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# AFRICA MEDICINES REGULATORY HARMONIZATION INITIATIVES

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*WHITE PAPER*

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## Acronyms

|        |   |
|--------|---|
| AMRH   | African Medicines Regulatory Harmonization                                |
| AMA    | Africa Medicines Agency   |
| AU     | African Union   |
| AUC    | African Union Commission  |
| BMGF   | The Bill and Melinda Gates Foundation                                     |
| CENSAD | Community of Sahel-Saharan States   |
| COMESA | Common Market for Eastern and Southern Africa                             |
| DFID   | United Kingdom Department of International Development                    |
| EAC    | East African Community  |
| ECCAS  | Economic Community of Central African States                              |
| ECOWAS | Economic Community of West African States                                 |
| EOI    | Expression of Interest (EOI)  |
| EU     | European Union  |
| GMP    | Good Manufacturing Practice   |
| IGAD   | Inter-Governmental Organization for Development                           |
| OCEAC  | Organization for the Fight Against Endemic Diseases in Central Africa     |
| MRH    | Medicines Registration Harmonization                                      |
| MER    | Medicines Evaluation and Registration                                     |
| NEPAD  | New Partnership for Africa's Development                                  |
| NDA    | National Drug Authority of Uganda   |
| NMRA   | National Medicines Regulatory Authority                                   |
| PAP    | Pan African Parliament  |
| PMPA   | Pharmaceutical Manufacturing Plan for Africa                              |
| RECs   | Regional Economic Communities   |
| RCORES | Regional Centres of Regulatory Excellence                                 |
| SADC   | Southern African Development Community                                    |
| SARPAM | Southern Africa Regional Programme on Access to Medicines and Diagnostics |
| SOP    | Standard Operating Procedure  |
| TWG    | Technical Working Groups  |

|       |  |
|-------|--|
| TFDA  | Tanzania Food and Drugs Authority            |
| UEMOA | The West African Economic and Monetary Union |
| WB    | The World Bank                               |
| WHO   | World Health Organization                    |
| WAHO  | West African Health Organization (WAHO)      |

## **Abstract**

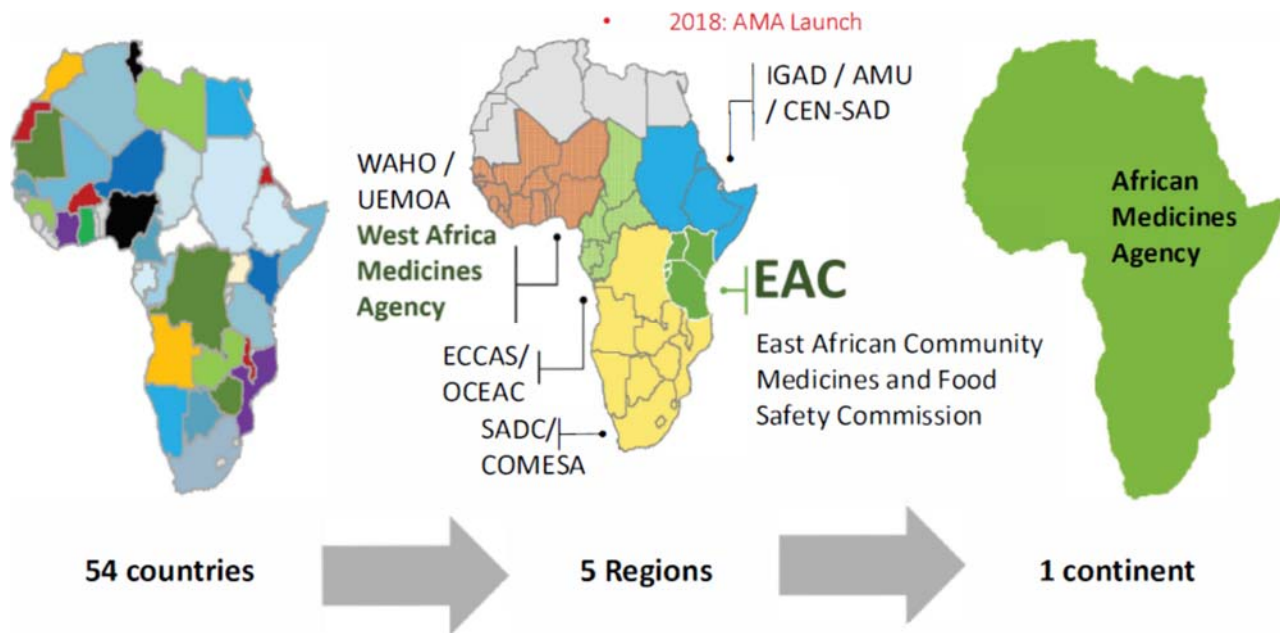
The lack of harmonized technical requirements and capacity for medicines registration jeopardizes timely access to essential medicines in many developing African countries. Due to shortages of human, technical, financial and other resources, many National Medicines Regulatory Authorities (NMRAs) in Africa do not have the full capacity to perform all the core regulatory functions. These shortfalls contribute to poor health outcomes and lower life-expectancy throughout the African continent. In response to these issues, African regulators and the international community mobilized technical and financial resources to create the African Medicines Regulatory Harmonization (AMRH) program. This program focuses on developing regional regulatory platforms, as opposed to independent country regulatory systems, while simultaneously strengthening capacity building efforts and encouraging harmonization of regulatory requirements. Various harmonization initiatives have been undertaken through the AMRH program and significant progress has been made during the last few years, notably in the East African Community (EAC). Similar initiatives are now being rolled out in other regions, including West Africa and the Southern African Development Community (SADC). Roughly 85% of sub-Saharan Africa is engaged in medicines regulatory harmonization (MRH) initiatives or similar projects at different levels. These initiatives are making significant progress in mobilizing the technical and financial resources needed to advance regulatory harmonization in Africa. However, there is still much work to be done to achieve the African Union's ultimate vision of a single and comprehensive African Medicines Agency by 2018.

## **Introduction**

The regulation of medicines is a critical component of every country's public health system. An effective medicines regulation system promotes and protects public health by ensuring that medicines are of the required quality, safety and efficacy<sup>3</sup>. One of the main obstacles to international approval of medical products is the different regulatory models and processes that exist throughout different countries. The lack of access to essential medicines remains one of the most serious global public health problems in Africa<sup>4</sup>. In many African countries, a lack of harmonized technical requirements and capacity for medicines registration jeopardizes timely access to essential medicines<sup>5</sup>. Harmonized medicine regulations in Africa could contribute to the achievement of the Millennium Development Goals relating to health (Goals 4, 5, 6 and 8)<sup>6</sup>. Lack of harmonized regulatory regulations in Africa means that registration regulations, timelines, costs and procedures differ across African countries, thereby discouraging manufacturers from pursuing product registrations in certain African markets.

In the 1980s, the European Union (EU) led the first effort to harmonize medicine regulatory requirements. This effort was successful in developing and implementing a structure for harmonizing the medicine regulatory laws and regulations in Europe, the results of which the AMRH program hopes to emulate in Africa. The African Union envisions the establishment of a single African Medicines Agency (AMA) by the end of 2018<sup>2</sup>. The AMA would contribute to an enabling environment for the development of the pharmaceutical industry and lead to better coordination between different partners and stakeholders undertaking medicines regulatory strengthening and harmonization efforts on the continent. The AMA would build upon the already existing structures of the five Regional Economic Communities (RECs) and Member States that have begun AMRH programs within the framework of the Pharmaceutical Manufacturing Plan for Africa (PMPA) as illustrated in **Figure 1** below. The PMPA was mandated and developed by the African Union Commission following DECISION 55 of the AU Assembly during the Abuja Summit in January 2005. Medicines regulatory harmonization is a key component of the African Union's PMPA, which was approved by the AU Conference of Ministers of Health in 2007 and which aims to enable African countries to fulfill their national obligations to provide all citizens with safe, quality and efficacious essential medicines<sup>2</sup>.

