First, donor funding tends to be short-term, and relies on financing from foreign governments, multi-lateral or non-government

[2] Bill & Melinda Gates Foundation, www.gatesfoundation.org

organizations, all of which are suffering from continued global economic instability. Second, donor funding has traditionally been focused on single ailments or conditions (the pandemic blind sight), rather than on the multi-condition, comprehensive healthcare system that Africa will require in the future. (21) The Global Fund cancelled its 11th funding round in December 2011, potentially putting many African countries' public health treatment programmes financed by this mechanism into turmoil.

2.4.1 HIV

East and Southern Africa remains the area most heavily affected by the HIV epidemic. Out of the total number of people living with HIV worldwide in 2009, 34% resided in 10 countries of Southern Africa. The epidemic continues to be most severe in Southern Africa, with South Africa having more people living with HIV (an estimated 5.6 million) than any other country in the world. (22) Almost half of the deaths from AIDS-related illness in 2010 occurred in Southern Africa.

In 22 sub-Saharan countries, research shows HIV incidence declined by more than 25% between 2001 and 2009. This includes some of the world's largest epidemics in Ethiopia, Nigeria, South Africa, Zambia and Zimbabwe. The annual HIV incidence in South Africa though still high, dropped by a third between 2001 and 2009 from 2.4% to1.5%. Similarly, the epidemics in Botswana, Namibia and Zambia appear to be declining. The epidemics in Lesotho, Mozambique and Swaziland seem to be levelling off, albeit at unacceptably high levels. (22)

Table 4 below summarizes some key HIV statistics for SADC Member States. The table shows a disturbing disparity between SADC countries in terms of Anti-retroviral Therapy (ART) coverage which ranges from a low 14% to a high 93%. Given the position of the SADC region as the worst hit by the epidemic, production of anti-retrovirals (ARVs) and related medicines should be concentrated in this region in order to safeguard the affected population against the vagaries of dependence on non-SADC countries, which is the current situation. South Africa is home to the world's largest HIV epidemic and it is not surprising that this country has the largest ART programme in the world which has motivated the country to embark on a project to locally manufacture selected active pharmaceutical ingredients for the local production of ARV finished pharmaceutical formulations.

Medicines registration harmonization in the SADC region with South Africa as a core component of the initial countries to be involved in the project, will benefit those companies in the region

who have aggressively embarked on attaining world class GMP standards together with developing and marketing appropriate product portfolios to meet the highly dynamic ART medicine regimens.

By 2022 continued global economic instability will lead to cuts in foreign aid budgets and leave many donor organizations overstretched, with the result that many of them will be forced to pull out of African countries. (21) The initial consequences of such a development could be empowering for many countries, as well as catastrophic for a smaller number. Countries with greater resources will use the opportunity to build their own local manufacturing capability. (21)

Table 4: Selected HIV Statistics in the SADC Region (22)[3]

Country	Estimated number of Adults and Children living with HIV, 2009	Estimated number of people needing ART based on 2010 WHO guidelines, 2010	Reported number of people receiving ART, 2010	Estimated ART coverage based on 2010, WHO guidelines, 2010
Angola	201 300	86 000	27 931	33%
Botswana	318 900	170 000	161 219	93%
Democratic Republic of Congo	-	300 000	43 878	14%
Lesotho	287 600	130 000	76 487	57%
Madagascar (suspended)	24 100	19 000	248	1%
Malawi	924 800	-	250 987	-
Mauritius	8 816	4 100	646	16%
Mozambique	1 400 000	550 000	218 991	40%
Namibia	177 200	98 000	88 717	90%
Seychelles	-	-	156	-
South Africa	5 600 000	2 500 000	1 389 865	55%
Swaziland	184 900	83 000	59 802	72%
United Republic of Tanzania	1 400 00	610 000	258 069	42%
Zambia	977 500	480 000	344 407	72%
Zimbabwe	1 200 000	560 000	326 241	59%

[3] www.unaids.org

2.4.2 Malaria

Malaria is one of Africa's biggest killer diseases. There is a diversity of malaria epidemiological settings and control activities among African countries. The African Region's countries which have malaria transmission are grouped into four categories namely: (23)

- Central Africa
- West Africa
- East Africa and high transmission countries in southern Africa; and
- Low transmission southern African countries

Countries which fall under the high transmission southern Africa group include Madagascar, Malawi, Mozambique, Zambia and the United Republic of Tanzania. The low transmission countries include Botswana, Namibia, South Africa, Swaziland and Zimbabwe and malaria is highly seasonal. Lesotho is entirely free of malaria transmission. Angola and the Democratic Republic of Congo are classified under Central Africa. In all nine countries of this subregion, all inhabitants live in areas with a high risk of malaria.

The following table summarizes the epidemiological profile of malaria in the SADC Region. The high transmission southern African countries are highlighted in yellow in Table 5. The United Republic of Tanzania is split into Mainland Tanzania and Zanzibar.

High transmission countries in southern Africa together with Angola and DRC which, in the context of the African Region malaria classification system, fall under Central Africa, present a high potential for medicines for malaria treatment and prophylaxis. As stated in the introductory part of this section, The Global Fund is responsible for at least 75% of the world malaria management programme. Whilst the population at risk in the aforementioned regions portray a huge market potential, reliance on donor funding narrows the actual available market and as discussed in the HIV section, diminishes the benefits of medicines registration harmonization in the SADC Region as medicine supply requirements will be largely met from outside the region. The situation is further worsened by the complexity of anti-malarial formulations which invariably require formulation technology skills higher than most of the basic ARV formulations. This is supported by the limited number of WHO pre-qualified anti-malarial formulations.

Table 5: Epidemiological Profile of Malaria in the SADC Region (23)[4]

Country	Population in High transmission (≥ 1 case per 1000 population), 2010	% of Total Population	Population in High transmission (0 – 1 cases per 1000 population), 2010	% of Total Population	Population in Malaria free (0 cases), 2010	% of Total Population
Angola	19 100 000	100	0	0	0	0
Botswana	361 000	18	943 000	47	702 000	35
Democratic Republic of Congo	64 000 000	97	1 980 000	3	0	0
Lesotho	0	0	0	0	0	0
Madagascar (suspended)	6 210 000	30	14 500 000	70	0	0
Malawi	14 900 000	100	0	0	0	0
Mauritius	-	-	-	-	-	-
Mozambique	23 400 000	100	0	0	0	0
Namibia	1 530 000	67	114 000	5	639 000	28
Seychelles	-	-	-	-	-	-
South Africa	2 010 000	4	3 010 000	6	45 100 000	90
Swaziland	0	0	332 000	28	854 000	72
United Republic of Tanzania (Mainland)	31 900 000	73	11 800 000	27	0	0
United Republic of Tanzania (Zanzibar)	1 360 000	100	0	0	0	0
Zambia	13 100 000	100	0	0	0	0
Zimbabwe	6 290 000	50	0	0	6 290 000	50

[4] Countries highlighted in yellow denote high transmission countries in Southern Africa

2.4.3 Tuberculosis

In 2010, there were an estimated 8.8 million incident cases of tuberculosis (TB) globally, of which 26% occurred in Africa. (24) The number of deaths caused by TB in the same period was estimated at 254 000. The table which follows shows the estimated epidemiological burden of TB in 2010 for high burden SADC countries namely the Democratic Republic of Congo, Mozambique, South Africa, United Republic of Tanzania and Zimbabwe. These high burden SADC countries currently represent 23% of the world's 22 high burden countries. South Africa was amongst the world's top five countries with the largest number of TB incident cases in the year 2010.

The proportion of TB cases coinfected with HIV is highest in countries in the African Region and overall, the African Region accounted for 25% of TB cases among people living with HIV. South Africa is the only SADC country that features in the world's 27 high Multiple Drug Resistant TB (MDR-TB) with an estimated 1.8% of new TB cases with MDR-TB and an estimated 6.7% of retreatment TB cases with MDR-TB.

Table 6: Estimated Epidemiological burden of TB in 2010 for high burden SADC Countries

Country	Estimated Mortality (1000s), 2010	Estimated Prevalence (1000s), 2010	Estimated Incidence (1000s), 2010	Estimated HIV-Positive Incident TB Cases (1000s), 2010
Democratic Republic of Congo	36	350	220	18
Mozambique	11	110	130	77
South Africa	25	400	490	300
United Republic of Tanzania	5.8	82	79	30
Zimbabwe	3.4	51	80	60

The arguments presented in sections on HIV and malaria above with respect to benefits of medicines registration harmonization in the SADC Region in terms of improvements in market access also apply to malaria. As pointed out earlier on, the GFATM currently finances at least

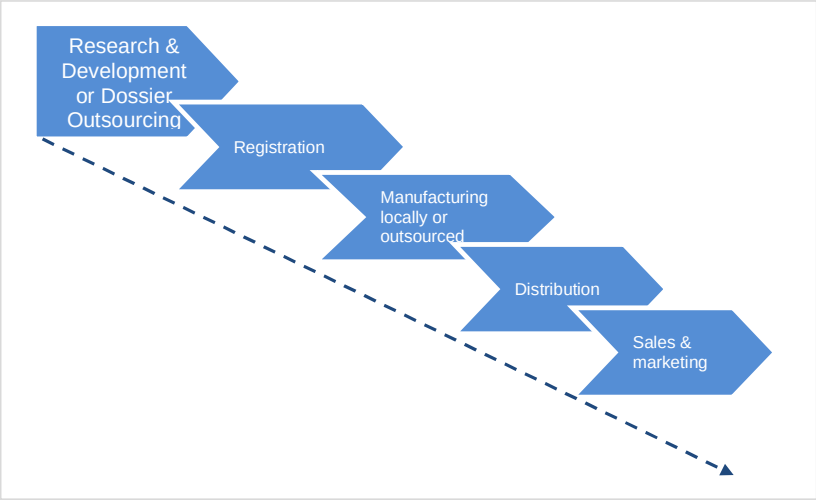
50% of the world's TB management programmes thus diminishing the potential market available for intra-SADC trade. As with anti-malarials, TB medicines also present formulation challenges and the number of TB medicines pre-qualified by the WHO is limited when compared to those of HIV. Technology thus acts as an additional non-tariff market access barrier for both malaria and TB medicines (additional to marketing authorization requirements).

2.5 Sector Structure And Key Players

The pharmaceutical industry is a knowledge-intensive sector, comprising research and development (R&D), manufacturing, sales and marketing of pharmaceutical products. Figure 2, below, summarises the key activities in a 'generic' pharmaceutical value chain. (25) The activities outlined in the value chain are in line with the sector definition and classification as given in section 2.1 above.

Within the Southern African Development Community pharmaceutical context, the amount of Research and Development (R&D) is limited to generic medicines formulation development, analytical method development and validation, improvements to existing formulations and troubleshooting of manufacturing processes. In the SADC Region, the level of development of the pharmaceutical sector varies with some countries only distributing medicines and very few countries doing manufacturing.

Figure 2: Pharmaceutical Value Chain



The table below summarizes the state of the SADC pharmaceutical sector in terms of Member States activities within the pharmaceutical value chain. (26)

Table 7: Pharmaceutical Value Chain Activities in SADC Member States

Country	Pharmaceutical Value Chain Activity			
	R&D[5]	Registration[6]	Manufacturing	Distribution
Angola				✓
Botswana		✓		✓
Democratic Republic of Congo		✓	✓	✓
Lesotho				✓
Madagascar (suspended)		✓	✓	✓
Malawi		✓	✓	✓
Mauritius		✓	✓	✓
Mozambique		✓	✓	✓
Namibia		✓	✓	✓
Seychelles				✓
South Africa	✓	✓	✓	✓
Swaziland			✓	✓
United Republic of Tanzania	✓	✓	✓	✓
Zambia	✓	✓	✓	✓
Zimbabwe	✓	✓	✓	✓

The table shows that only four (26.67%) of the fifteen SADC member states participate in the full pharmaceutical value chain. The strength of the SADC pharmaceutical value chain will determine the feasibility of the SADC Medicines Registration Harmonization Initiative. Whilst the United Republic of Tanzania is member state of SADC, it is heavily involved in the East African Community (EAC) Medicines Registration Harmonization Initiative which has now received funding for implementation. Even with the different value chain activities within SADC

[5] R&D is confined to formulation development and process/formulation improvements

[6] Legal provisions for marketing authorization

Member States, the level of development in these activities varies highly, with some countries not necessarily meeting international or other set levels of standards. Such disparities present some challenges in the regulatory harmonization process.

The sector can very broadly be divided into the R&D, or innovator / ethical drug industry, and the generic industry, although the boundaries between the segments have blurred significantly in the last few years, and a new hybrid model is gaining prominence. This is partly because of declining innovator pipelines, and slowing pharmaceutical industry growth in the developed economies (especially of innovator products) and the entry of innovator companies into the fast-growing generic segment, especially in the so-called emerging markets. (25)

The role-players in the pharmaceutical industry can broadly be classified as follows: (25)

- Innovator/multinational/foreign-owned importers, distributors and marketers
- Locally-owned manufacturing companies with plants
- Multinational manufacturing or packaging plants
- Importers of generic medicines, repackagers, marketers and distributors
- Suppliers of biological products,
- Government-funded research organisations, including universities
- Clinical trial units of universities, private medical practices and private organisations.

The number of manufacturers, distributors/wholesalers in SADC Member States has been established by the WHO in their publication, "Situational Analysis Study on Medicines Registration Harmonization in Africa – Final Report for the Southern African Development Community." However, the figures given in this paper are highly questionable, for example, South Africa is said to have the largest number of manufacturing plants numbering 112, followed by the DRC at 90 and Zimbabwe at 32. For this reason, this paper will not reproduce these figures.

South Africa has a relatively well-developed pharmaceutical industry, which consists of manufacturers, distributors and dispensers forming the supply-chain. It is by far the single largest pharmaceutical industry in the Southern African Development Community.

2.6 Local Production, Size And Value

The total pharmaceutical market in the SADC region was estimated at US$3 billion in the year 2006 with approximately 24% of this being local production and the balance being imports. It is

estimated that South Africa accounted for 90% of this total market value then. (27) Using the 2010 import value of US$3.23 (see section 2.7 below, and assuming the share of local production remained at 24%, the SADC pharmaceutical market would have been valued at US$4.25 billion in 2010 with a local production value of US$1.02 billion. Using this same assumption, table 8 below gives the projected pharmaceutical market values for the Southern African Development Community from the year 2004 to 2010 using import value given in table 9 below. It can be seen that the projected market value of the SADC was US$2.78 billion versus a value of US$3 billion quoted above from a different source. It can thus be said that the figures below are a good estimate of the Southern African Development Community pharmaceutical market values.

Table 8: SADC Projected Pharmaceutical Market Values

Year	2004	2005	2006	2007[7]	2008	2009	2010
Value of Imports (US$ billion)	**1.58**	**1.87**	**2.11**		**2.68**	**2.67**	**3.23**
Projected value of local production (US$ billion)	0.50	0.59	0.67		0.84	0.84	1.02
Projected total SADC Pharma market value (US$ billion)	2.08	2.46	2.78		3.52	3.51	4.25

Pharmaceutical spending in South Africa increased from USD2.34bn in 2008 to USD2.43bn in 2009. A compounded annual growth rate of 9.7% was projected from 2009 – 2014 to give an expected value of USD3.86bn by end of 2014. By 2019, the total drug market in South Africa is expected to be worth USD4.74bn with a 2014-2019 compounded annual growth rate of 4.2% in US dollar terms. (28)

Most pharmaceutical production outside South Africa is of non-complex, high volume, essential medicines. Within the SADC Region, only South Africa has a limited degree of API production. Local manufacturers only capture a small share of the donor market in southern Africa which is

[7] Figures not available

mostly focussed on treatments of HIV, TB and malaria. Most donor-funded contracts generally require product pre-qualification by the WHO or registration with the US Food and Drug Administration (FDA) or registration with a stringent regulatory authority. As at 7 February 2012, only two southern African manufacturers had WHO pre-qualified products, and only 8 of the 269 WHO pre-qualified HIV, TB, and malaria medicines were produced by these two southern African manufacturers.

The WHO pre-qualification is a difficult process for most SADC regional manufacturers and requires a commitment to significant financial and technical resources. Embarking on the WHO pre-qualification process should be done on the basis of the viability of the whole project. It is recommended that full pre-investment (support, pre-feasibility and feasibility) studies be carried out to support the feasibility of WHO pre-qualification before committing scarce resources.

2.7 Exports and Imports

Table 9 below shows the value of global pharmaceutical imports into the Southern African Development Community classified under the four digit Harmonized System (HS) code. Total imports in 2010 amounted to US$3.23 billion up from US$2.67 billion in 2009 an increase of 21% over a 12-month period. Finished pharmaceutical products (not in classes 3002, 3005 and 3006) accounted for 76% of the total value of imports in the year 2010. As discussed earlier on, SADC is home to the major three pandemics of HIV, TB and malaria and the high import given in table 8 illustrate the high dependence of the region on foreign supplies. This situation poses a considerable level of risk in terms of continuity of supplies if shocks hit foreign suppliers.

Table 9: Bilateral trade between SADC & the World, Product: 30 Pharmaceuticals, Unit: US Dollar Thousands

(Source WTO)

Product code	Product label	Value in 2004	Value in 2005	Value in 2006	Value in 2007	Value in 2008	Value in 2009	Value in 2010
'3001	Glands & extracts, secretions for organotherapeutic uses; heparin & its salts	2,600	2,223	2,043		6,086	6,997	20,803
'3002	Human & animal blood; antisera, vaccines, toxins, micro-organism culture	126,889	154,939	206,924		253,098	303,034	393,674
'3003	Medicament mixtures (not 3002, 3005, 3006) not in dosage	84,802	89,299	84,939		147,864	161,470	198,423
'3004	Medicament mixtures (not 3002, 3005, 3006), put in dosage	1,228,096	1,451,538	1,636,175		2,129,936	2,036,317	2,457,860
'3005	Dressings packaged for medical use	34,553	39,898	44,574		54,851	66,749	47,067
'3006	Pharmaceutical goods, specified sterile products sutures, laminaria, blood grouping reagents	99,835	128,747	138,502		87,045	97,160	115,578
Total Pharmaceutical Product Imports		1,576,775	1,866,644	2,113,157		2,678,880	2,671,727	3,233,405

Table 10 below gives a list of supplying markets for pharmaceutical products imported by Southern African Development Community with a cut-off supply value of US$20 million. Supply markets with values less that this limit are not shown.

