Food, Medicine and Health Care Administration and Control Authority

Expediting Medicine Market Authorization Strategy

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Addis Ababa, Ethiopia

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Acknowledgments

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Abbreviations and Acronyms

AMRP   Abbreviated Medicine review process

APIMF/DMF   Active pharmaceutical ingredients/Drug substances Master File

BP   British Pharmacopeia

cGMP   Current Good Manufacturing Practice

CPP   Certificate of pharmaceutical products

EDQM   European Directorate for Quality of Medicine

EFMHACA   Ethiopian Food, Medicine & Healthcare Administration and Control Authority

EMA   European Medicine Agency

FPP   Finished pharmaceutical ingredients

HSTP   Health Sector Transformation Plan

HRSTP   Health Regulatory Sector Transformation Plan

ICH   International Conference for Harmonization

MCC   Medicine Control Council

MRIS   Medicine Registration Information System

MoH   Ministry of Health

MOU   Memorandum of Understanding

OTC   Over the Counter

PQAD   Product Quality Assessment Directorate

QA   Quality Assurance

QC   Quality Control

SADC   South African Development Community

SRA   Stringent Regulatory Authority

TGA   Therapeutics Goods Administration of Australia

USFDA   United States Food and Drug Administration

WHO   World Health Organization

USP   United States Pharmacopoeia

Forward of Director General

Ethiopia has been putting tremendous efforts in implementing the National Medicine Policy (1993) and Health Sector Development Programme (HSDP) since the last two decades. During this period, our country has made huge strides to improve access to safe, quality and efficacious medicines to the public. The political commitment and good leadership, community mobilization with the concept of community ownership and strengthening collaboration & partnership has remarkably improved the health system in Ethiopia.

Currently, the government of Ethiopia has committed to improve quality and equity of the health services. This is expressed through the national Growth and Transformation Plan II (2015/16-2019/20), National Strategy and Plan of action for Pharmaceutical Manufacturing Development in Ethiopia (2015-2025) and National Health Sector Transformation Plan (2015/16-2019/20). Recognizing this, the Authority has developed Health Regulatory Sector Transformation Plan, HRSTP (2015/16-2019/20) and actively implementing regulatory activities and initiatives to ensure that medicine regulations are streamlined, effective and efficient. These strategies and plans aim to assist pharmaceutical companies and create conducive environment for the growth of the pharmaceutical industry and scaling up of medicine export.

Despite the impressive progresses made, the Authority still confronted with new and increasingly complex challenges. The infiltration of illegal medicines to the market, unprecedented shortages of critical medicines, limited number of approved quality medicines and long waiting time for registration are some of the challenges. The medicines dossier assessment, cGMP inspection and quality testing procedures did not keep pace with the increasing demand of the pharmaceutical industries for marketing authorization and the public need for quality and safe medicines. To overcome those challenges, the Authority has set a strategy having options to expedite medicine market authorization. This strategy builds upon previous successes and challenges, and the current global experiences.

In the strategy, we have set transformation procedures for medicines dossier assessment, cGMP inspection, quality testing, and communication and collaboration procedures. I believe that successful implementation of this strategy will help us to achieve the demands of our people to access safe, quality and effective medicines. Hence, I call up on health professionals, civil societies,

pharmaceutical organizations, development partners and all stakeholders to put a coordinated effort to realize these strategies.

I have no doubt that with the unwavering government commitment, engagement and ownership of regulations by the community, the commitment to comply regulatory requirements by the applicants for market authorization, the steadfast commitment of our staffs for our people, and the support of our development partners, we will prevail to meet the market authorization strategy.

Finally, I would like to take this opportunity to acknowledge and express my appreciation to the United States Agency for International Development (USAID) and the U. S. Pharmacopeial Convention Promoting the Quality of Medicines Program (USP/PQM) for the financial and technical support; United Nations Population Fund (UNFPA) for financial support and to all those experts who have directly or indirectly extended their helping hands in the preparation of this strategy.

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Yehulu Denekew Alemneh

Director General

Ethiopian Food, Medicine and Healthcare Administration and Control Authority

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1. Background

In the last two decades, the government of Ethiopia has been putting tremendous efforts in implementing policies and strategies including the National Medicine Policy (1993) and the 20-year Health Sector Development Programme (HSDP). The political commitment and good leadership, community mobilization with the concept of community ownership and strengthening collaboration and partnership has remarkably improved the health system in Ethiopia.

Currently, the government of Ethiopia has committed to improve the quality and equity of the health services to the public. This is vividly expressed in the national Growth and Transformation Plan II (2015/16-2019/20), national strategy and plan of action for pharmaceutical manufacturing development in Ethiopia (2015-2025) and national Health sector Transformation Plan, HSTP (2015/16-2019/20). These strategies and plans aim to assist local pharmaceutical companies and create conducive environment for the growth of the pharmaceutical industry which believed to be a success for the establishment of pharmaceutical industrial parks and scaling up of medicine export.

In line with those strategies and plans, the Authority has developed HRSTP and actively implementing regulatory activities and initiatives to ensure that medicine regulations are streamlined, effective, efficient and accessible to the community. As a result the accountability, transparency and effectiveness of the medicine regulations has improved and the Ethiopian medicines regulatory process is now characterized by an inclusive approach that relies extensively on consultation with public, trade and professional associations, academic institutes and other relevant stakeholders.

Although these efforts have shown significant progress towards the vision of the Authority; EFMHACA is still confronted with new and increasingly complex challenges. This can be expressed by the impact of increasing country's foreign trade with porous border that created the risk of infiltration of illegal medicines on one hand and unprecedented shortages and affordability of critical medicines on the other hands.

Moreover, the limited number of approved quality medicines and the existence of illegal medicines on the market reflect unaddressed assignment in pharmaceutical regulation and has a direct impact on the health systems as a whole. This means, medicines dossier assessment, cGMP inspection and laboratory testing process did not keep pace with the increasing demand of the pharmaceutical

industries for marketing authorization and the public need for quality and safe medicines. The slow pace at which medicines were being registered mainly is ascribed to a lack of skilled human resources, poor regulatory infrastructure and inefficient regulatory processes. These challenges have made the Authority accused of delaying patients' access to essential medicines in the past few years and put under considerable pressure to increase the rate of medicines market authorization.