**Figure 1: African Union Vision<sup>2</sup>**



## Overview of the AMRH Program

The AMRH Program is a partnership initiative formalized in 2009 and launched throughout the EAC countries in 2012 (Tanzania, Uganda, Kenya, Burundi, Rwanda). This program was created through a joint initiative of the New Partnership for Africa’s Development (NEPAD), the Pan African Parliament (PAP), and the African Union Commission (AUC), in collaboration with the World Health Organization (WHO), the World Bank, the Bill & Melinda Gates Foundation (BMGF), and the United Kingdom’s Department for International Development (DFID). The main objective of the AMRH program is to create regulatory mechanisms that are effective, efficient and transparent to achieve faster approval and subsequent availability of the products in various African markets. The strategy of this program is to develop regional regulatory platforms with harmonized standards (technical requirements/guidelines), joint regional dossier assessments and Good Manufacturing Practice (GMP) inspections, including work-sharing and streamlined decision-making processes<sup>2</sup>. Together, the NEPAD Agency (a technical body of the African Union) and the AUC defined and endorsed the regional networks for implementation of the AMRH program as indicated in **Table 1** below<sup>7</sup>. These networks build on existing RECs.

**Table 1: Regional Economic Communities**

| RECs                   | Community members  |
|------------------------|--|
| EAC                    | Burundi, Kenya, Rwanda, South Sudan, Uganda and United Republic of Tanzania.   |
| SADC/<br>COMESA        | SADC: Angola, Botswana, the Democratic Republic of Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Swaziland, Tanzania, Zambia and Zimbabwe.   |
|                        | COMESA: Burundi, Comoros, DRC, Djibouti, Egypt, Eritrea, Kenya, Libya, Madagascar, Rwanda, Sudan, and Uganda.  |
| IGAD                   | Djibouti, Ethiopia, Eritrea, Kenya, Somalia, the Sudan, South Sudan and Uganda.  |
| ECOWAS<br>(WAHO/UEMOA) | Benin, Burkina Faso, Cabo Verde, Côte d’Ivoire, The Gambia, Ghana, Guinea, Guinea Bissau, Liberia, Mali, Niger, Nigeria, Senegal, Sierra Leone and Togo.   |
| ECCAS/OCEAC            | Angola, Burundi, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of the Congo, Equatorial Guinea, Gabon, Rwanda and Sao Tome and Principe.  |
| CEN SAD/AMU            | AMU: Algeria, Libya, Mauritania, Morocco, and Tunisia.   |
|                        | CEN SAD: Benin, Burkina Faso, Central African Republic, Chad, the Comoros, Côte d’Ivoire, Djibouti, Egypt, Eritrea, the Gambia, Ghana, Guinea-Bissau, Libya, Mali, Mauritania, Morocco, Niger, Nigeria, Senegal, Sierra Leone, Somalia, the Sudan, Togo and Tunisia. |

Since 2014, the NEPAD Agency has spearheaded the designation of eleven (11) Regional Centers of Regulatory Excellence (RCOREs), leveraging existing academic, research and regulatory institutions<sup>8</sup> to strengthen regulatory capacity development. They were developed to streamline ad-hoc regulatory training programs and to support AU Member States in improving healthcare delivery. The aim of the designated RCOREs is to support a regulatory workforce that enhances human and institutional capacity in the following regulatory functions: Pharmacovigilance, Training in Core Regulatory Functions, Quality Assurance, Quality Control, Medicine Evaluation & Registration, Clinical Trial Oversight, and the Licensing, Inspection & Surveillance of Manufacturers, Importers and Inspections<sup>8</sup> as illustrated in **Figure 2** below. The RCOREs use multiple approaches that focus on the following important interventions: provision of academic and technical training in regulatory science applicable to different regulatory functions and managerial aspects; skills enhancement through hands-on training, twinning and exchange; and practical training through job placement in the pharmaceutical industry.

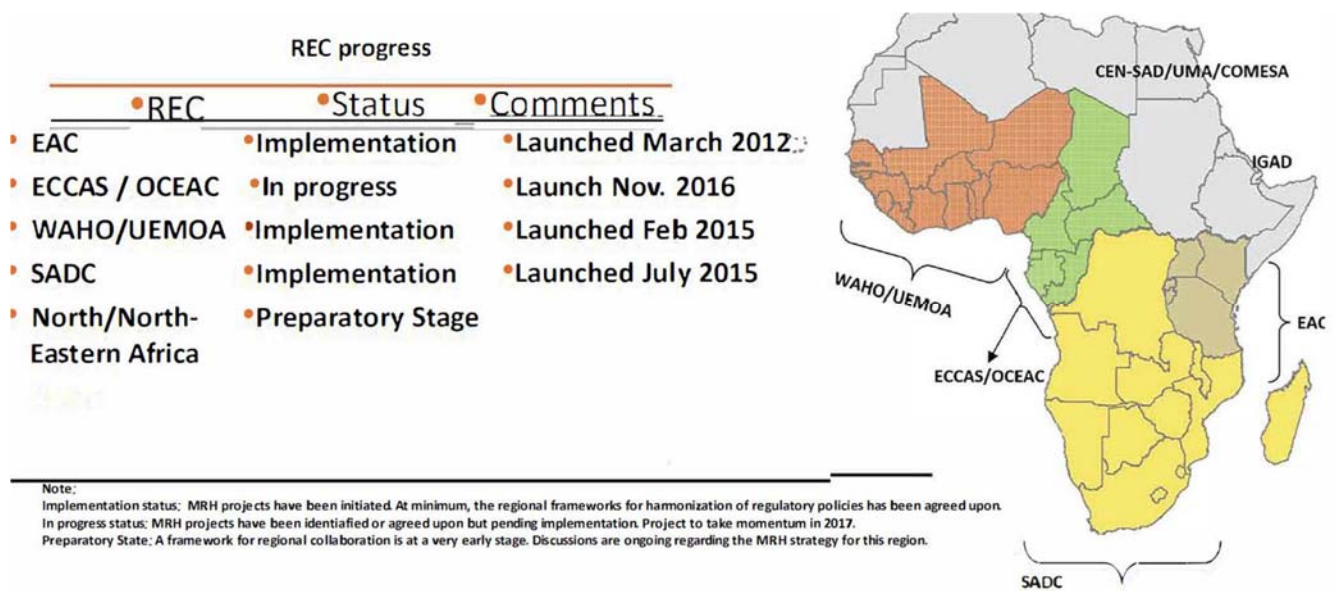
**Figure 2: Regional Centers of Regulatory Excellence (RCOREs)<sup>8</sup>**





Roughly 85% of Sub-Saharan Africa is engaged in medicines registration harmonization (MRH) projects, yet the level of progress and support varies across regions as shown on **Figure 3** below. Each MRH project is progressing at a different pace, with some RECs making significant progress while others require more time and attention to achieve AMRH milestones. This paper details the achievements and initiatives of various MRH projects.