Table 10: Top sources of pharmaceutical imports into the SADC sorted by value, in US$ thousands

(Source WTO)

	Exporters	Imported value in 2007	Imported value in 2008	Imported value in 2009	Imported value in 2010
	Total	**2,897,407**	**2,909,049**	**2,702,109**	**3,312,084**
1	India	270,387	425,656	447,328	601,945
2	France	365,084	331,276	400,821	505,826
3	Germany	201,211	207,641	192,653	278,593
4	United Kingdom	215,330	232,123	200,283	264,780
5	Switzerland	193,627	197,143	216,870	245,841
6	Belgium	211,619	197,616	201,229	234,757
7	Australia	678,395	453,378	169,335	223,816
8	Netherlands	151,916	133,146	153,430	136,770
9	Italy	77,960	83,724	94,782	116,418
10	United States of America	85,660	119,002	110,699	105,769
11	Ireland	35,612	19,560	40,362	77,097
12	China	62,173	73,181	64,763	75,880
13	Spain	47,680	55,252	48,455	66,911
14	Portugal	49,450	57,918	63,527	58,487
15	South Africa	40,945	60,052	66,261	47,091
16	Sweden	27,873	30,417	26,851	43,095
17	Republic of Korea	10,903	12,180	11,532	28,792
18	Denmark	25,397	25,722	18,502	23,867
19	Kenya	26,729	34,684	24,270	23,604
20	Austria	22,269	27,161	22,224	22,681

The table above shows that in the year 2010, India was the top supplier of pharmaceutical products to the Southern African Development Community followed by France, Germany, United Kingdom and Switzerland. South Africa is the only country within the region which features in the top 20 suppliers to the SADC Region. It is quite clear that import intra-SADC trade of reasonable magnitude is very limited with South Africa being the only SADC member

country accounting for 1.4% of intra-SADC trade in pharmaceutical products in 2010. There is a need to establish the causes of such low levels of intra-SADC trade. Harmonization of medicine registration in the SADC Region will be of minimal benefit to Member States if the situation is not turned around.

Table 11 below further disaggregates the SADC imports by importing country.

Table 11: SADC Pharmaceutical Product Imports by Member States, US$ thousands (Source WTO)

Importers	Imported value in 2007	Imported value in 2008	Imported value in 2009	Imported value in 2010
Southern African Development Community (SADC) Aggregation	**2,513,322**	**2,682,805**	**2,682,109**	**3,233,790**
South Africa	1,475,429	1,569,555	1,588,134	2,063,887
United Republic of Tanzania	167,019	136,743	105,464	153,080
Democratic Republic of the Congo	90,727	75,516	137,859	137,047
Botswana	109,632	107,374	112,395	136,686
Malawi	85,231	94,566	112,923	131,626
Mauritius	69,793	84,060	93,647	127,272
Angola	109,239	130,705	130,678	121,950
Zambia	96,014	159,448	155,620	115,000
Zimbabwe	75,099	60,632	80,802	83,725
Madagascar	50,595	66,587	60,540	66,397
Mozambique	52,645	61,319	43,668	45,139
Namibia	100,230	117,424	14,684	20,147
Swaziland	26,936	8,456	16,151	15,421
Lesotho	4,733	8,174	24,958	11,373
Seychelles		2,246	4,586	5,040

South Africa is by far the largest destination of pharmaceutical imports within the Southern African Development Community. In order to ascertain the level of pharmaceutical trade of SADC Member states with the rest of the world, the table which follows shows SADC exports to the rest of the world. Table 11 clearly indicates that the Southern African Development Community's level of exports is far below the level of imports. In the year 2010, SADC exported pharmaceutical products to the tune of US$207.6 million against an import bill of US$3.23 billion giving a pharmaceutical trade deficit of US$3.02 billion.

It is conclusive at this point in time to mention that intra-SADC pharmaceutical trade is very minimal and medicines registration harmonization would not result in increased market access amongst Member States. As pointed out earlier on, the region needs to embark on a serious local production agenda in order to increase the level of intra-SADC trade, failure of which regional registration harmonization would not be a viable project to embark on as the benefits will not outweigh the costs of project implementation and maintenance.

A decomposition of SADC pharmaceutical products exports given in table 12 would reveal the sources of exports in terms of Member States.

Table 12: List of Pharmaceutical Products Exported by SADC, in US$ thousands

(Source WTO)

Code	Product label	Exported value in 2008	Exported value in 2009	Exported value in 2010
'3004	Medicament mixtures (not 3002, 3005, 3006), put in dosage	165,165	207,431	143,721
'3002	Human & animal blood; antisera, vaccines, toxins, micro-organism culture	49,838	37,698	27,538
'3005	Dressings packaged for medical use	14,890	13,623	17,271
'3003	Medicament mixtures (not 3002, 3005, 3006) not in dosage	12,037	11,081	12,732
'3006	Pharmaceutical goods, specified sterile products sutures, laminaria, blood grouping	12,563	7,291	5,897
'3001	Glands & extracts, secretions for organotherapeutic uses; heparin & its salts	15	102	443
Total Pharmaceutical Product Exports		254,508	277,226	207,602

Table 13 shows such decomposition and as with imports, South Africa dominates exports of pharmaceuticals within SADC Member states. Export levels of the rest of the Southern African Development Community are very weak.

Table 13: List of SADC Exporters of Pharmaceutical Products, US$ thousands

(Source WTO)

Exporters	Exported value in 2007	Exported value in 2008	Exported value in 2009	Exported value in 2010
Southern African Development Community (SADC) Aggregation	**177,833**	**254,504**	**277,227**	**207,605**
South Africa	142,396	177,867	178,183	150,954
Mauritius	14,892	21,588	21,127	31,644
Swaziland	33	32,821	49,487	7,382
Botswana	8,227	14,353	11,871	6,491
Zimbabwe	1,645	934	1,976	3,046

United Republic of Tanzania	1,828	3,662	8,250	3,035
Zambia	1,126	1,166	1,020	1,556
Angola	32	132	12	1,057
Seychelles		135	900	828
Democratic Republic of the Congo	1,132	341	1,293	826
Namibia	1,030	1,220	108	645
Madagascar	10	38	271	90
Malawi	81	112	367	40
Mozambique	572	135	2,302	6
Lesotho	4,829		60	5

The last level of export analysis shows the destination of SADC exports. Table 14 below shows a list of importing markets for pharmaceutical products exported by Southern African Development Community.

Table 14: List of Importing Markets for Pharmaceutical Products Exported by SADC, US$ thousands

(Source WTO)

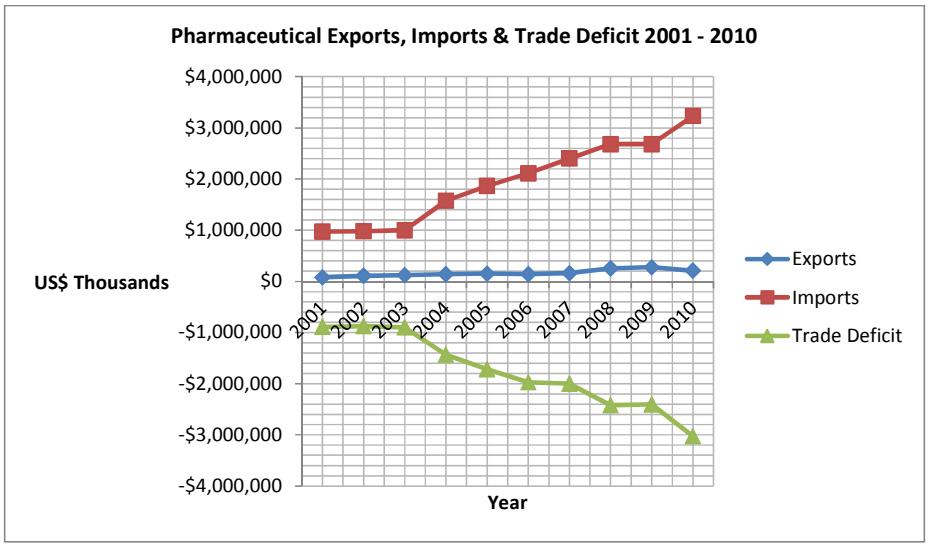
	Importers	Exported value in 2007	Exported value in 2008	Exported value in 2009	Exported value in 2010
1	Botswana	88,884	67,473	77,336	83,686
2	Zambia	42,384	42,866	51,235	36,950
3	Zimbabwe	12,640	10,402	15,721	27,872
4	United States of America	9,176	9,899	15,029	20,211
5	Kenya	14,005	18,428	24,545	15,698
6	China	1,652	2,255	6,509	8,284
7	Australia	7,933	7,485	6,864	7,815
8	Malawi	6,705	7,201	7,286	7,094
9	Mauritius	5,129	4,950	7,585	6,993
10	United Kingdom	8,467	21,581	7,320	6,946
11	Uganda	5,886	8,632	10,277	5,999
12	Madagascar	1,245	1,188	4,719	5,849
13	Germany	6,588	6,130	7,088	5,513
14	Hong Kong, China	1,321	1,163	1,463	5,171
15	Ghana	2,316	2,881	2,630	4,719
16	Mozambique	6,597	3,917	8,132	4,586
17	Brazil	5,616	3,445	3,269	4,541
18	Nigeria	322	1,373	32,298	4,270

19	Pakistan	754	24,740	22,684	2,743
20	United Republic of Tanzania	2,637	5,668	4,556	2,535

The level of intra-SADC trade remains very minimal as envisaged by the presence of only 35% of SADC Member States in the top 20 list of export destinations together with the magnitudes of trade when compared to imports as exemplified by the figures in Table 10. The table shows some exciting destinations like the USA and the European Union, with the most eligible players to service these markets being Aspen and Adcock Ingram of South Africa.

Figure 3 below summarizes the SADC pharmaceutical products exports, imports and the accompanying trade deficit. The figure shows that between 2001 and 2010, pharmaceutical products imports have been rising on the back of an almost flat rise in exports. This has resulted in the deficit worsening from a level of US$0.89 billion in 2001 to deficit level of US$3 billion in the year 2010.

Figure 3: SADC Pharmaceutical Products Exports, Imports & Trade Deficit, 2001 – 2010
(Source WTO)



What is clear from Figure 3 above is that the Southern African Community imports pharmaceutical products far in excess of what it produces and exports. With the envisaged medicines registration harmonization in the SADC Region, market access changes of significance will only take place for importing distributors especially those from South Africa.

The long standing debate of industrial policy versus public health policy then comes into play. It could be argued that medicines registration harmonization in the region will improve access to affordable, quality generics through imports. However, this would not be in the interests of local producers.

The question to be raised then is, will medicines registration harmonization in the Southern African Development Community be open to goods not manufactured within the SADC Region? As an example, many countries/regions including the EU, USA, Canada, Japan and others, have concluded mutual recognition agreements with countries with equivalent levels of GMP and registration standards. These agreements are meant to assure the quality of drugs imported into the country/region issuing market authorization through mutual acceptance of GMP inspection and exchange of information on the drugs distributed in the two countries and/or regions. India being not a signatory to many of these mutual recognition agreements is not able to export to such countries. (19)

2.8 Drivers of Growth

The growth of the Southern African Development Community pharmaceutical sector, especially the generic segment, has been largely driven by the following factors:

- Patent expiries of many blockbuster[8] molecules
- The HIV/AIDS epidemic
- Increasing acceptance and use of generic medicines
- An increase in lifestyle diseases
- An aging population requiring chronic care
- A greater number of people now accessing health services

2.9 SWOT Analysis

The figure below shows a SWOT analysis of the Southern African Development Community pharmaceutical sector. The SADC pharmaceutical sector is burdened with a myriad of weaknesses and threats. The sector does not possess any considerable strength to capitalize on the many opportunities available. The high market concentration of the sector with South Africa accounting for almost 90% of the total regional market value is a major weakness. Despite the abundant opportunities available within the SADC pharma market, all SADC

[8] A blockbuster molecule is a drug product with sales of US$1 billion or more per annum.

Member States except for South Africa do not possess the necessary strengths to capitalize on these opportunities. The large pharmaceutical import bill of the region is a consequence of the low level of local pharmaceutical production.

Figure 4: SADC Pharmaceutical Market SWOT Analysis

Strengths	Weaknesses
▪ High regional population pool ▪ High regional total income	▪ Low government health expenditure in most member states ▪ large pool of member states with a weak private sector characterized by high out-of-pocket expenditure and lack of pre-paid private medical plans ▪ limited number of local manufacturers and high proportion of importing distributors/wholesalers ▪ lack of adequate clinical trials facilities ▪ Low level of regional exports ▪ limited manufacture of APIs ▪ High market concentration in one country, South Africa
Opportunities	**Threats**
▪ Potential for marked generic sector growth through use of TRIPS flexibilities ▪ huge potential market for HIV, TB and malaria ▪ Potential for establishment of clinical trials CROs ▪ huge potential market for non-communicable disease especially life-style related ▪ Local production expansion in view of the global financial crisis and the resulting lower donor support	▪ Costs of GMP compliance are rising ▪ Increase in imports from the rest of the world and especially from Asia ▪ Cost containment programmes ▪ High regulatory barriers to market access ▪ Skills flight ▪ Global financial crisis and declining donor support

The low level of pharmaceutical exports from the Southern African Development Community is also a symptom of the weak pharmaceutical production within the region. Earlier on, it was pointed out the global financial crisis with its resultant decline in donor support, could bring

opportunities for local production and decrease dependence on foreign supply of critical medicines. This will however only benefit Member States with sufficient resources to capitalize on this opportunity. The opportunity arising from the high prevalence of the three pandemics in the SADC region is difficult to capitalize on due to the inability of Member States to finance procurement of medicines using own resources.

Trade Related Aspects of Intellectual Property Rights (TRIPs) present some opportunities for generic companies in the region. These include product portfolio enlargement through development and commercialization of products still protected by patents. It is however disheartening to note that only one country within the SADC, Zimbabwe, has been able to realise benefits from this opportunity. Most Member States have either not amended their intellectual property rights laws in conformance with TRIPs provisions or lack the political will to utilize TRIPs flexibilities.

The high burden of the three pandemics of HIV, TB and malaria in the region presents a market opportunity for the supply of medicines for these diseases. However, the financing mechanisms for the procurement of medicines for these diseases is largely donor driven and attracts barriers to access through stringent requirements such as WHO pre-qualification, FDA registration or registration with stringent medicines regulatory authorities. Only one company in the SADC Region has benefited from this vast opportunity.

Bioequivalence studies are required for the registration of some generic pharmaceuticals by national regulatory authorities. Within the SADC, only South Africa conducts bioequivalence studies using local contract research organizations, the other countries do not have bioequivalence facilities. Conducting bioequivalence studies using South African CROs is expensive with a cost range of US$40 000 to US$100 000. An opportunity exists for the establishment of a bioequivalence CRO outside of South Africa. There is however a need to establish the feasibility of such an opportunity.

Comment [A1]: The fact that we mention that there is a need to establish the fasibility of a local bio study center means we are not concluding that it is necessarily going to be cheaper to conduct these studies locally.

Chapter 3: Stakeholders' Analysis

This section presents findings of the primary research on medicines registration harmonization in the SADC region from a perspective of the private sector. The findings of this paper are presented according to the following areas:

a) Background of the respondents
b) Respondents' comments on opportunities arising from medicines registration harmonization
c) Threats to stakeholders arising from pharmaceutical registration harmonization
d) Challenges to medicines registration harmonization
e) Suggested road map to medicines registration harmonization

SAGMA convened a workshop in Gaborone, Botswana from the 21st to the 22nd of March 2012 to discuss Medicines Registration Harmonization in the Southern African Development Community. During the workshop, two breakaway sessions covering the interests of wholesalers/distributors and manufacturers were held. The proceedings of these breakaway sessions are included in the stakeholder analysis.

3.1 Background

The 12 responses received were from four countries namely, Namibia, South African, Swaziland and Lesotho. Of these 12 responses, 50% were from Zimbabwe, 25% from South Africa, 16.7% from Namibia and 8.3% from Swaziland.

The following table summarizes the key background statistics of the respondents:

Table 15: Background statistics of respondents

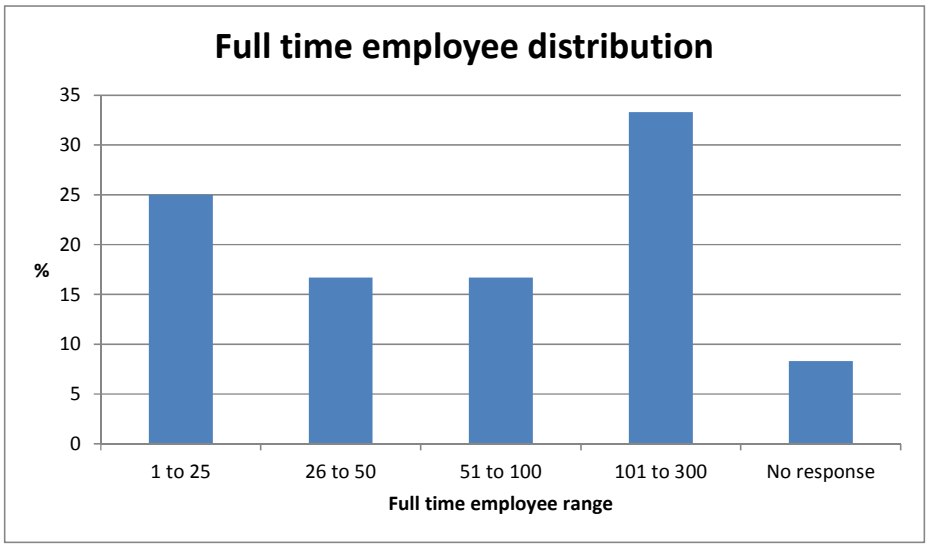
Statistic/Activity	% Respondents
Marketing and Sales	25
Manufacturing & Non-importing wholesaler	25
Importing and non-importing wholesaler	16.7
Manufacturer & importing wholesaler	16.7
Manufacturer, importing & non-importing wholesaler	8.3
Consulting	8.3
Innovative medicines	25

Generic medicines	75
Vaccines (in addition to generics and/or innovative medicines)	25
Full time employees (1-25)	25
Full time employees (26-50)	16.7
Full time employees (51-100)	16.7
Full time employees (101-300)	33.3
Full time employees (no responses)	8.3
Awareness of SADC Medicines Registration harmonization Initiative	66.7
Awareness of the AMRH Initiative	25
Awareness of the EAC Medicines Registration harmonization Initiative	41.7
Awareness of the EU Centralized Procedure	50
Awareness of all Initiatives	16.7
Awareness of other initiatives	8.3

The respondents were fairly spread amongst the key activities of manufacturing, importing wholesalers/distributors, non-importing wholesalers and marketing and sales. In South Africa, a pharma company cannot have a dual function of a manufacturer and wholesaler/distributor as this is outlawed by the competition act. The marketing and sales function presented in the responses above represents the activities of innovative multinationals in South Africa. 75% of the respondents were involved in the generics medicines business with 25% of them carrying out pharmaceutical business in the innovative medicines arena. 25% of the total respondents were involved in the vaccines business.

