Jimma University Institute of Health

Faculty of Health Sciences

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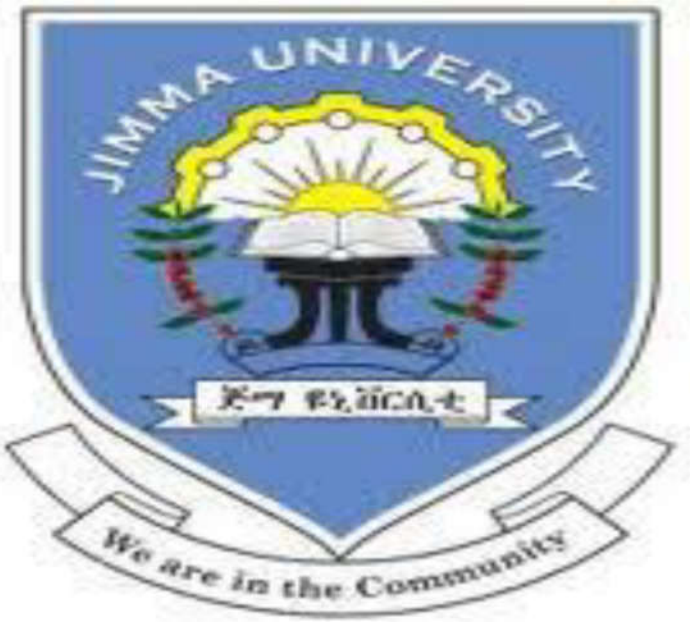
Medicines registration process in Ethiopia: Its challenges and their impacts on the timely approval and procurement of essential medicines in the country



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June 2018

Jimma, Ethiopia

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Abstract

***Background**: Although the provision of safe, effective, quality, and affordable essential medicines and supplies is one of the elements of health for all indicators set by world health organization (WHO), one third of the world's population lacks reliable access to required medicines and the situation is even worse in developing countries. Among the various factors that can be attributed to this poor access to medicines in the developing countries are the regulatory processes required to bring the medicines to the market and patients that require significant human, financial, and material resources from national medicines regulatory authorities (NMRAs) as well as considerable information from applicants.*

***Objective:** This study was conducted to identify the challenges of the medicines registration process (MRP) in Ethiopia and assess their impacts on the timely approval and procurement of essential medicines in the country.*

***Methods:** A descriptive, cross-sectional, questionnaire-based study was conducted from July 19,2017 to September 25,2017 to collect information from the dossier evaluators, good manufacturing practice(GMP) inspectors, quality control laboratory(QCL) analysts, technical persons of local and multi-national pharmaceutical industries(TPLMNPIs), local agents of foreign pharmaceutical industries (LAFPIs), and pharmaceutical fund and supply agency procurement officers(PFSAPOs) about the challenges they face while performing their respective activities all aimed to facilitate the availability of safe, effective, and quality medicines for human use in Ethiopia. A retrospective review of the medicines registration applications (MRAs) submitted to Ethiopian food, Medicines and health care administration and control authority (EFMHACA) from 11 April 2014 to 05 September 2017 was also done to assess the impacts of these challenges on the timely approval and procurement of essential medicines in Ethiopia.*

***Results:** This study found shortage of qualified personnel at the EFMHACA and poor quality of the submitted MR dossiers as the two major challenges facing the EFMHACA in carrying out its MR activities. These challenges with other multifaceted challenges facing the EFMHACA and the applicant pharmaceutical industries(PIs) and/ or their local representatives, are significantly delaying the MRP in Ethiopia as it was found that only 17(1.8%) of MRAs approved by the EMHACA were completed within the expected time.*

***Conclusion and Recommendations:** The various challenges facing the EFMHACA and the applicant PIs and/ or their local representatives are delaying the MRP decreasing the availability of alternative registered medicines in the country. So, all stakeholders directly and/or indirectly involved in MR in Ethiopia should work their best to solve these challenges and improve the availability of medicines in the country.*

***Key Words:** Approval, applications, challenges, Ethiopia, impacts, medicines, procurement, registration, time*

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Abbreviations and Acronyms

AMRAs	Approved Medicines Registration Applications
cGMP	Current Good Manufacturing Practice
CSD	Customer Service Directorate
CTD	Common Technical Document
DRC	Democratic Republic of Congo
EFMHACA	Ethiopian Food, Medicine, and Health Care Administration and Control Authority
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
IQR	Inter-quartile Range
ITFS	Information Technology Facilities and Services
LAFPIs	Local Agents of Foreign Pharmaceutical Industries
MMRT	Median Medicines Registration Time
MR	Medicines Registration
MRA	Medicines Registration Applications
MRD	Medicines Registration Directorate
MRIS	Medicines Registration Information System
MRP	Medicines Registration Process
MRT	Medicines Registration Time
NMRAs	National Medicines Regulatory Authorities
OMRDA	Outsourcing of Medicines Registration Dossier Assessment
PFSA	Pharmaceutical Fund and Supply Agency
PFSAPO	Pharmaceutical Fund and Supply Agency Procurement Officers
PIs	Pharmaceutical Industries
QCL	Quality Control Laboratory
SPSS	Statistical Package for Social Sciences
SRA	Stringent Regulatory Authority
TFDA	Tanzanian Food and Drug Administration
TPLMNPIs	Technical Persons of Local and Multi-national Pharmaceutical Industries
WHO	World Health Organization

1. Chapter One: Introduction

1.1. Background

Health is one of the basic rights for human beings. Medicines are developed to maintain the public health [1]. Access to safe, effective and quality medicines improves the chances of successful treatment for individual patients and promotes better outcomes for public health in general [2]. Thus, the constant availability of affordable medicines of assured quality, safety and efficacy is an important aspect of any national health system [3]. Ideally, medicines prevent, treat or heal diseases and related symptoms. However, it must be kept in mind that taking medicines is also associated with several risks. Hence, medicines are not regarded as ordinary consumer products [4].

In most instances, consumers are not in a position to make decisions about when to use medicines, which medicines to use, how to use them and to weigh potential benefits against risks as no medicine is completely safe. Therefore, professional advice from healthcare professionals is needed in making these decisions. However, even the healthcare professionals nowadays are not in capacity to take informed decisions about all aspects of medicines without special training and access to necessary information as the production of medicines, their distribution and dispensing requires special knowledge and expertise [5]. As a result, there is an 'information asymmetry' between the manufacturers of medicines on one side and the patients/consumers and medical practioners , who are not equipped to make independent assessments of the quality, safety or efficacy of their medicines, on the other side [6, 7].

Unless this information asymmetry is minimized to the required extent, it may result in potentially adverse outcomes for patients/consumers. They may use ineffective, poor quality, and harmful medicines leading to therapeutic failure, exacerbation of disease, resistance to medicines and sometimes death, loss of confidence in the health systems, health professionals, pharmaceutical manufacturers and distributors, and wastage of patients/consumers or insurance schemes/governments money [5, 6, 8].

So, this information asymmetry derives the need for medicines regulation and the establishment of strong NMRAs by national governments as they have the responsibility to guide and protect the public from unsafe, inefficacious, and poor quality medicines [5, 6, 9].

Medicines regulation is a process that incorporates several mutually reinforcing activities aimed at promoting and protecting public health [6]. These regulatory activities vary from country to country in scope and implementation, but generally include those provided table 1 [5].

Table 1: Principal Medicines Regulatory Functions [5]

S.No.	Regulatory Functions
1	Licensing of the manufacture, import, export, distribution, promotion and advertising of medicines
2	Assessing the safety, efficacy and quality of medicines, and issuing marketing authorization for individual products
3	Inspecting and surveillance of manufacturers, importers, wholesalers and dispensers of medicines
4	Controlling and monitoring the quality of medicines on the market
5	Controlling promotion and advertising of medicines
6	Monitoring safety of marketed medicines including collecting and analyzing adverse reaction reports
7	Providing independent information on medicines to professionals and the public

Until the 20th century, there was virtually no regulatory supervision of medicines at all. PIs were allowed to put their products on the market without major restrictions by governments. The initial regulatory standards were originally developed to control the quality of medicines; subsequent developments on safety and quality were later emphasized in 1960. The breakthrough of medicines regulation process was triggered only by unfortunate events. In 1937, over 100 people in the United States died of diethylene glycol poisoning following the use of a sulfanilamide elixir, which used the chemical as a solvent without any safety testing. Consequently, this event led to the adoption of the Food, Drug and Cosmetic Act in 1938. Another catastrophic event that

influenced the development of medicines regulation far more than any event in history was the thalidomide disaster. Thalidomide was a sedative and hypnotic that first went on sale in Western Germany in 1956. Between 1958 and 1960, it was introduced in 46 different countries worldwide resulting in an estimated 10,000 babies being born with phocomelia and other deformities. This tragedy catalyzed the development of the rigorous drug approval and pharmacovigilance monitoring system at the United States Food and Drug Administration (FDA) and the regulatory authorities of other countries today [4, 5, 10, 11].

In Ethiopia, "The Pharmacists and Druggists Proclamation No 43/1942" was the basis for pharmaceutical regulation. Comprehensive regulation of the pharmaceutical sector was started in the early stages by a regulation called "Pharmacy Regulation No. 288/ 1964" that formed the legal basis for official establishment of drug regulation in the history of the country [12, 13].The chronology and scope of pharmaceutical regulation in Ethiopia is presented in table 2.

The EFMHACA is the executive body assigned to regulate medicines in Ethiopia by the EFMHACA Establishment Council of Ministers Regulation No.189/2010 [14].

MR is one of the principal activities of NMRAs carried out to ensure that a medicine has been adequately tested and evaluated for safety, efficacy and quality and that the medicine information provided by the manufacturer is accurate. It involves the evaluation of technical and administrative data submitted about medicine, deciding whether to approve or reject the product, issuing a MR certificate and conducting adverse drug reactions monitoring [15].

In Ethiopia, the MRP is carried out by the EFMHACA and includes manufacturing premise inspection for GMP compliance, assessment of product dossiers and laboratory testing, where applicable. Inclusion of the medicinal product in the national medicines list; certification and approval of the manufacturing site for current good manufacturing practice(cGMP) compliance either by the EFMHACA or other recognized stringent regulatory authorities (SRAs); submission of application/s for dossier evaluation and product quality assessment accompanied with application fee; and fulfillment the expected safety, quality and efficacy profiles after evaluation of the submitted dossier and quality assessment of the product sample/s through laboratory testing are the requirements for MR in Ethiopia [13, 16].

Table 2: The chronology and scope of pharmaceutical regulation in Ethiopia [12, 13, 17-20]

Year	Proclamation/Regulation No. and Year	Scope of Regulation
1942	The Pharmacists and Druggists Proclamation No. 43	Pharmacists and Druggists
1964	Pharmacy Regulation No. 288	Drugs, psychotropic substances, pharmacists, druggists, and the facilities where the pharmacists and druggists were practicing their professional activities
1999	Drug Administration and Control Proclamation No. 176	Human and veterinary drugs, traditional medicines, pesticides, animal food additives, poisons, blood and blood products, vaccines, sera, narcotic drugs ,psychotropic substances, radio pharmaceuticals ,cosmetics, sanitary items, medical instruments and medical supplies Drug manufacturers, wholesalers, retail outlets as well as pharmacy units in health care facilities
2009	Food, Medicine and Health Care Administration and Control Proclamation No. 661	Human drugs and food, narcotic drugs, psychotropic substances and precursor chemicals, traditional medicines, complementary or alternative medicine; poisons, blood and blood products, vaccine, radio pharmaceuticals, cosmetics and sanitary items and medical instruments Manufacturers, wholesalers, retail outlets, health institutions, health professionals, and environmental health

.

The EFMHACA has developed a guideline in June 2014 to inform manufacturers what documentation should be submitted with requests for the registration of medicines for human use in Ethiopia. This guideline provides recommendations on the quality, safety and efficacy information for both active pharmaceutical ingredients and finished pharmaceutical products that should be submitted to support medicine dossiers for MR in the country [21]. The registration of medicines in Ethiopia is generally conducted as presented in figure 1.