**Figure 3: AMRH Progress (November 2016)<sup>2</sup>**



**Figure 3** shows that MRH initiatives have been implemented in the EAC, ECOWAS and SADC regions, with uneven levels of progress. At a minimum, a framework for harmonization of regulatory policies and activities has been initiated in all three of these RECs. An MRH initiative is pending implementation in the Central African region. As it stands, the NEPAD Agency, in collaboration with ECCAS, OCEAC and WHO, have developed a collaborative framework to outline activities and clearly defined roles and responsibilities for partners involved in the implementation of the MRH initiative in this region. In the North or North Eastern Africa region, the MRH project is in consultation stage only. The Member States of this Northern region recently signed the Khartoum Declaration to Call for Action supporting movement toward the implementation of a regional medicines regulatory collaboration and harmonization program<sup>12</sup>.

## East African Community-MRH Project

The AMRH program selected the EAC as the first region to begin implementation of its regulatory harmonization plan. The program was officially launched on 30<sup>th</sup> March 2012. The stated purpose of the program was to implement harmonized technical requirements, information management systems and quality management systems in each EAC Member State and to build regional and national capacity to implement an EAC-MRH program. The program was also initiated to create a platform for information-sharing and to develop and implement a framework for mutual recognition of regulatory decisions based on Chapter 21, Article 118 of the East African Community Treaty<sup>12</sup>. The EAC-MRH has made significant progress to-date. In September 2014, the EAC-MRH finalized and approved harmonized registration guidelines, the Common Technical Dossier (CTD), Good Manufacturing Practice (GMP) and the Quality Management System (QMS) compendia<sup>2</sup>. These harmonized guidelines were launched in January 2015 and have been used for several national registrations as well as EAC joint dossier assessments.

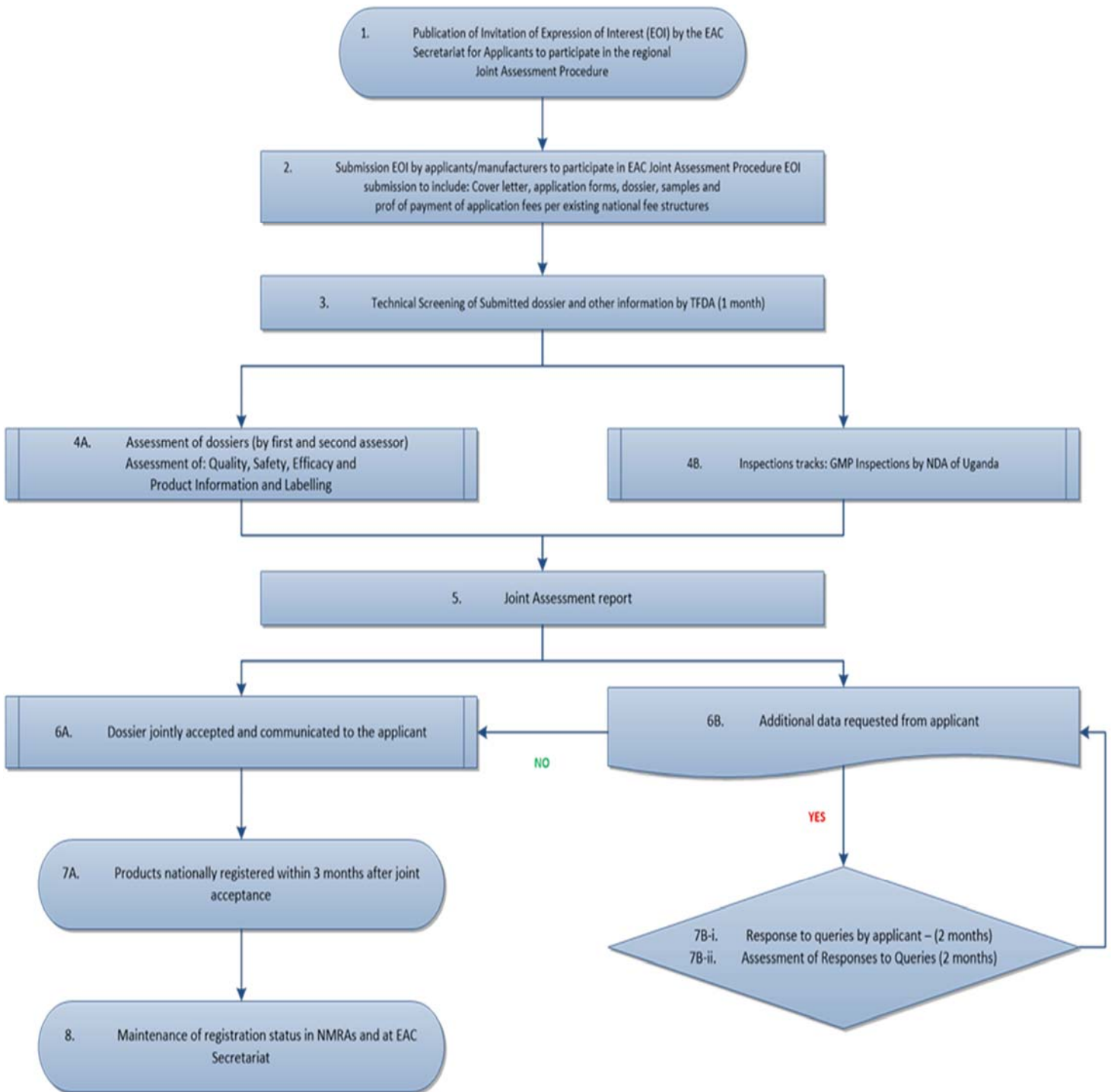
It is important to note that the EAC does not have a regional medicines regulatory agency with legal mandate for issuing marketing authorization of medicinal products. In view of this, and within the framework of the EAC-MRH project, medicines are authorized through one of three channels: The National Authorization Procedure, the WHO Collaborative Procedure and the EAC Joint Assessment Procedure. Under the National Authorization Procedure, each EAC Member State has its own procedures for the authorization of medicines. However, each uses the EAC harmonized guidelines for registration of medicines. This procedure will yield marketing authorization in EAC Member State(s) where the application was submitted. The WHO Collaborative procedure is a collaboration between the WHO Prequalification of Medicines Program (WHO/PQP) and interested NMRAs. This procedure can be used for the assessment and accelerated national registration of WHO prequalified pharmaceutical products. Applicants interested in registration in two or more EAC Member States can submit product registration dossiers through the EAC Joint Assessment Procedure. This procedure entails joint assessment of selected medicinal products and joint inspection of their respective manufacturing site(s) by designated assessors.

**Figure 4** below illustrates the EAC Joint Assessment Procedure. The process begins with the submission of Expression of Interest (EOI) by applicant to the Tanzania Food and Drugs Authority (TFDA) for screening. TFDA serves as the region's lead Medicines Evaluation and Registration (MER) country. The list and scope and list of products invited under the EOI is reviewed and decided by the EAC Member States' NMRAs. An invitation for the EOI is published and managed by the EAC Secretariat and is available on the websites of all Member State NMRAs. In situations of high public health concern, the EAC Secretariat in consultation

with all Member States' NMRAs may directly invite relevant manufacturers to submit specified products for assessment under this procedure without publication of an invitation for EOI.