The figure below summarizes the distribution of full time employees of the respondents.

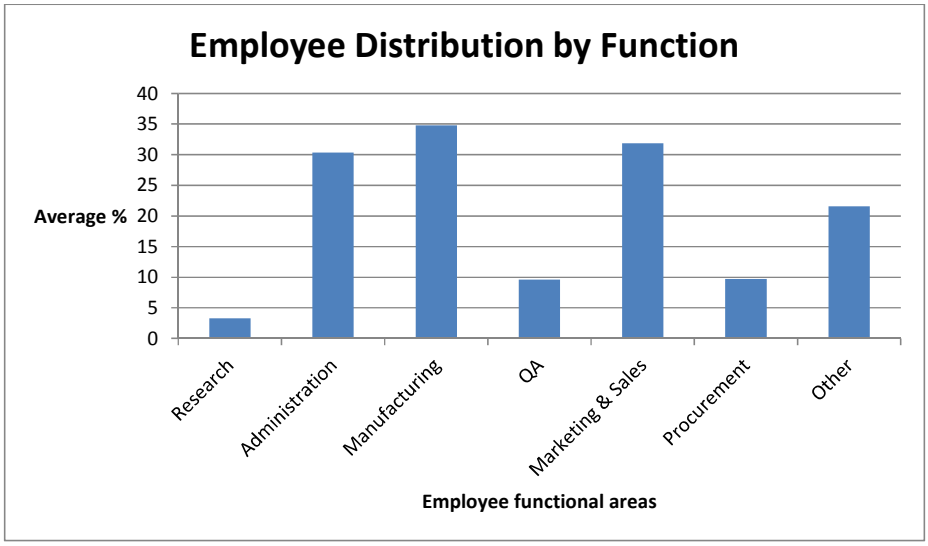
Figure 5: Full time employee distribution



Given the employee numbers presented in the figure above, the respondents' organizations can be termed 'micro', 'small', and 'medium' sized enterprises (SMMEs) according to the South African National Small Business Act of 1996.

The figure below summarizes the distribution of employees of the respondents by functional area. It can be seen from the figure that the level of employees assigned to Research and Development is very small when compared to other functional areas. Marketing and sales employee distribution is almost comparable to that of manufacturing staff. Although the respondents sample is not representative of the whole SADC pharmaceutical sector, this functional distribution which is weak in R&D staff level distribution with manufacturing staff levels of distribution almost being equalled by those in marketing and sales, almost confirms the structure of the SADC pharmaceutical sector which is characterised by the dominance of high import levels (requiring a high level of marketing and sales staff) as revealed in chapter 2 of this paper. The weak distribution levels of R&D staff points to a weak generic drug product development base in the industry which further weakens the manufacturing base of the sector as a constant pipeline of new generic products is required to keep manufacturing activity of the pharmaceutical value chain well oiled.

Figure 6: Employee distribution by function



Of the total respondents, 50% of the organizations were locally owned and the balance being foreign owned. The majority of the respondents (66.7%) did not have any foreign partners. The lack of foreign partners confines the business activities of the respondents to internally generated R&D in the case of manufacturers and internal financing with no outside equity partners. This scenario can weaken the ability of these businesses to compete nationally and regionally.

Table 16: Ownership, partnership & knowledge summary stats

Statistic	% Respondents (Yes)	% Respondents (No)
Locally owned	50	50
Foreign partners	33.3	66.7
Difference between regulatory & registration harmonization	100	0
Registration Harmonization an important agenda	91.7	8.3

All the respondents were aware of the differences between regulatory and registration harmonization (see section 1.3) and the majority of the respondents (91.7%) pointed out that medicines registration harmonization in the SADC was an important agenda because of the resultant streamlined registration process and its associated benefits. The respondent not viewing medicines registration harmonization in the SADC as an important agenda cited the long standing nature of this initiative with no visible results as their reason for the negative response. Most respondents were aware of the EU centralized procedure for medicines marketing authorization, the SADC and EAC medicines registration harmonization initiatives. Only 25% of the respondents were aware of the African Medicines Regulatory Harmonization initiative.

3.2 Opportunities For Stakeholders

The table below summarizes the opportunities identified by respondents which might arise as a result of medicines registration harmonization in the Southern African Development Community. Increased market access, streamlined marketing authorization/registration and faster access to medicines of public health value were perceived as the most valuable opportunities, each of these areas receiving a minimum percentage response of 90%. Other opportunity areas that received high respondent ratings can be seen in the table. The opportunity classified under other was a respondent's view that medicine registration harmonization will result in high pharmaceutical product quality in the region because of a strong and common regulatory framework.

A strong regulatory framework as a result of harmonization was perceived as an opportunity to reduce counterfeits. It was mentioned that the more the region develops a framework of medicines control, the lower the number of weak linkages that are most likely to act as sources of counterfeits. Some respondents indicated that increased competition will result in increased manufacturing efficiencies in the industry leading to lower prices. From a private sector perspective, a streamlined registration process will lead to faster to market opportunities.

In the breakaway session for manufacturers, technology sharing and standardization of essential medicines lists and standard treatment guidelines were identified as additional opportunities arising from regional medicines registration harmonization. It was also felt that pharmaceutical harmonization will also lead to a reduction in the number of GMP audits carried

Table 17: Pharma harmonization opportunities

Opportunity	% Respondents
Increased market access	100
Streamlined marketing authorization/registration process	100
Faster access to medicines of high public value (quality, efficacy, affordable and safe)	91.7
Increased competitiveness from newly developed common markets	75
More likely acceptance of local products for export to other countries	66.7
Reduction in the amount of human and animal experimentation due to the generation of only one set of data for all regions	66.7
Streamlined post-marketing authorization process	66.7
Reduction in registration fees	66.7
Elimination and/or reduction of substandard medicines	66.7
Other	8.3

out by different national medicines regulatory authorities for different markets, resulting in tremendous reduction in cost of compliance.

Import and export activities of respondents are summarized in the table below. It should be noted that the importing activity figure does not add up to 100% as a result of some non-responses. The table reveals that the majority of the respondents (58.7%) are importers with only 41.7 percent of respondents currently exporting pharmaceutical products. The level of exports as a percentage of sales ranged from a low of 1% to a high of 5%.

Table 18: Import & Export Activities

Activity	% All Respondents (Yes)	% All Respondents (No)
Exporting	41.7	58.3
Importing	58.3	25

Table 19 below gives a summary of the current export destinations of respondents who are currently exporting to the region. This export destination profile is similar to that cited in chapter

Table 19: Current SADC countries export destinations

Current Export SADC Country Destination	% Respondents
Botswana	25
Swaziland	25
Namibia	16.7
Zambia	16.7
Zimbabwe	16.7
Angola	8.3
Lesotho	8.3
Malawi	8.3
Mozambique	8.3
South Africa	8.3

2 of this paper. Only 8.3% of the respondents mentioned South Africa as an export destination despite the revelations in chapter 2 citing South Africa as the largest pharmaceutical market in the region. Tables 21 and 23 below will shade more light on this anomaly.

South Africa being the largest market and producer of pharmaceuticals in the Southern African Development Community emerged as the largest source of imports for pharmaceuticals with 58.3% of the respondents citing the country as their source of imports.

Table 20: Current SADC countries import sources

Current Import SADC Country Source	% Respondents
South Africa	58.3
Zimbabwe	8.3

Laborious registration requirements and long registration lead times were cited as the major barriers to pharmaceutical exports in the region by the respondents. High registration fees were not perceived to be a major hurdle to exports as only 25% of the respondents cited this area as a barrier to exports. Other barriers to exports cited by respondents include market specific requirements like packaging and labelling, laborious export procedures, inability to meet minimum GMP standards of the importing country and presence of unregulated markets in the region which are populated by a high level of cheap counterfeits and substandard products.

Table 21: Barriers to exports

Barrier to exports	% Respondents
Registration requirements laborious	66.7
Long registration lead times	50
Other	41.7
High registration fees	25

Market specific requirements such as packaging and labelling were seen as not viable given the low level of intra-SADC trading in pharmaceutical products.

Similarly to exports, laborious registration requirements and long registration lead times were seen as major hurdles to imports of pharmaceutical products. One respondent cited that it would appear that some regulatory authorities demand data that they have no capacity to evaluate and GMP inspection reports take too long to be made available. In contrast to export barriers, high registration fees were cited as a barrier to imports by 50% of the respondents versus 25% of the export respondents. The 'other' response generated a high level of response (41.7%) as a barrier to imports. This category included stringent registration requirements which are not commensurate with the level of business activity, high import permit fees which increase the cost of business and importation delays as a result of poor communication between customs and regulatory authorities.

Table 22: Imports barriers

Barrier to Imports	% Respondents
Registration requirements laborious	58.3
Long registration lead times	58.3
High registration fees	50
Other	33.3

With medicines registration harmonization in the region, respondents would like to export to the SADC member countries listed in the table below. It is not surprising that 50% of the respondents would like to export to South Africa given its position as the largest market for pharmaceuticals in the Southern African Development Community. Export market priorities were based on a number of factors including access to transport and proximity of the market to the exporter, the need to be present in all SADC member countries for key product areas and the sharing of common health problems and similarity of cultures.

Table 23: Target export SADC country destination

Target Export SADC Country Destination	% Respondents
South Africa	50
Zambia	50
Botswana	33.3
Malawi	25
Democratic Republic of Congo	25
Zimbabwe	25
Angola	16.7
Mozambique	16.7
Namibia	16.7
Swaziland	16.7
Tanzania	16.7
Swaziland	16.7
Mauritius	8.3
Madagascar	8.3

South Africa still remains as a preferred import source of pharmaceuticals with 33.3% of respondents revealing that they intend to source products from this country with the harmonization of medicines registration. The cited reasons for the choice of target import sources from the SADC region included low transport costs, South Africa as the number one source of pharmaceutical imports and the poor quality of products from other SADC member countries.

Table 24: Target imports SADC country sources

Target Import SADC Country Source	% Respondents
South Africa	33.3
Zambia	25
Botswana	8.3
Zimbabwe	8.3
Namibia	8.3

The section on the background of the respondents revealed that the responses received covered a diverse number of pharmaceutical activities (manufacturing, wholesaling, marketing &

sales etc) in a balanced manner and all respondents were of the idea that medicines registration harmonization in the SADC was an important agenda. The results of the stakeholders' analysis with regards to opportunities arising from medicines registration harmonization point to a picture of a common end result for all stakeholders (manufacturers, distributors, marketers) of pharmaceutical harmonization. This is illustrated in table 17 by the common opportunities responses amongst all stakeholders.

3.3 Threats To Stakeholders

In this section, stakeholders' responses on the possible threats posed by medicines registration harmonization in the Southern African Development Community and their possible actions to counter any threats are discussed. 58% of the respondents are of the opinion that medicines registration harmonization would be a threat. The balance of the respondents, 42% were not of the opinion that pharmaceutical harmonization in the region will be a threat as a result in the flooding of local markets with non-SADC imports. Increase in substandard and counterfeit products was seen a threat to arising from medicines registration harmonization. This in direct contrast to the responses outlined in section 4.2 on opportunities, which showed that 66.7% of the respondents thought that pharma harmonization will result in the elimination and/or reduction of substandard products.

One respondent indicated that big Asian generic pharma companies have brought in headaches for large regulatory agencies like the FDA through falsifying of data and manufacturing in unapproved facilities through misrepresentation after successful pre-approval inspection at different facilities. This would invariably cause more problems for small regulatory authorities in the region in the face of pharmaceutical harmonization and therefore result in substandard and/or counterfeit products being shipped into the region.

16.7% of the respondents did not consider the harmonization of medicines registration as posing any threats. The respondents thought that threats can be avoided with adequate registration standards and proper systems with monitoring and control mechanisms. Loss of revenues by national medicines regulatory authorities was seen as a threat resulting from pharma harmonization by one respondent.

Table 25: Threats to pharma harmonization

Threat	% Respondents

Flooding of local markets with non-SADC imports	58.3
Increase in counterfeit products	41.7
Increase in substandard products	25
None	16.7
Other	8.3

For those respondents who cited threats from medicines registration harmonization, the following table summarizes actions such respondents will take in order to mitigate against these threats. Developing and/or registering new products (innovation) faster, improving manufacturing efficiencies, increasing skills base and exports to other countries were cited as the most probable actions by the respondents.

Table 26: Respondents actions to increased competition

Comment [A2]: Here we are merely tabling results of the survey, your question would need to be answered by the respondents through a separate survey

Mechanism to counter increased competition	% Respondents
Develop/register new products at a faster rate	50
Improve manufacturing efficiencies	50
Increase skills base	50
Increase exports into other countries	41.7
Other	25
None	16.7

Respondents noted that improved skills and manufacturing efficiencies were key to success in the pharma manufacturing industry. Companies should embark on faster product development and transform themselves in order to be able to compete globally as intervention and protection from governments was short lived. Increased competition was not seen as an outcome of medicines registration by others as pharma harmonization will result in a broader product and market space for all players leading to a wider product choice and reduction in prices for the patient.

Tables 27 and 28 below summarize respondents' views on perceived negative and positive effects of pharmaceutical regulatory harmonization in the region. These are centred on the areas of employment, local investment and skills. The manufacturing respondents citing decrease in employment levels, local investment and skills flight as a negative consequence of pharmaceutical regulatory harmonization are only in the magnitude of 16.7%. One respondent cited the consolidation of manufacturing activities in one country as a result of loss of business

arising from harmonization with the resultant closures and loss of employment. Others revealed that there would be no negative effects on manufacturers as competition arising from pharmaceutical regulatory harmonization will lead to improved efficiencies, improved quality standards and reduction in costs.

Table 27: Manufacturers' perceived negative effects of pharma harmonization

Manufacturer perceived negative effects	% Respondents
Decrease in employment levels	16.7
Decrease in levels of local investment	16.7
Skills flight	16.7
None	8.3
Other	8.3

Importers noted that pharmaceutical harmonization in the region will lead into an increase in the level of investment and skill development in the region with some increase in employment levels. Generally, it was felt that pharmaceutical regulatory harmonization in the Southern African Development Community will benefit all participating member countries through skills development necessitated by the need to bring industry to a certain level of competency. Other cited positive effects of pharmaceutical harmonization were increase in profits and the variety of products on the regional pharmaceutical market, faster responses to local demand, improved local manufacturing capabilities and better service levels.

Table 28: Importers' perceived positives effects of pharma harmonization

Importer perceived positive effects	% Respondents
Increase in levels of local investment	41.7
Skills development	41.7
Increase in employment levels	25
Other	16.7

3.4 Challenges To Medicines Registration Harmonization

In this section we look at challenges to medicines registration harmonization in the SADC region. It is important to note the differences between a challenge and a threat. Challenge is

experienced when there is an opportunity for redemption with available coping strategies, whereas threat is experienced when the situation is perceived as leading to failure with no available strategies to cope with it.

Table 29 below summarizes respondents' views on the perceived challenges posed by pharmaceutical regulatory harmonization in the region. The major challenge cited with a 91.7% response rate was the lack of political will with the associated sovereignty issues and loss of regulatory autonomy. This was followed by the possibility of the region not being able to fund and sustain the harmonization project with a 75% response rate, with the lack of parity in existing regulatory capacity in SADC member countries coming in third with a 66.7% response.

Table 29: Challenges to pharma regulatory harmonization

Challenges to pharma harmonization	% Respondents
Lack of political will, associated sovereignty issues & loss regulatory autonomy	91.7
Lack of financial resources	75
Lack of parity in existing regulatory capacity in SADC member countries	66.7
Disparate intellectual property laws in the SADC member countries with no provisions for use of TRIPS flexibilities	50
Conflicting interest of importing wholesalers and manufacturers	50
Low socioeconomic development in SADC member states	33.3
Other	16.7

Disparate intellectual property laws with no provisions for the use of TRIPs flexibilities and conflicting interests of importing wholesalers and manufacturers gather a 50% response rate each as possible challenges to pharmaceutical regulatory harmonization in the region. Other cited challenges were protectionist measures by some member states and the lack of understanding of the pharmaceutical regulatory harmonization process.

With regards to the need to balance the conflicting interest of importing wholesalers/distributors and manufacturers, the following issues were raised by respondents:

- Make use of negative import lists based on products commonly manufactured locally. During a breakaway session at the SAGMA workshop on pharma harmonization, the manufacturing group felt that this was a retrogressive protectionist intervention as it can result in a zero sum game as other SADC member countries institute such a measure in favour of their local pharma manufacturing companies.

- Make use of preferential clauses in pharma harmonization process where local manufacturers would be received some form of registration prioritization.
- Discourage importation of locally manufactured products by raising tariffs on such products.
- Help manufacturers to reduce costs and increase capacity to produce cheaper medicines.
- Educate both players on the need to balance business interests and community interests.
- Involvement of both parties in the harmonization process, emphasizing the need to form strategic partnerships to strengthen the regional pharmaceutical value chain.
- Preferences for local manufacturers on local tenders
- A level playing field in all member states should be created; currently some member countries levy duties and taxes on raw material inputs for manufacturing with no such levies on finished pharmaceutical products.
- Financial incentives on research and development
- Financial incentives on pharmaceutical facility upgrades and greenfield projects
- Other acceptable incentives

Some respondents felt that there were no conflicting interest between importing wholesalers/distributors as pharmaceutical harmonization in the region will result in a common goal of increased access and a wider range of products and markets for the benefit of all stakeholders. Others felt that pharmaceutical product imports reduce price abuses by local manufacturers.