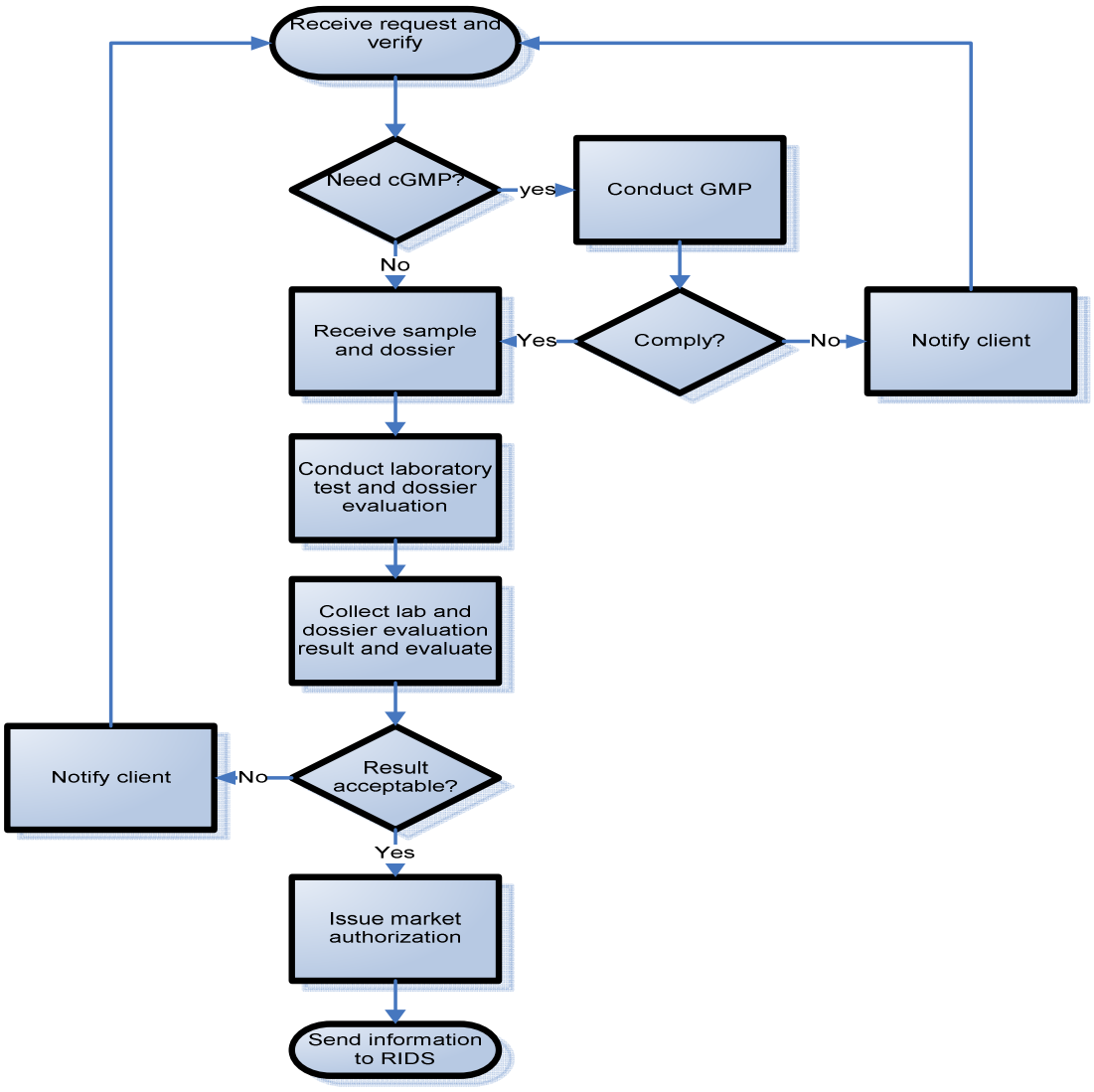

Figure 1: Work flow chart for the registration of medicines in Ethiopia [16]

RIDS: Registration Information Dissemination System

1.2. Statement of the Problem

Provision of safe, effective, quality, and affordable essential medicines and supplies is one of the elements of health for all indicators set by the WHO in Alma Ata in 1978 and revitalized in 2008 [22]. However, global access to safe, effective, and quality medicines is grossly unequal [23]. The WHO reported that one third of the world's population lacks reliable access to required medicines and the situation is even worse in developing countries [24].

The situation in the African continent is not different as access to medicines remains a big challenge in the continent. Among the various factors that can be attributed to this poor access to medicines are the regulatory processes that are required to bring the medicines to the market and patients [25]. Even when medicines are available and affordable, they may be unsafe, ineffective, or of poor quality, or all of these things in various combinations [23].

Unsafe, ineffective, and/ or poor quality medicines present a serious public health problem, especially in emerging economies and developing countries [26]. Their use is associated with increased mortality and morbidity; engendering of drug resistance and loss of medicine efficacy; loss of confidence in health systems and health workers; economic loss for patients, their families, health systems, and the producers and traders in good-quality medicines; adverse effects from incorrect active ingredients; wastage of enormous human effort and financial outlay in development of medicines, optimizing dosage, carrying out clinical trials, discussing policy change, and manufacturing medicines; and increased burden for health workers, and customs officials and police officers [27].

To protect their citizens from the unwanted effects of unsafe, ineffective, and poor quality medicines, governments need to establish strong NMRAs [5, 6, 9]. National registration of medicines is one of the principal activities of NMRAs aimed to ensure the quality, safety and efficacy of medicines provided to the population. However, MR is cumbersome, requiring significant human, financial, and material resources from NMRAs as well as considerable information from applicants. As a result, it is sometimes difficult to get PIs to comply fully with the MRP and NMRAs in many developing countries especially those of Africa which face

particularly significant challenges in meeting their mandate to register medicines circulating on their markets [3-5, 28-31].

To further complicate this, the number of MRAs submitted to the NMRAs in African countries is increasing beyond their capacities [4]. This is also true for Ethiopia as the number of applications submitted for MR is increasing from time to time [32]. This increase in the number of MRAs in Ethiopia can play a major role in minimizing the shortage of medicines in the country as the demand for pharmaceutical products in the country is high[33, 34]. The implementation of the Social Health Insurance Scheme (SHIS) will also significantly increase the demand for pharmaceutical products in the country [35].

On the other hand, the participants of a consultative meeting with pharmaceuticals importers and local agents of international manufacturing companies organized by Pharmaceutical Fund and Supply Agency(PFSA) on 24th December 2015 in Sarem International Hotel, Addis Ababa, Ethiopia, indicated that the EFMHACA takes a very long time to register medicines in the country [35].The EFMHACA itself also admitted, in a new strategy developed to expedite the MRP and officially published in October 2017, that long waiting time for MR is one of the challenges facing the authority [36].

Similarly, a study conducted in America to determine the time taken for registration of new medicines in 192 countries around the world in 2014 also found that it takes about 730 days (2 years) to register a new medicine in Ethiopia[10]. This is about 7.6 times longer than the longest timeline set by the authority as indicated in its citizen charter (3 months + 5 days+1 hour for new or variation applications from foreign manufacturers without SRA approval certificate) [37].

However, the study determined the registration time for applications for standard medicines, not priority or orphan medicines as well as applications for re-registration and variation of medicines. As to our review of the literature, there are no studies that identify the challenges of MRP of a specific developing country and its impacts on access to essential medicine in that country except one study conducted in Tanzania in 2013 [38]. However, the study did not involve GMP inspectors, QCL sample analysts, and Pharmaceutical Supply Agency officers.

In addition, the study did not determine the time taken for the registration of medicines as well as the impacts of the challenges of MR and the medicines registration time (MRT) on access to medicines in the country but the status of MRAs received in 2010 and 2011 by the Tanzanian food and drug administration (TFDA).

Therefore, other more comprehensive studies that address all the limitations of the above study are crucial so as to have a detailed understanding of the challenges of the MRP and their impacts on the MRT and their impacts on the timely approval and procurement of essential medicines in various countries of interest to minimize the delay in MR and improve patients access to safe, effective, and high quality medicines as delay in MR is a significant challenge that prevents access to essential medicines in many developing countries especially those in sub-Saharan Africa due to the lack of harmonized technical requirements and capacity for MR [39].

As a result, this study was conducted to identify the challenges of MR and assess their impacts on the timely approval and procurement of essential medicines in Ethiopia.

1.3. Significance of the Study

As explained earlier, there is delay in MR in Ethiopia [35-36] and this delay can hamper patients' access to safe, effective, and quality drugs potentially opening the door for counterfeit and substandard drugs to enter into the country. So, the country is in a high time to identify the challenges facing its MRP and assess their impacts on timely approval and procurement of essential medicines in the country.

The findings of this study may help EFMHACA and applicant PIs to formulate strategies to minimize, if possible to avoid, the challenges they are facing during the MRP. It may also help the applicant PIs to have a better understanding of the MR requirements of the country.

The WHO Prequalification of medicines programme facilitates the NMRAs of developing countries by enhancing their regulatory capacity through regulator engagement and training [40]. So, this study will also help the prequalification programme and other stakeholders to identify the pressing challenges facing the NMRA of Ethiopia during the registration of medicines in the country so that the programme and the stakeholders will be effective in the allocation of their resource in solving/ minimizing these challenges.

The ultimate beneficiaries of this study are the patients as it may lead to smooth and timely registration of medicines and increase the number and quality of registered medicines increasing competition among registered medicines. This could eventually lower prices; significantly increasing the availability and affordability of essential medicines in the country.

2. Chapter Two: Literature Review

Medicines quality, safety, and efficacy are the three common pillars of medicines regulation. Only medicines that can satisfy all these three criteria should be allowed on to the market [41]. MR is one way to ensure that medicines that fulfill these three criteria are provided to the population [3].

Thus, MR is a requirement for NMRAs in any country of the world. This enables the countries to control and monitor medicines circulating on the market. However, MR is generally a very resource-demanding process. The medicine's quality, safety and efficacy must be proven by a detailed dossier including all relevant scientific data about chemistry, manufacturing and control (CMC), preclinical and clinical studies. Moreover, prospective risk monitoring and management are increasingly within the NMRAs' area of responsibilities. These complex and comprehensive data should be assessed thoroughly by qualified staff at the NMRA, which often takes several months or even years. Accomplishing these tasks is challenging for NMRAs even in developed countries let alone in the developing countries. Approximately two-thirds of all countries around the world lack any adequate and operational medicines regulation [4].

Many developing countries have poorly developed regulatory systems, procedures and processes to ensure adequate quality, safety and efficacy assessment or evaluation of medicines and other health products due to limitations and resource constraints including poor access to quality control laboratories, poor regulatory standards, lack of trained regulatory personnel and limited financial resources [28, 29].

Therefore, NMRAs in many developing countries [30] especially those of Africa face particularly significant challenges in meeting their mandate. African regulatory capacity overall is below that of Europe, Latin America and much of Asia [31].

A WHO study conducted between 2002 and 2009 to assess the status of medicine regulation in 26 countries in sub-Saharan Africa found that the regulatory authorities in most countries did have both financial and human resource constraints. It was reported that 90% of NMRAs in sub-Saharan Africa were not in a capacity which could allow them to adequately carry out regulatory

functions, and thus could not guarantee the safety, efficacy and quality of medicines to be used in their country. A total of 92% of the NMRAs noted that a lack of qualified experts to evaluate the regulatory dossiers inhibited the efficiency of the regulatory authority [28, 31]. Another WHO study conducted in 2002 also showed that shortage of qualified personnel was the major problem facing the NMRAs in ten countries involved in the study [15].

Similarly, in a study conducted in 2015 to describe the historical context that led to the establishment of the WHO collaborative registration procedures for medicines in developing countries, Donatien Kabamb Kabey, Chief of Division of Direction de la Pharmacie et du Médicament of the Democratic Republic of Congo (DRC) confirmed that they have actually a problem of technical capacity for the assessment of all the technical parts of the dossier. A similar situation was described by the NMRAs of Malawi, Cameroon, Namibia. Dr Kouakap Solange, Sub-Director of Drugs at the Direction de la Pharmacie, du Médicament et des Laboratoires (DPML) in Cameroon explained that they did not have enough personnel for all the work and they were also facing many financial problems [4].

To further complicate all these previously explained problems of the African NMRAs, the number of MRAs submitted to these NMRAs for MR is increasing beyond their capacities. For example, the NMRA of Zimbabwe received twice as many MRAs as they could handle within one year in 2012. Similarly, the NMRA of DRC received approximately 1,000 dossiers a year which was too many to be evaluated within an acceptable timeframe [4].

The poor capacity of NMRAs, the technical complexity of the MRPs, and the increasing number MRAs submitted to the African NMRAs coupled with the difficulties for some applicant PIs to comply fully with the MRP requirements in these countries delay the MR and patients' access to safe, effective, and quality new medicines in the countries [4, 29, 32, 41].

As a result, most NMRAs in these countries rely on approvals from a "stringent' regulatory authority" such as the FDA or European Medicines Agency (EMA) to foster the registration of new medicines in their country. According to the decision of the SRA about the new medicine, the NMRA in these countries grants or denies an MR certificate in its country. This approach

reduces the workload for regulators in those resource-limited NMRAs enormously while maintaining high international quality standards for the medicinal product/s [4, 28, 30].

However, this concept does not take into account that the disease burden and consequently the health needs in Africa and developing countries as they often differ significantly. Therefore, medicines in urgent need in African countries are not registered at all by SRA as there is no pressing health need in the Western countries, which eliminates the option of referencing to an SRA approval in such cases. Furthermore, it cannot be ensured that the MR dossier submitted to the SRA and the one at the NMRA are the same because the NMRA may not access the data submitted to the SRA and vice versa [4]. So, this approach has a major impact on the time taken for MR and affects market access, especially for medicines used for diseases endemic to developing countries and not necessarily developed countries [28].

Therefore, NMRAs in Africa and other developing countries should be strengthened to allow them to adequately carry out their MR activities and other regulatory functions so that they could guarantee the safety, efficacy, and quality of medicines to be used in their country by themselves. The regulatory approval timeline is the key metric NMRAs use for the evaluation of their performance [11, 42]. The time taken to assess and register medicines should be long enough to ensure that the medicines are effectively assessed for safety, efficacy and quality, however should not lead to loss of lives, disincentive to research and development. Moreover, it should not be compromised to endangering the health of patients and the public [15].

Many countries have legislated maximum times allowed for the review of application dossiers for MR. For example, the target time-frame for completing the review process in the European Union centralized system is 210 days [42]. The length of the MRT in a country may be affected by a number of factors, such as the availability of alternative therapies for similar indications, national regulations, the regulatory authority's access to data from other NMRAs, and the authority's policies, procedures and resources [43]. These factors decide the type of products to be registered, the requirements of the MRP and the type of review to be carried out for the MR in a specific country [42].

Over the last decade, there have been major improvements in the global regulatory environment, leading to a reduction in the time needed by NMRAs to register new medicines. However, regulatory review timing is under constant scrutiny, by patients seeking quicker availability of new medicines, regulatory authorities looking to improve processes and PIs seeking a timely and high-quality review [44]. Several studies have been conducted to examine the MRTs and identify their trends. However, most of the studies compare the MRTs of only new active substances approved in few developed countries [43-50].

A study conducted to compare the MRTs for applications for new active substances submitted between January 1, 2004 and December 31, 2006 in 13 emerging markets showed that the MRTs vary widely around the overall median of 290 calendar days from 127 days in Argentina to 1388 days in Egypt [51]. Another study conducted in 2010 showed that there were significant differences in the length of time taken by various NMRAs to evaluate MRAs. The average period was 3 to 6 months for developing countries while middle income countries like Russia, Brazil, China, India and Thailand took 12-18 months [52].

A study conducted in America to determine the time taken for registration of standard applications (not priority or orphan medicines studied) for new medicines in 192 countries around the world in 2014 also found that there is variability in many of the countries where most developed countries are the troughs at approximately 365 days and developing countries at 1095 days (3 year mark) [10].