If the dossier is complete upon screening, the manufacturer can submit copies of the dossier to other NMRAs within the region. The Joint Assessment Procedure will be done by a team of assessors from EAC Member States; external expertise may be sought from other Regulatory Authorities, WHO and Academia under confidentiality agreements. Under the EAC Joint Assessment Procedures, the product information submitted in the dossiers is sent to two lead EAC Member State NMRAs by the lead MER country (TFDA) for first and second assessment. The selection of the assessors follows the EAC Standard Operating Procedure (SOP) for selection of medicines assessors to participate in joint assessment of medicinal product dossiers. Guidelines state that this first assessment is to be performed within a period of one month from the date of acceptance of the application by the selected lead country. The second assessment is to be completed within one week of completion of the first assessment. An assessment report is then circulated to a team of assessors appointed by the EAC Member State NMRAs. The team reviews and makes comments on the report prior to convening in a joint meeting wherein comments are compiled from all assessors and the assessment report is finalized. The dossier assessment is performed prior to GMP assessment. The National Drug Authority of Uganda (NDA) serves as the lead country for evaluation of Good Manufacturing Practice (GMP) and conducts all GMP evaluations under the EAC Joint Assessment Procedure. Registration fees are paid by the applicants to all NMRAs for each country where the applicant intends to register its products. The letter which confirms the final registration outcome is communicated by the respective country-level NMRAs. Please refer to **Annexure 1** for the EAC procedure for marketing authorization of medicinal products.

**Figure 4: EAC Joint Assessment Procedure**



The EAC Joint Assessment Procedure has received a total of 32 applications, of which it has evaluated 27, resulting in 4 product registrations and 23 applications queried<sup>9</sup>. The EAC-MRH committee estimates that the evaluation procedure was completed 30 - 40% faster than usual at national levels, resulting in significant cost and time savings<sup>9</sup>. The EAC-MRH completed joint GMP inspections of nine (9) manufacturing facilities between 2015 and 2016<sup>9</sup>. In 2016, the EAC also adopted the AU Model Law on Medical Products Regulation. The Model Law provides a guide for AU Member States and RECs in harmonizing country-level regulatory systems. In addition, it provides an enabling environment for the development and scale-up of health technologies. The model law is expected to accelerate the regulation of the safety, quality and efficacy of medical products and technologies in the EAC Member States. This will be achieved through the process of domestication whereby a country can adapt the Model Law to ensure alignment with its constitutional principles and legal systems and can also amend or repeal any inconsistent national laws. The Model Law was developed in line with WHO recommendations and international safety and quality standards. Once adopted and implemented by RECs and countries, the goal of the Model Law is to resolve discrepancies in current regulatory legislation and improve the efficiency and effectiveness of regulatory systems across Member States.

Though the EAC-MRH has recorded significant progress, more work remains to achieve mutual recognition, which would enable automatic registration in all Member States once the joint dossier and GMP evaluations are completed via the EAC Joint Assessment Procedure. A Co-operation Agreement for NMRAs in the EAC has been drafted, and approval is anticipated in 2017. This co-operative agreement will provide the legal framework for mutual recognition, which would eliminate the national country procedures, i.e. payment of different NMRA registration fees and receipt of final registration approval and certificates from each NMRA. The EAC-MRH initiative is also working on expanding its scope to include Pharmacovigilance (PV), Devices and Diagnostics, Vaccines, Clinical Trials Oversight, and Variations & Renewals.

## SADC-MRH Project

Harmonization efforts in the Southern African Development Community (SADC) region are facilitated by the Southern African Regional Program Access to Medicines and Diagnostics (SARPAM). SARPAM was initiated as a support program for the SADC Pharmaceutical Business Plan, through the Department for International Development (DFID-UK) between 2009 and 2014. The program was designed in consultation with the SADC Secretariat, Member States and other stakeholders who committed to regulatory harmonization in line with Article 29 of the Protocol on Health, in 1999<sup>12</sup>. SARPAM provides technical and logistical assistance to SADC Member States. Some of the notable achievements of the SARPAM include the development of the SADC Medicines Regulatory Strategic Framework 2015-2020 and the adoption of the International Conference Harmonization (ICH) Common Technical Dossier (CTD) format for medicine registration by SADC ministers in November 2013<sup>12</sup>. The SADC Regional registration guidelines have since been updated and aligned to CTD format. SARPAM also facilitated the review and benchmarking of the Lesotho Draft Medicines Bill and facilitated work-sharing and collaboration for dossier assessments and Good Manufacture Practice (GMP) inspections among SADC countries. SARPAM further supported the ZAZIBONA project, which was initiated in 2013 and established a collaborative procedure for medicines registrations between four SADC countries, namely Zambia, Zimbabwe, Botswana and Namibia<sup>14</sup>. In 2014, the ZAZIBONA approach was officially adopted as part of the broader SADC Framework for Regulatory Harmonization. The SADC Regulators Forum endorsed the implementation of an MRH Program, using the ZAZIBONA approach. South Africa and Swaziland (non-active status) officially joined the ZAZIBONA scheme in 2016.

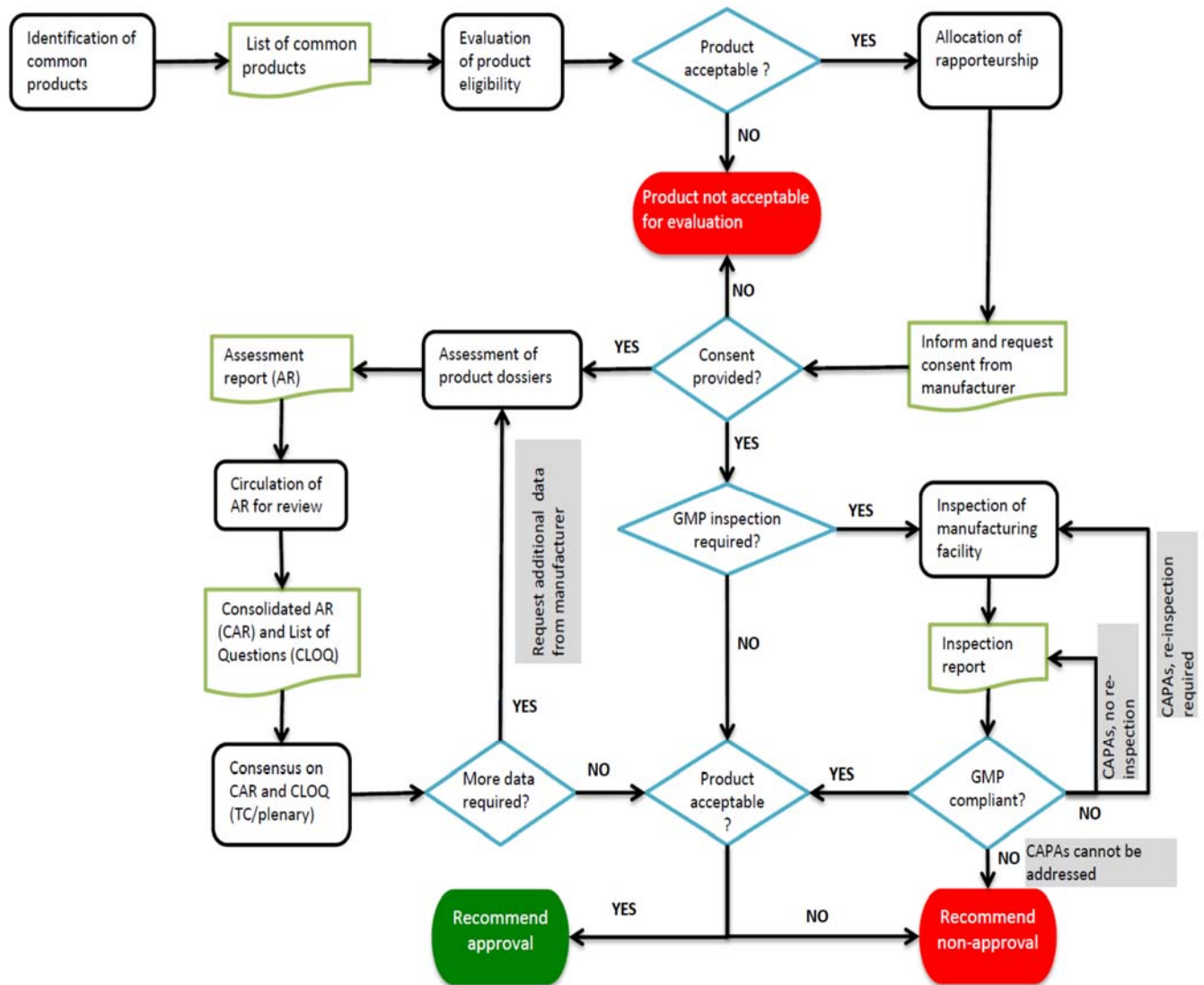
The standard guideline to register medicines via the ZAZIBONA collaborative was published and implemented in June 2015. Any medicine meeting the criteria of being an essential medicine is invited to submit for registration via the ZAZIBONA collaborative process. However, given the SADC focus on ten priority disease conditions (see **Table 2** below) and on reproductive health, special consideration may be given to medicines that are vital to effective treatment of these conditions and to expanding treatment programs. Priority is also given to the products included in the List of UN Commission for Live-Saving Commodities for Women and Children, refer to **Annexure 2** for the ZAZIBONA registration guideline.