Study respondents cited the following as possible interventions to improve political will and by in for medicines registration harmonization in the SADC region:

- Make use of evidence based lobbying (see 6.2.6 on the South African ARV tender motivation for preference for local manufacturers).
- Promote the benefits of pharma harmonization based on patient priority, increased access, time and cost savings etc
- Promote concept of self-reliance
- Promote concept of economic and industrial development
- Involve politicians right from project inception

With respect to different regulatory capacity levels within SADC member countries as a challenge to pharmaceutical harmonization, respondents pointed the following as possible solutions:

- Member countries should work towards the achievement of an acceptable regulatory standard within a specified time period.
- Embark on centralized training programmes and institutionalize training in all NMRAs.
- Work on a progressive approach to pharmaceutical harmonization with set qualifying criteria and starting with ready member countries adding more as they meet the set criteria.
- Fund NMRAs technical support and training
- NMRAs to share and exchange experiences

Intellectual property laws in SADC member countries are quite disparate and non-supportive to regional medicines regulatory harmonization. The following solutions were respondents' contribution towards resolving such non-supportive IP laws:

- Overhaul of intellectual property laws in the Southern African Development Community in order to stimulate pharmaceutical production and regional pharmaceutical harmonization initiatives.
- Increased transparency and harmonization of IP legislation.
- Use of TRIPs flexibilities by all member countries after overhaul of IP laws.

3.5 Suggested Road Map To Medicines Registration Harmonization

Pharmaceutical harmonization is a process which does not happen overnight. Case studies developed in chapter 5 of this paper will make testimony of this. The Southern African Development Community is a regional organization with peculiar fundamentals not similar to those of regional economic communities cited in chapter 5 case studies. Although lessons from these case studies will be of great value to SADC member countries, private sector stakeholders were tasked to suggest a road map to medicines registration harmonization in the region based on their experiences and knowledge of harmonization processes. Table 30 below summarizes the respondents' views on the pharmaceutical harmonization process.

The table gives guidance on the options/steps available for pharma harmonization which respondents were asked to use in building a road map for the SADC initiative.

Table 30: Pharma regulatory harmonization suggested road map/steps

Harmonization road map option/steps	% Respondents
Strengthening the technical & administrative capacity of participating NMRAs	75
Harmonizing technical requirements for regulation of medicines	75
Stepwise approach starting with a few countries with a reasonable parity of regulatory capacity (gradual & carefully balanced harmonization)	58.3
Development of information management systems & promotion of the exchange of information	58.3
Establishing a framework for joint evaluations of application dossiers & inspection of medicines manufacturing sites	50
Limiting the scope of harmonization project to generic applications in early stages	41.7
Centralized procedure with a permanent secretariat in one country	25
Decentralized procedure	25
Centralized procedure with a rotating secretariat in different countries	16.7
Establishment of a steering committee of representatives of participating member countries to give oversight & act as a coordinating body	16.7
Centralized procedure with rotating national staff in terms of time-limited secondment	8.3
Other	0

Five areas received a response rate of at least 50% according to results tabulated in table 30. These steps in order of highest response rate (with some equally rated) are as follows:

- Strengthening the technical & administrative capacity of participating NMRAs.
- Harmonizing technical requirements for regulation of medicines.
- Stepwise approach starting with a few countries with a reasonable parity of regulatory capacity
- Development of information management systems & promotion of the exchange of information
- Establishment of a framework of joint evaluations of application dossiers & inspection of medicines manufacturing sites.

The above steps form the pillars of any sound pharmaceutical harmonization process and it is commended that the respondents are quite knowledgeable in the subject matter. The other area which received a high response rate was that of limiting the product scope of the harmonization initiative to a specific class of pharmaceutical namely generics. Case studies presented in chapter 5 show that the two pharmaceutical harmonization models namely the centralized and decentralized procedures tend to have different product class scope.

Respondents were however unfamiliar with the actual harmonization model after having identified the key pillars identified above. Pharmaceutical harmonization initiatives are a hybrid of both the centralized and decentralized procedures (see case studies in section 5). Some respondents felt that these models where mutually exclusive. The centralized procedure can take many variants as exemplified in table 30 above and the response rates received seem to indicate ignorance on this.

Respondents noted that the SADC medicines registration harmonization project should be time bound with everyone working towards set targets and deadlines. It was also noted that open communication to all stakeholders was of paramount importance during project implementation.

Chapter 4: Case Studies

In this chapter we present case studies of successful regulatory harmonization initiatives together with those that are in progress and have so far resulted in some success in the process. We have chosen the Association of South East Asian Nations (ASEAN), the Gulf Co-operation Council (GCC) and the European Union as our examples as they represent diverse economies with different levels of development and hence offer some insight into challenges arising from such differences.

4.1 Association Of South East Asian Nations (ASEAN)

The Association of Southeast Asia was established on 8th August 1967 when the founding countries of Indonesia, Malaysia, Philippines, Singapore and Thailand signed the Bangkok Declaration. (30)

The Bangkok declaration states that the aims and purposes of the Association shall be, amongst others, to accelerate the economic growth of the region, to promote regional peace and stability, to promote active collaboration and mutual assistance on matters of common interest in the economic, social, cultural, technical, scientific and administrative fields.

After its independence Brunei Darussalam acceded to ASEAN on the 8th of January, 1984, becoming the sixth member of ASEAN. The first six countries are often called the ASEAN-6.

Vietnam became a member on the 28th of July, 1995, followed by Laos and Myanmar, which acceded to the Association on 23rd July. 1997. Cambodia was the last of the ten member association to join by acceding on the 30th of April, 1999. The last four members to join are usually referred to as the CLMV group. Even though they had to accept all agreements of ASEAN at the time of accession, they got prolonged timeframes to reach the set targets[9].

ASEAN covers a land area of 4.46 million km², which is 3% of the total land area of Earth, and has a population of approximately 600 million people. The sea area of ASEAN is about three times larger than its land counterpart. In 2010, its combined nominal GDP had grown to US$1.8 trillion.[10] If ASEAN were a single entity, it would rank as the ninth largest economy in the world.

[9] www.asean.org

ASEAN now has Dialogue Partners from all corners of the world: Australia, Canada, China, the EU, India, Japan, South Korea, New Zealand, Russia, the United States and the United Nations.

ASEAN Secretariat

The ASEAN Secretariat was established on the 24th of February, 1976, by the ASEAN foreign ministers and has its legal basis in the Agreement on the Establishment of the ASEAN Secretariat, 1976 which has been constantly amended.

The Secretariat is located in Jakarta, Indonesia and consists of a professional staff of around 100 members. The Secretariat is headed by Secretary-General of ASEAN, who is appointed on merit and accorded ministerial status. The Secretary-General of ASEAN has a five-year term and is mandated to initiate, advise, coordinate, helps effective decision making within the ASEAN bodies, monitors work plans and implements ASEAN activities. This includes participation to the heads of Government Meetings, ASEAN Ministerial Meetings, attend or dedicate a representative at all ASEAN committees. He acts as the channel for formal communications between, ASEAN permanent committees, ad hoc committees, experts groups, and other ASEAN bodies as well as international organizations and governments.

In addition to its usual function of servicing meetings and conferences, and helping to facilitate coordination and monitoring of ASEAN activities, the ASEAN Secretariat also started a modest publishing program aimed at keeping everyone involved in ASEAN abreast of developments in the Association.

ASEAN Free Trade Area (AFTA)

The ASEAN Heads of State and Government decided to establish an ASEAN Free Trade Area or AFTA in 1992. The objective of AFTA is to increase the ASEAN region's competitive advantage as a production base geared for the world market. A vital step in this direction is the liberalization of trade through the elimination of tariffs and non-tariff barriers among the ASEAN members. This activity has begun to serve as a catalyst for greater efficiency in production and long-term competitiveness. Moreover, the expansion of intra-regional trade is giving the ASEAN consumers wider choice and better quality consumer products.

Background of the ACCSQ

In 1992 the ASEAN Consultative Committee for Standards and Quality (ACCSQ) was formed to facilitate and complement the ASEAN Free Trade Area (AFTA). ACCSQ's agenda was as follows:

- Facilitation of the realization of the ASEAN economic community.
- Establish Working Groups and Product Working Groups.
- Cooperation with dialogue partners and other organizations on standards and conformance.
- ASEAN Free Trade Agreement negotiations.

ASEAN regulatory bodies were authorized to achieve the mandate of eliminating technical barriers to trade in 1997. Efforts to harmonize regulatory requirements amongst ASEAN were initiated through the ACCSQ in 1998 culminating in the presentation by Malaysia of the concept of ASEAN pharmaceutical harmonization which was agreed upon by the Senior Economic Officials Meeting (SEOM).

Pharmaceutical Product Working Group (PPWG)

Efforts toward harmonization of ASEAN pharmaceutical regulations were initiated in 1992 through the ASEAN Consultative Committee for Standards and Quality (ACCSQ). The 13th Meeting of the ACCSQ held in March 1999 in Manila, agreed that a Product Working Group on Pharmaceuticals (PPWG) be set up, with Malaysia as the lead country. This led to the formation of ACCSQ-PPWG in September 1999 in Kuala Lumpur, Malaysia.[10]

The case study will focus on the activities of the ASEAN Consultative Committee for Standards and Quality's Product Working Group on Pharmaceuticals (ACCSQ-PPWG) which is primarily responsible for spearheading the harmonization of pharmaceutical regulatory processes in the ASEAN region.

Objective and Activities of the ACCSQ-PPWG

The objective of the ACCSQ-PPWG is to develop harmonization schemes of pharmaceuticals' regulations of the ASEAN member countries to complement and facilitate the objective of ASEAN Free Trade Area (AFTA), particularly, the elimination of technical barriers to trade posed by these regulations, without compromising on drug quality, safety and efficacy. Below is the scope of its activities:

- Exchange of information on the existing pharmaceutical requirements and regulations implemented by each ASEAN member countries;
- Review and preparation of comparative study of the requirements and regulations;

[10] www.asean.org

- Study of harmonized procedures and regulatory system currently implemented in others regions on pharmaceutical trade;
- Development of harmonization of technical procedures and requirements, including appropriate MRAs (full harmonization equivalence of conformance, equivalence of results and/or acceptance of test procedures) applicable to the ASEAN pharmaceutical industry, taking into account other regional and international developments on pharmaceuticals

Summary of Achievements and Meeting Updates of the early meetings

The Meetings were attended by delegates and observers from all the ASEAN member countries, comprising of both regulatory and industry representatives. A staff of the ASEAN Secretariat and a representative from the World Health Organisation (WHO) were also in attendance.

First Meeting 6-7 September, 1999 in Kuala Lumpur, Malaysia

The First Meeting of the ACCSQ P-PWG held on 6 - 7 September 1999 in Kuala Lumpur, Malaysia deliberated on various key issues including the terms of reference and proposed work-plan. The meeting also provided an update on the progress in implementation of the Common Effective Preferential Tariff (CEPT) Scheme for ASEAN Free Trade Area (AFTA) and important features of the pharmaceutical sector towards of AFTA.

Second Meeting 5-6 March, 2000 in Bangkok, Thailand

The Second Meeting which was held on 5 - 6 March 2000 in Bangkok, Thailand discussed study reports of various core activities and also highlighted other important issues as Trend of Pharmaceutical Harmonization: WHO and ICH, Report on the APEC Workshops on the Food/Drug Interface and overview of the ASEAN Working Group on Technical Co-operation in Pharmaceuticals. Formation of Ad-hoc Committees on Quality, safety (Pre-clinical Study), Efficacy (Clinical Data) and Administrative Data were proposed with the respective lead countries Indonesia, Philippines, Thailand and Malaysia.

Third Meeting 6-7 February, 2001 in Ho Chi Minh City, Vietnam

The meeting focused on plenary sessions of Ad-Hoc Committees, as well drafting of ASEAN Common Technical Requirements (ACTRs). Deliberations were held on scientific and technical aspects of medicines registration i.e. pharmaceutics quality, pharmacological/toxicological data-safety, clinical data-efficacy and administrative data and product information.

Of note is that the Meeting noted with satisfaction the presence of representatives of the business sectors as part of delegations of some countries.[11]

Fourth Meeting 28-29 September, 2001 in Bali, Indonesia

The fourth meeting saw the PPWG focusing on the following:

- Consideration of the ACTR and ASEAN Common Technical Dossier (ACTD) on Administrative data and product information.
- Consideration of the ACTR and ACTD on Quality
- Consideration of the ACTR and ACTD on Safety
- Consideration of the ACTR and ACTD on Efficacy
- Consideration of ASEAN glossary
- Revision of the work programme of ACCSQ-PPWG

Fifth Meeting 25-27 February, 2002 in Yangon, Myanmar

The fifth meeting saw the PPWG focusing on the following:

- Consideration and confirmation of guidelines on ACTR- Quality, Safety (non-clinical study), Efficacy (clinical data) and Administrative data and product information.
- Consideration of the first draft of overall ACTD's organization
- Adoption of ACTR and first draft of ACTD together with the proposed ASEAN guidelines
- Adoption of draft ASEAN glossary
- Consideration of implementation issues of ACTD
- Cooperation with international organizations and dialogue partners
- Revision of the work programme of ACCSQ-PPWG

7th Sixth Meeting 4-6 September, 2002 in Siem Reap, Cambodia

The meeting was preceded by the Technical Meeting of PPWG on product information and stability. It focused on the following:

- Adoption of final draft of ASEAN glossary
- Adoption of the final drafts of ACTRs, ACTD on safety, efficacy and administrative data and product information
- Consideration of ACTD's organization and proposal to compare it with ICH CTD

[11] http://www.tcvn.gov.vn/en/about_stameq/cooperation/asean/p_pwg.htm

- Agreement of first draft of working guidelines namely :
  - -Draft Guidelines on Stability Studies-Indonesia
  - -Draft Guidelines on Analytical Validation-Thailand
  - -Draft Guidelines on Process Validation-Singapore
  - -Draft Guidelines on Bioavailability and Bioequivalence (BA/BE) Studies
- Formation of Implementation Working group (IWG) – comprising of the following members ; Singapore as Chair , Indonesia as Co-chair, Malaysia, Philippines and Thailand - in view of the implementation of the ACTD in 2003
- Cooperation with international organizations and dialogue partners : (i) WHO-ASEAN Harmonization project, (ii) ACCSQ-US Cooperation – with three PPWG project proposals ;(i) Developing the Guidelines on Quality, (ii) Training on Clinical Data and(iii) Developing and Implementing the "Guideline & Implementation SOP" of an ASEAN Bridging Study Requirement
- Revision of the work programme of ACCSQ-PPWG which has been expanded to cover the new goals: Implementation of the harmonized ASEAN Documents and looking into the possible "Sectoral MRA".

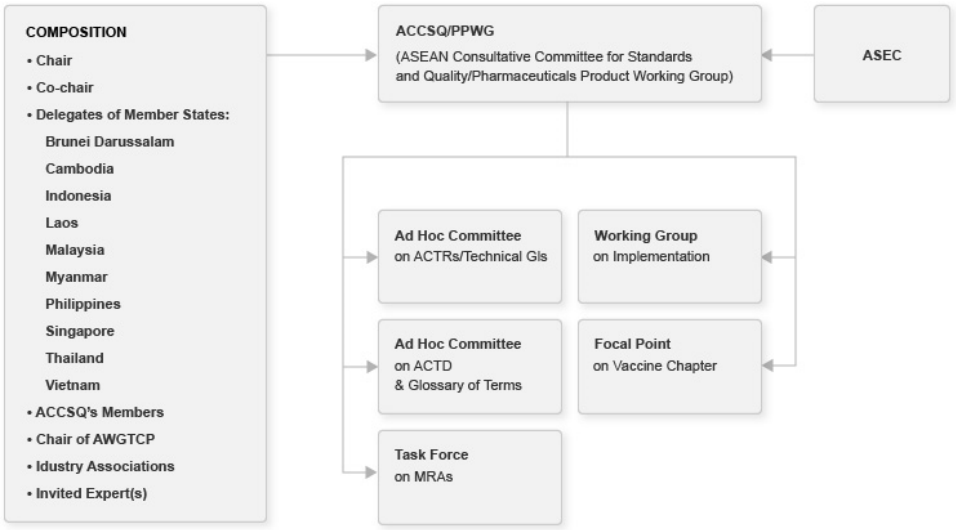
Overall, the ACCSQ-PPWG has made considerable progress over the years, despite limitations in the existing capability and capacity of the Regulatory Authorities of ASEAN member countries. Due to varying readiness expressed by some member countries to conform to the harmonized requirements a transition period of two years is provided.

Comment [A3]: We do not have any information on industry support, if one had carried out personal visits and interviews with the respective authorities, may be one would have come up with any other support initiatives.

ASEAN PPWG Organisation[12]

Figure 7 below gives the organizational structure of the ASEAN PPWG.

Figure 7: ASEAN PPWG Organization



ASEC = ASEAN Secretariat; **ACTRs** = ASEAN Common Technical Requirements; **ACTD** = ASEAN Common Technical Dossier; **AWGTCP** = ASEAN Working Group on Technical Cooperation in Pharmaceuticals

Norms and procedures[13]

The PPWG is governed by written norms and procedures relating to the organisation and conduct of PPWG meetings. PPWG meetings, which are held at least once a year, are convened by the Chair of the PPWG, and in the absence of the Chair, by the Co-Chair. With the approval of the Chair and Co-Chair, any member of the PPWG can request a meeting. Members are given at least 3 months advance notice of meetings, with confirmation on the scheduling of the next "regular" meeting of the PPWG taking place at the end of each meeting. All decisions taken by the PPWG are reached by consensus agreement of the PPWG's members. The PPWG reports its recommendations and proceedings to the ACCSQ.

[12] http://www.ich.org/about/organisation-of-ich/coopgroup/asean/organisation.html

Harmonisation process[14]

The PPWG works to harmonise, and if necessary, develop common technical documents and requirements which are appropriate and applicable to the ASEAN region, with a view to achieving alignment with international technical documents and requirements.

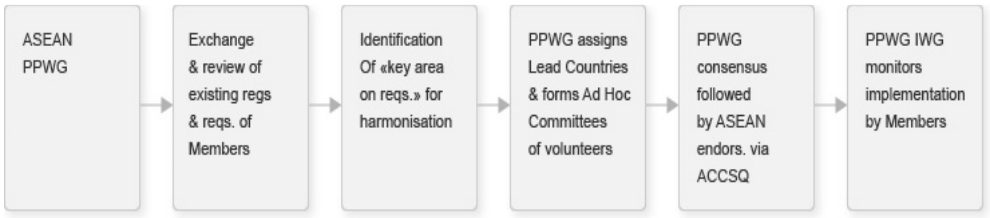
When considering the development/adoption of ASEAN guidelines, the PPWG considers existing guidelines including those of ICH, WHO and other national regulatory authorities (e.g. USFDA and EMEA non EMA).