A WHO study conducted in 2002 to compare, contrast and synthesize country experience in drug regulation on the basis of data collected in 1998-1999 in the 10 countries found that the average time needed for MR ranges from 5 to 18 months for new medicines and from 2 to 18 months for generic medicines also indicating that the average time taken to register a generic medicines is not different from that taken to register a new medicines in Cyprus, Estonia, Malaysia, the Netherlands, Uganda and Zimbabwe (Figure 2). The study revealed that fast-track registration system shortens the registration process, particularly in Estonia, the Netherlands, Tunisia and Venezuela [15].

As explained earlier, this WHO study also showed that there was a shortage of qualified personnel in 92% of the countries involved the study [15]. This problem is also not different for Ethiopia as the participants of a study conducted in 2013 to assess the pharmaceutical regulatory system in the country revealed that there was significant shortage of qualified and skilled human resource for medicine regulation in Ethiopia due to low salary, lack of attractive career structure and incentives that create problems in hiring and retaining qualified and skilled personnel within the regulatory system [13]. To complicate this, the number of MRAs submitted for MR in Ethiopia is increasing from time to time [32].

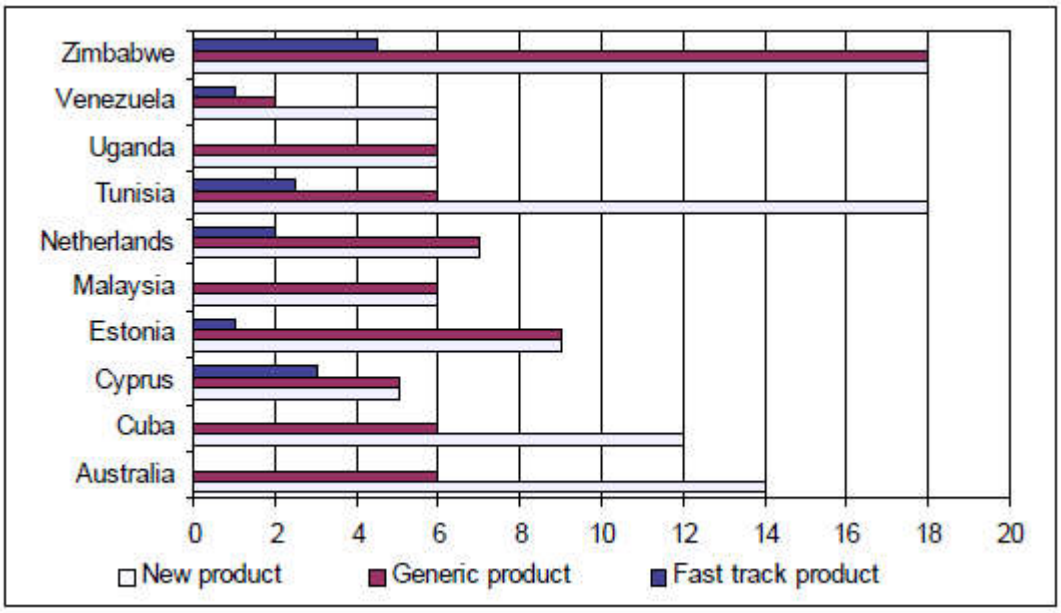

Figure 2: Average time taken to register different categories of drug (months) [19]

The delay in MR in Ethiopia could be attributable to this shortage of qualified experts and the increasing number of MRAs as well as a number of other internal and/or external challenges which need to be investigated.

Literature on the challenges of MRP of a specific country is rare. One study conducted in Tanzania in 2013 found inadequate evaluators (85.7%), lack of training and expertise (76.2%), and poor dossier quality (73.8%) were the three most common challenges facing the dossier evaluators while long registration time(92.7%), inadequate number of evaluators(75.6%), and

inefficient registration database(70.7%) were the three most common challenges facing the representatives of manufacturers [38] (Figures 3 and 4).

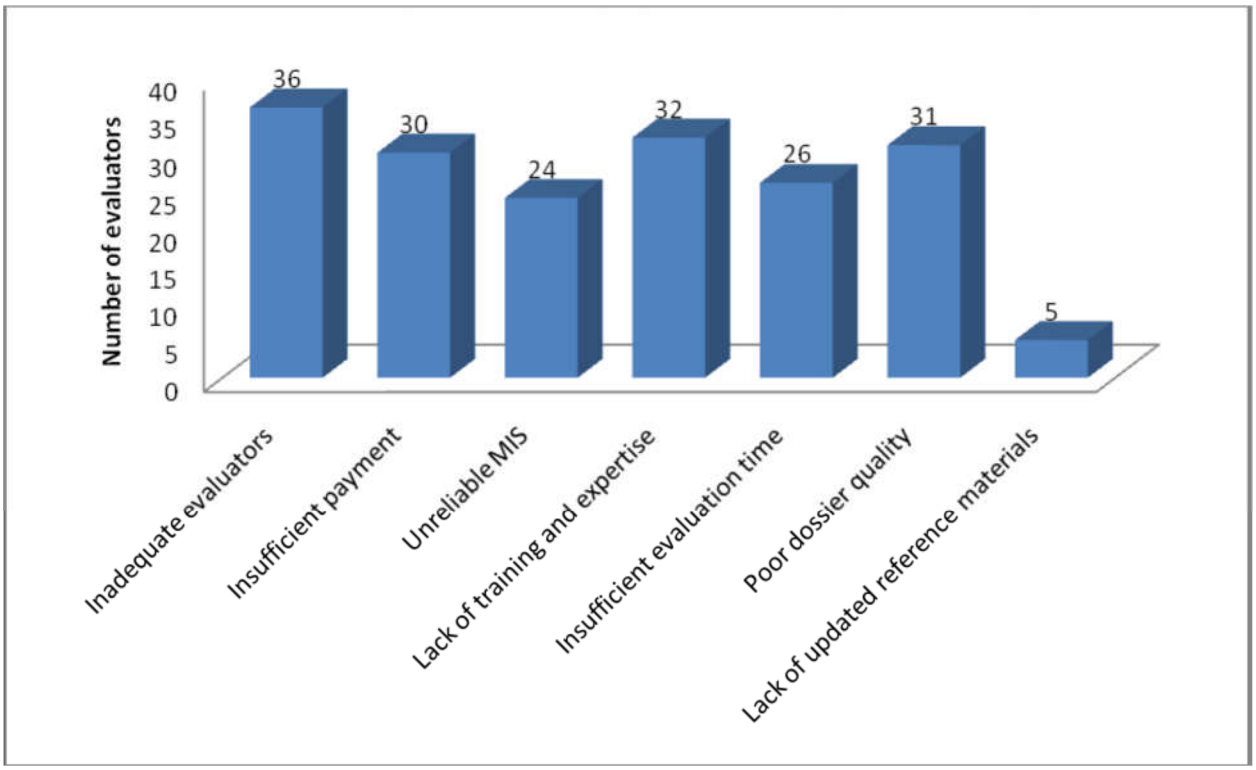

Figure 3: Challenges encountered by evaluators (n=42)

The study also assessed the quality of dossiers undergoing evaluation in 2010 and 2011 with respect to the registration guidelines and found that out of the 478 dossiers which were evaluated, more than half (60%) of them were either rejected or queried indicating that the quality of submitted dossiers was not adequate as was also highlighted as one of the challenges facing evaluators in MR. In this study, 265 applications had no status remarks indicating that they were not yet evaluated. For the applications submitted in 2010, 152 dossiers had no status remarks by April 2013 indicating that such dossiers would take more than three years to be evaluated [38].

However, the study did not include QCL analysts and GMP inspectors at the TFDA, It also failed to assess the impacts of the challenges of MR on the timely approval and procurement of medicines in the country.

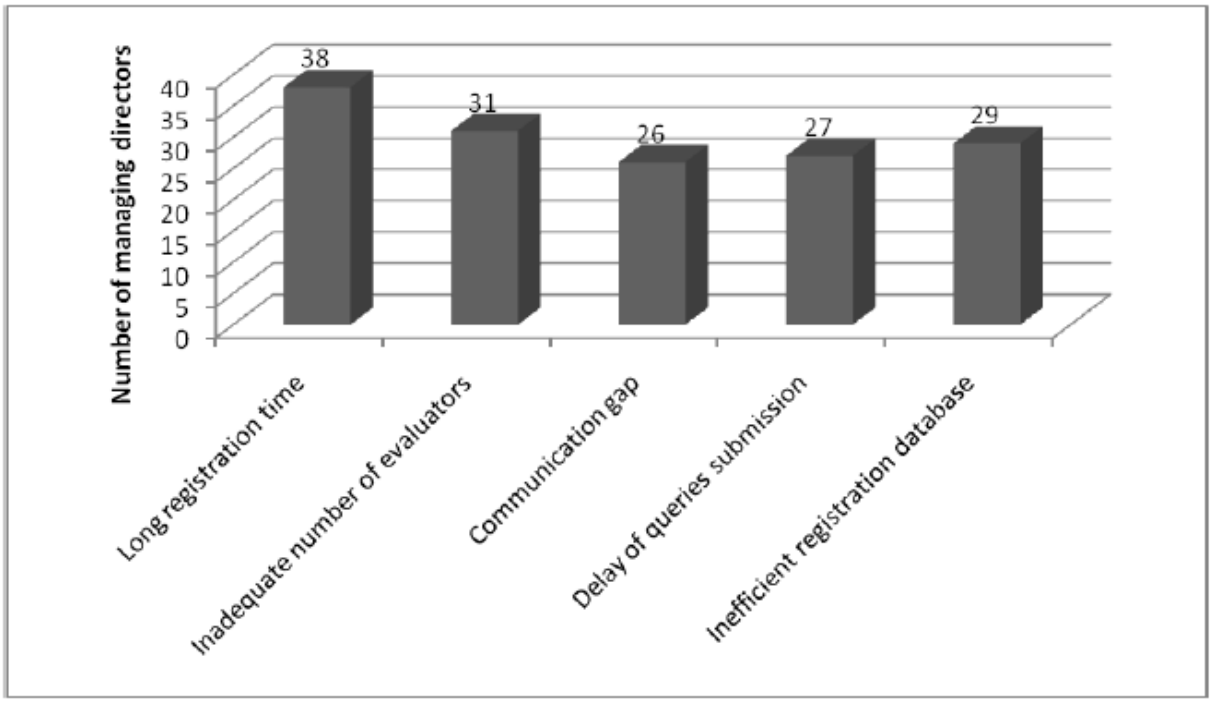

Figure 4: Challenges encountered by representatives of manufacturers regarding MRP (n=41) [38]

3. Chapter Three: Objectives of the Study

3.1. General Objective:

- To identify the challenges of MRP in Ethiopia and assess their impacts on the timely approval and procurement of essential medicines in the country.

3.2. Specific objectives:

- To identify the MR related challenges facing the EFMHACA
- To identify the MR related challenges facing PIs to register their medicines in Ethiopia
- To determine the time taken for MR in Ethiopia
- To assess the impacts of the challenges of the MRP on the timely approval of essential medicines in Ethiopia
- To assess the impacts of the challenges of the MRP on the procurement of essential medicines by the PFSA
- To identify any trends in the time taken for the approval of medicines registration applications (AMRAs) submitted to EFMHACA from 11 April 2014 to 05 September 2017.

4. Chapter Four: Methods and Materials

4.1. Study Area and Period

This study was conducted in Addis Ababa, the capital city of Ethiopia, from July 19, 2017 to September 25, 2017. The reason why Addis Ababa was chosen is because the central office of the medicines regulatory authority of Ethiopia (EFMHACA), the PFSA, and most applicant PIs as well as their local representatives are located in Addis Ababa.

4.2. Study Design

A descriptive, cross-sectional, questionnaire-based study was conducted from July 19, 2017 to September 25, 2017 to collect information from the dossier evaluators, GMP inspectors, QCL sample analysts, TPLMNPIs, and LAFPIs about the challenges they face while performing their respective activities all aimed to facilitate the registration of safe, effective, and quality medicines for human use in Ethiopia.

In the study to assess the impacts of the challenges of the MRP on the timely approval and procurement of medicines in Ethiopia, a retrospective review of the MRAs submitted to EFMHACA from 11 April 2014 to 05 September 2017 that passed the pre-screening procedure at the customer service directorate (CSD) and were sent to the medicines registration directorate (MRD) was done. The reason why data was collected only for applications submitted to EFMHACA from 11 April 2014 onwards was because there was no complete data on the applications submitted before 11 April 2014. It was also difficult to get a complete data of the applications submitted to EFMHACA and failed the pre-screening at the CSD. So, this study includes only applications that passed the pre-screening procedure and were sent to the MRD for further processing.

This study also included PFSAPOs so as to assess the impacts of the challenges of the MRP on the medicines procurement activities of the PFSA and access to medicines in Ethiopia.

4.3. Population

4.3.1. Source Population

- All People working at the EFMHACA, PFSA, local and multi-national PIs in Ethiopia, and medicines importers in Ethiopia.
- All MRAs submitted to EFMHACA

4.3.2. Study Population

- All regulatory personnel working at medicines registration, medicines manufacturers inspection, and medicines quality assessment directorates at EFMHACA; procurement department officials at PFSA; regulatory personnel working at the local and multi-national PIs as well as medicines importers in Ethiopia.
- All MRAs submitted to the EFMHACA from 11 April 2014 to 05 September 2017.

4.4. Inclusion and Exclusion Criteria

4.4.1. Inclusion Criteria

- Dossier evaluators, GMP inspectors, QCL sample analysts, PFSAPOs, TPLMNPIs, and LAFPIs who were willing to participate in the study.
- MRAs submitted to the EFMHACA from 11 April 2014 to 05 September 2017

4.4.2. Exclusion Criteria

- Dossier evaluators, GMP inspectors, QCL sample analysts, PFSAPOs, TPLMNPIs, and LAFPIs who were not be available for various reasons during the data collection time or were not willing to participate in the study.
- MRAs which were found to be incomplete with regard to the information required for this study like the generic and brand names, strength, and dosage form of the drug , country of manufacture, and name of the manufacturer, application and approval dates, type of application, and name of the local agent in Ethiopia.