**Table 2: Top Conditions/Diseases in SADC with Overall Priority Ranking**

|                                     |    |
|-------------------------------------|----|
| HIV/AIDS                            | 1  |
| Tuberculosis                        | 2  |
| Malaria                             | 3  |
| Acute Respiratory infections        | 4  |
| Diarrhea                            | 5  |
| Diabetes                            | 6  |
| Pneumonia                           | 7  |
| Cardiovascular                      | 8  |
| Cancer                              | 9  |
| Obstetrics, Gastroenteritis & colic | 10 |

The ZAZIBONA collaboration does not replace the need to submit applications for registration in participating countries in line with national requirements. However, it provides an accelerated application for manufacturers of essential medicines to obtain marketing authorization in two or more countries participating in this scheme. **Figure 5** below shows the ZAZIBONA process design, which includes selection of eligible products, assignment of rapporteurs and the generation of assessment reports from which final recommendations can be made for consideration by individual ZAZIBONA Member States. Products that have already been registered in any ZAZIBONA country or other products jointly accepted by participating authorities are eligible to use the collaborative process, provided there is an agreement between the participating countries. It is important to note that the invited generic products exclude those which have been WHO prequalified and/or registered by Stringent Regulatory Authorities (SRA); other accelerated registration mechanisms can be used for such products. Innovator products which have not been registered by SRAs are accepted for the ZAZIBONA collaborative procedure. Manufacturers based in the six countries involved in the collaboration are also encouraged to apply.

**Figure 5: ZAZIBONA Process Design<sup>13</sup>**



The ZAZIBONA initiative has evaluated 154 product applications over 13 meetings from October 2013 to November 2016. Out of these 154 product evaluations, they have made a final decision for 90 products (56% approved, 33% rejected and 11% withdrawn). The remaining 64 products have been queried. The mean time to recommendation is estimated at 9 months.



## **ECOWAS-MRH Project**

The MRH program in the West African region was launched in 2015 in Accra, Ghana<sup>12</sup>. The NEPAD Agency, together with the AMRH partners, facilitated the program launch, which included the establishment of a joint MRH Program Steering Committee and formation of seven Technical Working Groups (TWGs). The Steering committee has managed to align the Common Technical Document (CTD) requirements for the West African Health Organization (WAHO) and the West African Economic and Monetary Union (UEMOA) with technical support from WHO<sup>2</sup>.

WAHO has provided support to the Economic Community of West African States (ECOWAS) since 2009, when a five-year plan was implemented to strengthen registration harmonization, regulatory management, quality control of medicines, pharmaceutical production, current Good Manufacturing Practices (cGMP) and pharmacovigilance across the region<sup>12</sup>. UEMOA is the organization representing the francophone west African countries. Additionally, WAHO and WAEMU have an established collaboration framework and a joint three-year plan of action (2014-2016) for implementation of the MRH program in this region. Through the TWGs, the region will now begin developing technical guidelines. A series of collaborative activities between regional agencies have also been undertaken as part of capacity and confidence building among the NMRAs.

## **Other-MRH Projects**

- North/Northeastern Africa

The consultations regarding AMRH in North/Northeastern Africa began in December 2010 in the Intergovernmental Authority on Development (IGAD) region<sup>12</sup>. In April 2016, the IGAD Member States signed the Khartoum Declaration to Call for Action towards the implementation of a regional medicines regulatory collaboration and harmonization program. This took place during the 2<sup>nd</sup> IGAD Regional Medicine Regulatory Authorities Conference on Regulatory Collaboration and Harmonization held in Khartoum. One of the recommendations of the Khartoum Declaration was to strengthen NMRAs with inadequate regulatory systems, as well as to strengthen partnerships between IGAD Member States to ensure regulatory harmonization<sup>2</sup>.

- Central Africa

In 2013, the Heads of State of the Economic and Monetary Community of Central Africa (CEMAC) Member States adopted the Common Pharmaceutical Policy (CPP)<sup>12</sup>. The Organization for the Fight Against Endemic Diseases in Central Africa (OCEAC) is responsible for the coordination of health programs in the region. To initiate activities in the Central Africa region, the NEPAD Agency, in collaboration with ECCAS, OCEAC and the WHO, developed a collaborative framework to spell out activities with clear roles and responsibilities for partners involved in the implementation of the AMRH Program. A mapping exercise was carried out in 2016 to establish the status of regulatory systems in Member States. This will help inform the AMRH project development process. A Steering Committee for the implementation of the MRH Project in the CEMAC was launched in November 2016 to provide oversight in the implementation of joint activities. This committee will serve as an entry point for the implementation of the MRH Project in the Economic Community of Central African States (ECCAS).

## **Conclusion**

In recognition of the obstacles in the field of medicines registration, the AMRH program has made significant progress and has mobilized both technical and financial resources to advance the medicines regulatory harmonization in Africa. The program has recorded concrete milestones, especially in the EAC and SADC regions, where harmonized regulatory frameworks have been established and implemented. However, more work is required to realize the African Union Vision, which is to establish a single African Medicines Agency (AMA) by the end of 2018. The establishment of the AMA will build upon the preexisting structures of the Regional Economic Communities (RECs) and Member States that have already started implementing the AMRH programs within the framework of the Pharmaceutical Plan for Africa (PMPA). More work is required to drive the AMRH implementation processes in other Regional Economic Communities, such as the North/Northern East Africa and the Central Africa.