To overcome those challenges; the Authority has been implementing different initiatives for expedited medicine market authorization. The following are the main initiatives that have been implemented at national level by the Authority.

- Set and implemented different Market Authorization procedures such as" **fast track registration procedure**", and "**SRA procedure**"
- Created pool of trained assessors by giving training to pharmacy professionals from different directorates of the Authority, regional regulatory bodies and universities; and involving them in dossier assessment work.
- Undertaken initiative called *"zero backlogs flagship initiative"* to take the backlog of applications to zero.
- Consultation and collaboration with the academic institutions with respect to dossier assessment works and introducing the teaching of the regulatory sciences at MSc level.
- Developed medicine registration information system (MRIS) to automate the medicine registration process

Thus, taking these efforts further including extending to the other functions of the Authority such as cGMP inspection and quality control analysis and sighting in to additional strategies is found crucial. It is also equally important to follow risk based approach in implementing the activities performed in the marketing authorization process. This is because all activities have not the same risk and not all medicines carry similar risk to end users. Hence, designing an expedited marketing authorization strategy is critical to the Authority's efforts to realize its obligation for effective and efficient protection and promotion of public health.

Therefore, the aim of this strategy will be to expedite market authorization of medicines and thereby increase access to safe, quality and efficacious medicines to promote and protect the public health.

2. Scope of the Strategy

This Strategy is applicable to medicines market authorization at national level

3. Objectives

3.1. General Objectives

The main objective of this strategy is to transform regulatory review processes and dramatically boost access to safe, quality and efficacious medicines through expedited market authorization process.

3.2. Specific objectives

- To ensure transparency and accountability in medicine market authorization
- To implement risk based regulatory approach in medicines dossier assessment, GMP inspection and quality testing there by ensure regulatory service quality.
- To establish mechanism to effectively utilize skilled human resources available inside and outside the regulatory Authority.
- To consistently and timely provide market authorization services that meet the needs and expectations of customers and enhance customer satisfaction.

4. Definitions

Market Authorization	An official document issued for the purpose of marketing or free distribution of a medicines after evaluation of safety, quality and efficacy of the product.
Stringent Regulatory Authority	Regulatory authorities which are recognized and listed as a stringent by the Authority
Abbreviated approval	An approval process that applied for medicines that had evidence of Stringent Regulatory Authority market authorization and had obtained cGMP inspection waiver from the Authority.
Risk based approach	A process that allows the regulatory Authority to classify or categorize medicines based on the risk they impose to the end user.
Regulatory review	A process which involves dossier assessment, cGMP inspection and quality testing of medicines to make regulatory decisions.
Authority	The Ethiopian Food, Medicine and Healthcare Administration and Control Authority

5. Mission, Vision and Values of the Authority

5.1. Mission

"To promote and protect the public health by ensuring safety and quality of products and health service through registration, licensing and inspection of health professionals, pharmaceuticals, food establishments and health institutions and provision of up-to-date regulatory information while promoting rational medicine use."

5.2. Vision

''Quality health services and products to all citizens''

5.3. Values and beliefs

The following values & beliefs are considered:-

- **Community first:** we'll serve the customer first, give priority to our customers with a sense of urgency in our service provision.

- **Integrity:** we will be honest, frank, dependable and willing to accept corrections from our customers

- **Openness:** we will be honest and will not be hiding anything to our customers. We'll provide information, be informative and a source of knowledge and excellence to our clients

- **Courtesy:** we want to be polite and very well-mannered in our relation to our customers and stakeholders

- **Responsiveness:** we want to reply and positively react to inquiries and complaints of our customers and collaborators

- **Timeliness:** we will be punctual with our customers encounters, would always be in time and on time.

- **Professionalism:** we will provide services that need special knowledge and training, which require expertly doing

- **Impartiality:** we will serve our customers, not favouring one side more than the other and with complete fairness.

- **Consistency:** we will provide our services in a regular or same manner

- **No compromise on quality**: we will serve without agreement to accept sub standards.

6. Situational Analysis of market authorization

ENABLERS	BARRIERS
1. Strength	2. Weakness

• Enthusiasm in achieving the mission of EFMHACA with the available human resource
 	
• Maintenance of ISO accreditation in Medicine Quality Control Laboratory
 	
• Top management commitment for change and to introduce automated information management system
 	
• Implementation of SRA and fast rack procedure
 	
• Creating training opportunities for dossier evaluators and inspectors
 	
• Implementation of MRIS system
	• Current regulatory review tends to treat all products equally.
	  ✓ A disproportionate amount of regulatory attention is devoted to low-risk products
	  ✓ Weak regulation of the distribution channel and availability of illegal medicine on the market.
	  ✓ Major focus was given to premarket testing of samples than post market monitoring
	
	• The existing fast track registration procedure focuses only on program medicines.
	
	• Limited information on the quality and quantity of medicines on the market
	
	• cGMP inspection is not well-connected to knowledge gained from dossier assessment.
	
	• Re-registration is not supported with cGMP inspection result
	
	• Approval of registration renewal for medicines which have not been marketed within the validity period of the license
	
	• Lack of list of EFMHACA approved APIMF: Repeated assessment of the same DMF from the same DMF holder when submitted by different FPP manufacturers
	