4.5. Sample Size and Sampling Technique /Sampling Procedures

A convenient sampling technique [38] was used to get the sample size due to the small numbers of dossier evaluators, GMP inspectors, QCL sample analysts, PFSAPOs, TPLMNPIs, and LAFPIs. The study to determine the time taken for MR in Ethiopia also includes the retrospective review of MRAs received from 11 April 2014 to 05 September 2017. The applications received and evaluated in the 4 years were classified as new, new SRA, re-registration, variation and fast track based on their type. Some applications that were submitted for both re-registration and variation were classified as applications for variation.

4.6. Data Collection Procedures (Instrument, Personnel, Data Collection Technique)

Data was collected using a semi-structured self-administered questionnaire developed by reviewing relevant literature and questionnaires used previously in similar studies [15,38,42, 53-55]. Pre-testing was done only for the questionnaire for LAFPIs due the small number of the other respondents. Comments from the MR team leader at EFMHACA were incorporated in development of the questionnaires for LAFPIs and the other respondents. The data collection was done by two trained data collectors under the supervision of the principal investigator. Survey questions focus on the demographic data, training, work experience, views (challenges) in dealing with regulatory requirements, and their recommendations to avoid/minimize these challenges. The questionnaires were developed in English language and took an average of 20 minutes to be completed by the individual respondent.

In the retrospective review of the MRAs received from11 April 2014 to 05 September 2017, an excel data collection tool that includes the generic and brand names, strength, and dosage form of the drug, country of manufacture, name of the manufacturer, application date, type of application, name of the local agent in Ethiopia, and approval date was developed. All data except the approval date was obtained from the authority. Data on approval date was collected online (from mregistration.fmhaca.gov.et/ethiopia) by the principal investigator.

The number of days taken for MR in each application were calculated by subtracting the application date from the approval date using excel sheet. To classify the registered medicines as

those registered on time or not, the time the authority set in its citizen charter for each application type (New SRA:17 days+1 hour=18days, New Local:1 month+15 days+1 hour=46 days, New Foreign: 3 months+5days+1hour=96 days, Re-registration Local:2days+1 hour+40 minutes=3 days, and Re-registration Foreign(New/New SRA):2 days +1 hour+40 minutes= 3 days) was subtracted from the number of days previously obtained by subtracting the application date from the approval date. If the result of this subtraction is less or equal to zero, the drug was considered as registered onetime otherwise, not registered onetime.

The applications were classified as those submitted before or after the beginning of medicines registration information system (MRIS) based on date of application (before or after September 20, 2016). The applications were also classified as those submitted before or after the beginning of the outsourcing of medicines registration dossier assessment (OMRDA) based on date of application (before or after April 17, 2015).

The various dosage forms of the medicines submitted for MR were classified as solid, semi-solid, liquid, inhalational, and trans-dermal dosage forms [56] while the countries of the manufacturers of the medicines were classified as high, upper middle, lower middle, and low income countries based on the United Nations' world economic situation and prospects report published in 2017 [57].

Applications for the registration of antiretroviral medicines, ant malarial medicines, anti-TB medicines, reproductive health medicines, vaccines, anticancer medicines, orphan medicines, and locally manufactured medicines were considered as fast-track applications. There were no applications for the registration of medicines for emergent humanitarian aid.

4.7. Study Variables

4.7.1. Independent Variables

- Demographic data of the respondents such as age, gender, etc
- Dosage forms of the medicines, country of manufacture of the medicines, continent of the country of manufacture of the medicines, level of income of the country of manufacture of the medicines, types of applications, and application and approval dates of the applications

4.7.2. Dependent Variables

- Challenges facing to EFMHACA, TPLMNPIs, LAFPIs, and PFSA in the MRP
- Time taken for MR in Ethiopia
- Impacts of delayed MR in Ethiopia

4.8. Operational Definitions

Challenges: are the constraints that face the different stakeholders involved in MR and related activities. These may be human, financial, material, and/or technical.

Dossier: is a document that contains detail chemical, pharmaceutical, efficacy and safety profile of the medicine submitted by the applicant to the NMRA as part of for the fulfillment of getting MR certificate.

Dossier Evaluator: An EFMHACA medicines registration and licensing directorate staff who is authorized by the authority to assess the dossiers submitted to the authority for MR.

GMP Inspector: An EFMHACA medicines registration and licensing directorate staff who is authorized by the authority to inspect the medicines manufacturers for GMP compliance in the manufacture of medicines.

Local Agent: is an EFMHACA approved local company/importer which represents the foreign PIs to process the registration of medicines in Ethiopia.

Medicines Registration Time: The number of days taken the registration of medicines calculated by subtracting the date of application from the date of approval using excel sheet.

Technical Person: is someone who is assigned by the local manufacturing industries and is responsible for the compilation, submission and/ or follow up of the application status and the progress including responding to queries.

4.9. Data Quality Management and Analysis Procedures

The collected questionnaire data was checked for completeness and consistency, categorized, and coded. After that, it was entered using EpiData Manager Version 4.2.0.0 .Then; it was exported to and analyzed using the Statistical Package for the Social Sciences (SPSS), version 20.0 software. Descriptive statistics was used to summarize the respondents' characteristics and the key results.

In the retrospective review of the MRAs received from 11 April 2014 to 05 September 2017, data was collected using Microsoft Excel 2007 online from mregistration.fmhaca.gov.et/ethiopia and checked by looking the data for every application on the website for a second time. Then, the collected data was checked for completeness and consistency, categorized, coded, and finally exported to and analyzed using the SPSS version 20.0 software.

Median, inter-quartile range (IQR), percentages, as well as mean and range were used to summarize the applications' characteristics and the key findings while Mann-Whitney *U* test and Kruskal-Wallis test were used to test whether there was a statistically significant difference between and/or among the variables or not and a p-value of less than 0.05 was considered as statistically significant difference.

4.10. Ethical Consideration

Before conducting the study, an ethical clearance from the institutional review board (IRB) of Jimma University and consent from EFMHACA were obtained. To obtain the consent of the study participants prior to data collection, a detailed explanation on the aim of the study was explained; and they were also informed that confidentiality would be ensured and their participation was totally voluntary.

4.11. Dissemination Plan

The results of this study were presented to the pharmaceutical quality assurance and regulatory affairs course and research team of Jimma University in June 2018. They will also be presented to the management of the EFMHACA and published in international scientific journals.

5. Chapter 5: Results

5.1. Socio-demographic Characteristics of Respondents:

5.1.1. Socio-demographic Characteristics of EFMHACA Staff Respondents (Dossier Evaluators, QCL Analysts, and GMP Inspectors)

Out of the eight dossier evaluators who were at EFMHACA at the time of data collection, six filled the questionnaire. The remaining two joined the MRD from the medicines quality assessment directorate few months before the data collection. Hence, they and other 13(10 out of 13 QCL analysts in the Physicochemical laboratory and all of the three QCL analysts in the microbiological laboratory) filled the questionnaire for QCL analysts. At the time of data collection, there were only seven GMP inspectors out of the ten GMP inspectors in the organization.

Majority of the respondents (100 % of the dossier evaluators, 86.7% of the QCL analysts, and 71.4% of the GMP inspectors) were males with a mean age of 32.83, 31.87, and 29.57 years respectively. Two-third of the dossier evaluators, 80% of the QCL analysts, and 85.7% of the GMP inspectors were first degree holders. Most of the respondents (66.7 % of the dossier evaluators, 46.7% of the QCL analysts, and 57.1% of the GMP inspectors) had 2-4 years experience in their respective work environment (Table 3).

5.1.2. Socio-demographic Characteristics of Non-EFMHACA Staff Respondents (TPLMNPIs, LAFPIs), and PFSAPOs)

Out of the 15 PIs (8 Local and 7 multi-national with a branch office and/ or manufacturing site in Addis Ababa) at the time of the data collection, 6(75%) the local and all the multi-national PIs completely filled the questionnaire for PIs.

There were also 63 LAFPIs that were actively involved in the registration of human medicines in Ethiopia at the time of data collection. Five out of these 63 local agents participated in the pre-testing of the questionnaire. So, they were not included in the study. Out of the remaining 58 local agents, 53(91.4%) filled the questionnaire completely. Ten (83.3%) out of the 12

procurement officers at PFSA at the time of the data collection completely filled the questionnaire for PFSAPOs.

Most of the respondents (90% of the PFSAPOs, 69.2% of the TPLMNPIs, and 62.3% of the respondents from the LAFPIs) were males with a mean age of 30.70, 34.46, and 35.36 years respectively. All of the PFSAPOs, 53.8% of the TPLMNPIs, and two-third of the respondents from the LAFPIs were first degree holders (Table 4).

Table 3: Socio-demographic characteristics of EFMHACA staff respondents (dossier evaluators (N=6), QC lab analysts (N=15), and GMP inspectors (N=7))

Socio-demographic characteristics		**Dossier Evaluators**	**QCL Analysts**	**GMP Inspectors**
Gender	Males	6(100%	13(86.7%)	5(71.4%)
	Females	0(0.00%)	2(13.3%)	2(28.6%)
Age(Years)	Mean	32.83	31.87	29.57
	Standard Deviation	3.488	5.383	3.690
Profession	Pharmacist	6(100%	14(93.3%)	6(85.7%)
	Others	0(0.00%)	Micro: 1(6.7%)	BE: 1(14.3%)
Educational Level	First Degree	4(66.7%)	12(80%)	6(85.7%)
	Masters Degree	2(33.3%)	3(20%)	1(14.3%)
Field of Specialization(If available)		MSc in P/ceutics:1(50%)	MSc in PQRA:1(33.3%)	MSc in PQA: 1(14.3%)
		Others:1(50%)	Others:2(66.7%)	0(0.00%)
Experience	≤1 year	1(16.7%)	1(6.7%)	2(28.6%)
	2-4 years	4(66.7%)	7(46.7%)	4(57.1%)
	5-7 years	0(0.00%)	6(40%)	1(14.3%)
	≥8 Years	1(16.7%)	1(6.7%)	0(0.00%)

BE: Biomedical Engineer, Micro: Microbiologist, P/ceutics: Pharmaceutics, PQA: Pharmaceutical Quality Assurance, PQARA: Pharmaceutical Quality Assurance and Regulatory Affairs

Table 4: Socio-demographic characteristics of non-EFMHACA staff respondents (TPLMNPIs (N=13), LAFPIs (N=53), and PFSAPOs (N=10))

Characteristics		TPLMNPIs	LAFPIs	PFSAPOs
Gender	Males	9(69.2%)	33(62.3%)	9(90%)
	Females	4(30.8%)	20(37.7%)	1(10%)
Age(Years)	Mean	34.46	35.36	30.70
	Standard Deviation	4.274	8.979	2.869
Profession	Pharmacists	12(92.3%)	50(94.3%)	10(100%)
	Others	1(7.7%)	3(5.7%)	0(0.00%)
Educational Level	First Degree	7(53.8%)	35(66%)	10(100%)
	Masters Degree	6(46.2%)	18(34%)	0(0.00%)
Field of Specialization(If available)		MSc in P/ceutics: 2(33.3%) Others (MBA):2(33.3%) NI: 2(33.3%)	MSc in P/ceutics:1(5.6%) MSc in P/logy: 4(22.2%) MSc in CP: 1(5.6%) Others: 7(38.9%) NI: 5(27.8%)	
Type of Organization		Local: 6(46.2%) Multi-national:7(53.8%)		

Position in the Organization		RDM: 3(23.1%) RAM: 7(53.8%) QAM: 2(15.4%) NI: 1(7.7%)	TM: 28(52.8%) RAP: 15(28.3%) TMM: 1(1.9%) Others: 8(15%) NI: 1(1.9%)	
Experience	≤1 year	4(30.8%)	8(15.1%)	≤ 1 years: 2(20%) 2-4 years:5(50% 5-7 years: 3(30%)
	2-5 years	6(46.2%)	29(54.7%)	
	6-10 years	2(15.4%)	9(17%)	
	≥11 Years	1(7.7%)	7(13.2%)	

CP: Clinical Pharmacy, NI: Not Indicated, P/ceutics: Pharmaceutics, P/logy: Pharmacology, PQARA: Pharmaceutical Quality Assurance and Regulatory Affairs, QAM: Quality Assurance Manager, RAM: Regulatory Affairs Manager, RAP: Regulatory Affairs Pharmacist, RDM: Research and Development Manager, TM: Technical Manager, TMM: Technical and Marketing Manager

5.2. Challenges of MR in Ethiopia

All the dossier evaluators and the GMP inspectors as well as 93.3% of the QCL analysts received training on their respective work after they started working at EFMHACA. Majority of the EFMHACA staff respondents (all the GMP inspectors, 83.3% of the dossier evaluators, and 80% of the QCL analysts) received an average of 1 to 2 trainings per year (Figure 5).

Two- third of the dossier evaluators, one-half of the QCL analysts, and 57.1% of the GMP inspectors think the number of training per year they got is adequate(Figure 6). The same number of the dossier evaluators and 64.3% of the QCL analysts also think the trainings they got were very relevant while all of the GMP inspectors think the trainings were relevant (Figure 7).

All the EFMHACA staff respondents think there was no enough number of staff in their respective work environment. All the dossier evaluators,93.3% of the QCL analysts, and 85.7% of the GMP inspectors think EFMHACA did not initially hired enough number of staff. Difficulty in attracting qualified personnel on the market for financial and other resource and incentive related reasons was the main reason for not initially hiring enough number of staff by EFMHACA as reported by two-thirds of the dossier evaluators and GMP inspectors as well as 71.4% of the 14 QC lab analysts who said there was no enough number of staff in their work environment.

Majority (83.3% of the dossier evaluators, 93.3% of the QCL analysts, and 85.7% of the GMP inspectors) of the respondents also think there is high turnover of staff at EFMHACA. Low salary and lack of attractive career structure and incentives were the two main reasons reported by most of the dossier evaluators, GMP inspectors, and QCL analysts for the high turnover of staff in their respective work environment (Table 5).