## About WCG

WCG is a non-profit organization committed to empowering, educating and enabling women and girls to make informed choices and access critical reproductive health products and services. WCG excels at forming strategic partnerships to introduce and create access to new contraceptive methods around the world. WCG's Quality and Regulatory department is experienced in global registration of drugs and devices, and in aiding manufacturers to improve their processes to meet international best practices. WCG's credentials in product introduction have made it a preferred partner of organizations looking to move products from laboratories and manufacturing plants to the women who need them. We create options for women when it comes to their reproductive health-no matter where they live. For more information, please visit [www.wcgcares.org](http://www.wcgcares.org)



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## **ANNEXURE 1**



**EAST AFRICAN COMMUNITY**

## **NOTICE TO APPLICANTS**

**EAST AFRICAN COMMUNITY'S PROCEDURE FOR MARKETING  
AUTHORIZATION OF MEDICINAL PRODUCTS**

## 1. INTRODUCTION

Marketing Authorization (MA) is the process of assessing and accepting the dossier to support a medicinal product in view of its marketing, finalized by granting of a document also called marketing authorization. This process is performed within a legislative framework which defines the requirements necessary for application to the concerned medicine regulatory authority, details on the assessment procedure (based on quality, efficacy and safety criteria) and the grounds for approval or rejection of the application, and also the circumstances where a marketing authorization already granted may be withdrawn, suspended or revoked.

As part of implementation of provision of EAC Treaty on Regional Cooperation on Health, Chapter 21, Article 118, the EAC Secretariat in collaboration with EAC Partner States National Medicines Regulatory Authorities (NMRAs) initiated the process of harmonizing requirements for the regulation of medicines through the legal mandate of the existing National Medicines Regulatory Authorities (NMRAs) in each of the EAC Partner States with the primary goal of increasing access to and affordability of safe, efficacious and good quality medicines in the region. The East African Community Medicines Regulatory Harmonization (EAC-MRH) programme is implemented collaboratively by all the six (6) NMRAs in the region, namely **Department of Pharmacy, Medicines and Laboratories (DPML)** - Republic of Burundi, **Pharmacy and Poison Board (PPB)** Republic of Kenya, **National Drug Authority (NDA)** - Republic of Uganda, **Pharmacy Task Force (PTF)**, Ministry of Health - Republic of Rwanda and **Tanzania Food and Drugs Authority (TFDA)** and **Zanzibar Food and Drugs Board (ZFDB)** - United Republic of Tanzania.

The EAC Medicines Regulation Harmonized guidelines, requirements and standards for Medicines Evaluation and Registration (MER), Good Manufacturing Practice (GMP) and Quality Management System (QMS) as approved by the EAC Council of Ministers (**EAC/CM29/DECISION 36/09/20/2014**) on 20<sup>th</sup> September 2014 will become effective, January 2015.

## 2. Procedures for marketing authorization in the EAC

Currently, the East African Community has no Regional Medicines Regulatory Agency, which has legal mandate for marketing authorization of medicinal products. In view of this, and within the framework of the East African Community Medicines Regulatory Harmonization (EAC MRH) project, medicines will be authorized through the national authorization procedure, joint assessment procedure and WHO collaborative procedure.

### 2.1 National authorization procedure

2.1.1 Each EAC Partner State has its own procedures for the authorization of medicines, within their own territory, that fall outside the scope of the joint assessment procedure and WHO Collaborative procedure. Information about

these national procedures can be found on the website of the National Medicine Regulatory Authority (NMRA) in the country concerned.

2.1.2 This procedure will give marketing authorization in EAC Partner State(s) where application was submitted.

## **2.2 Joint assessment procedure**

2.2.1 This is a procedure for joint assessment by the National Medicines Regulatory Authorities (NMRAs) of the EAC Partner States in the assessment of selected medicinal products, inspection of their respective manufacturing site(s) followed by national approval of jointly accepted medicinal products.

2.2.2 Once the assessment of medicinal products dossiers is complete and jointly accepted, the EAC NMRAs will grant marketing authorization within three (3) months from the date of final assessment and joint acceptance.

2.2.3 The Marketing Authorization Holder (MAH) can begin to make the medicine available to patients and healthcare professionals in EAC countries where marketing authorization has been granted.

## **2.3 WHO Collaborative procedure**

2.3.1 This is a procedure for collaboration between the WHO Prequalification of Medicines Programme (WHO/PQP) and interested National Medicines Regulatory Authorities (NMRAs) in the assessment and accelerated national registration of WHO prequalified pharmaceutical products.

2.3.2 In this procedure, participating authorities are those NMRAs that voluntarily agree to implement this collaborative procedure and accept the task of processing applications for registration of WHO-prequalified pharmaceutical products in accordance with the terms of the Procedure. A list of participating authorities including EAC Partner States' NMRAs is posted on the WHO/PQP web site (<http://www.who.int/prequal/>).

## **3. Scope of products under the EAC Joint Assessment Procedure**

The scope of medicinal products covered in joint assessment procedure includes the following:-

- (a) Priority medicines as defined in the Essential Medicine List of individual Partner States;
- (b) Medicines termed as Life Serving Commodities (LSC) by the UN Commission on Life Serving Medicines for Women and Children;
- (c) Officially designated 'orphan medicines' (medicines used for rare human diseases)/ medicines for treatment of neglected tropical diseases;
- (d) Anti-cancer medicines;



- (e) Paediatric preparations;
- (f) Medicines not invited for assessment within the scope of WHO Prequalification Programme.

#### **4. Mode of application in the EAC Joint assessment procedure**

##### **4.1 Invitation of Expression of Interest (EOI)**

- 4.1.1 At regular intervals and in consultations with EAC NMRAs, the EAC Secretariat will publish an invitation for expression of interest, requesting the interested parties to participate in this procedure in respect of the products mentioned in the invitation.
- 4.1.2 By submitting an expression of interest, the applicant undertakes to share same information with all EAC-Partner States NMRAs on all relevant aspects of quality, safety and efficacy of the specified medicinal products along with changes carried out and/or planned. The invitations will be published on the EAC Secretariat and NMRAs websites and other media as may be required.
- 4.1.3 In situations of high public health concern as determined by EAC NMRAs, the EAC Secretariat in consultation with EAC Partner States' NMRAs may directly invite relevant parties to submit specified products for assessment under this procedure without publication of an invitation for expressions of interest.

##### **4.2 Data and Information to be submitted**

- 4.2.1 Applicant should submit soft copies of the product dossier(s) with the required information to all EAC NMRAs.
- 4.2.2 In submitting an EOI for medicinal product evaluation, the applicant should send to all EAC NMRAs the following:-
  - a) A covering letter, expressing interest in participating in the EAC MRH programme and confirming that the information submitted in the product dossier is complete and correct;
  - b) A product dossier, in the format specified in the EAC Guidelines on Submission of Documentation for Registration of Human Medicinal Products;
  - c) Product samples, to enable visual examination and laboratory analysis;
  - d) A site master file for each manufacturing site listed in the product dossier, in the required format specified in the EAC harmonized guidance documents for submitting a site master file;
  - e) Evidence of payment to all EAC Partner States' NMRAs where the product is not registered;

4.2.3 Fees to be paid by the applicants to the EAC NMRA will continue to follow national fees regulations.

### **4.3 Screening of Dossiers submitted**

4.3.1 Each product dossier submitted by an applicant will be screened within two weeks by the lead country in medicines evaluation and registration for completeness.

4.3.2 In the event the dossier is incomplete, the applicant will be informed and requested to complete the dossier.

4.3.3 Dossiers that are considered complete as the result of the administrative screening will be retained by the lead country for evaluation process.

### **4.4 Dossier Assessment**

4.4.1 The product information submitted in the dossiers will be sent to two selected lead EAC Partner States NMRA for first and second assessment.

4.4.2 The allocation of the application for assessment will be done by a coordination committee established.

4.4.3 First assessment by the selected lead country will be done within a period of one month from the date of acceptance of the application after screening and second assessment will be done after conclusion of first assessment within a period of one week.