	• Medicine registration were supported through premarket testing on samples brought to the Authority directly from the facility irrespective

	of risk categorization
	• Limited human resource
	✓ Shortage of trained/experienced dossier assessors, cGMP inspectors and laboratory analysts
	✓ Experienced & skilled personnel turnover
	• Weak regulatory communication, coordination and collaboration
	✓ Weak regulatory collaboration with other countries regulatory Authority
	✓ Weak inter-sectoral coordination and integration within the country
	• Limiting local agents into three
3. Opportunity	**4. Threat**
• Quality and equity are taken as core transformation agendas in the health sector	• Corruption and rent seeking attitude
• The current government initiatives on local pharmaceuticals manufacturing.	• Unlimited number of local agent may create pressure on the regulatory Authority in traceability of medicines they distribute
• Government commitment to revise the existing proclamation No.661/2009	• Rapid technological advancement in the pharmaceutical industry
• Government commitment to implement good governance and supporting local manufacturing of medicines	• Availability of uncontrolled ports of entry and porous border
• Rapid technological advancement in the pharmaceutical industry	• Anti-microbial resistance and availability of illegal products that may be counterfeited
• Introduction of automated medicine registration information system	• Limitation of resources
• Better interests of teaching institutions on regulatory sciences and engagement	• Misunderstanding of the strategy by stakeholders during implementation

in of dossier evaluation initiatives • Availability of pool of trained dossier evaluators and cGMP inspectors • High willingness of international organization to support medicine registration system • The move on global community on medicine regulatory harmonization including IGAD initiative on regulatory harmonization • Better understanding of the impacts of pharmaceutical regulation in the health sector • High need for excellence in regulatory functions (Centre of excellence)	

7. Current problems and root cause analysis

SN	Current market authorization related gaps/problems	Root cause of the problems
1.	Current regulatory review, cGMP and laboratory testing tend to treat all medicines equally without considering the risk they might impose	• Applying the same Medicine Registration Guideline for all categories of medicines • Disproportionate regulatory attention is devoted to low-risk products and premarket controls • Major focus was given to the premarket testing of the samples than post market monitoring • Premarket sample testing as a prerequisite for marketing authorization for all medicines • Shortage of medicines
2.	The existing fast track procedure focuses only on program medicines	• Program medicines were assumed to be of priority importance in the medical system and lack of frequent updating of the list in collaboration with the responsible programs of MOH. • Weak implementation of regulatory incentives for orphan medicines. • The fast track concept is not applied for cGMP inspection by considering the medical need
3.	Limited information is available about quality and quantity of medicines on the market	• Lack of web based pharmaceutical information management system. • Insufficient survey on the quality and quantity of medicines on the market • Poor documentation and information handling
4.	Weak GMP inspection system	• cGMP inspection is not well-connected to knowledge gained from product dossier assessment. • Lack of site cGMP re-inspection and re-registration is not supported with cGMP re-inspection results

SN	Current market authorization related gaps/problems	Root cause of the problems
		• cGMP inspection is not conducted timely • Delay in response of cGMP report
5.	Lack of list of EFMHACA approved APIMF	• GMP inspection of the API supplier and assessment of DMF yet not started by EFMHACA • Repeated assessment of the same DMF from the DMF holder when submitted by different FPP applicant
6.	Existence of backlog applications for medicine registration	• Limited human resource in terms of experience, speciality and training • Market authorization processing is not as per the promised timeline • Increased demand for essential and innovative medicines • Incomplete dossier submission for registration • Experienced and skilled personnel turnover • Attitude of assessors towards balancing scientific knowledge with the existing medicine shortage
7.	Weak regulatory communication, coordination and collaboration	• Absence of system that enable regulatory communication, coordination and collaboration with other regulatory Authorities. • Weak inter-sectoral and inter-directorate coordination and integration • Absence of regulatory communication strategy

8. Country Experiences

Various countries experiences were reviewed using desktop review during the development of this strategy. Best practices on medicine market authorization were taken from developing and developed countries. The regulatory bodies whose experience on expediting medicine market authorization reviewed include USFDA, EMA, Health Canada, Japan, New Zealand, East African

community like Burundi, Kenya, Rwanda, Uganda and Tanzania; ZAZIBONA which includes Zambia, Zimbabwe, Namibia, and South Africa. Although the ground on which they expedite the review of regulatory approvals varies, all have procedure in place to expedite for marketing authorization. The details of these experiences are presented in annex II of this document.

9. Market Authorization Strategy

Health Authorities globally have recognized the need to provide a faster access for medicines with a high unmet clinical need for life-threatening conditions through establishing legal framework for the regulatory agency to work closely with sponsors during the development of the medicines and expedite the dossier assessment for registration based on early clinical data including the use of surrogate endpoints while confirmatory clinical studies are on-going and/or expediting the assessment of finished medicines by considering the medical need of the products based on established prioritization and assessment criteria.

In contrast, Ethiopia currently has limited formal expedited dossier assessment process including applications related to antimalarial, antiretroviral, anti-tuberculosis, reproductive health, anti-cancer, vaccines, medicines for orphan diseases, and medicines for emergent humanitarian aid that applied through fast track registration. Even though the time prioritization during the initial assessment of the dossier was taken in to consideration, assessment of the further information reply will follow the normal path and end up with the delay of the registration process. Moreover, the requirements for all medicines are the same. This means, the requirements for all application is the same except the time prioritization in case of fast track registration.

This is mainly due to the fact that the current EFMHACA medicine registration process tends to treat all products equally and requires a comprehensive suite of supporting data without considering the medical need of medicinal products. Furthermore, the registration process requires complete set of supporting scientific data in accordance with adopted ICH and WHO-guidelines limiting opportunities for early applications for registration based on early-phase clinical trials and for new generic and brand medicines which are already marketed for years in other countries, but not in Ethiopia, further delaying access to the medicine. As such medicines are considered to be new medicines in Ethiopia; registering such medicines is not a simple task for an applicant. For many Ethiopians suffering from life-threatening diseases who have run out of those treatment options, this timeframe is simply long and results in delay of the market authorization process.

Moreover, cGMP is a vital component of the pharmaceutical regulation and hence, compliance with cGMP is necessary condition for marketing authorization, in other words domestic and foreign products of pharmaceutical companies cannot sell or market their medicines without it in developed and some less developed countries. While cGMP compliance has not been universally adopted in developing world, the governments' in developing countries like Ethiopia are under pressure to ensure and comply with cGMP requirements when granting marketing authorization to products manufactured & imported from non-stringent regulatory agencies and to domestic pharmaceutical companies respectively.