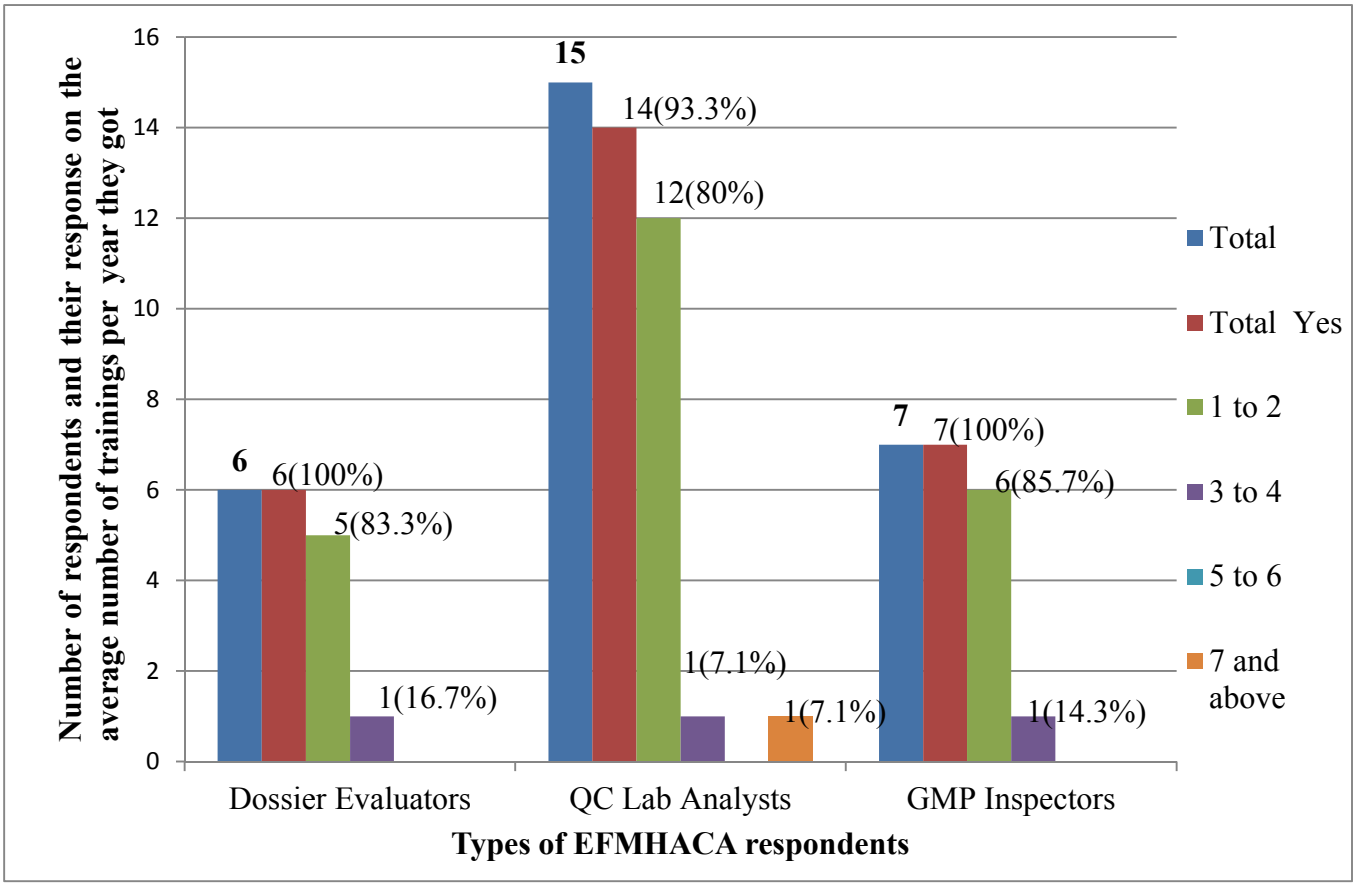

Figure 5: Number of dossier evaluators, QCL analysts, and GMP inspectors by the average number of trainings they get per year after they started working in their current work environment

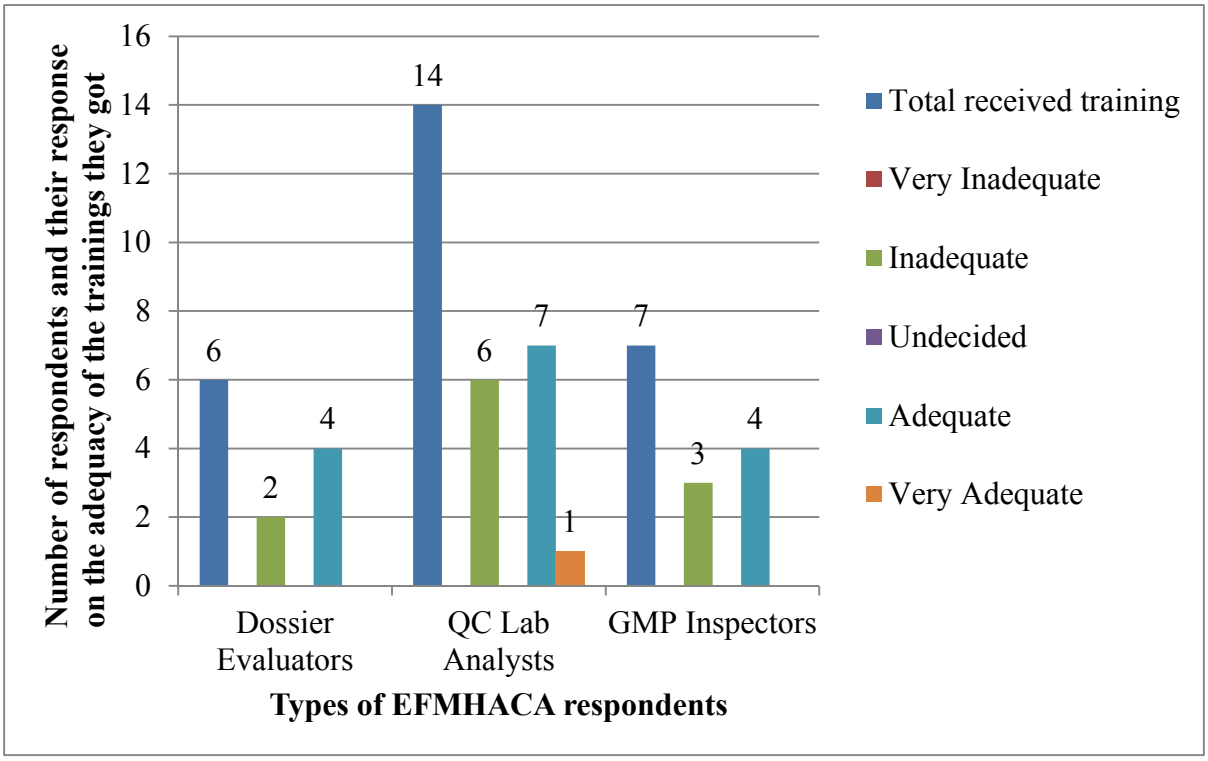

Figure 6: Number of dossier evaluators, QCL analysts, and GMP inspectors by the level of the adequacy of trainings they get per year after they started working in their current work environment

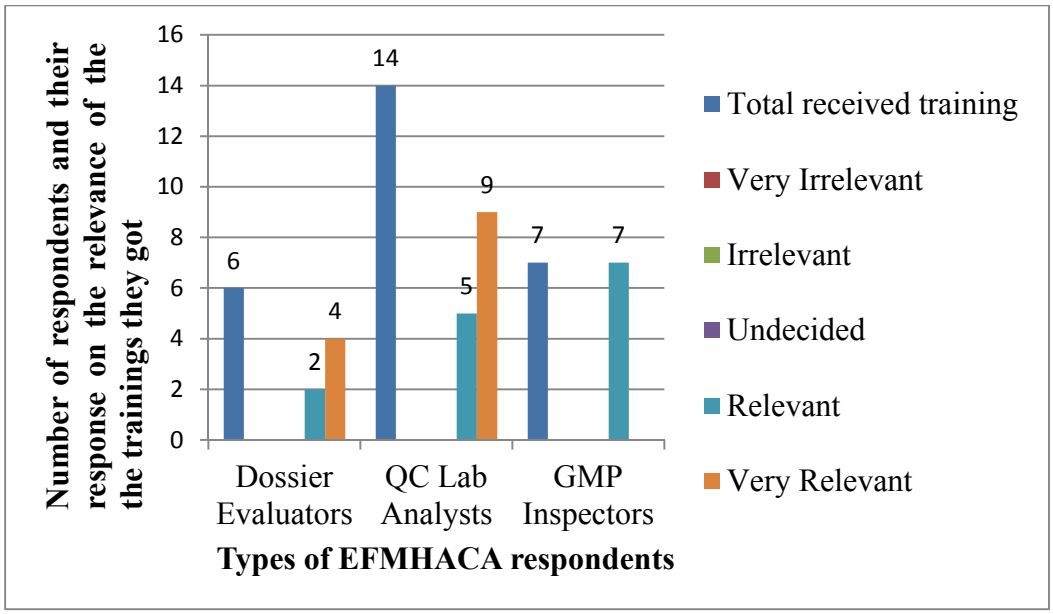

Figure 7: Number of dossier evaluators, QCL analysts, and GMP inspectors by the level of the relevance of trainings they get per year after they started working in their current work environment.

Table 5: Dossier evaluators (N=6), QCL analysts (N=15), and GMP inspectors (N=7) response to questions related the reasons for shortage of staff in their respective work environment

Reasons		**Number(Percentage) of Respondents**		
		Dossier Evaluators	QCL Analysts	GMP Inspectors
The organization didn't initially hire enough number of staff?	Yes	6(100%)	14(93.3%)	6(85.7%)
	No	_ _ __	1(6.7%)	1(14.3%)
Reasons for not initially hiring enough number of staff by the organization as the respondents said	Shortage of qualified and skilled personnel on the market	_ _ __	2(14.3%)	2(33.3%)
	Difficulty in attracting qualified personnel on the market for financial and other resource and incentive related reasons	4(66.7%)	10(71.4%)	4(66.7%)
	The organization believes the currently available number of staff is enough	3(50%)	4(28.6%)	2(33.3%)
	Others (e.g. civil service did not allow more)	2(33.3%)	1(7.1%)	1(16.7%)
There is high turnover of staff?	Yes	5(83.3%)	14(93.3%)	6(85.7%)
	No	1(16.7%)	1(6.7%)	1(14.3%)
Reasons for high for high turnover of staff as the respondents said	Low Salary	5(100%)	8(57.1%)	5(83.3%)
	Lack of attractive career structure and incentives	4(80%)	8(57.1%)	4(66.7%)
	Poor retention mechanisms	4(80%)	7(50%)	3(50%)
	Others (e.g. unfriendly working environment)	2(40%)	3(21.4%)	2(33.3%)

Most (53.3%) of the QCL analysts said they have reliable information technology facilities and services (ITFS) in their work environment. However, two-third of the dossier evaluators and 57.1% of the GMP inspectors said they do not have reliable ITFS in their work environment. The dossier evaluators and QCL analysts reported erratic power supply and lack of commitment by the institutional management as the two main reasons for the absence of reliable ITFS in their work environment. The GMP inspectors reported the lack of commitment by the institutional management as the main reason for the absence of reliable ITFS in their work environment (Figure 8).

All the QCL analysts, 85.7% of the GMP inspectors, and two-third of the dossier evaluators said they have all the necessary guidelines, standard operating procedures/SOPs, and templates in their work environment. Most of the GMP inspectors (57.1%) and QCL analysts (53.3%) reported the general limitation of resource in their work environment as a moderate problem to their activities. However, 66.7% of the dossier evaluators reported it as a major problem (Figure 9).

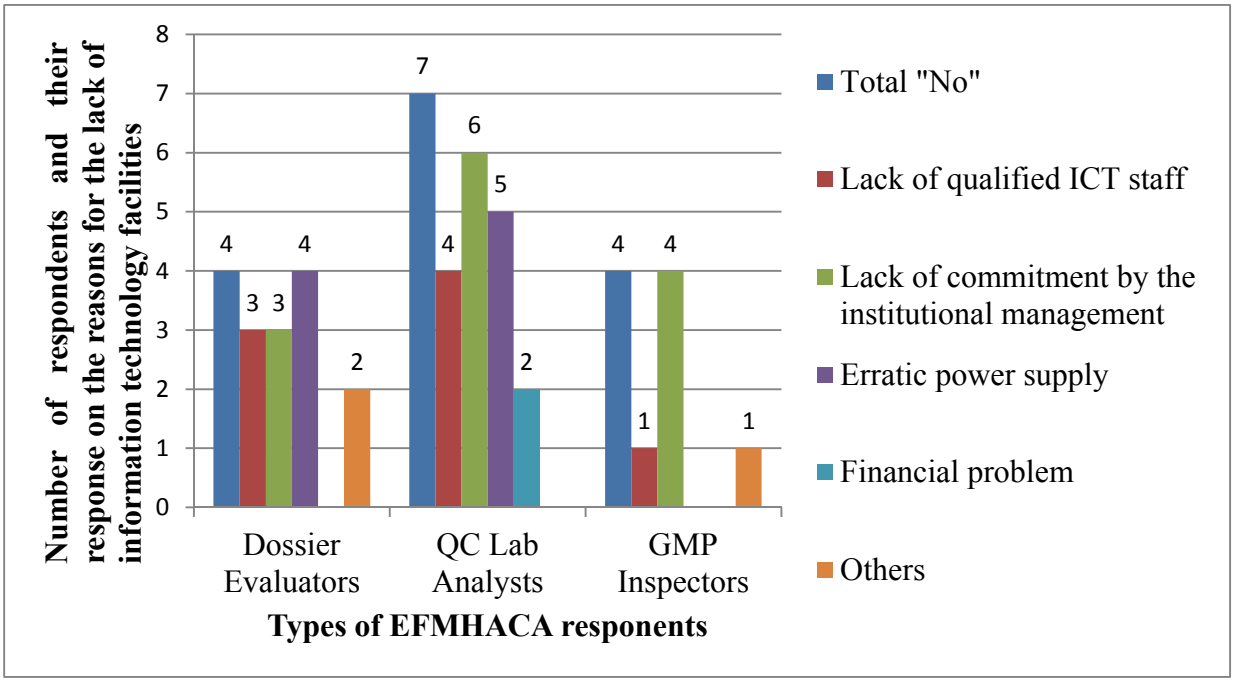

Figure 8: Reasons the dossier evaluators, QCL analysts, and GMP inspectors raise for the lack of reliable ITFS in their work environment

Equal number of dossier evaluators described the management support they get as good and satisfactory (33.3% each); 53.3% of the QCL analysts described it as satisfactory while 42.9% of the GMP inspectors described it as good. Half of the dossier evaluators and 53.3% of the QCL analysts were satisfied in their respective work environments. However, only 28.6% of the GMP inspectors were satisfied and majority (57.1%) were not able to decide their level of satisfaction. Table 6 shows the respondents response to the management support they get and their satisfaction level related questions.