4.4.4 Selection of the assessors will follow the EAC Standard Operating Procedure (SOP) for selection of medicines assessors to participate in joint assessment of medicinal product dossiers.

4.4.5 Dossier assessment shall be done prior to GMP and if applicable, GLP and GCP inspections.

4.4.6 The assessment report shall be circulated to team of assessors appointed by the EAC Partner States NMRA for comments prior to convening of the joint meeting.

4.4.7 There shall be a joint assessment session to compile comments from all assessors and finalize the assessment report.

4.4.8 Queries/ Communications arising from the meeting will be compiled by the lead country Medicines Evaluation and Registration and sent to the applicants/manufacturers within two weeks.

4.4.9 If any additional information is required, applicant will be required to provide such additional information to the lead country within 60 days. EWG on MER will

postpone its decision of the acceptability of the respective product dossier, until such information has been evaluated and found satisfactory in light of the specified standards.

- 4.4.10 Upon receipt, the responses to the queries shall be assessed immediately by the Partner State, which did first assessment and circulated for comments by all NMRAs.
- 4.4.11 The assessment reports will be shared to the departments responsible for registration in the NMRAs.
- 4.4.12 The EAC Partner States NMRAs, during the process of execution of the mandate has the right to bring on board technical support and expertise from WHO or any other stringent MRA, for the purpose of support and capacity building.

#### **4.5 Site Inspection**

Site(s) inspection shall be conducted in accordance with the EAC procedure for conducting GMP inspections

#### **4.6 Reporting and communication of the results of assessment**

- 4.6.1 The team of assessors will finalize its report from the joint assessment session according to the established EAC SOP and format, describing the findings and including recommendations and issues to communicate to applicant, manufacturer(s) and/or testing unit(s) or organization(s), where relevant.
- 4.6.2 The EAC NMRAs reserve the right to terminate the procedure of assessment of a specific product if the applicant is not able to provide the required information within six months and no written request for extension of time has been submitted.
- 4.6.3 In the event of any disagreement between an applicant and EAC NMRAs, an SOP established by the EAC NMRAs for the handling of appeals and complaints will be followed to discuss and resolve the issues.
- 4.6.4 The EAC NMRAs shall be entitled to use and publish public assessment reports, subject to the protection of any commercially confidential information of the applicant, manufacturer(s) and/or testing organization(s) [5].

#### **4.7 Outcome of Joint Assessment Procedure**

- 4.7.1 Once the EAC NMRAs are satisfied that the assessment process is complete for the relevant product, and that the EAC harmonized requirements and standards are met, the product, as produced at the specified manufacturing site(s), a notification letter on completion of assessment of the dossier will be issued by the EAC Secretariat to the applicant/manufacturer.

4.7.2 The letter shall state that the final registration outcome will be communicated by the respective NMRAs.

#### **4.8 Maintenance of registration status**

The registered products shall be maintained in each NMRA's list of registered products subject to:-

- 4.8.1 Continued compliance with requirements of quality, safety and efficacy.
- 4.8.2 Payment of retention fees in accordance with respective NMRA's Fees Regulations in force.
- 4.8.3 The MAH communicates details to EAC NMRAs of any changes (variations) made to the registered product following the EAC harmonized guidelines on variations to a registered product.
- 4.8.4 The MAH applies for renewal of their products in accordance with EAC Guidelines on Procedural Aspects for registration of medicinal products.
- 4.8.5 Continued GMP compliance of the manufacturing site(s).
- 4.8.6 Continued compliance with National Health Policies and any other directives.

## **ANNEXURE 2**

# ZAZIBONA Collaborative Medicines Registration

## Alternative/Expedited process to register medicines via the ZAZIBONA collaborative process

Version 01

Date 9 June 2015



Zambia



Zimbabwe



Botswana



Namibia

## **Introduction**

The ZAZIBONA process is a collaboration between national medicines regulatory authorities (NMRAs) in Botswana, Namibia, Zambia, and Zimbabwe. These are four neighbouring countries in Southern Africa which have a combined population of around 34 million. This process may be extended to include participation by other interested SADC Member States.

The vision of the ZAZIBONA process is :

- a region in which good-quality medicines are available to all those who need them;
- significantly reduce time taken to grant marketing authorisation in the individual countries; and
- efficient utilisation of resources within regional national regulatory through work sharing.

The process objective is to promote a collaboration model to facilitate access to good-quality medicines through worksharing in assessment of medicines and inspection of medicine manufacturing and testing facilities. Products that meet assessment criteria are then granted marketing authorisation in the participating countries, in which applications for registration would have been submitted. Where countries agree that is necessary, variations to the products which have been registered under this collaboration may be handled through the same process.

The ZAZIBONA collaboration does not represent the replacement of the need to submit applications for registration in participating countries in line with national requirements. However, as described in this document, in order to facilitate cooperation among ZAZIBONA authorities, certain modifications are expected. Although there is close collaboration on assessments and inspections, final national registration decisions are the responsibility of individual participating authorities.

It is envisaged that manufacturers of needed medicines will benefit from accelerated registration processes, a single set of questions during the registration process and in principle harmonized registration decisions, which will facilitate easier review of any post-registration variations. Applications may be submitted by any person that qualifies to be an applicant in each participating country as per national requirements.

### ***Scope of products***

Any medicine meeting the criteria of being an essential medicine is invited for submission to be considered for registration via the ZAZIBONA collaborative process. Special consideration may be given to medicines that are vital to effective treatment and to expanding treatment programmes, where there are currently limited options for health practitioners in the participating countries. This includes medicines identified for special regional programmes and initiatives.

The focus will however be on the 10 priority disease conditions identified by SADC (Annex 1) plus reproductive health products. Priority will be given to the products included in the List of UN Commission for Live-Saving Commodities for Women and Children.

Any other medicines that are important from a public health perspective may be considered on a case-by-case basis.

### ***Other eligibility criteria***

To be eligible for the ZAZIBONA collaborative process an application should have been lodged with at least two (2) ZAZIBONA participating countries.

Products registered by stringent regulatory authorities (SRA) are eligible for an abridged review process provided there access to the assessment reports for which the authorisation was based on.

### ***Applications not eligible***

The invited generic products exclude those which have been prequalified by the World Health Organization (WHO), for which an accelerated registration mechanism (WHO PQ Collaborative Registration Process) can be applied.

Applicants are encouraged to make pre-submission consultations on eligibility of their products with their respective national authorities.

### ***Application submission process***

As a condition for a medicines dossier to be included in the collaborative process an application should be submitted according to current country requirements plus the additional ZAZIBONA requirements which include an agreement to consent to information sharing among participating regulatory authorities. All participating countries shall treat the shared information as confidential in line with applicable national legislation and arrangements.

In applying for a product registration through the ZAZIBONA collaborative process, applicants are requested to submit a covering letter (clearly indicating their interest to participate in the ZAZIBONA process), a product dossier in the Common Technical Document (CTD) format, product samples and a Finished Pharmaceutical Product (FPP) site master file to all the participating countries according to the individual national requirements. The submissions should comply with the harmonised SADC Registration Guidelines.

The national specific requirements include especially:

- Application fees
- Statutory forms to be completed and to accompany a specific national application
- Country specific labelling requirements

Potential applicants are further advised that participating countries reserve the right to accept or refuse submissions to be considered for this collaboration on a case by case basis. Each NMRA retains the right to assess submitted data and organize site inspections to the extent they deem appropriate.

Applicants are encouraged to submit applications for inclusion in the collaborative process at least 1 month before the meeting of assessors which considers applications received and assignment of rapporteurs. Early submissions facilitate the administrative screening of applications before the meeting of assessors. Assessment meeting dates are published on participating authority websites.