Manufacturing of medicines requires inbuilt quality products and ensure quality assurance system to produce products that meet marketing authorization requirements. In other words, quality of product should be built in the process of product design and manufacture rather than testing on the end products. Moreover, there are several quality requirements that can't be tested in the product such as processing conditions, systems and manufacturing premises. Thus, inspection of manufacturing premises to assure consistency in production and avoid mix ups and contamination, on site audit of the manufacturing premises is indispensable without creating unnecessary delay to put the product on the market.

In general, the quality of medicines is a topic of global concern. The lack of reliable medicine quality assurance systems in many developing countries contributes to the proliferation of diseases, particularly those that have become resistant to first line medicines. Recent reports indicate that the availability of substandard and counterfeit medicines has reached disturbing proportions in many resource-limited countries. Some countries are addressing this problem by developing a medicines policy that has a country-specific quality control system. Ideally, a country's medicines regulatory authority conducts product pre-approval and post-marketing surveillance for locally produced and imported medicines. In reality, few countries do both, and priority shall be given to post-marketing surveillance.

Comprehensive evaluation of quality on premarket samples was a requirement for granting market authorization for the last couple of years in Ethiopia. Premarket testing may or may not always be an indicative of the expected quality of the products under investigation. Although there are a number of countries still required premarket testing as a prerequisite for authorization, they are facing time delay and associated grievance. The current thinking of laboratory testing worldwide are shifting on

samples withdrawn from commercial batches found in the market and/or from consignment at the port of entry rather than on samples submitted by the applicant for the purpose of marketing authorization.

Recognizing the negative impacts of premarket testing on market authorization delay and recalling the frequent recommendations from international organization on strengthening post registration regulatory activities, it is required to re-design the testing scheme, cut unnecessary processing times at different stages so as to contribute to improve medicine access on the market.

Thus, the Authority has designed strategic shifts to address those problems related to dossier assessment, cGMP inspection and quality testing so as to expedite the marketing authorization that enable the Authority to solve problems related to quality, access, and affordability of medicines.

Conducting GMP inspection following product dossier assessment will create an opportunity for recommendations for the inspectors. Hence, cGMP inspection will be carried out after Dossier assessment. cGMP re-inspection is as equally important as new inspection and the re-inspection on EFMHACA cGMP approved or waived sites may be conducted as appropriate within the validity period of marketing authorization. Products from re-inspected sites will be directly re-registered based on the re-inspection report provided that annual retention fee is introduced and no variation was made to the exiting registration.

The achievement of marketing authorization strategy requires the implementation of several measures and creation of conducive regulatory environment for local and foreign pharmaceutical manufacturers as well as for professional expertise working in the regulatory sector. Once this strategy is translated in to practice by the Authority, it will positively influence the Health Regulatory Sector Transformation Plan. The strategy sets out details how to expedite the market authorization process in Ethiopia. Considering this, the following strategic directions will be taken in to action.

Strategic Directions for Market Authorization

9.1. Dossier Assessment Strategic Directions

9.1.1. Risk based dossier assessment approach

9.1.2. Expedited assessment (conditional, Abbreviated and Collaborative)

9.1.3. Fast track designation of priority products

9.1.4. API suppliers and APIMF approval scheme

9.1.5. Mutual recognition approach

9.1.6. Waiving re-registration assessment

9.1.7. Outsourcing of dossier assessment

9.1.8. Use of external assessors

9.2. GMP Inspection Strategic Directions

9.2.1. Risk based inspection approach

9.2.2. Mutual recognition approach

9.2.3. The fast track designation of priority for cGMP inspection

9.2.4. Outsourcing of cGMP inspection

9.2.5. Use of external inspectors

9.3. Laboratory Testing Strategic Directions

9.3.1. Risk based testing approach

9.3.2. Consignment testing

9.3.3. Premarket testing for sterile products and local produced medicines

9.3.4. Strengthen pharmacovigilance and post market surveillance

9.3.5. Outsourcing of laboratory testing

9.3.6. Use of external analysts

9.4. Common Strategies

9.4.1. Strengthen regulatory communication and collaboration

9.4.2. Establish training capacity building system and research centre

9.4.3. Support local manufacturing of medicines

9.4.4. Regulatory collaboration and Harmonization

10. **Description of each Strategic Directions**

10.1. Strategic Direction for Dossier Assessment

10.1.1. **Risk based dossier assessment approach**

Considering the risk the products may impose on patients, medicines can be classified into low risk and high risk products based on their type, dosage forms, their origin etc.; and depth of dossier assessment. Hence, the Authority will limit itself to a 'partial review' concentrating on the assessment of administrative requirements, product information and specifications, stability and shelf life, and others as applicable. However, full and rigorous dossier assessment will be conducted for the dossier of the product designated as high risk product.

a. **Dossier evaluation of low risk products**:- Waiving routine dossier assessment for low risk medicines based on their history of registration and market history in other countries for which their categorical list will be developed & updated by the Authority annually. Market authorization from other countries of such products will be used as an evidence for registration purpose. However, administrative documents will be required. Low risk products classification or categorization will be based on the criteria set in annex I of this document. Examples of products that are certain category of OTC including any medicines having medical claim with low risk and multivitamins**.**

b. **Dossier evaluation of high risk products:-** For the assessment of high risk medicines, full dossier data will be required and hence much time of the assessors will be spent on rigorous and extensive evaluation of such products. The general approach for categorization of high risk products are described in annex I of this document. Examples of products considered as high risk class during assessment are; New products (not marketed in the country); biological and immunological products; generic products with poor bioavailability, complex formulations etc. (e.g. sterile product, products with poor stability); medicines with narrow therapeutic index; medicine for major public medical problems of the country: ARV, anti-TB, anti-Malaria etc. To successfully implement the risk based approach, the medicine registration guideline will be revised. This should be the first action to be taken by the Authority. So that, well defined procedures and science based regulatory requirements ensuring transparency, optimal use of resources within specified timelines will be in place for the benefit of patients.

c. The dossier assessment processes should rely on quality risk management principles in the management of resources as well as in the management of product-related risk factors and the medical need of such products. The prioritization of dossiers for assessment based on identification of the specific risk factors will be used for allocation of resources (time and assessors) on a dossier for a given product based on their expertise. That means the current generalist approach will gradually shifted to the area of expertise based on the professional background and experiences.

d. Certificate of pharmaceutical product as a requirement for registration could be optional provided that valid cGMP Certificate or Market Authorization Certificate were submitted. If CPP is submitted along with the medicine registration dossier; the requirement for CPPs to be authenticated by the consulate of the certifying country and or the nearby Ethiopian Embassy at the country of origin is not mandatory.