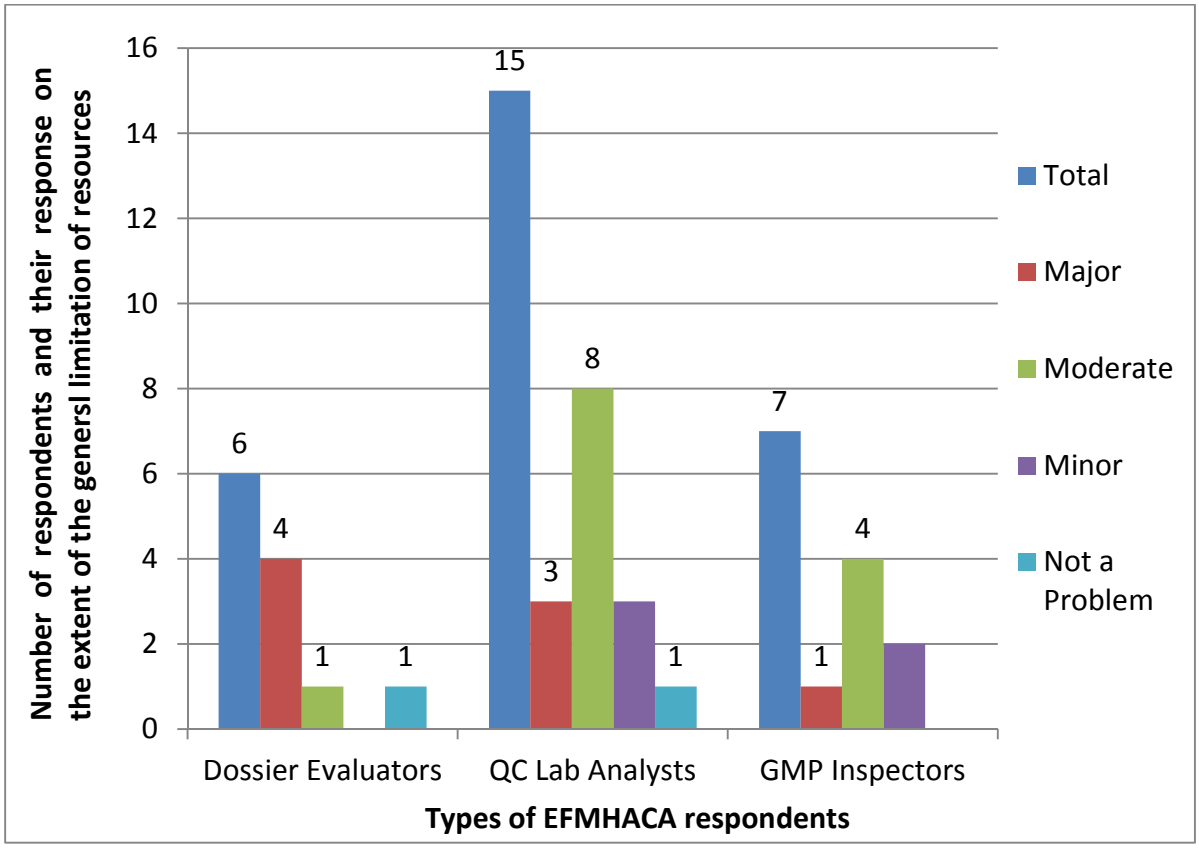

Figure 9: The extent to which the general limitation of resource is a problem in the work environment of the dossier evaluators (N=6), QCL analysts (N=15), and GMP inspectors (N=7)

One-half of the dossier evaluators think the comprehensiveness of the MR dossiers the applicant PIs submit with respect to the registration guideline is poor while 33.3% think it is satisfactory. The remaining 16.7% think it is good. Majority (86.7%) of the QCL analysts said they rarely encounter samples that fail the QCL analysis tests while the remaining 13.3% encounter this

problem moderately. Most (71.4%) of the GMP inspectors rated the compliance of the local MR applicants they inspected for GMP as poor. About 43 % of the GMP inspectors rated the compliance of the foreign MR applicants they inspected for GMP as good (Figure 10).

Table 6: Dossier evaluators (N=6), QCL analysts (N=15), and GMP inspectors (N=7) response to the management support and their satisfaction level related questions.

Respondents' response		**Number and Percent of Respondent**					
		Dossier Evaluators		QCL Analysts		GMP Inspectors	
		Frequency	Percent	Frequency	Percent	Frequency	Percent
How do you describe the support you get from the management?	Excellent	1	16.7%	-------	-----	-------	-------
	Good	2	33.3%	4	26.7%	3	42.9%
	Satisfactory	2	33.3%	8	53.3%	------	------
	Undecided	---------	--------	1	6.7%	2	28.6%
	Poor	1	16.7%	2	13.3%	2	28.6%
How do you describe your level satisfaction in your work environment?	Very Satisfied	1	16.7%	-------	-----	-------	-------
	Satisfied	3	50%	8	53.3%	2	28.6%
	Undecided	1	16.7%	3	20%	4	57.1%
	Dissatisfied	1	16.7%	4	26.7%	1	14.3%
	Very Dissatisfied	------	------	-------	-------	---------	-------

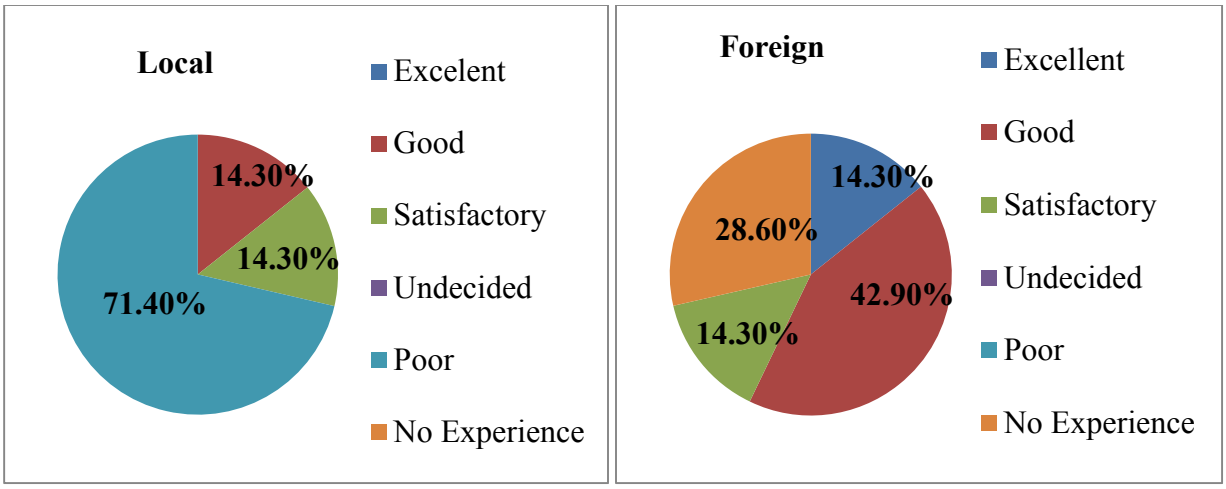

Figure 10: The extent of GMP compliance of local and foreign MR applicants as rated by the GMP inspectors (N=7) they inspected for GMP

Poor Quality of submitted dossiers (83.3%), power supply and/or internet connection problems (50%), lack of relevant periodic trainings (50%), inadequate time for dossier evaluation (50%), and poor documentation (50%) were most common challenges most of the dossier evaluators were facing during dossier evaluation for MR. Lack of continuing education/training (60%), limited numbers of qualified professionals (46.7%), and unavailability of certain reagents, solvents and indicators (40%) were the three most common challenges most of the QCL analysts were facing in their work environment. The lack of continuing education/training (71.4%) and limited numbers of qualified professionals (57.1%) were also the two most common challenges most of the GMP inspectors. Limited access to relevant information on inspection (42.9%) was the other most common challenge facing the GMP inspectors. The Challenges facing the dossier evaluators, QCL analysts, and GMP inspectors as well as their recommendations to solve these challenges are given in tables 7-9 respectively.

Majority (64.2%) of the respondents from the LAFPIs said they did not receive any training on dossier pre-screening and compilation for registration purpose. Of the 19 respondents who received training, only 4(21.1%) said that the training has adequately prepared them to pre-screen dossiers for completeness and proper compilation before submission of the dossiers for registration purpose. However, all except one of the TPLMNPIs said they have received training on dossier preparation and compilation for registration purpose. Most (75%) of those who received training also said that the training has adequately prepared them to prepare and pre-

screen dossiers for completeness and proper compilation before submission of the dossiers for registration purpose.

Most of the respondents from the LAFPIs (84, 9%) and the TPLMNPIs (76.9%) said EFMHACA did not register the product/s they requested for registration on time. EFMHACA's failure to notify clients the results of the dossier evaluation within the specified time (30 days) was the most common reason raised by most respondents for this delay in the registration of the product as raised by 88.9% of the respondents from the LAFPIs and 80% the TPLMNPIs who said EFHACA did not register the product/s on time. Figure 11 shows the reasons the respondents raised for the delay in the registration of medicines.

All except two (84.6%) of the TPLMNPIs and 79.2% of the respondents from the LAFPIs think the timeline for MR could be shortened. Employing well trained man-power in the registration, QCL and cGMP inspection departments (64.35) as well as training the existing staff in these departments (40.5%) were the two most common ways to shorten the timeline for MR raised by the respondents from the LAFPIs. Employing well trained man-power in the registration, QCL and cGMP inspection departments (63.6%) was also the most common way to shorten the timeline raised by the TPLMNPIs. Encouraging the existing staff in these departments to avoid/ minimize leaving the organization (46.4%) was the second most common way to shorten the timeline raised by the TPLMNPIs. Table 10 shows the ways the respondents from LAFPIs and the TPLMNPIs raised to shorten the timeline for MR.

Nearly half of the respondents from the LAFPIs (49.1%) and 30.8% of the TPLMNPIs think the current guidelines for MR should be updated. However, 46.2% of the respondents from the LAFPIs and one of the 4 TPLMNPIs who think the current guidelines for MR should be updated did not indicate the sections/requirements that need to be updated. Majority of the respondents who indicated the sections /requirements that need to be updated said that all sections/requirements of the guideline should be updated (Table 11).However, more than half of the respondents from the LAFPIs (52.8%) and more than two third (69.2%) of the TPLMNPIs said the guideline is easy to understand (Figure 12).

Table 7: The Challenges facing the dossier evaluators and their recommendations to solve these challenges (N=6)

Challenges	**Frequency (Percent)**	**Their recommendations**	**Frequency (Percent)**
Power Supply and/or Internet Connection Problems	3(50%)	Working to solve the power supply and internet connection problems	3(50%)
Poor Quality of Submitted Dossiers(Lack of Authenticity and Compliance to Common Technical Document (CTD) Requirements)	5(83.3%)	Training and informing applicants to submit the dossiers in CTD format	5(83.3%)
Uncomfortable work environment	2(33.3%)	Working hard to improve the work environment	2(33.3%)
Lack of relevant periodic trainings(Technical capability problems)	3(50%)	Provision of relevant periodic trainings for the dossier evaluators	4(66.7%)
Inadequate time for dossier evaluation	3(50%)	Allocating enough time for dossier evaluation	3(50%)
Non-proportionality of responsibilities/burdens and incentives/salary	2(33.3%)	Increase in commitment of the authority to solve the incentive problems	2(33.3%)
Poor Documentation	3(50%)	Establishing proper document management system	2(33.3%)
Lack of reference materials	1(16, 7%)	Availing adequate relevant references	2(33.3%)
Not Indicated	1(16, 7%)	Employ additional dossier evaluators	3(50%)
		Not Indicated	1(16, 7%)

Table 8: The Challenges facing the QCL analysts and their recommendations to solve these challenges (N=15)

Challenges	**Frequency(Percent)**	**Their recommendations**	**Frequency(Percent)**
Financial Constraints(Low Budget)	3(20%)	Provision of need based trainings to the QC lab analysts	5(33.3%)
Limited Numbers of Qualified Professionals	7(46.7%)	Employ additional QC lab analysts	4(26.7%)
Lack of Continuing education/Training	9(60%)	Direct purchase of reference standards and other chemicals	1(6.7%)
Limited Quantity of Functional Lab Equipments/Instruments	1(6.7%)	Increase in commitment of the authority to solve these challenges	5(33.3%)
Unavailability of Certain Reference Standards/Substances	4(26.7%)	Working to minimize staff turnover by increasing incentives(such as risk allowance),implementing health insurance and making the working environment more safe	5(33.3%)
Unavailability of Certain Reagents, Solvents and Indicators	6(40%)	Organization of the authority as an independent authority/Independent from the ministry of health and other institutions	1(6.7%)
		Not-Indicated	2(13.3%)

Table 9:The Challenges facing the GMP inspectors and their recommendations to solve these challenges (N=7)