Documents to be submitted are in Annex I



The collaborative process is designed to achieve registration within a total time of 11 months, during which the applicant will have two windows of opportunity to respond to consolidated lists of regulatory assessment questions within a period of 60 days. Total regulatory time for collaborative process is therefore 210 days, which corresponds to regulatory deadlines of established regulatory authorities. Timelines for collaborative process starts at the point of allocation of rapporteurship i.e. within 1 month of the submission, followed by 10 weeks for initial assessment, 2 weeks for sharing assessment report, 8 weeks for the manufacturer/supplier or applicant to respond, and 2 weeks to process the response. The specified timelines are only indicative and may vary depending on the specific dates of the assessment sessions. Products are only considered for 2 review cycles (for the responses) thereafter a final recommendation will be made. The target timelines may vary depending on the number of submissions relative to the available technical capacity of the participating NMRAs. A NMRA reserves the right to make a final determination on any application and may request further information.

Each NMRA will be required to finalise the registration process within a reasonable timeframe after the final recommendation from the collaborative process depending on the schedules of the meetings for the Authorities/Boards/Committees responsible for final regulatory decision at national level.

Additional information can be obtained from focal persons in ZAZIBONA participating NMRAs.

#### Annex 1: Top conditions/diseases in SADC with an overall regional priority ranking

|  |    |
|--|----|
| HIV/AIDS                               | 1  |
| Tuberculosis                           | 2  |
| Malaria                                | 3  |
| Acute respiratory infections           | 4  |
| Diarrhoea                              | 5  |
| Diabetes                               | 6  |
| Pneumonia                              | 7  |
| Cardiovascular                         | 8  |
| Cancer                                 | 9  |
| Obstetrics,<br>Gastroenteritis & colic | 10 |

**Annex I: Documents to be Submitted with an Application for the ZAZIBONA  
Collaborative Process**

NB: You should read the current Alternative/Expedited process to register medicines via the ZAZIBONA collaborative process. The document gives information on which products are invited for assessment in this collaborative process.

1. Covering letter, in English, expressing
  - 1.1. interest in participating in the ZAZIBONA process and information, whether the product is already registered in any ZAZIBONA participating country,
  - 1.2. confirmation/attestation that the information submitted in the product dossiers is "true and correct",
  - 1.3. confirmation/attestation that the same<sup>1</sup> dossier and data have been submitted to all participating countries,
  - 1.4. consent with sharing of the product related information during registration and in the post-registration period among ZAZIBONA participating authorities and with WHO staff and external experts, who support the process and are bound by confidentiality undertaking; and
  - 1.5. commitment to apply for the same variations and post-registration changes in all ZAZIBONA participating countries where the product is registered.
2. Product dossier, in English, organized in CTD format for submitting product data and information. For the purpose of generic medicine registration, data demonstrating quality of raw materials (Active Pharmaceutical Ingredients and Excipients) and FPP are necessary, as well as demonstration of bioequivalence with an acceptable comparator. Details are specified in the relevant guidelines that reflect the harmonized SADC position. Paper and electronic copies of the dossier should be submitted as per national requirements.
3. A product sample (for example a package of 100 tablets), for evaluation of product appearance, container material and labelling, and also to enable, under exceptional circumstances, chemical and pharmaceutical analysis. Where sample labelling does not comply with national requirements or the proposed final labelling, mock-up labels demonstrating design of final labelling should be submitted.
4. A site master file, for each manufacturing site of the medicine, in the requisite format.

## **How to organize the documentation**

*The documentation should be submitted in English in the format described below. Please follow specific country requirements for number of copies required.*

For the product dossier the structure and format of the Common Technical Document (CTD), agreed within the framework of the International Conference on Harmonisation (ICH, see web site: <http://www.ich.org>) or the SADC CTD Format should be followed.

The submission of the documentation should be both electronic and paper copy (as per specific country requirements) otherwise only electronic should be submitted.

The submission should therefore include

1. A cover letter expressing interest (See template), and
2. An appropriately filled out QOS-PD<sup>2</sup> (Quality Overall Summary - Product Dossier) in Word format, and

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<sup>1</sup> Specific national administrative documents, labelling and product information texts as submitted in the module 1 of the dossier do not represent a difference between dossiers of the same technical content.

3. An appropriately filled out QIS<sup>3</sup> (Quality Information Summary) in Word format, and
4. An appropriately filled out BTIF (Bioequivalence Trial Information Form) or BW-BCS<sup>4</sup> Biowaiver Application Form: Biopharmaceutics Classification System) (where applicable) - in Word format or BW-BCS Add Strength <sup>5</sup> (Biowaiver Application Form: Additional Strength) (where applicable) - in Word format, and
5. The dossier according to CTD format *in word or text selectable PDF* (see documentation requirements section); and
6. A copy of the current Site Master File for all the proposed FPP manufacturing sites.

Currently the only accepted word formats of the summaries and forms are as per WHO PQ. Please follow links below to access the current version.

#### *Electronic submission*

A well labelled CD or DVD containing the electronic documentation should be organized according to the CTD structure (Modules 1, Module 2, Module 3, Module 4 and Module 5) and this should be reflected in the corresponding file names. All CDs/DVDs should be numbered and the first folder should contain a Table of Content, reflecting the location of files as cross-referenced to the CTD format

The summaries of quality and bioequivalence files (QOS-PD, QIS and BTIF/BW-BCS) should be submitted in Word-format to facilitate the evaluation process.

Scanning of documents for electronic submission should lead to a file, which is readable and of reasonable size to allow scrolling (i.e. less than 5–10 MB).

#### *Paper copies*

Paper copies should be well organized according to the CTD structure, bound and paginated, and should include a Table of Contents. No loose sheets should be provided for any information submitted.

#### *Site master file (SMF) requirements*

An SMF<sup>6</sup> must be submitted - as an electronic copy (CD/DVD) only - for each proposed FPP manufacturing site. An SMF is a document prepared by the manufacturer containing information with respect to the production and/or control of pharmaceutical manufacturing operations carried out at the named site and to any closely integrated operations at adjacent and/or nearby buildings. If only part of a pharmaceutical operation is carried out at the site, the SMF need describe only those operations, e.g. analysis, packaging.

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<sup>2</sup> [http://apps.who.int/prequal/info\\_general/documents/generic\\_guide/QOS-PD\\_Nov2014.doc](http://apps.who.int/prequal/info_general/documents/generic_guide/QOS-PD_Nov2014.doc)

<sup>3</sup> [http://apps.who.int/prequal/info\\_general/documents/generic\\_guide/QIS\\_Dec\\_2013.doc](http://apps.who.int/prequal/info_general/documents/generic_guide/QIS_Dec_2013.doc)

<sup>4</sup> [http://apps.who.int/prequal/info\\_applicants/Guidelines/GuideGenericSubmitDocFPPs\\_01\\_2010\\_Annex7.doc](http://apps.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_01_2010_Annex7.doc)

<sup>5</sup> [http://apps.who.int/prequal/info\\_applicants/BE/BW-AddStrengthsApplicationForm\\_May2012.doc](http://apps.who.int/prequal/info_applicants/BE/BW-AddStrengthsApplicationForm_May2012.doc)

<sup>6</sup> [http://apps.who.int/prequal/info\\_general/documents/TRS961/TRS961\\_Annex14.pdf](http://apps.who.int/prequal/info_general/documents/TRS961/TRS961_Annex14.pdf)