10.1.2. Expedited Assessment (Conditional, Abbreviated and Collaborative)

The designation for priority review to dossiers should take into account the therapeutic needs of the Ethiopian population and the availability of medicines on the market. Medicines with high demand in the health sector and those used for unmet medical needs will receive priority review during regulatory approvals to enhance availability and access to these products. Hence, the following approaches will be taken in to consideration while dossier screening and assessment

   a) **Conditional approval:** For new chemical entities claimed to treat seriously debilitating or life-threatening disease, or are used in emergency situations (conditions which cannot be adequately managed by medicines marketed in Ethiopia or which is not yet available in Ethiopia), the authority can designate "priority review"; issue conditional approval for one year and allow for submission of additional data or rolling submission based on the clinical data review by national advisory committee provided that the submitted limited clinical data demonstrates satisfactory benefit/risk ratio.

   b) **Abbreviated approval:** this is an approach by which the authority will limit the assessment to certain sections of the dossier based on an evidence of cGMP waiver and availability of market authorization certificate by the claimed SRA. Evidence of sample testing by the EFMHACA is not a prerequisite for the issuance of market

authorization. For products approved by stringent regulatory authorities, evidence of cGMP inspection waiver should be checked.

c) **Collaborative registration:** for products prequalified by World Health Organization and notified to focal persons of the national regulatory Authority available under the collaborative registration procedure, the focal persons will check the existence of WHO prequalified applications in the Authority. For applications which are prequalified by WHO, the authority's assessors will confirm the sameness of the submitted dossier with the prequalified product from the WHO public assessment report. If they are the same, the Authority will register directly otherwise it will follow the full assessment procedure. For prequalified products, cGMP inspection of the manufacturing sites will be exempted.

10.1.3. Fast track designation of priority products:

a. The existing fast track registration procedure will be revised based on risk/benefit concept. The current list of the fast track products (HIV/AIDs, Malaria, TB, Vaccine, and reproductive health products) will be updated to include anticancer, orphan medicines, and other rarely used medicines for orphan diseases. Otherwise, the designation for priority of medicine registration will follow the principle of service fee payment to expedite the registration process.

b. Locally produced medicines will be prioritized for fast track registration.

10.1.4. API suppliers and APIMF approval scheme
- Accept APIMF approved by organization such as WHO selected products
- Prepare EFMHACA approved APIMF list
- Waive the assessment of DMF submitted from the same DMF holder by different FPP applicants provided that no change has been made since the previous approval

10.1.5. Mutual recognition approach

This is an acceptance of the product for registration based on the joint assessment. After developing mutual trust, EFMHACA will evaluate the system of its counterpart before signing an agreement. If the system is found to be acceptable, EFMHACA and the national medicine regulatory authority of that country will establish an information exchange system in between them and sign Memorandum of Understanding (MOU) for mutual recognition.

Decision making procedures, confidentiality, conflict of interest, and appointments of assessors etc. will be considered in the MOU.

10.1.6. Waiving re-registration assessment

Any technical documents shall not be requested upon re-registration; unless change is declared by the pharmaceutical manufacturer or change is identified by the Authority during application reviewing in the MRIS. But all necessary administrative documents such as cGMP compliance status shall be submitted. If variation is declared during the re-registration application, the re-registration process will be treated by the variation guideline of the Authority.

10.1.7. Outsourcing of dossier assessment

The Authority will use outsourcing of dossier assessment to credible organizations as one of the strategies to decrease backlog applications. This will be considered based on the flow of the applications whenever the Authority gets it necessary.

10.1.8. Use of external assessors

The Authority will have pool of experts from different organizations including academia and train them to use as an external dossier assessors whenever deemed necessary. To effectively implement this procedure, the authority will set guiding documents.

10.2. Strategic Direction for cGMP Inspection

10.2.1. Risk based cGMP Inspection

This is an acceptance of manufacturing facility for cGMP based on the cGMP compliance certificate or other GMP compliance documents which may be product specific or production line specific for that specific dosage form from SRA. The list of Stringent Regulatory Authorities which are recognized by the Authority as Stringent Regulatory Authority will be developed and updated annually. The Authority will create a procedure for the access of public assessment and inspection report by SRA as appropriate. In this option onsite audit of the manufacturing facility by the Authority will be waived. However, based on case by case and where found to be necessary, the Authority may inspect the manufacturing site prior to or after marketing authorization.

10.2.2. Mutual recognition approach

This is an acceptance of manufacturing facility for cGMP compliance based on the certificate issued by internationally recognized cGMP consulting organization (e.g. WHO) or national regulatory authorities. After developing mutual trust, EFMHACA will evaluate their system before signing an agreement. If the system is found to be acceptable, EFMHACA and the international organization or national regulatory authority will establish an information exchange system in between and sign Memorandum of Understanding (MOU) for mutual recognition. In the MOU, the decision making procedure, confidentiality, conflict of interest, appointments of Authority's inspector as an observer and where applicable on site audit for verification will be considered.

10.2.3. Fast track designation of priority for cGMP inspection

The designation for priority of cGMP inspection should take into account the therapeutic needs of the Ethiopian population and the availability of medicines on the market. Medicines with high demand in the health sector/medicines in shortage and those used for unmet medical needs will receive priority cGMP inspection without additional fee for the purpose; to enhance availability and access to these products on the Ethiopian market. Otherwise, the designation for priority of cGMP inspection shall follow the principle of service fee payment to expedite the cGMP inspection process. Priority of cGMP inspection will be given for products listed under fast track registration. Furthermore, cGMP data base for approved sites will be established.

10.2.4. Outsourcing of cGMP inspection

The Authority will use outsourcing of cGMP inspection activities to credible organizations as one of the strategies to manage backlog applications. This will be considered based on the flow of the applications whenever the authority gets it necessary.