The PPWG process of harmonisation is initiated with an exchange and review of information on the existing pharmaceutical requirements and regulations of the Member States. This is followed by a comparative study of the requirements and regulations, and the identification of the "key area on requirements" for harmonisation.

A Lead county is assigned, and an Ad Hoc Committee established to prepare the draft "harmonised product", which may be a guideline or a recommendation on an international guideline. The draft is then circulated to all Member States for comments. The resulting comments are consolidated into a revised draft "harmonised product" which is then submitted to the PPWG for discussion and a decision at the next PPWG meeting.

Once a consensus agreement on the “harmonized product” is reached by the PPWG, endorsement is sought via the ACCSQ from the higher bodies within ASEAN. Implementation by the Member States of the 'harmonised product' is compulsory, and is supported / facilitated by an Implementation Working Group (IWG), which is under the PPWG.

Figure 8: PPWG Decision making process



[14] http://www.ich.org/about/organisation-of-ich/coopgroup/asean/operating-procedures-and-processes.html

PPWG Communications

Final adopted documents and information on the activities of the PPWG can be found the ASEAN website (www.aseansec.org) which is available in English. Information is also communicated to stakeholders through meetings with patient organisations, healthcare professionals, industry associations, individual companies and media. Workshops may also be held on specific topics, and presentations made in national and international congress or conferences.

PPWG Participation (31)

The participants to the PPWG are representatives from the ASEAN Secretariat, representatives from national health authorities and any ACCSQ member wishing to participate. The first PPWGs were not open to foreigners or industry. As of 2001 members from international organisations like the WHO and ICH are invited to hold presentations and to participate in working sessions. Most PPWG plenary sessions are now open to invited guests and observers from local industry associations. There around three hundred (300) participants at each PPWG meeting.

During the PPWG meetings industry usually raises their voice through representatives from local trade associations that are in dialogue with Health Authority delegates. Lately dialogue between health authority and industry is channeled via two 'regional' trade associations to the PPWG. These are the ASEAN Pharmaceutical Club (APC), composed of members from local generic trade associations and the ASEAN Pharmaceutical Research Industry Associations (APRIA), mainly with representatives of multinational companies situated in ASEAN. It has been decided that these regional industry associations shall submit position papers 3 months prior the PPWG meetings to the PPWG Chair[15]

PPWG Training

The PPWG organises on-going training to increase understanding of the ASEAN harmonised product and the ASEAN technical guidelines. Seminars are also organised on quality issues and on relevant ICH guidelines. While the PPWG organises many training activities back-to-back with PPWG meetings, training activities are also co-developed with or developed by external organisations and some ASEAN Dialogue Partners, who may also sponsor the activities.

[15] 12th PPWG Meeting (2006).

Individual Member States also organise and sponsor training activities. In general, training activities are open to all sectors including the government and industry. For some training activities a registration fee may apply, and for sponsored events restrictions may apply to the number of participants per Member State.

PPWG Sources of Funding

The PPWG operates through self-sponsorship, with each Member State responsible for its own funding to either attend or host PPWG meetings. Discretional amounts may also be received from International Organisations, such as WHO, which in the past supported a special project relevant to the PPWG's work programme.

Progress to date, ASEAN ACTD and ACTR (10)

The same regulatory requirements apply for the registration of a medicinal product among the ASEAN member countries. To facilitate this, the PPWG developed the ASEAN Glossary of terms, the ASEAN Common Technical Dossier (ACTD), the ASEAN Common Technical Requirements (ACTR) and its guidelines.

The **ACTD** gives information on the format and structure of the dossier that shall be commonly used for applications in the ASEAN region. The ACTD serves as a locator for documentation that has been compiled for a marketing authorization application. It does not give any recommendations on the actual content of the dossier. The ACTD is similar to the European Notice to Applicants Volume 2B Presentation and Format of the Dossier (EU-CTD).

The ACTD organization and its structure were adopted at the 7th PPWG Meeting in 2003. After a trial period which started in 2003, it was agreed that the ACTD shall be implemented by all ASEAN member countries originally by 31 December 2006. The due date for implementation was postponed to 31 December 2008 in order to allow member countries to transpose ACTD requirements into their local regulations. During the transition period 2003-2008, the following dossier formats were optional to use, either national dossier format or the ICH-CTD format.

The **ACTR** is a set of written material intended to guide applicants to prepare an application in a way that is consistent with the expectations of all ASEAN Drug Regulatory Authorities. It is guidance for the preparation of the ACTD and has been divided into three areas namely quality, efficacy and safety. It can be compared to the EU Notice to Applicants (NTA) Volume 2C.

The **ACTD check-lists** give recommendations to which extent documentation has to be provided for the different product classifications. The different ASEAN product classifications are namely New Chemical Entity, Biotechnology derived products, Major/Minor Variations or Generic Products. It is envisaged that a product category will be assigned for products with a high impact on public health. These will require fast access to the ASEAN markets.

A **Question and Answers** (Q&A) document for the ACTD quality has been established and is updated on a regular basis by the relevant expert working group. Further Q&A documents are in progress for the other parts of the dossier.

The **ACTD Glossary** of terms is valid for the ACTD and ACTR and helps to have a common understanding when working in different expert working groups. The PPWG agreed that the ASEAN glossary be based on regional definitions and international guidelines. The different ASEAN member countries realised that different terms were used by different organizations, e.g. WHO, ICH. The PPWG therefore created the ASEAN glossary which was adopted in 2002.

The table below summarizes the transition and implementation dates of the ACTD and the ACTR.

Table 31: Transition and implementation dates of the ACTD and ACTR

Countries	Start of transition period	National due dates for implementation
Singapore	April 2004	Dec 2005
Malaysia	July 2003	Dec 2005
Thailand	June 2004	Dec 2007
Indonesia	2005	Dec 2007
Vietnam	Not determined	Dec 2007
Philippines	Jan 2005	Dec 2008
Brunel Darussalam	April 2006	Dec 2008
Cambodia	Not determined	Dec 2008
Lao PDR	Not determined	Dec 2008
Myanmar	Not determined	Dec 2008

By 2009, the ACTD had been fully implemented.

There are four ASEAN specific ACTR-quality guidelines and several other international guidelines that have been adopted as reference guidelines to be followed when planning a submission. These are discussed below.

Progress to date, ASEAN Quality Guidelines (10)

The majority of pharmaceutical products reviewed by ASEAN Drug Regulatory Authorities are generics. For generic applications, the quality part of the ACTD (Part II) is of importance as the non-clinical (Part III) and the clinical (Part IV) do not need to be submitted. With this I mind, the PPWG reviewed available international guidelines and determined which ones were applicable to the ASEAN member countries. Four ASEAN ACTR Quality Guidelines were developed to set standards and provide for guidance especially for the local generic manufacturers. Existing international guidelines were more or less transposed into simplified ASEAN guidelines with the exception of the ASEAN stability guideline.

The ACTD and ACTR clearly indicate that for NCE and Biotechnology products, the ICH reference guidelines should be followed. For generics and variations, the respective ASEAN guidelines apply. The following table summarizes the list of quality guidelines and the respective adoption year.

Table 32: ASEAN Quality guidelines and years of adoption

Quality Guideline	Year of Adoption
Analytical Validation	2003
Process Validation	2003
BA/BE Studies	2004
Stability Studies	2004

The ASEAN stability guideline sets adequate quality standards for hot and humid conditions (Zone IV/IVb) of the region and goes beyond ICH requirements. This guideline must be followed for all product classifications NCE, Biotech, generics and variations.

ASEAN adopted all WHO guidelines for quality, the existing pharmacopoeias of the UK, USA and 12 ICH guidelines namely Q1A, Q1B, Q2A, Q2B, Q3A, Q3C, Q5A, Q5B, Q5C, Q5D, Q6A and Q6B.

Progress to date, Reference Guidelines for Safety and Efficacy (10)

ASEAN documentation for safety and efficacy are not required for generic product registrations, minor variations and some major variations. Usually, only non-clinical and clinical overviews and summarised need to be submitted for NCE, biotechnology products and major variations if the originator products are already registered and approved for marketing authorization in a reference country.

ACTR Safety:

The following ICH guidelines have been adopted by the PPWG, and thereby been defined as applicable ACTR Safety Guidelines for the ASEAN region. These are S1A, S1B, S1C & S1C(R), S2A, S2B, S3B, S4, S4A, S5A, S5B (M), S6, S7A and M3.

ACTR Efficacy

After long debates, the PPWG came to the following decision regarding the ACTR Efficacy Guidelines, some ICH guidelines were adopted, others declared as reference only and two were not adopted.

Adopted as ACTR Efficacy Guidelines, were the following ICH guidelines, E1, E2A, E2C, E3, E4, E6, E7, E8, E9, E10 and E11.

Accepted as Reference Guidelines were E2C(A), E2D, E2E and E12A. This means that each ASEAN member country may refer to these guidelines as reference, but there is no obligation to implement them into national guidelines.

The two ICH efficacy guidelines E5(R1) and E2B(R3) were not adopted and there is no obligation to implement these in the national member states.

Progress to date, Mutual Recognition Agreements (10)

A new initiative in the ASEAN pharmaceutical harmonization project is the implementation of Mutual Recognition Agreements (MRA). The PPWG identified that mutual recognition of marketing authorizations is only possible once the ACTR and ACTD have been fully implemented in all Member States.

The identified areas for MRA are:

1. **MRA on the Post-Marketing Alert System (PMA)** has been set up. Its objective is to establish an efficient and effective system of alert on post-marketing issues affecting the safety and quality of pharmaceutical products. After a trial phase between Singapore and Malaysia since December 2005 its acceptability, the PMA has been compulsory for all ASEAN member countries since then.
2. **MRA on Good Manufacturing Practice (GMP) Inspections:** The signing of the ASEAN Sectoral Mutual Recognition Agreement (MRA) for Good Manufacturing Practice Inspection of Manufacturers of Medicinal Products was done in 2009.
3. **MRA on Bioavailability and Bioequivalence:** A task force to follow-up on the implementation of the BA/BE was established with Indonesia and Singapore as co-chairs. The main issues to be addressed by the task force hinge on the selection of comparator products for bioequivalence studies. There being a number of different variants of innovator products in the region, the task force saw the need to establish one common list of comparators valid for the whole region. Further it was agreed to encourage member countries to accept BE studies conducted by recognized BE centres in the region, in order to reduce unnecessary repetition of BE studies and transaction costs for the industry.

Summary

The PPWG is one of the longest standing in the region since its formation in 1999. It has covered much ground and made significant achievements to bring about the integration of the pharmaceutical sector through the harmonisation of technical requirements for pharmaceutical products in the ASEAN region. However, mutual recognition agreements on marketing authorizations, still remains to be achieved.

PHARMACEUTICAL MARKET AND TRADE

Below we summarize the salient features of the ASEAN pharmaceutical market and also give the details of trade in pharmaceutical products in the ASEAN member countries. The extent of intra-ASEAN trade in pharmaceuticals will give an indication of the benefits of the ASEAN pharmaceutical harmonization project. Does pharmaceutical harmonization lead to access of essential medicines from all sources of supply and/or does it encourage local production together with improved intra-ASEAN trading in pharmaceuticals?

Pharmaceutical Market

In the South East Asia region, pharmaceutical trends and developments vary from one market to another. Despite the negative impact of the global recession, eight markets of the region namely Indonesia, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand and Vietnam had a pharmaceutical market value of US$23.1 billion in 2009 and were expected to continue to grow. South Korea and Taiwan are not members of ASEAN. Indonesia, Thailand and the Philippines are fairly large emergent pharmaceutical markets, with large populations and steadily growing economies. Malaysia and Vietnam are small pharmaceutical markets typified by rapid economic growth, increasing foreign investment and support from national government. These five markets have significant over the counter (OTC) sectors and rapidly expanding generic sectors, and present previously untapped populations for potential foreign pharmaceutical companies. (32)

All ASEAN member countries are net importers of pharmaceuticals. With the exception of Brunei and Singapore, most have a pharmaceutical industry that remains at a ‘formulation” stage. This means that all these countries import most raw materials to produce finished pharmaceutical products. (33)

Pharmaceutical Trade

Tables 33 and 34 below summarize the pharmaceutical trade of the Association of South East Asian. Table 33 gives the imports of pharmaceutical products by the region from the period 2007 to 2010. Imports of pharmaceutical products have grown at a compounded annual growth rate of 12% between the years 2007 and 2010. Total pharmaceutical imports for the ASEAN region in 2010 amounted to US$7 billion. Five countries namely Singapore, Thailand, Vietnam, Malaysia and the Philippines accounted for 88% of the total imports in the year 2010. Singapore alone accounted for 27% of the total ASEAN pharmaceutical import bill.

Table 33: Pharmaceutical products imports of Association of South East Asian Nations, US$ thousands

Importers	Imported value in 2007	Imported value in 2008	Imported value in 2009	Imported value in 2010
Association of South-East Asian Nations (ASEAN) Aggregation	4,970,488	5,704,713	6,541,085	7,027,441
Singapore	1,326,807	1,521,081	1,705,287	1,896,263
Thailand	999,829	1,226,679	1,342,714	1,538,822
Viet Nam	775,769	905,012	1,178,484	1,060,824
Malaysia	755,380	816,855	938,609	962,713
Philippines	539,905	611,576	676,758	736,497
Indonesia	296,976	338,048	380,418	482,339
Myanmar	124,862	149,562	171,673	179,197
Cambodia	94,557	79,958	88,028	103,639
Brunei Darussalam	45,971	43,176	41,003	49,510
Lao People's Democratic Republic	10,432	12,766	18,111	17,637

Table 34 below shows the list of the top 20 supplying markets for pharmaceutical products imported by the ASEAN member countries during the period 2007 through to 2010. The table shows that the majority of pharmaceutical imports into the ASEAN region emanate from non-ASEAN member countries except for two member states, Thailand and Malaysia who rank 8th and 10th respectively in the top 20 countries supplying pharmaceutical products to the Association of South East Asian Nations.

The top 5 supplying markets for ASEAN pharmaceutical product imports are France, Switzerland, Australia, the United States of America and the United Kingdom. This most likely resembles the skewedness of the imports towards high value innovator products. The structure of imports, which are mainly dominated by non-ASEAN member countries, point to a similar situation as that of SADC. With the full harmonization of pharmaceutical regulations in the ASEAN region, the major impact of this initiative will be on access to medicines which will be positively impacted on by an increase in imports from non-ASEAN member countries who currently dominate the import bill.

Although Thailand and Malaysia are ranked 8th and 10th in the top 20 supplying markets to the ASEAN market, any increase in exports from local production from these countries together with other member countries will not likely have a considerable positive impact in the change of market access of ASEAN member states as exports and imports are dominated by one country Singapore. The volume of trade in pharmaceutical products flowing in and out of Singapore is disproportionately large compared with the size of the country. Table 19 below summarizes the pharmaceutical products exports of the Association of South East Asian Nations. Singapore exports more pharmaceuticals than any other ASEAN member country by a significant amount and the majority of this is from re-exported goods. The country acts as a key trading hub to connect South East Asia and the Western world and is a major re-exporter of pharmaceuticals. (32)

The relatively high level of exports from Singapore (net of re-exports), Thailand, Indonesia and Malaysia, point to a well-developed local pharmaceutical manufacturing industry in these countries. Thailand, Indonesia and Malaysia accounted for some 13% of the total ASEAN pharmaceutical exports (including re-exports by Singapore).

Table 34: List of top 20 supplying markets for pharmaceutical products imported by the Association of South-East Asian Nations, US$ thousands

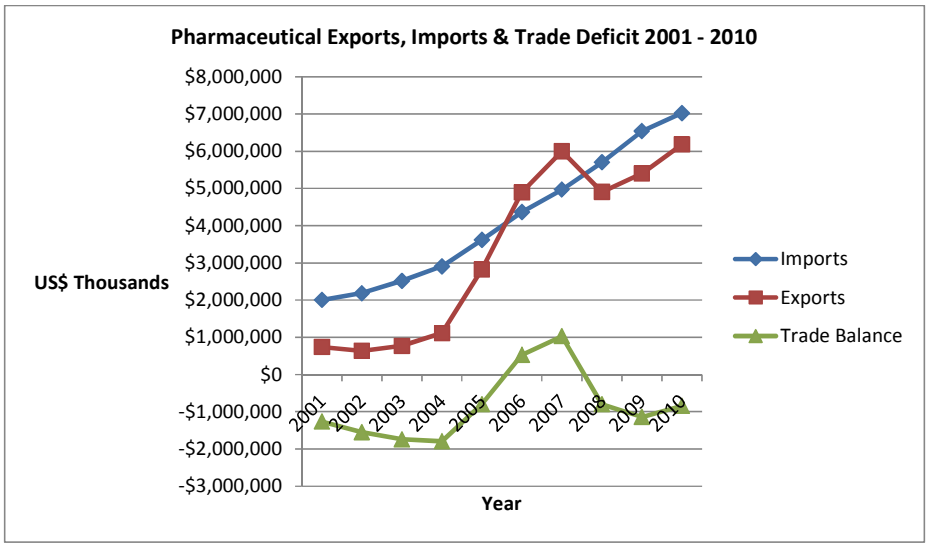
	Exporters	Imported value in 2007	Imported value in 2008	Imported value in 2009	Imported value in 2010
	Total	4,961,784	5,706,608	6,346,990	7,068,827
1	France	659,434	724,771	771,250	990,643
2	Switzerland	500,474	534,696	572,326	664,173
3	Australia	505,154	539,649	538,218	590,667
4	United States of America	239,418	280,853	357,727	430,549
5	United Kingdom	340,883	344,547	359,623	385,131
6	China	141,833	179,861	234,652	242,619
7	Republic of Korea	130,338	149,901	179,036	220,365
8	Thailand	128,125	151,690	154,355	188,368
9	Japan	72,802	93,324	103,741	132,055
10	Malaysia	102,159	89,579	83,954	102,237
11	Chinese Taipei	37,415	42,515	51,142	54,100
12	Canada	40,063	36,778	35,005	60,333
13	Brazil	5,990	13,692	31,638	39,329
14	Turkey	7,403	7,933	9,171	13,972
15	Colombia	332	3,342	4,308	9,598
16	Norway	16	483	275	53
17	South Africa	1,296	2,262	2,848	3,609
18	Czech Republic	936	901	1,561	1,906
19	Malta	0	0	1,103	1,195
20	Chile	339	414	506	1,361

Table 35: Pharmaceutical products exports of ASEAN member countries, US$ thousands

Exporters	Exported value in 2007	Exported value in 2008	Exported value in 2009	Exported value in 2010
Association of South-East Asian Nations (ASEAN) Aggregation	5,998,741	4,908,190	5,401,443	6,186,342
Singapore	5,378,885	4,231,418	4,685,772	5,278,735
Thailand	215,064	269,780	269,130	332,757
Indonesia	176,399	205,335	212,970	306,791
Malaysia	163,967	133,944	142,466	173,854
Viet Nam	26,874	33,845	45,721	47,170
Philippines	35,006	31,829	38,427	40,544
Cambodia	2,004	758	3,312	3,199
Brunei Darussalam	94	409	1,293	2,207
Lao People's Democratic Republic	110	450	2,334	608
Myanmar	338	422	18	477

Figure 9 below summarizes the pharmaceutical products trade balance of the Association of South East Asian Nations.