Challenges	Frequency (Percent)	Their recommendations	Frequency (Percent)
Financial Constraints(Low Budget	1(14.3%)	Increasing the number of competent and experienced staff at FMHACA	3(42.9%)
Limited Numbers of Qualified Professionals	4(57.1%)	Working to improve the motivation and satisfaction of staff members to minimize/avoid turn over	1(14.3%)
Lack of Continuing education/Training	5(71.4%)	Provision of relevant training to the staff	6(85.7%)
Limited access to relevant information on inspection	3(42.9%)	Training of clients on GMP and Institutional management	1(14.3%)
		Improving access to all relevant documents and information	1(14.3%)
		Apply Multi-professionalism	1(14.3%)
		Not Indicated	1(14.3%)

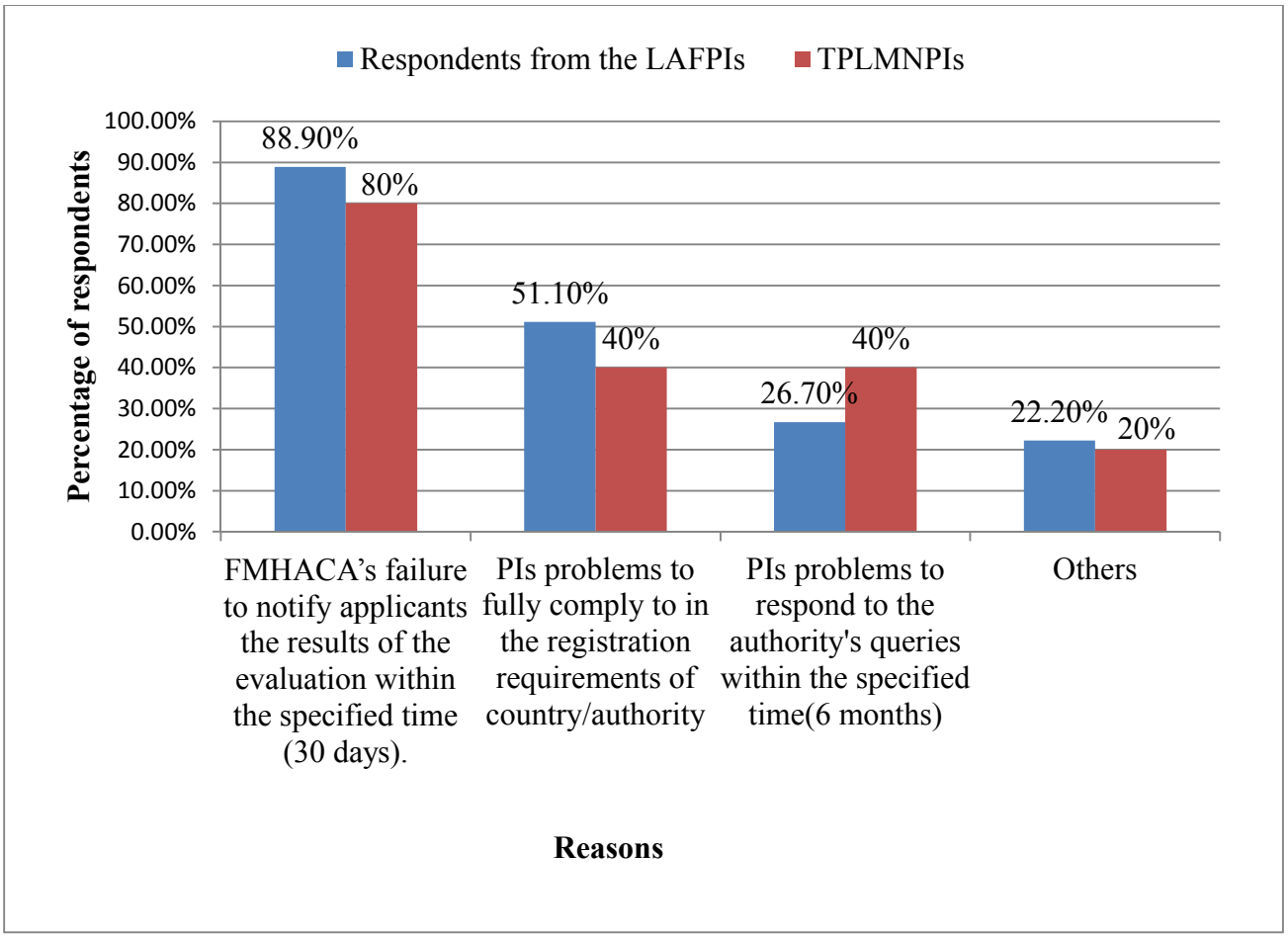

Figure 11: Reasons the respondents from the LAFPIs and the TPLMNPIs raised for the delay in the registration of medicines by the EFMHACA

Most of the respondents from the LAFPIs think the fees EFMHACA ask for local (43.4%) and foreign (45.3%) MR applicants is reasonable as compared to the fees nearby countries ask for local and foreign MR applicants. About 54% of the TPLMNPIs think the fees EFMHACA ask for local MR applicants is reasonable as compared to the fees nearby countries ask for local MR applicants while 30.8% of them think the fees EFMHACA ask for foreign MR applicants is also reasonable as compared to the fees nearby countries ask for foreign MR applicants. However, there were also a number of respondents who said they do not have the experience on the fees nearby countries ask for MR (Table 12).

Table 10: The ways the respondents from LAFPIs and the TPLMNPIs raised to shorten the timeline for MR

LAFPIs	Frequency (Percent)	TPLMNPIs	Frequency (Percent)
Training dossier evaluators, QC lab analysts and cGMP inspectors	17(40.5%)	Training dossier evaluators, QC lab analysts and cGMP inspectors	3(27.3%)
Benchmarking other countries experience	2(4.8%)	Harmonizing the registration process with the registration process of other Sub-Saharan African countries	1(9.1)
Employing well trained man-power in the registration, QC lab and cGMP inspection departments	27(64.3%)	Employing well trained man-power in the registration, QC lab and cGMP inspection departments	7(63.6%)
Encouraging the existing staff to avoid/ minimize leaving the organization	8(19%)	Encouraging the existing staff to avoid/ minimize leaving the organization	4(46.4%)
Decreasing meeting time	5(11.9%)	Strengthening the online registration process	3(27.3%)
Strengthening the online registration process	10(23.8%)	Using External Evaluators	1(9.1%)
Harmonizing the registration process with the registration process of other sub-Saharan African countries	2(4.8%)	Focusing on the critical aspects	1(9.1%)
Training and involving clients in policy development	4(9.5%)	Establishing time limit for prescreening and conducting dossier evaluation and QC lab analysis within the time limit	1(9.1%)
Making the process more transparent	3(7.1%)	Parallel Implementation of Dossier Evaluation and QC Lab Analysis	1(9.1%)
Not-Indicated	2(4.8%)		

Majority (39.6%) of the respondents from the LAFPIs rated the quality of the FMHACA's scientific opinions provided after evaluation of the MR dossier and /or laboratory analysis of the sample as good while equal number of TPLMNPIs rated it as satisfactory (38.5%) and poor (38.5%). Figure 13 shows us the respondents rating of the quality of the FMHACA's scientific opinions provided after evaluation of the MR dossier and /or laboratory analysis.

Table 11: Sections/requirements the respondents from the LAFPIs and the TPLMNPIs think should be updated

Requirements/Sections that should be updated			
LAFPIs	**Frequency(Percent)**	**TPLMNPIs**	**Frequency(Percent)**
All aspects	9(34.6%)	All aspects	2(50%)
Clinical study reports	1(3.8%)	SRA Registration	1(25%)
Module 3	1(3.8%)	Not-Indicated	1(25%)
BE for old molecules	2(7.7%)		
Minor Variation	2(7.7%)		
Not-Indicated	12(46.2%)		

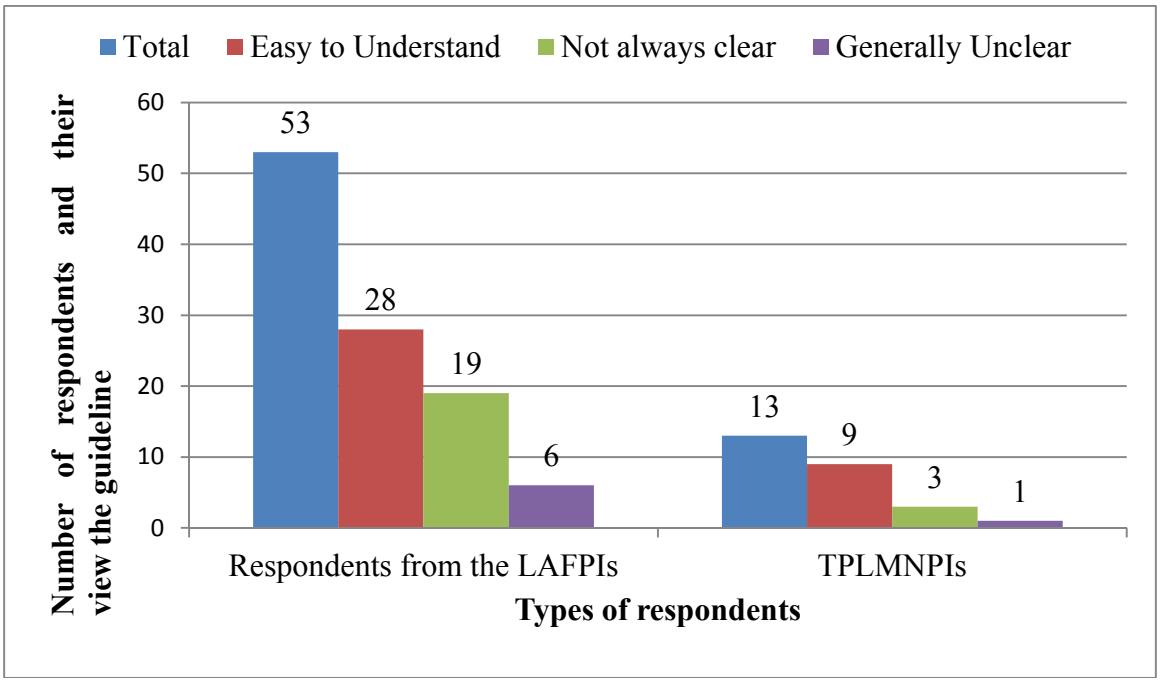

Figure 12: LAFPIs and TPLMNPIs view on the Ethiopian MR guideline

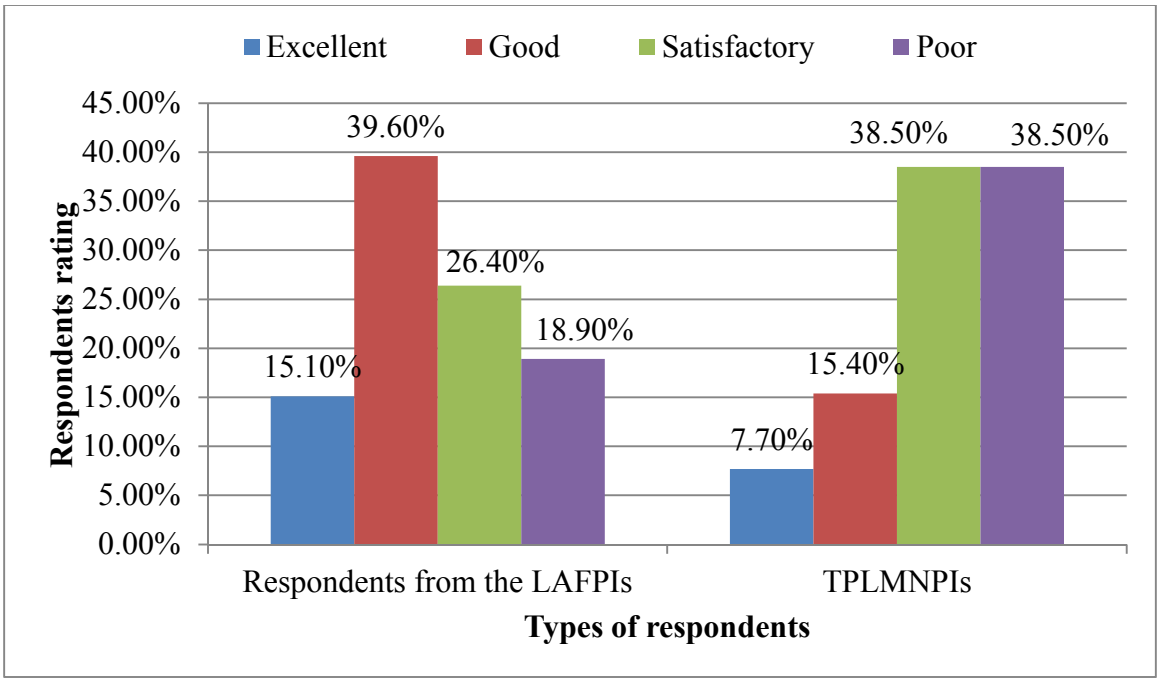

Figure 13: LAFPIs (N=53) and TPLMNPIs (N=13) rating of the quality of the FMHACA's scientific opinions provided after evaluation of the MR dossier and /or laboratory analysis

Delay in MR(64.2%), delay in providing pre-screening, dossier evaluation, cGMP inspection, and/ or QCL analysis results feedback(41.5%), poor documentation process(difficulties in tracing, loss, misplacement)(28.3%), communication problems(lack of willingness, skills, and /or time) in some staff members(28.3%), lack of cooperativeness in some members of the staff(28.3%), and lack of transparency and accountability(22.6%) were the most common challenges that face the respondents from the LAFPIs during the MRP. Provision of relevant training to the staff (47.2%), increasing the number of competent and experienced staff at EFMHACA (45.3%), working to improve the motivation and satisfaction of the staff members to minimize/avoid turn over (32.1%), developing proper documentation process (26.4%), and increasing the transparency and accountability in decision making (22.6%) were the most common recommendations of the respondents from the LAFPIs to solve these challenges (Table 13).