10.2.5. Use of external assessors

The Authority will have pool of experts from different organizations including academia and train them to use as an external inspectors whenever deemed necessary. To effectively implement this procedure, the Authority will set guiding documents.

10.3. Strategic Direction for Quality Testing

10.3.1. Risk based testing approach

a. Waiving pre-market testing as appropriate

Premarket sample testing shall be waived and greater focus will be given to the consignment testing and/or post market surveillance. Hence, the pre-market testing by EFMHACA is no more a prerequisite for market authorization except for medicines which require sterility test, products manufactured locally and shelf life extension unless justified for those. For products with known variation of shelf life extension, testing shall be carried out on samples of actual products that meet the requirements for expiry information. Thus, actual samples shall be requested in that case before granting market authorization. However, SRA approved products will be exempted from sterility testing.

b. Limiting the Testing Parameter and Critical Attributes based on Risks without Compromising Quality.

- Testing parameter shall be based on information from individual monograph in officially accepted pharmacopeias (USP, BP, int.Phar, EDQM) and/or manufacturer method of analysis if not official in either of the above pharmacopeias.

- Testing parameter will be based on the type of products under investigation. However, identity, active ingredient quantity determination and sterility (when required) are the first priorities. Dissolution test shall be taken as a critical testing parameter and critical attributes for planned consignment testing scheme.

- In cases where there is a known or likely safety, quality or effectiveness issue with a product; EFMHACA shall perform tests specifically for this vulnerability. For example, if an active pharmaceutical ingredient is likely to become contaminated with a harmful impurity during the manufacturing process, EFMHACA tests for that specific impurity, rather than testing for all potential impurities.

- Based on the dossier evaluation input, specific tests parameters shall be tested out before granting market authorization.

10.3.2. Consignment Testing

a. New Consignment

- Regardless of the source of the medicines, except for sterile medicines for which compendia requirements microbial laboratory testing will be used for market

authorization; all newly incoming medicine consignments for the first time will be subjected for consignment testing based on pre-defined list and their test parameters. Consignments from which the sample for laboratory testing was taken upon arrival at entry-exit ports will be hold at the local importer's warehouse based on signed and approved official commitment letter of the importer. Respective importer shall keep its consignees until the consignment testing report is released. If the sample taken for testing is failed to pass the required test parameter(s) for the first time; the whole consignment will be rejected and ordered to return to the country of origin; and the applicant will be supposed to investigate and submit the investigation results to the authority. If the Authority is not satisfied with the investigation report, another investigation may be requested or inspectors may be assigned for additional investigation.

- If the same product is failed to pass the laboratory test for the second round, the regulatory Authority may come to the final decision of market authorization cancelation unless otherwise scientifically justified and accepted by the regulatory Authority.

b. **Planned Consignment Testing Procedure based on Risks.**

- Planned consignment samples testing shall be employed on selected types of products at least on three consecutive consignees throughout their valid registration period.
- Newly approved or first time generic prescription medicines shall be covered in planned consignment testing. List of products has to be renewed every calendar year.
- Manufacturers with a history of consistent quality of products shall be exempted from initial and planned consignment testing for defined period of time in the future.

10.3.3. Premarket Testing for Sterile Products and Locally Produced Medicines

- Sterile finished pharmaceutical products shall be registered and granted a market authorization only when it is found to be manufactured by cGMP compliant pharmaceutical plants, fulfils dossier assessment criteria and proved to meet the compendia requirements of microbial laboratory testing. On the other hand sterile medicines having SRA approval are not subjected for such rigorous premarket microbiological testing.

- All locally manufactured medicines will be subjected for laboratory testing and the test result will be used as an input for issuance of market authorization.

10.3.4. Strengthen Pharmacovigilance and Post Market Surveillance

a. Conducting continual monitoring, assessment, and reporting on the state of safety and quality across the inventory of medicines shall be strengthened. Quality surveillance testing and laboratory-based investigational activities as needed for public medical emergencies are of high priority. Despite rigorous consignment testing, active post marketing surveillance of medicines shall also be essential. Because all possible side effects of medicines can't be anticipated based on preapproval studies, EFMHACA shall maintain and strengthen a system for pharmacovigilance, post marketing surveillance and risk assessment programs.

b. EFMHACA shall establish and utilize computerized information database for adverse event reporting system to support the EFMHACA's post-marketing quality and safety surveillance program for all approved medicines.

c. Extensive post market quality surveillance shall be in place for products whose quality was not justified through planned consignment testing.

d. Develop, implement, and manage a new inspection program focusing on the surveillance of quality, which is distinct, but complementary to inspections for compliance with cGMP. Therefore, selected quality defects in post market surveillance programme shall be supported with sudden cGMP inspection.

10.3.5. Outsourcing of laboratory Testing

The Authority may introduce system to outsource quality testing of medicines to certified laboratories as one of the strategies. This will be considered based on the flow of testing requests whenever the Authority gets it necessary. For the purpose of this, both local and foreign WHO Prequalified and/or ISO 17025 certified medicine quality control laboratories will be used.

10.3.6. Use of external assessors

The Authority may have pool of analysts from different organizations including academia and with appropriate training whenever deemed necessary. To effectively implement this procedure, the authority will set guiding documents.

10.4. Common Strategies

10.4.1. Strengthen Regulatory Communication and Collaboration

- Establish web based pharmaceutical information management system
- Develop synchronized alert system regarding shortage of medicines and illegal medicines.
- The regulatory Authority shall serve as center of excellence in the area of medicines scientific data assessments, GXP and medicines quality testing.
- Promote the market authorization process to national and international organizations. The promotion of Ethiopian medicine registration system will be done at national and international level through various communication means. In addition, the market authorization process will be advocated at international medicine regulatory meetings and scientific medical conferences.
- Establish data repository system and handling of information at one place for common access as an evidence for regulatory decision.
- Strengthen communication and collaboration within EFMHACA
- Establish communication system within national and international counterparts

10.4.2. Establish Capacity Building Training System and Research Center

- Create a system for capacity building trainings of internal and external expertise including formal education in regulatory affairs and establish training programmes including attachments with WHO and other SRAs.
- Design, develop, and implement specific training and developmental programs to ensure the skills and competencies of staff that shall be maintained and continually improved.
- Establish pharmaceutical regulation research unit and conduct research to support the development of scientific standards, create and implement new technologies, modernize current regulatory pathways or indicate new regulatory pathways.
- Create conducive working environment and incentive mechanism to retain qualified professionals.