Figure 9: Pharmaceutical products trade balance of the ASEAN member countries



The pharmaceutical products trade balance of the ASEAN member countries is distorted by re-exports of pharmaceutical products by Singapore. Even with the re-exports, the pharmaceutical products trade balance has largely been negative except for the two consecutive years 2006 and 2007. Thus largely to a certain extent, the ASEAN region is a net importer of pharmaceutical products.

4.2 Gulf Co-Operation Council (GCC)

Here, we present a very short but quite informative case study of the Gulf Co-operation Council regulatory authorities. The Gulf Co-operation Council (GCC), uniting 6 Arabian Gulf states (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and the United Arab Emirates (UAE) was established on 25 May 1981. The GCC spans over the area of about 2.3 million square kilometres and has around 40 million inhabitants. The combined Gross Domestic Product (GDP) of the GCC in 2010 was around US$1 trillion.

Gulf Co-operation Council regulatory authorities

Gulf Central Committee for Drug Registrations (GCC-DR)

- Approved in May 1999
- Located in the executive office for Health Ministers, Riyadh, Saudi Arabia
- The GCC-DR consists of two members nominated by each state

Scope of GCC Drug Regulatory Activities

- Pre-marketing evaluation
- Marketing authorization
- Post-marketing review
- GMP inspection
- Technical guidelines

The GCC-DR Steering Committee

- Responsible for product registration and selection and prioritization of topics
- Guidelines drafting and approval
- Composed of two members from each of the member states including Yemen
- Steering committee holds a minimum of four meetings per year

The GCC-DR Secretariat

- Facilitates the activities of the harmonization initiative through administration, co-ordination and communication
- Receiving and reviewing registration files for completeness
- Prepares the agenda for the steering committee meetings

Norms and procedures

The GCC-DR harmonization process is governed by standard practices and operating procedures. These procedures relate to:

- The registration process for products and companies
- Procedures which describe file flow
- Implementation of guidelines
- Working groups and secretariat
- Funding

Harmonization process

- The GCC primarily uses ICH guidelines as the basis of developing regional guidelines
- Other international guidelines as well as selected regional and national technical documents are also used as basis for harmonization and as reference material
- Once developed by a working group, a draft guideline is circulated to all member states for comment
- The draft document is also posted on the website to solicit comments from stakeholders
- The working group reviews all comments received, and recommends the adoption of the guideline to the GCC-DR Steering Committee
- Once adopted by the GCC-DR Steering Committee, the General Director of the Executive Office submits the guideline to the Council of Ministers of Health for approval

Drug registration: there are two processes of drug registration;

1. Centralized registration procedure
2. Decentralized registration procedure

A. Centralized registration procedure

i. The executive office of GCC-DR assumes the receipt of registration files after ensuring the fulfilment of registration requirements and upon duly filling the following forms:
    - The drug company's registration form
    - A pharmaceutical chemical entity/preparation registration form
ii. Eight complete files for each chemical entity and 17 samples have to be submitted to the executive office and two samples shall be dispatched to each country along with registration file.
iii. Every country shall study the registration files forwarded to it and then return those files with its recommendation to the committee.
iv. The company needs to provide the laboratory for the analysis with standard materials, methods etc.
v. The executive office dispatches the samples of chemical entity to reference accredited laboratory for the analysis.
vi. After approving the registration of the company and/or chemical entity centrally, the remaining authentication and documentation, fees are finalized on a country basis, as per their prescribed and established policies.
vii. The executive office issues the registration certificate.
viii. The companies reserve their rights to lodge their grievances to the executive office within a period of two months effective from the date of notification about the registration by GCC-DR.

The validity of the central registration

a. The Central Gulf committee's resolutions for drug registration are binding for consolidated purchasing
b. All countries must sanction and approve export prices, which have been approved by the committee upon completion of the registration procedure in the country.

Issues of Centralization of registration of drugs

It is not mandatory to centralize the registration of drugs in GCC, as of now. For special classes of drugs, registration through the centralized process is necessary. These are as follows:

1. Generic drugs for which bioequivalence studies cannot be done, e.g. inhalable medicines and some nasal inhalers.

2. Biotechnology products for which bioequivalence studies cannot be done and which require clinical or pharmacodynamics studies.
3. Drugs with narrow therapeutic spectrum, which are administered orally.

B. Decentralized registration procedure

Although there is a centralized procedure and a harmonized process for drug registration in GCC countries, the regulatory requirements of a few big countries like Saudi Arabia and UAE separate. These countries have their well-established regulatory systems and enforcement.

Sources of Funding

- The activities of the GCC-DR harmonization initiative are financed by established quotas of contributions from Member States.
- Fees obtained from both company and product registration
- The GCC-DR initiative operates through cost recovery, and is audited by a certified accounting firm.

Pharmaceutical Market and Trade

The total GCC pharmaceutical products market was valued at approximately U$6 billion in 2010 with the majority of the region's pharmaceutical requirements being imported. Table 36 shows GCC imports of pharmaceutical products between the years 2006 and 2010. Imports increased at an average value rate of 23% over the period 2006 to 2010, and amounted to US$5.78 billion in 2010.

Table 37 shows a list of top supplying markets for pharmaceutical products imported by the GCC member states. Intra-GCC trade on pharmaceutical products only accounted for 5.6% of the total imports of US$3.94 billion in the year 2008 with the rest being imported. The GCC pharmaceutical harmonization initiative seems to have a public health agenda as opposed to an industrial and economic agenda.

Table 36: List of GCC members states imports of pharmaceutical products, US$ thousands

Importers	Imported value in 2006	Imported value in 2007	Imported value in 2008	Imported value in 2009	Imported value in 2010
Gulf Cooperation Council (GCC) Aggregation	2,606,408	3,863,691	3,935,790	4,608,533	5,782,627
Saudi Arabia	1,921,128	2,199,994	1,777,093	2,380,722	3,353,023
United Arab Emirates		843,648	1,037,008	1,219,916	1,383,248
Kuwait	394,053	447,562	602,093	422,312	469,737
Oman	110,062	133,133	177,808	231,469	196,528
Qatar	139,715	163,071	206,189	181,230	190,422
Bahrain	41,450	76,283	135,599	172,884	189,669

Table 37: List of top supplying markets for pharmaceutical imports of GCC, US$ thousands

	Exporters	Imported value in 2007	Imported value in 2008
	GCC aggregates	3,863,691	3,935,790
1	Germany	593,487	567,827
2	Switzerland	408,356	474,656
3	United Kingdom	434,051	437,681
4	France	350,024	334,592
5	Belgium	225,547	232,064
6	United States of America	388,762	214,924
7	Jordan	153,370	197,255
8	Sweden	103,515	178,471
9	Italy	178,648	175,795
10	Ireland	119,239	166,407
11	United Arab Emirates	126,286	146,328
12	Austria	72,906	142,272
13	Netherlands	140,391	137,896
14	Denmark	134,087	129,302
15	Spain	51,442	81,422
16	Saudi Arabia	46,426	57,072
17	India	38,889	44,527
18	Poland	705	39,979
19	Canada	50,570	26,253
20	Australia	33,643	19,831
21	Kuwait	11,833	18,098

4.3 European Union (EU)

The European Medicines Agency (EMA) is a European agency for the evaluation of medicinal products. The agency was set up after nearly thirty years of efforts to harmonize national approval procedures for medicines in the European Community (EC). (34) The European Medicines Agency was known as European Agency for the Evaluation of Medicinal Products. Set up by EC Regulation No. 2309/93 as the European Agency for the Evaluation of Medicinal Products, and renamed by EC Regulation No. 726/2004 to the European Medicines Agency, it had the acronym EMEA until December 2009. The European Medicines Agency does not call itself EMA either - it currently has no official acronym.[16]

Roughly parallel to the U.S. Food and Drug Administration (FDA), but without FDA-style centralization, the European Medicines Agency was set up in 1995 with funding from the European Union and the pharmaceutical industry, as well as indirect subsidy from member states, in an attempt to harmonize (but not replace) the work of existing national medicine regulatory bodies. The hope was that this plan would not only reduce the €350 million annual cost drug companies incurred by having to win separate approvals from each member state but also that it would eliminate the protectionist tendencies of states unwilling to approve new drugs that might compete with those already produced by domestic drug companies. Based in London, the EMA was born after more than seven years of negotiations among EU governments and replaced the Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products, though both of these were reborn as the core scientific advisory committees.[17]

The legislation establishing the new approval procedures leaves much room for continued national regulation. Enforcement of requirements concerning such matters as good manufacturing practices, distribution controls, and advertising rules will remain subject to national control. The legislation also leaves some important questions unresolved, including the effect of the new approval procedures on parallel trade between high- and low-price markets, arrangements for market exclusivity, and protection against abridged applications for follow-on products. The Agency does represent a major step toward further consolidation of the pharmaceuticals market in Western Europe. (34)

[16] http://www.ema.europa.eu/

[17] http://en.wikipedia.org/wiki/European_Medicines_Agency

The European regulatory system for medicines is complex for the simple reason that the Member States regulate medicine together. This means that there are national agencies in addition to one central regulatory body, the European Medicines Agency, created in 1995. The recent expansion of the European Union membership is a challenge to every aspect of integration, and pharmaceutical regulation is no exception. Consequently, the EMEA's main responsibility and mission is to coordinate the scientific resources of the EU Member States, with a view to providing European citizens with high quality, safe, and effective medicines for humans and animals and, at the same time, to advance towards a single market for medicines. (35)

The “Centralized European Procedure” provides the applicant (usually a pharmaceutical company such as Novartis, Pfizer or BASF) with a license that is valid in all E.U. Member States, and is mandatory for an increasing range of pharmaceuticals explicitly mentioned in the basic regulation.

For all other pharmaceuticals the “Centralized European Procedure” is voluntary. The national pharmaceutical authorities remain in existence, and remain indispensable in terms of law enforcement, even if the significance with regard to licensing is decreasing. Having a European license makes perfect sense in most cases. According to the association of researching pharmaceutical companies in Germany, the invention and development of every new pharmaceutical takes an estimated ten to twelve years, and costs 800 million Euros.

Since no domestic European market is big enough for refinancing these expenses, the economic success of every single pharmaceutical depends on its distribution in other European countries and beyond. (36)

What the agency does[18]

 The Agency is responsible for the scientific evaluation of applications for European marketing authorizations for both human and veterinary medicines (centralized procedure). Under the centralized procedure, companies submit a single marketing-authorization application to the Agency.

[18] http://www.ema.europa.eu/

Once granted by the European Commission, a centralized (or 'Community') marketing authorization is valid in all European Union (EU) and EEA-EFTA (European Economic Area-European Free Trade Association) an international free-trade organization with four Member States – Iceland, Liechtenstein, Norway and Switzerland.

 All medicines for human and animal use derived from biotechnology and other high-tech processes must be approved via the centralized procedure. The same applies to all advanced-therapy medicines and human medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, as well as to all designated orphan medicines intended for the treatment of rare diseases. Similarly, all veterinary medicines intended for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals have to go through the centralized procedure.

 For medicines that do not fall under any of the above-mentioned categories, companies can submit an application for a centralized marketing authorization to the Agency, provided the medicine constitutes a significant therapeutic, scientific or technical innovation, or is in any other respect in the interest of patient or animal health.

 The Agency constantly monitors the safety of medicines through a pharmacovigilance network, and takes appropriate actions if adverse drug reaction reports suggest that the benefit-risk balance of a medicine has changed since it was authorized. For veterinary medicines, the Agency has the responsibility to establish safe limits for medicinal residues in food of animal origin.

 The Agency also plays a role in stimulating innovation and research in the pharmaceutical sector. The Agency gives scientific advice and other assistance to companies for the development of new medicines. It publishes guidelines on quality-, safety- and efficacy-testing requirements. A dedicated SME Office, established in 2005, provides special assistance to small and medium-sized enterprises.

 Six scientific committees, composed of members of all EU and EEA-EFTA states, some including patients' and doctors' representatives, conduct the main scientific work of the Agency: the Committee for Medicinal Products for Human Use (CHMP), the Committee for Medicinal Products for Veterinary Use (CVMP), the Committee for Orphan Medicinal Products (COMP),

the Committee on Herbal Medicinal Products (HMPC), the Paediatric Committee (PDCO) and the Committee for Advanced Therapies (CAT).

 The Agency works with a network of over 4,500 'European experts' who serve as members of the Agency's scientific committees, working parties or scientific assessment teams. These experts are made available to the Agency by the national competent authorities of the EU and EFTA states.

 The Agency can be considered as the 'hub' of a European medicines network comprising over 40 national competent authorities in 30 EU and EEA-EFTA countries, the European Commission, the European Parliament and a number of other decentralized EU agencies. The Agency works closely with its European partners to build the best possible regulatory system for medicines for Europe and protect the health of its citizens.

 In view of the continuing globalization of the pharmaceutical sector, the Agency works to forge close ties with partner organizations around the world, including the World Health Organization and the regulatory authorities of non-European nations. The Agency is continually involved in a wide range of cooperation activities with its international partners, designed to foster the timely exchange of regulatory and scientific expertise and development of best practices in the regulatory field.

 The Agency is also involved in referral or arbitration procedures relating to medicines that are approved or under consideration by Member States in non-centralized authorization procedures.

What the Agency doesn't do[19]

Evaluate all medicines in use in the European Union

The Agency is involved in the scientific evaluation of the hundreds of medicines that fall within the scope of the centralized procedure. However, thousands of other medicines that do not fall within this scope are marketed in the European Union either in individual Member States, in accordance with their national authorization procedures, or in multiple Member States through the decentralized or mutual-recognition procedures. The Agency only becomes involved in the

[19] http://www.ema.europa.eu/

assessment of such medicines when they have been referred to the Agency due to a disagreement between two or more Member States about the authorization or use of the medicine, or due to some other issue that requires resolution in the interest of protecting public health.

The Agency also doesn't do the following:

- Research or develop medicines
- Evaluate the pricing or availability of medicines in individual countries
- Establish ethical codes in relation to the development of medicines or evaluate applications based on ethical considerations.

How the agency works

Key information on funding quality management budget SOPs Work Instructions[20]

The European Medicines Agency has developed a comprehensive body of scientific evaluation practices and respects the highest scientific standards. Members of its Management Board, scientific committees and all staff sign annual declarations of interests, detailing their financial and professional relationship with the pharmaceutical industry. The Agency implements a quality assurance system to continually review and strengthen the quality of its scientific work, while the work carried out by the Agency is underpinned by strict legal criteria.

The Agency has its own legal personality and, while partially funded from the European Union's budget, it operates independently of the EU institutions such as the European Commission and the Parliament. It is not, therefore, managed by the European Commission, but by an Executive Director, who in turn is answerable to an independent Management Board.

Since its creation in 1995, the Agency has established key operating principles and rules, which have been adopted by its Management Board. In addition, the Agency is bound by EU legislation on issues such as public access to documents. In accordance with its Founding Regulation, the Agency is legally obliged to publish on its website the decisions of its six scientific committees, as well as main management documentation such as budgets, accounts and contracts. The Agency conducts its activities in accordance with a set of guiding principles.

[20] http://www.ema.europa.eu/

Incentives for Small to Medium Enterprises

The European Medicines Agency implemented Commission Regulation (EC) No 2049/2005 by providing incentives for micro, small and medium-sized enterprises (SMEs) that are developing medicines for human or veterinary use.

Comment [A4]: See comment on the ASEAN case study, we could not establish any other incentives received through literature review

The Regulation describes implementing provisions relating to SMEs in the European Union pharmaceutical legislation and was adopted on 15 December 2005. It aims to promote innovation and the development of new medicines by SMEs.

The Agency's SME Office has the sole remit of offering assistance to SMEs. It aims to facilitate communication with SMEs through dedicated personnel within the Agency who respond to practical or procedural enquiries, monitor applications, and organize workshops and training sessions for SMEs.

The some of the incentives offered to SMEs apply to the human and veterinary sectors. They include:

- Administrative and procedural assistance from the SME Office;
- Fee reductions for scientific advice, scientific services, inspections and the establishment of maximum residue limits for veterinary medicines;
- Fee exemptions for certain administrative services of the Agency;
- Deferral of the fee payable for an application for marketing authorization or related inspection;
- Conditional fee exemption where scientific advice is followed and a marketing authorization application is not successful;
- Assistance with translations of the product information documents submitted in the application for marketing authorization;
- Inclusion in the public SME register.

Regulatory and procedural guidance

EMA has developed extensive guidance documents on pre-market authorization and post-marketing authorization. On the website, guidance documents for pre-submission, data exclusivity, dossier submission requirements, dossier format as well as application and evaluation can be downloaded. An even more extensive list is available for post-marketing authorization, covering different types of variations to the original submissions, annual

reassessment, renewals and a host of other relevant post-marketing procedures. Perusing the website will show that EMA takes communication with its stakeholders very seriously. Most guidances under this section are based on ICH processes.

European Experts

The European Medicines Agency's peer-review evaluation system works through a network of European experts.

These experts serve as members of the Agency's scientific committees, working parties or scientific assessment teams. The Agency's experts are made available by the regulatory authorities of the 27 European Union (EU) Member States and Iceland, Liechtenstein and Norway.