10.4.3. Support Local Manufacturing of Medicines

- Promoting and supporting the current government initiative to boost local manufacturing of medicines

- Provide priority for exporting manufacturers

- Create access to regulatory information

- Introduce market protection for locally produced medicines

- Give priority to locally produced medicines during dossier assessment, inspection and testing

10.4.4. Regulatory Collaboration and Harmonization

- Strength harmonization with neighboring countries regulatory agencies specially strengthening IGAD harmonization

- Introducing mutual recognition for specific pharmaceutical products in the area of cGMP inspection and dossier assessment.

- Inter-sectoral collaboration within ministry and other law enforcing bodies

11. Monitoring and Evaluation

Implementation success will be gauged through monitoring and evaluation processes that are linked to continuous feedback, and adds value through support for taking corrective measures and sharing lessons learnt. The key feature of monitoring on each strategic direction and respective activities will be done on quarter and annual consultative meetings among respective directorates to discuss progresses and challenges, and to collectively seek solutions that could work. Furthermore, stakeholders' engagement is very crucial to evaluate the status of the implementation of the strategy. Finally, progresses, challenges and opportunities of the market authorization process will be monitored and evaluated through wide range of assessments at national level and interventions will be introduced based on the assessment findings.

12. Revision of the strategy

This strategy may be subjected for revision whenever there is science and technology change, legal change; and national and international regulatory environment change

13. Annexes

Annex I: Product Risk Categorization

Each product will be categorized into two risk categories for the subsequent dossier assessment, laboratory testing and premises requirement for cGMP. This risk classification can be changed based on changes in sciences.

Parameters	*Low Risk*	*High Risk*
Over the counter medicines	Products which have the following characteristics are in general considered as low risk • The potential for misuse and abuse is low • Consumer can use them for self-diagnosed condition safely and effectively • Adequately labelled • Their benefit outweigh their risk	Products containing problematic API such as bioavailability, solubility, polymorphism, manufacturability and stability
Orphan medicines	Categorized in this list are products intended to be marketed for small group of subjects not more than 200,000 population and the product contains non-problematic medicines substance with wide therapeutic window **OR** products with low market value such as antidotes	Orphan products containing problematic API and narrow therapeutic window
Multivitamin and minerals	Multivitamin and minerals under the category of OTC medicines as listed in the OTC medicine list issued by the Authority	Prescription only vitamins

Antihelmentics	Antihelmentics having local action	Antihelmentics with problematic API
Dermatological medicines	Dermatological products having local action	Dermatological products containing potent steroids
Anti-inflammatory /ant allergic medicine	Non-steroidal and antihistaminic having wide therapeutic index	Narrow therapeutic index products and products having potential for causing dependence are considered high risk products.
Other Products	Products containing substances with the property such as High solubility and permeability, Wide therapeutic index, Non-significant effect in the event of treatment failure, Products full filling SRA requirements	- Products containing problematic API such as bioavailability, solubility, polymorphism, manufacturability and stability - New chemical entity - Products with narrow therapeutic window - Biological and immunological products - Medicine for major medical problems of the country: ARV, anti- TB, anti-Malaria etc.

Annex II: Countires Experiences

1.   FDA Programs to Expedite Medical Products Development and Review

FDA procedures designed to expedite product development and/or the regulatory review and approval includes: Fast track designation, accelerated approval, breakthrough therapy, and designation priority Review.

1.1. Fast Track Designation

Fast track is a process designed to facilitate the development, and expedite the review of medicines that fill an unmet medical need for serious conditions. The designation is requested by the sponsor any time during the medical products development process and a decision made by the FDA within 60 days. The FDA's Fast Track Designation has two mechanisms to help speed up access to important medicines:

- An early and frequent interaction between the FDA and sponsor ensures the most efficient development program. This includes working together on trial design to collect the data needed to support registration. Frequent communication between the sponsor and FDA assures that issues are resolved quickly, marketing applications are submitted earlier, and patients access important medicines sooner.
- A "rolling review" allows sponsor to submit sections of the marketing application for review by FDA as they are completed rather than waiting for all sections to be complete before regulatory review begins.

1.2. Breakthrough Therapy Designation

A breakthrough designation requires medical products to potentially demonstrate a large effect compared with available therapies. Medical products granted breakthrough therapy designation receives intensive guidance by the FDA for an efficient medical products development program, beginning as early as Phase 1 and the development program may be considerably shortened. It is important to note that the compressed development program must still generate adequate data to meet the FDA's rigorous standards for safety and effectiveness. Breakthrough therapy designation is described as an "all hands on deck" approach to expedite the development of promising new medical products. A breakthrough product have been approved for marketing includes are those used for

cancer, Hepatitis C, and for cystic fibrosis. The most recent breakthrough approval was for Zykadia (ceritinib) for certain patients with late stage non-small cell lung cancer. The medical products was approved less than three and a half years after the first patient entered a clinical trial and its safety and effectiveness were established in a clinical trial of only 163 patients.

1.3. Accelerated Approval

The accelerated approval procedure has been successful in speeding up access for patients to targeted cancer products, like Gleevac for CML, Herceptin for breast cancer and Xalcori for lung cancer. More than 80 new products have been approved under accelerated approval since the program was established in 1992, about 75% of which were to treat cancer and HIV infection.

1.4. Priority Review

A Priority Review designation means FDA commits to take action on an application within 6 months after the application is filed. For standard applications (those not deemed to be priority), FDA's review time commitment is 10 months. Priority review is determined at the time a marketing application is submitted to the FDA. It does not speed the medical products development and testing process.

2. EMA Programs to Expedite Medical Products Development and Review

2.1. Conditional Marketing Authorization

Commission Regulation (EC) 507/2006 provides the legal basis for conditional approval by the EMA as a means to expedite medical products development and review process. 'Conditional Marketing Authorization' may be requested by the applicant or proposed by the committee for medical products for human use (CHMP) provided that the sponsor can justify that the medical products falls into at least one of the following categories:

- Medical product that treat a seriously debilitating or life-threatening disease
- Medical product to be used in emergency situations, or
- Orphan medical products

Products which fall into the above categories may be approved on the basis of surrogate markers and/or other less complete data than is normally the case but is subject to the following specific obligations:

- The supporting data demonstrates a positive risk-benefit balance
- It is likely that the applicant will be able to provide comprehensive data after granting of a conditional marketing authorization,
- The product fulfils unmet medical need, and
- The benefits to public medical outweighs the risks inherent in the fact that additional data are still required.

A conditional marketing authorization is valid for 1 year and may be renewed annually provided a positive benefit–risk is demonstrated at each renewal, which ensures sponsor fulfill their post marketing requirements. Conditional marketing authorization as a route to approval has expedited patient access for numerous life-saving medical products, such as Xalkori (Crizotinib) for non-small cell lung cancer, and Tyverb (lapatinib) for HER2 positive breast cancer.

2.2. Accelerated Assessment

Commission Regulation (EC) 725/2004 provides the legal basis for accelerated assessment by the EMA as a means to expedite medical products review, in which it is stated under Recital 33 that "in order to meet, in particular the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, accelerated assessment procedures should be set up, reserved for medical products of major therapeutic interest, and procedures for obtaining temporary authorization subject to certain annually reviewable conditions". As outlined in the current EMA guidance document EMEA/419127/05 applications accepted for 'Accelerated Assessment', the time limit is reduced from the standard 210 days to 150 days. The decision by the CHMP to grant medical product accelerated assessment is based on the applicant providing adequate justification that the product meets an unmet clinical need or provides significant improvement over existing therapy.

3. Other Programs to Expedite Medical Products Development and Review World-wide.

3.1. Canada

In recognition of the need to providing expedited review of critical new medical products and breakthrough therapies, Medical Canada has established a framework for granting medical products a 'Priority Review' status. Priority review status allows for the submission review target to be shortened from the standard 215 days to 180 days

In order to qualify for priority review, the medical product must address a serious/life-threatening or severely debilitating disease. Applicants requesting for priority review for a medical product must demonstrate that it:

- is an effective treatment, prevention or diagnosis for a disease or condition for which no medical products is presently marketed in Canada, or
- has significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies, preventive or diagnostic agents for a disease or condition that is not adequately managed by a medical products marketed in Canada.

"Substantial clinical evidence" of clinical effectiveness must be provided to support the above qualifying criteria. In general, Medical Canada requires at least two adequate and well controlled clinical studies, each convincing on its own to establish effectiveness of the medical products involved. However in some instances, Medical Canada may deem clinical evidence consisting of a single, large-scale, adequate and well controlled study or one pivotal trial; or "promising" clinical evidence including the use of non-validated surrogate markers, or Phase II studies to be "substantial clinical evidence".

3.2. Japan

The Ministry of Medical, Labour and Welfare (MHLW) have also established a priority review system for medical products designated as **orphan medical products** and other medical products considered especially important from a medical standpoint. Granting of priority review to a medical product is based on the following assessment criteria:

A. Seriousness of indicated diseases: Diseases with effects on patient's survival (fatal diseases) and progressive and irreversible diseases with marked effects on daily life

B. Overall assessment of therapeutic usefulness: when there is no existing method of treatment or therapeutic usefulness with respect to existing treatment with respect to the standpoint of efficacy and safety and reduction of physical and mental burden on the patient is taken in account

In addition, to expedite medical products development and review process, the MHLW has also the framework for medical products to be designated 'priority face-to-face advice' at the development stage. To qualify for this designation, applicants are requested to submit results of clinical studies up to late Phase II as an estimate of clinical usefulness, and the designation is decided after input of expert opinion in the field.

3.3. New Zealand

In New Zealand, Medsafe have adopted policy for priority assessment as well as provisional consent. Medsafe will grant priority status to a medical product (upon application) on the basis of significant clinical advantage or significant potential cost savings for the tax payer; with the principle being to shorten the time to consent and hence realize the potential of these new medicines. Granting of priority assessment status is conditional on applicants responding to a Medsafe request for information within 28 days. In cases where the sponsor cannot obtain the information requested within the 28 day timeframe, it can still be provided after this deadline but the priority status of the application will be revoked.

3.3.1. African Countries

East African Community, EAC

The East African Community (EAC) is a regional intergovernmental organization of six partner states namely the Republics of Burundi, Kenya, Rwanda, South Sudan, Uganda and the United Republic of Tanzania. In September 2014, the EAC-MRH finalized and approved harmonized medicine registration guidelines, the Common Technical Dossier (CTD), Good Manufacturing Practice (GMP) and the Quality Management System (QMS) compendia. 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 country 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 collaboration between the WHO Prequalification of Medicines Program (WHO/PQP) and interested NRAs. 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. The EAC Partner States supported by the EAC Secretariat are currently pursuing several initiatives to increase the availability of affordable, safe and quality assured medical products and health technologies to the EAC citizens. In general, the EAC member countries has implemented harmonized technical requirements, information management systems and quality management systems in each EAC Member State and this enable them to build regional and national capacity which in turn dramatically help them to increase the access to essential registered medicines in the region.

Expedited process to register medicines via the ZAZIBONA collaborative process
Similar to that of EAC Medicine regulatory harmonization, the ZAZIBONA process is collaboration between national medicines regulatory authorities in Botswana, Namibia, Zambia, and Zimbabwe. These are four neighboring countries in Southern Africa which have a combined population of around 34 million. 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 MRH Program, using the ZAZIBONA approach. South Africa and Swaziland officially joined the ZAZIBONA scheme in 2016. Through this initiative, these countries are successfully benefitted from the harmonized procedure and they share the workload and building the capacity of their expertise.