The Agency maintains an online list of its experts: the list includes the experts' annual declaration of financial and any indirect interests that could relate to the pharmaceutical industry. The Agency requires all experts to submit these declarations every year, to ensure that they are acting in the public interest and in an independent manner.

Details of the specific areas of expertise of individual experts are accessible to the public on request at the Agency's offices. These documents may not be copied or further distributed in order to avoid misuse of confidential and personal information.

Operations[21]

The European Medicines Agency operates as a decentralized scientific agency (as opposed to a regulatory authority) of the European Union and its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. More specifically, it coordinates the evaluation and monitoring of centrally authorized products and national referrals, developing technical guidance and providing scientific advice to sponsors.

Its scope of operations is medicinal products for human and veterinary use including biologics and advanced therapies, and herbal medicinal products. The agency is composed of the Secretariat (ca. 600 staff), a management board, six scientific committees (human, veterinary and herbal medicinal products, orphan drugs, pediatrics and advanced therapies) and a number

[21] http://en.wikipedia.org/wiki/European_Medicines_Agency

of scientific working parties. The Secretariat is organized into five units: Directorate, Human Medicines Development and Evaluation, Patient Health Protection, Veterinary Medicines and Product Data Management, Information and Communications Technology and Administration. The Management Board provides administrative oversight to the Agency: including approval of budgets and plans, and selection of Executive Director. The Board includes one representative of each of the 27 Member States, two representatives of the European Commission, two representatives of the European Parliament, two representatives of patients' organizations, one representative of doctors' organizations and one representative of veterinarians' organizations. The Agency decentralizes its scientific assessment of medicines by working through a network of about 4500 experts throughout the EU. The EMA draws on resources of over 40 National Competent Authorities (NCAs) of EU Member states.

Centralized marketing authorizations and CHMP/CVMP[22]

The centralized procedure allow companies to submit a single application to the Agency to obtain from the European Commission a centralized (or 'Community') marketing authorization valid in all EU and EEA-EFTA states (Iceland, Liechtenstein and Norway). The centralized procedure is compulsory for all medicines derived from biotechnology and other high-tech processes, as well as for human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, and for veterinary medicines for use for growth or yield enhancers. The centralized procedure is also open to products that bring a significant therapeutic, scientific or technical innovation, or is in any other respect in the interest of patient or animal health. As a result, the majority of genuinely novel medicines are authorized through the EMA.

For products eligible for or requiring centralized approval, a company submits an application for a marketing authorization to the EMA. A single evaluation is carried out through the Committee for Medicinal Products for Human Use (CHMP) or Committee for Medicinal Products for Veterinary Use (CVMP). If the relevant Committee concludes that the quality, safety and efficacy of the medicinal product are sufficiently proven, it adopts a positive opinion. This is sent to the European Commission to be transformed into a marketing authorization valid for the whole of the EU. A special type of approval is the paediatric-use marketing authorization (PUMA), which can be granted for medical products intended exclusively for paediatric use.

Comment [A5]: The issue of standards was not relevant in the EU, as mention earlier on within this case study, the main driver of harmonization was the issue of market access

[22] http://www.ema.europa.eu/ema

The CHMP and CVMP are obliged by the Regulation to reach decisions within 210 days, though the clock is stopped if it is necessary to ask the applicant for clarification or further supporting data. This compares well with the average of 500 days taken by the U.S. FDA.

Management Board[23]

The Management Board is an integral governance body of the Agency. It has a supervisory role with general responsibility for budgetary and planning matters, the appointment of the Executive Director and the monitoring of the Agency's performance.

The Board's operational tasks are very broad, ranging from adopting legally binding implementing rules, to setting strategic directions for scientific networks, to reporting on the use of European Union (EU) contributions for the Agency's activities:

- It has legally enforceable rule-making authority for implementation of certain parts of the fee regulation, with the implementing rules being adopted and published as decisions of the Board. The Board also adopts the Agency's financial regulation and its implementing rules, which are binding texts for the Agency, the Board and the Executive Director. See financial management and budgetary reporting for more information.
- It has a key role to play in the process whereby the EU budgetary authority gives discharge to the Executive Director for the Agency's budget. The Board conducts an analysis and assessment of the Executive Director's annual activity report, which is part of the package of controls and reports that lead to the discharge of the budget. The Board also gives its opinion on the Agency's annual accounts.
- It has close ties with the Agency's accounting officer, who is appointed by the Board, and with the internal auditor, who reports to the Board and to the Executive Director on audit findings.
- It is consulted on the rules of procedure of some of the Agency's scientific committees, and on their membership.
- It is responsible for adopting the implementing provisions necessary for the practical application of the rules and regulations applicable to officials and other staff of the European Communities.

[23] http://www.ema.europa.eu/ema

Full details on the tasks and responsibilities of the Management Board are described in the Agency's founding legislation and financial regulation.

Composition

The members of the Management Board are appointed on the basis of their expertise in management and, if appropriate, experience in the field of human or veterinary medicines. They are selected to guarantee the highest levels of specialist qualifications, a broad spectrum of relevant expertise, and the broadest possible geographical spread within the EU.

Achievements

In addition to its original task of drug authorization, the EMEA has set up several initiatives under its extended mandate. Particular achievements mentioned in the 2005 Annual Report include the successful launch of an SME Office, the provision of early stage scientific advice to companies developing "breakthrough" medicines, and the introduction of new measures to accelerate the assessment of medicines that are of critical importance to public health.

The European Medicines Agency (EMA) has recently launched a four-month electronic submissions pilot that will allow pharma companies to file centralized marketing authorization applications using an interactive PDF form. (13 March 2012).

It marks an attempt by the European regulator to kick-start its delayed move towards accepting electronic applications through the Electronic Common Technical Document (eCTD) as standard.

The eCTD has been available for pharma to use, in parallel with companies' paper submissions, since June 2003, but uptake has been limited because of the complexity of the process.

The EMA said the pilot, and ultimately the transition to accepting the eCTD as standard, is "expected to simplify and speed up the application process" by:

- Improving data quality and consistency
- Providing access to data in Extensible Markup Language (XML) format
- Integrating application data with controlled vocabulary lists

The pilot will initially offer access to the human medicines electronic application forms, which are supported by Data Exchange Standards documentation, XML schema definitions, and user guidance. A second phase will provide access to veterinary medicines electronic forms

If the EMA's pilot is judged a success the regulator expects that electronic application forms will become an alternative, recommended format for submitting eCTD applications to the EMA.

The electronic application forms for the pilot were published in early March, 2012, and their content is identical to that of the current application forms published by the European Commission in the EudraLex – Volume 2. The electronic application forms will be updated in parallel to any update of EudraLex – Volume 2. The forms were developed by the European Medicines Agency, working together with the European Commission services and medicines regulatory authorities in European Union Member States.[24]

EU PHARMACEUTICAL MARKET AND TRADE (37)

In this section we summarize the salient features of the European Union pharmaceutical market and also analyze the level of trade between EU member states and the rest of the world. The EU pharmaceutical harmonization initiative is a mature one and thus it is expected that the level of intra-EU pharmaceutical products trade should be high.

Pharmaceutical Market

The European Union is the current name of the former European Community. Since January 1995 the EU has consisted of 15 member states. Ten new countries joined the EU in May 2004. In January 2007 two more countries – Bulgaria and Romania – joined the EU. Negotiations are in progress with a number of other candidate member states. In this discussion of the EU market, the EU is referred to as the EU27, unless otherwise stated.

According to the European Federation of Pharmaceutical Industries (EFPIA), the global pharmaceutical market was estimated at €484.1 billion at ex-factory prices in 2007. North America, the world's leading market, accounted for a share of 46%. Europe (excluding Russia, Ukraine and Belarus) was the region with the second largest pharmaceutical market in the world in 2007, accounting for approximately 31% of total sales of pharmaceutical products. Despite

[24]http://www.pmlive.com/digital_intelligence_blog/archive/2012/mar_2014/ema_pilots_ectd_electronic_regulatory_submissions

its smaller size, the European market outpaced the North American market in terms of growth. Whereas the North American market increased at an estimated rate of approximately 4% in 2007, the European market increased at an estimated rate of around 7%. The Asian market was the fastest growing market in the world, increasing at an estimated rate of over 13% in 2007.

The size of the pharmaceutical market in the individual EU countries is shown in the table below.

Table 38: EU Pharmaceutical market 2003-2007, in million Euros, at ex-factory prices

	2003	2004	2005	2006	2007	Annual change %	% EU
Total EU	**106,455**	**116,160**	**125,502**	**129,365**	**141,289**	**7.3%**	-
France	21,320	22,760	23,838	24,353	25,501	4.6%	18%
Germany	22,670	21,551	24,846	24,353	25,241	2.7%	18%
Italy	14,606	15,195	15,749	16,472	16,734	3.5%	12%
United Kingdom	16,713	16,110	15,569	14,548	14,493	-3.5%	10%
Spain	9,890	10,671	11,332	12,154	13,209	7.5%	9.3%
Greece	3,020	3,468	3,821	4,244	5,503	16%	3.9%
The Netherlands	3,477	3,579	3,795	4,230	4,616	7.3%	3.3%
Poland	n.a.	2,939	3,546	4,009	4,237	13%[3]	3.0%
Belgium	3,291	3,539	3,657	3,684	3,932	4.5%	2.8%
Portugal	2,715	2,879	3,105	3,321	3,490	6.5%	2.5%
Sweden	2,553	2,608	2,673	2,802	3,052	4.6%	2.2%
Austria	2,148	2,312	2,411	2,544	2,736	6.2%	1.9%
Hungary	n.a.	1,556	1,844	1,954	1,955	7.8%[3]	1.4%
Ireland	1,130	1,306	1,514	1,706	1,902	14%	1.3%
Denmark	1,351	1,410	1,536	1,685	1,860	8.3%	1.3%
Finland	1,571	1,689	1,740	1,740	1,848	4.1%	1.3%
Romania	n.a.	n.a.	1,083	1,352	1,601	22%[4]	1.1%
Czech Republic	n.a.	1,163	1,338	1,467	1,586	11%[3]	1.1%
Slovakia	n.a.	487	565	671	846	20%[3]	0.6%
Bulgaria	n.a.	n.a.	489	538	542	5.3%[4]	0.4%
Slovenia	n.a.	413	442	468	487	5.6%[3]	0.3%
Lithuania	n.a.	276	322	411	404	13%[3]	0.3%
Latvia	n.a.	144	181	213	257	21%[3]	0.2%
Cyprus	n.a.	n.a.	n.a.	177	174	-1.7%[5]	0.1%
Estonia	n.a.	105	106	189	137	9.2%[3]	0.1%
Malta	n.a.	n.a.	n.a.	80	77	-3.8%[5]	0.1%

The EU pharmaceutical market increased by an annual average rate of 7.3% between 2003 and 2007, amounting to approximately €141.3 billion at ex-factory prices in 2007. Five countries namely France, Germany, Italy, the United Kingdom and Spain accounted for 67% of the total EU pharmaceutical market production in 2007.

As seen in Table 38, France and Germany were the largest markets in the EU, each accounting for approximately 18% of the total pharmaceutical market sales in 2007. Italy, the third largest market in the EU, accounted for 12% of the total pharmaceutical market and the UK, the fourth largest market, accounted for a 10% share. Spain, the fifth largest market, accounted for 9.3% of the total pharmaceutical market in the EU.

The EU market for generic medicines has gone through major changes in the past few years. By the end of 2004, EU patents expired for approximately 35% of the most frequently sold pharmaceutical products. This created a major opportunity over the ensuing years to increasing the share of generics, both in the pharmacy and hospital sector. Generic medicines accounted for approximately 50% of the volume of pharmaceutical products in the EU in 2006. In terms of value (at ex-factory prices), the EU market for generic medicines was worth approximately €27.4 billion in 2007, accounting for around 21% of the total EU pharmaceutical market. The size of the market for generic medicines in the EU varies widely from country to country.

Pharmaceutical Trade

Table 39 below shows a list of top 20 supplying markets for pharmaceutical products imported by the EU between 2006 and 2010. Total EU imports of pharmaceutical products increased by an annual average rate of 13% in value between 2006 and 2010, amounting to US$239 billion. Intra-EU imports accounted for more than 78% of the total EU imports in 2010. This is in direct contrast to the low levels of intra-SADC and intra-ASEAN imports as given earlier on. Indirectly, this shows a high level of success of the EU pharmaceutical harmonization initiative together with a highly developed pharmaceutical production infrastructure. It would have been ideal to study the level of intra-EU pharmaceutical products imports prior to the establishment of EMA and comparing this post EMA establishment in order to assess the level of change in pharmaceutical products trade between EU member states. However, pre-1995 pharmaceutical products trade data is could not be accessed.

Table 40 shows a list of top 20 importing markets for pharmaceutical products exported by the European Union. Between 2006 and 2010, total EU pharmaceutical products exports increased by an average rate of 11% in value, amounting to US$306 billion. Exports to intra-EU countries accounted for more than 63% of total exports in 2010. This again shows the success of EU pharmaceutical harmonization.

Table 39: List of top 20 supplying markets for pharmaceutical products imported by European Union **(EU 27), US$ thousands**

	Exporters	Imported value in 2006	Imported value in 2007	Imported value in 2008	Imported value in 2009	Imported value in 2010
	European Union aggregation	166,061,985	199,011,802	232,459,529	236,382,407	239,017,378
1	Germany	29,432,156	39,590,282	47,157,679	42,860,237	42,053,451
2	United States of America	21,956,301	24,096,628	32,538,054	37,583,685	33,801,651
3	Ireland	23,902,832	25,943,362	29,567,749	28,751,854	25,067,567
4	Switzerland	12,434,237	16,270,525	18,189,390	18,610,860	18,937,351
5	France	14,185,323	16,384,480	18,112,226	18,219,127	18,358,787
6	United Kingdom	12,282,896	13,499,045	15,420,974	15,618,716	15,260,532
7	Belgium	9,764,413	11,149,973	13,564,592	14,041,425	14,711,570
8	Netherlands	7,443,515	9,431,843	10,391,064	9,677,543	11,187,710
9	Italy	8,944,024	11,274,608	10,195,799	10,005,276	10,348,414
10	Spain	4,458,340	5,672,398	6,580,281	7,038,583	10,290,203
11	Sweden	4,658,822	5,159,809	5,492,074	5,194,708	5,277,098
12	Denmark	2,804,763	3,449,602	4,219,725	3,950,997	3,901,786
13	Austria	2,253,062	2,560,744	2,950,885	3,010,221	3,185,640
14	Singapore	594,471	794,862	1,403,757	1,887,452	2,845,434
15	Hungary	828,577	1,364,974	1,621,441	1,531,284	1,883,442
16	Israel	568,253	793,608	1,019,095	1,091,071	1,793,366
17	Japan	1,324,849	1,340,977	1,498,132	1,977,493	1,787,673
18	China	402,153	550,219	643,851	1,043,087	1,701,802
19	Poland	369,477	611,836	959,732	1,370,331	1,694,711
20	Area Nes	98,095	228,206	549,763	1,152,809	1,542,583

Table 40: List of top 20 importing markets for pharmaceutical products exported by the European Union (EU27), US$ thousands

	Importers	Exported value in 2006	Exported value in 2007	Exported value in 2008	Exported value in 2009	Exported value in 2010
	European Union aggregation	204,501,634	243,605,594	283,237,824	294,171,086	306,516,634
1	United States of America	26,775,066	31,915,086	33,260,921	38,541,108	40,831,637
2	Belgium	27,111,556	30,818,130	33,478,359	34,735,281	34,821,718
3	Germany	23,786,003	28,313,855	37,350,143	37,977,980	34,425,593
4	France	12,385,674	14,519,301	16,999,155	19,008,246	20,062,427
5	United Kingdom	10,946,628	12,698,996	14,329,436	14,721,166	15,036,274
6	Netherlands	7,340,080	10,195,266	12,933,650	12,081,430	14,326,471
7	Italy	8,734,462	11,209,800	12,110,642	12,414,006	13,000,433
8	Switzerland	10,697,866	12,540,398	11,460,566	11,556,842	11,721,659
9	Spain	8,033,596	9,712,671	11,389,890	12,120,603	11,630,250
10	Russian Federation	4,492,365	5,059,597	7,046,571	6,458,580	8,320,796
11	Japan	3,630,493	3,981,674	4,738,275	5,965,260	6,852,246
12	Poland	2,963,866	3,796,510	5,014,004	4,239,400	4,965,001
13	Canada	4,021,200	4,628,091	5,036,185	5,141,584	4,964,630
14	Australia	2,975,458	3,397,534	3,794,495	4,270,896	4,688,873
15	Special categories	2,601,126	3,058,766	3,062,555	3,071,221	3,864,517
16	Ireland	2,869,899	2,877,311	3,420,673	3,351,480	3,807,363
17	Austria	2,602,067	3,034,076	3,593,004	3,730,159	3,804,998
18	China	985,846	1,487,821	2,480,312	2,965,333	3,609,073
19	Greece	2,774,849	3,359,232	4,117,689	3,982,497	3,448,710
20	Turkey	2,017,960	2,557,707	3,521,926	3,504,393	3,324,695

The main destinations of EU exports of pharmaceutical products in 2010 included Belgium (11%), Germany (11%), France (6.5%) and the United Kingdom (5%). Amongst the extra-EU markets, the USA was the main destination for EU exports of pharmaceutical products. Approximately 13% of the total EU exports were directed to the USA market in 2010.

Chapter 5: Lessons Learnt and Recommendations

5.1 Lessons from the Case Studies

Below are the key lessons that can be drawn from the three case studies,

- Pharmaceutical regulatory harmonization in the EU and the ASEAN regions was largely driven by the need to create free trade in pharmaceuticals
- Adoption with modification of international and regional guidelines as a basis of regional guidelines development is key to early realization of pharmaceutical harmonization initiatives.
- The pharmaceutical harmonization process should take into account of the level of development of member states and adoption and implementation of various activities in the regulatory harmonization process should be progressive.
- Self-financing of the pharmaceutical harmonization process is important.
- Pharmaceutical harmonization process should take into account different product categories e.g. generics, innovative medicines etc. in order to be effective.
- Co-operation with international organizations and other partners is essential.
- Implementation of pharmaceutical harmonization activities by member states should be compulsory once adopted.
- Pharmaceutical harmonization models are a hybrid of a centralized and decentralized procedures
- The centralization procedure is targeted for certain types of medicines which are normally of common interest to member states.
- Mutual recognition agreements are critical for the adoption of a decentralized pharmaceutical harmonization system.

Comment [A6]: The main issue here is not re-inventing the wheel by originating own guidelines. I am not sure what you mean by "What does this mean for quality standards"

- Robust arbitration procedures relating to medicines that are approved or under consideration by Member States in a decentralized procedure authorization are critical for the success of the system.
- Robust information sharing systems are critical for the adoption of a decentralized pharmaceutical harmonization procedure.
- Involvement of private sector stakeholders in the development of the system right from the inception stage is important.
- A pool of experts from the region is critical for the implementation of pharmaceutical harmonization initiatives.
- The decentralized procedure requires a lot of political will because of multiple legislative instruments required for successful implementation of this model.

5.2 RECOMMENDATIONS

The following recommendations are made based on the study findings:

5.2.1 Education and project redefinition

The two words regulatory and registration have been used interchangeably in many regional pharmaceutical harmonization initiatives. However, these two words have different meanings with regulatory being broader and encompassing. Registration harmonization is too specific and for it to be feasible, other elements of regulatory harmonization need to be undertaken. It is with this in mind that the SADC pharmaceutical harmonization projection should be redefined as the "SADC Medicines Regulatory Harmonization" project. There is need for SAGMA to embark on an education programme to concertize stakeholders on the subject of medicines regulatory harmonization.

5.2.2 Realignment of project purpose with industrial and economic perspectives

The purpose of the SADC Medicines "Registration" Harmonization Project is "To improve public health by achieving rapid and sustainable access to safe, affordable essential medicines of acceptable quality." The SADC Medicines "Registration" Harmonization project is silent on the need to promote local pharmaceutical manufacturing. In the absence of this important element of the project, the SADC which is currently a net importer of finished pharmaceutical products will end up having no local pharmaceutical manufacturing capacity. It is recommended that this local pharmaceutical production element be captured in the project.

Comment [A7]: It was mentioned in the theoretical part of this paper that registration harmonization does not take place in a vacuum, and in fact it is a misnomer to talk about registration harmonization, it is appropriate to talk about regulatory harmonization. To give a simple example, cGMP manufacturing inspections are a requisite of most registration processes, however, it would be incorrect to call a cGMP a registration process, the term regulatory harmonization is therefore a more accurate description of what would happen in practice.

5.2.3 Scope of Medicines Regulatory Harmonization Initiative

There is need to determine the scope of medicines regulatory harmonization in the South African Development Community in terms product classes and stakeholders to be included or excluded in the project (product and stakeholder scope). With regards to product classes, it has to be clear which products are to be part of the project, all medicines including innovative and generic medicines, variations to current registrations, complimentary and traditional medicines. Even within these broad product classes, there might be a need to further look at narrowing the product classes to specific therapeutic classes. This will simplify the harmonization process in the initial stages of implementation. The other area which needs addressing in the project scope is the type of stakeholders to be included in the harmonization process. Will harmonization be broad based and open to all products as agreed in the product classes originating from non-SADC countries or will it be restricted to products from the SADC member countries only?

The SADC project proposal envisages a broadened scope of products (new chemical entities, vaccines and biologicals) for pharmaceutical harmonization. However the project purpose dwells on public health through sustainable access to safe, affordable essential medicines of acceptable quality. This purpose therefore limits the product scope in that most innovative products will not meet the public health element of the project as envisaged in the project purpose statement. There is thus a need to address this anomaly.

The three case studies presented in this paper reveal that the pharmaceutical harmonization process in the cited regions had a narrower scope of products when the centralized procedure is used. The SADC project proposal states that “At the regional level, the harmonization project will be implemented in accordance with existing SADC Secretariat organizational and institutional structures”. This in essence refers to the centralized procedure. The project proposal further states that “At national level, the project will be implemented through each of the region NMRA’s in accordance with their existing national organizational and institutional structures, systems and procedures.” This last stated approach is similar to the decentralized procedure cited in the case studies. The decentralized procedure uses the broader product scope according to the case studies cited.

5.2.4 Road map to Medicines Regulatory Harmonization Initiative

As pointed out in the section above, the SADC proposal intends to use both the centralized and decentralized procedures of pharmaceutical harmonization. Based on the experiences of other regional initiatives, it is quite clear that the pharmaceutical harmonization process is a long one

which involves a number of step wise sub-processes and cannot be done overnight. It is recommended that this step wise process be adopted both in terms of member countries to be involved and the technical process. Member countries should be assessed in terms of their readiness for inclusion into the project right from the project inception. Those ready should proceed with the adoption and implementation whilst those not ready, are given transition periods for adoption and implementation. During the transition periods, capacity building should be undertaken in order to strengthen these countries' ability to join the rest of the region in pharmaceutical harmonization. The case studies also point out to a clear step wise process where the pre-requisites for full pharmaceutical harmonization (technical requirements and institutional arrangements) are developed first, adopted and implemented before full regulatory harmonization can be achieved.

5.2.5 Adoption and adaptation of existing technical requirements for medicines registration

The case studies of the less developed RECs clearly illustrate the importance of adoption and adaptation of existing technical requirements for medicines registration based on the regional settings. Given the limited resources of the SADC region, there is no need to re-invent the wheel when it comes to the development of guidelines required for the pharmaceutical harmonization process. Systematic adoption and adaptation of technical requirements for the registration of medicines based on scientific principles is recommended for the SADC region.

5.2.6 Safe guarding local pharmaceutical production

If the pharmaceutical harmonization project in the SADC region is implemented within the current regional pharmaceutical sector characterized by week production and heavy imports of finished pharmaceutical products, local pharmaceutical production will experience serious challenges which can result in its collapse. Whilst developing and implementing a sector development strategy to strengthen local pharmaceutical production, there is need to put in place interim measures to safeguard local pharma production. These interim measures were discussed in the stakeholder analysis section as proposed by respondents.

The manufacturing group at the harmonization workshop discussed the merits of the negative import list as an interim measure to protect local pharma industry and concluded that such an incentive would lead to a zero-sum game with member countries implementing this type of protectionism to its local industry. The group was of the opinion that more subtle measures be pursued without necessarily imposing more technical barriers to market access which the pharma harmonization project seeks to eradicate. The group also pointed out that experience

with national governments with regards to incentives for the pharmaceutical manufacturing sector need to be backed up by some evidence based studies to strengthen lobbying.

For example, the Industrial Development Corporation of South Africa undertook a quantitative analysis of the potential economic benefit to the South African economy should the government decide to pay a premium for domestically produced anti-retroviral drugs for distribution by the South African Department of Health. The study by the Industrial Development Corporation concluded that the maximum premium that should be paid to a domestic producer (over the contract value paid by a foreign producer) is 32.5%. In other words, a contract for the manufacture of ARVs should be allocated to a domestic producer if the domestic producer's price does not exceed the price charged by a foreign competitor by more than 32.5%. If the premium paid to a domestic producer is less than 32.5% (compared to that of an imported product), the South African economy will benefit to a greater extent than the value associated with the additional cost of the contract. (38)

5.2.7 Development of a sector strategy

In the pharmaceutical market overview section, it was revealed that the SADC region is a net importer of finished pharmaceutical products and intra-SADC trade is very low. Exports in the regional pharmaceutical sector are very weak. Pharmaceutical harmonization without strengthening local pharmaceutical production will open flood gates for more importation of finished pharmaceutical products and destroy the current weak pharmaceutical manufacturing base. Chapter 2 of this paper highlighted some of the reasons cited for the existence of a weak pharmaceutical manufacturing sector in the SADC region. The section pointed out that aggressive R&D in new generic products required to keep the pharmaceutical manufacturing base is lacking mainly because of the lack of adequate financial and human capital resources. It is recommended that a Sector Development Strategy for the regional pharmaceutical industry be put in place. The regional pharmaceutical sector strategy should articulate a shared vision and a growth path for sector. The pressing need is to develop a sector strategy upon which other strategies and initiatives can be built. The sector development strategy should be balanced and thus should also articulate how the distribution part of the pharmaceutical value chain can also be developed.

Comment [A8]: There are no opportunities as the sector is weak with old age product portfolios which cannot be exported

5.3 Action Plans For SAGMA

Below we summarize the suggested action plans SAGMA can initiate in order to translate the recommendations of this paper into tangible beneficial solutions for its members. In the

suggested action plans we take into consideration the limited resources of the Association which can hinder implementation of the suggested action plans.

Figure 10: Suggested SAGMA Action Plans

Recommendation area	Suggested action plan(s)
Education and project redefinition	1. Develop a SAGMA series of newsletters specifically addressing the subject of pharmaceutical harmonization 2. Develop evaluation material to check stakeholders understanding the pharmaceutical harmonization subject matter 3. Disseminate newsletter on a determined interval basis 4. Carry out evaluations of stakeholders to ascertain understanding of the subject matter 5. Engage AMRH consortium and SADC Secretariat on the need to standardize pharmaceutical harmonization projects in line with the suggested “regulatory harmonization” concept

Realignment of project purpose with industrial and economic perspectives	1. Assimilate and consolidate material/information on the state of the SADC region pharmaceutical market with clear breakdown of the performance of the local producers and distributors 2. Engage AMRH consortium and the SADC Secretariat on the need to address industrial and economic issues in all regional pharmaceutical regulatory harmonization projects in view of the back-up information gathered above
Safe guarding local pharmaceutical production	1. Determine incentives which have been used in other regions to safeguard local pharma producers against international imports 2. Carry out economic impact analysis on the effects the suggested incentives on the regional and national economics (see South African example cited in section 6.2.6) 3. Based on the outcome of the economic impact analysis carried out above, gain regional and national political buy in to introduce incentives with positive regional and national economic impacts.

Development of a sector strategy	1. Develop a sector vision of the SADC pharmaceutical sector 2. Develop elements of the SADC pharmaceutical sector development strategy 3. Develop activity packages of the SADC pharmaceutical sector development strategy 4. Develop a SADC pharmaceutical sector strategy taking into consideration elements of the Pharmaceutical Manufacturing Plan for Africa Business plan so as not to duplicate activities 5. Translate the SADC Regional Pharmaceutical Sector Development Strategy into Member States National Pharmaceutical Sector Development Strategies through national pharma trade associations
Scope of Medicines Regulatory Harmonization Initiative	1. Determine the product and stakeholder scope of pharmaceutical harmonization from the private sector perspective for each pharmaceutical harmonization model (centralized and decentralized procedures) 2. Fully motivate for the suggested product and stakeholder scope for pharmaceutical harmonization 3. Engage SADC Secretariat in order to agree on pharmaceutical harmonization project scope

Road map to Medicines Regulatory Harmonization Initiative	1. Determine a suggested step-wise pharmaceutical harmonization process road map with adequate monitoring and evaluation systems 2. Fully motivate for the suggested pharmaceutical harmonization process road map 3. Engage SADC Secretariat in order to agree on the suggested pharmaceutical harmonization process road map
Adoption and adaptation of existing technical requirements for medicines registration	1. Critically study and evaluate available regional and international technical requirements for medicines registration 2. Determine the applicability and suitability of relevant regional and international technical requirements for registration to the SADC situation 3. Develop a list of regional and international technical requirements for medicines registration to be adopted and/or adapted 4. Engage SADC Secretariat and propose private sector participation in any working groups that are set up for the development of technical requirements for medicines registration.

6.4 ACTION PLAN DRIVERS

Participants at the pharmaceutical harmonization workshop unanimously agreed that pharmaceutical regulatory harmonization in the Southern African Development Community is a noble agenda and there is a common harmonization objective amongst wholesalers/distributors and local pharmaceutical manufacturers, that of access to medicines. Workshop participants agreed that for the recommendations and suggested working plans to be implemented; there was a need for a group of people to act as drivers of the project. This group would further crystalize and prioritize the recommendations and action plans in this paper to form the basis for the way forward. The SAGMA board was tasked with the formation of such a reference group with clear terms of reference. It is recommended that the SAGMA Board embarks on an aggressive fundraising initiative to finance the activities of the reference group. Participants of the SAGMA workshop on pharma harmonization pointed out to the need for adequate funding for the project to progress forward. This paper could serve as a selling tool for the fund raising initiative.

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Appendices

Appendix I: Sample Design

1. Target Population
   The target population of the Medicines Registration Harmonization Initiative in the Southern African Development Community (SADC) Region – A private sector Perspective is the full membership of the SADC. The full membership of the SADC is as follows:

Angola	Botswana
Democratic Republic of Congo	Lesotho
Malawi	Mauritius
Mozambique	Namibia
Seychelles	South Africa
Swaziland	Tanzania
Zambia	Zimbabwe

   The 15th member state Madagascar is currently under suspension.

2. Selecting appropriate sampling method
   This study is a qualitative one and does not involve the calculation of any variables and therefore precision is not an issue in sampling design. On this basis and given the small size of the population, the two appropriate sampling methods in this situation are judgemental and convenience sampling. Convenience sampling would entail a long engagement process with various stakeholders to ascertain their willingness to participate in this study. This leaves judgmental sampling as the only alternative method for this study.

3. Method of picking sample
   Given the limited time and financial resources allocated to this study, all non-English speaking countries will be excluded from the sample. Translation of study document into the other two main languages of the SADC namely French and Portuguese and backwards would require time and financial resources not provided for within the study. The following countries are therefore excluded from the study on this basis:

Angola	Democratic Republic of Congo
Mozambique	

   Mauritius and Seychelles have English as part of their official languages and are therefore eligible for sampling.

   A combination of the following criteria will be used to select the country study sample:
   a. The presence of a National Medicines Regulatory Authority (NMRA) in the country

b. Strength of the NMRA
c. Presence of local pharmaceutical manufacturers
d. Presence of local pharmaceutical wholesalers

The country sample size shall not be below a minimum of 50% of the eligible countries.

Within each country, the top 5 wholesalers and manufacturers will be sampled.

Below is a table which summarizes the categorization of eligible member states based on the criteria given above.

Criteria	**Category 1** **(meeting 2 or less criteria?)**	**Category 2** **(meeting 3 criteria)**	**Category 3** **(meeting all 4 criteria)**
• The presence of a National Medicines Regulatory Authority (NMRA) in the country. • Strength of the NMRA. • Presence of local pharmaceutical manufacturers. • Presence of local pharmaceutical manufacturers.	Lesotho, Swaziland, Seychelles, Mauritius	Malawi, Botswana, Namibia	South Africa, Tanzania, Zambia, Zimbabwe

Based on the categorization above, the country sample for the study will include countries in categories 2 and three as those in category 1 lack the majority of the criteria given above.

4. All SAGMA members will be included in the sample.

Appendix ii: Companies/Associations Sampled

COUNTRY	PERSON/COMPANY /ASSOCIATION	Email Addresses
BOTSWANA	Gemi Pharmacure, Abba Pharmaceuticals, Alred Medicals, Delta Pharmaceuticals, Embassy Scientific Group, Orthosurge Pharmaceuticals, Premier Pharmaceuticals, Kalahari Medical, Medswana, CAPS Botswana, DHL Pharmaceuticals	'georgeproctor@gemigroup.com'; 'brian@hoptialsuppies.co.bw'; 'ckatholo@alredmedical.com'; 'tebogo.moumakwa@dhl.com'; 'msibanda@caps.co.zw'; 'sjsenwelo@medswana.co.bw'; 'krichardson@upd.co.za'; 'narendra@premierpharma.co.bw'; 'george@orthosurge.co.bw'; 'dental.sup@info.bw'; 'murali@deltapharma.co.bw'
NAMIBIA	Geka Pharma Omapango, Erongomed, Cargo Dynamics, Newmed Holdings, Esindano Pharmaceuticals, Global Pharmaceutical Exchange, NamPharm, Swavet, Intersana, Windhoek medical supplies	'auasvetmed@agra.com.na'; 'Cheryl@geka.com.na'; 'cosmas@erongomed.com'; 'hjmurorua@yahoo.com'; 'ghabimana@cms-namibia.com'; 'Pharmacist1@cdp.com.na'; 'cosmas@erongomed.com'; 'info@comex.com.na'; 'ruanda@nampharm.com.na'; 'swavet@iway.na'; 'u.ritter@intersana-na.com'; 'willie@geka.com.na'; 'wms@medicineworld.biz'
SOUTH AFRICA	Fresenius Kabi, Cipla Medpro, Pharma Dynamics, Amayeza Abantu, Zans African Medical, MSD, Ethelm Healthcare Resources, AstraZeneca, Bayer, Pfizer, Nycomed, Glenmark Pharma South Africa, Merck, Roche,	Maria.Vilar@fresenius-kabi.com 'ansie@ciplagauteng.co.za'; 'sarusha@ciplamedpro.co.za'; 'c.page@pharmadynamics.co.za'
ZAMBIA	Got list, but do not have specific named except for Pharmanova Zambia and Tejay Pharmaceuticals.	'murugappan@zamnet.zm'; 'idcl@iconnect.zm'; 'kings@coppernet.zm'; 'Tejaypharma@yahoo.com'; 'kings@coppernet.zm'; 'idcl@iconnect.zm'
ZIMBABWE	Plus Five Pharmaceuticals, Datlabs, Greenwood	

	Wholesalers, CAPS Pharmaceuticals, Varichem Pharmaceuticals, Graniteside Chemicals, Fivet, New Avakash, Pharmanova, Pulse Pharmaceuticals, Sky Pharmaceuticals, Link Medical Supplies, Savanna Pharmaceuticals, Pharmaceutical & Chemical Distributors,	
OTHER	All SAGMA members	'alois.muchabaiwa@varichem.co.zw'; 'chitemerere.stratdigm@gmail.com'; 'docskhu@gmail.com'; 'gmothibe@yahoo.co.uk'; 'starros@realnet.co.sz'; 'murugappan@zamnet.zm'; 'sjsenwelo@medswana.co.bw'; 'mujpfive@mweb.co.zw'; 'georgeproctor@gemigroup.com'; 'wychalira@globemw.net'; 'mbodhania@medreich.co.za'; 'piet@medswana.co.bw'; 'promedlabo@gmail.com'; 'victor.basopo@datlabs.co.zw'; 'hwesa09@gmail.com'; 'ceo@vantagehealth.co.za'
	National Association of Pharmaceutical Manufacturers (NAPAM) South Africa	Through their Chairman
	PIASA –South Africa	Through their Chairman
	Ethical Drugs Association (Zimbabwe)	Through their Chairman