Table 12: LAFPIs and TPLMNPIs view on the MR fees EFMHACA asks local and foreign MR applicants as compared the fees nearby countries ask for local and foreign MR applicants

Respondents from the LAFPIs		
Rating	Fees EFMHACA ask for local MR applicants as compared to the fees nearby countries ask for local MR applicants in their countries	Fees EFMHACA ask for foreign MR applicants as compared to the fees nearby countries ask for foreign MR applicants outside of their countries
Lower	6(11.3%)	4(7.5%)
Reasonable	23(43.4%)	24(45.3%)
Higher	4(7.5%)	10(18.9%)
No Experience	20(37.7%)	15(28.3%)
TPLMNPIs		
Rating	Fees EFMHACA ask for local MR applicants as compared to the fees nearby countries ask for local MR applicants in their countries	Fees EFMHACA ask for foreign MR applicants as compared to the fees nearby countries ask for foreign MR applicants outside of their countries
Lower	1(7.7%)	2(15.4%)
Reasonable	7(53.8%)	4(30.8%)
Higher	1(7.7%)	2(15.4%)
No Experience	4(30.8%)	5(38.5%)

Delay in MR(84.6%), delay in providing pre-screening, dossier evaluation, cGMP inspection, and/ or Qc lab analysis results feedback(84.6%), poor Inter-communication among the directorates(30.8%), communication problems(lack of willingness, skills, and /or time) in some staff members(30.8%), frequent changes in requirements without proper notification of clients(30.8%), and shortage of qualified man-power at EFMHACA (23.1%) were the most common challenges that face the TPLMNPIs during the MRP. Increasing the number of competent and experienced staff at EFMHACA (38.5%%), facilitating the pre-screening process (38.5%), applying and strengthening the online registration process (30.8%), making clear definitions of the roles and responsibilities of each member of the staff (30.8%), provision of relevant training to the staff (23.1%), and developing proper documentation process (23.1%) were the most common recommendations of the TPLMNPIs to solve these challenges (Table 14).

Table 13: Challenges the LAFPIs face during MR and their recommendations to solve these challenges (N=53)

Challenges	Frequency (Percent)	Recommendations	Frequency (Percent)
Delay in MR	34(64.2%)	Increase the number of competent and experienced staff at FMHACA	24(45.3%)
Internet connection problems	5(9.4%)	Apply and strengthen the online registration process	10(18.9%)
Poor Documentation Process(Difficulties in tracing, loss, misplacement)	15(28.3%)	Work to improve the motivation and satisfaction of staff members to minimize/avoid turn over	17(32.1%)
Non-flexibility of some staff in decision making	5(9.4%	Develop proper documentation process	14(26.4%)
Delay in providing pre-screening, dossier evaluation, cGMP inspection, and/ or Qc lab analysis results feedback	22(41.5%)	Solve internet connection problems	7(13.2%)
Shortage of qualified man-power	14(26.4%)	Provision of relevant training to the staff	25(47.2%)
Lack of commitment of some staff members	8(15.1%)	Training and involvement of clients and stakeholders when planning to implement new requirements	9(17%)
Communication Problems(lack of willingness,skills, and /or time) in some staff members	15(28.3%)	Creating favorable conditions for proper communication with the staff member	7(13.2%)
Errors in the provided certificates	3(5.7%)	Make fees paid in birr by the daily dollar-birr exchange	4(7.5%)
Dollar Problems	4(7.5%)	Make clear definitions of the roles and responsibilities of each member of the staff	5(9.4%)
Frequent changes in requirements without proper notification of clients	2(3.8%)	Increasing transparency and accountability	12(22.6%)
Lack of transparency and accountability	12(22.6%)	Increasing the capacity of QC lab rooms	3(5.7%)
Lack of cooperativeness in some members of the staff	15(28.3%)	Transformation of the working environment	4(7.5%)
Asking unnecessary FIRs	5(9.4%	Update the guideline and/or the system as a whole	9(17%)

Companies compliance problems to the requirements of the medicines registration guideline	3(5.7%)	Facilitate the pre-screening process	8(15.1%)
Subjective interpretation of the registration guideline	3(5.7%)	Limit the number of agents	2(3.8%)
Company data security problems	2(3.8%)	Focusing on critical aspects	3(5.7%)
Undefined roles of some staff members	2(3.8%)	Reduce subjectivity in the interpretation of the guideline	3(5.7%)
Payment of cGMP inspection fee for cGMP exempted manufacturers	1(1.9)	Establish performance evaluation department	3(5.7%)
Delay in cGMP inspection process	4(7.5%)		
The issue of multiple agency problems	2(3.8%)		
Vast and demanding medicines registration guideline	6(11.3%)		

Table 14: Challenges the TPLMNPIs face during MR and their recommendations to solve these challenges (N=13)

Challenges	Frequency (Percent)	Recommendations	Frequency (Percent)
Delay in MR	11(84.6%)	Increase the number of competent and experienced staff at FMHACA	5(38.5%)
Poor Documentation Process(Difficulties in tracing, loss, misplacement)	2(15.4)	Apply and strengthen the online registration process	4(30.8%)
Delay in providing pre-screening, dossier evaluation, cGMP inspection, and/ or Qc lab analysis results feedback	11(84.6%)	Work to improve the motivation and satisfaction of staff members to minimize/avoid turn over	1(7.7%)
Communication Problems(lack of willingness, skills, time) in some staff members	4(30.8%)	Develop proper documentation process	3(23.1%)
Frequent changes in requirements without proper notification of clients	4(30.8%)	Provision of relevant training to the staff	3(23.1%)
Lack of transparency and accountability	1(7.7%)	Training and involvement of clients and stakeholders when planning to implement new requirements	2(15.4%)
Subjective interpretation of the registration guideline	1(7.7%)	Creating favorable conditions for proper communication among the directorates	4(30.8%)
Shortage of qualified man-power	3(23.1%)	Increasing transparency and accountability	2(15.4%)
Vast and demanding medicines registration guideline	2(15.4)	Make clear definitions of the roles and responsibilities of each member of the staff	4(30.8%)
Errors in the provided Letters(alphabetical, grammatical, and/ copy of other unrelated product)	2(15.4)	Focusing on critical aspects	1(7.7%)
Undefined roles of some staff members	2(15.4)	Facilitate the pre-screening process	5(38.5%)
Poor Inter-communication among the directorates	4(30.8%)	Reduce subjectivity in the interpretation of the guideline	1(7.7%)
Poor perception towards local manufacturers	1(7.7%)	Establish performance evaluation department	1(7.7%)

Not clear and constant prescreening, evaluation and laboratory analysis fees	2(15.4)	Reduce fees paid by local manufacturers to motivate them	2(15.4%)
Request for non-scientific justification/Irrelevant Questions	3(23.1%)	Work to improve perception towards local manufacturers	2(15.4%)
		Harmonization of the registration system with that of other countries	1(7.7%)
		Not Indicated	1(7.7%)

5.3. Impacts of the Challenges of MR on the Timely Approval of Essential Medicines in Ethiopia

5.3.1. Number of MRAs Submitted to the EFMHACA

A total of 2787 applications were submitted from 11 April 2014 to 05 September 2017. Most (41.5%) of the applications were submitted in 2015(Figure 14). New (40.7%) and re-registration (23.1%) were the two types of applications with the highest number of application submitted from 11 April 2014 to 05 September 2017(Table 15).

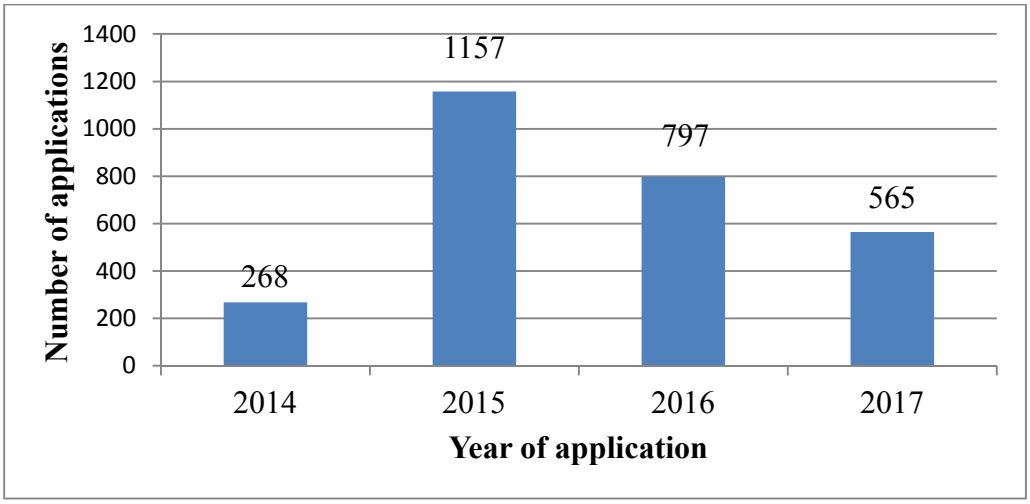

Figure 14: Total number of MRAs submitted to the EFMHACA by application year (11 April 2014 to 05 September 2017)(N=2787).

Table 15: Total number of MRAs submitted to the EFMHACA by type (11 April 2014 to 05 September 2017)

Type of Application	Frequency	Percent
New	1134	40.7
New SRA	414	14.8
Re-registration	643	23.1
Variation	596	21.4
Total	2787	100.0

India (41.5%), Germany (8.1%), and United Arab Emirates (3.8%) were the three countries of origin of the medicines manufacturers with the highest numbers of applications submitted to the authority. Most of the applications (61.75%) were from Asia while only 2.30% were from North America (Figure 15). Only 98 applications (3.5%) were from PIs located in Ethiopia.

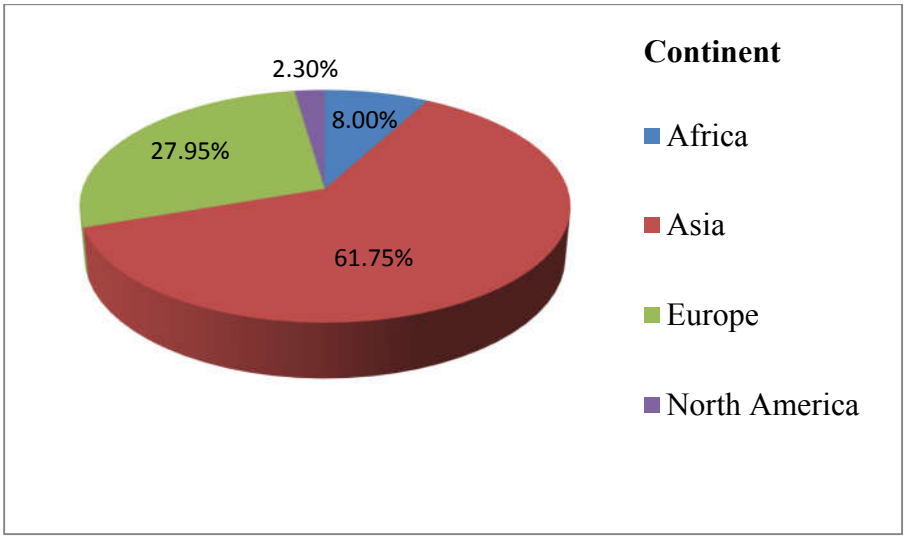

Figure 15: Total number of MRAs submitted to the EFMHACA by continent of the country of origin of the manufacturer expressed in percentages (N=2787)

Only two out of the 223 applications from Africa were New SRA applications while more than half (54.62%) of the 1721 applications from Asia were new applications. Twenty five (39.06%) of the 64 applications from North America were variation applications (Table 16).

Table 16: Total number of MRAs submitted to the EFMHACA by type and continent of the country of origin of the manufacturer (11 April 2014 to 05 September 2017)

Continent of Country of Manufacturer	**Type of Application**				**Total**
	New	**New SRA**	**Re-registration**	**Variation**	
Africa	123	2	60	38	223
Asia	940	80	386	315	1721
Europe	55	314	194	216	779
North America	16	18	3	27	64
Total	1134	414	643	596	**2787**

5.3.2. Number of MRAs Approved by the EFMHACA

Out of the 2787 MRAs submitted to the authority between 11 April 2014 and 05 September 2017, 596 were applications for variations. Excluding these 596 variation applications, only 933(42.58%) out of the 2191 submitted applications were approved for MR of in Ethiopia. This number includes new applications approved until 08 September 2017, new SRA applications approved until 14 September 2017, re-registration applications approved until 19 September 2017 and fast track applications. Since there was no separate list of fast track applications at EFMHACA at the time of data collection, these applications were separated later from the three application types by their therapeutic category. More than two-third (67.2%) of the approved medicines registration applications (AMRAs) were submitted after the OMRDA was started (after 17 April 2015). However, vast majority (82.7%) of the AMRAs were submitted before the beginning of the MRIS by the authority (Before 20 September 2016).

More than one-third (35.3%) of the AMRAs were re-registration application type while 31.1% of the AMRAs were new application type. Less than quarter (21.5%) of the AMRAs were new SRA application types while 12.1% of the AMRAs were applications for fast track registration. Most of the approved medicines (61.7%) were in solid dosage forms followed by liquid dosage forms (29.4%), semi-solid dosage forms (7.6%). Inhalational dosage forms, trans-dermal patches and implants constitute only 1.3% of the applications.

Based on the continent and economic status of the country of origin of the manufacturer of the medicines, most of the approved applications were from Asia (57.7%) and high income countries (44.2%) (Table 17). Only 23(2.5%) of 933 AMRAs were from PIs located in Ethiopia.

None of the 130 applications submitted in 2014 was approved in that year. More than half (56.2%) of them were approved in 2016. Most (59.8%) of the 445 submitted in 2015 were also approved in 2016 (Table 18). Only 17(1.8%) of the 933 applications were approved within the expected time.

Table 17: Number of MRAs approved by EFMHACA until 19 September 2017 by the continent and economic status of the country of origin of the manufacturer of the medicines (N=933)

Continent and Economic Status		Frequency	Percent
Continent of the country of origin of the manufacturer of the medicines	Africa	59	6.3%
	Asia	538	57.7%
	Europe	320	34.3%
	North America	16	1.7%
	Total	933	100,0%
Economic status of the country of origin of the manufacturer of the medicines	High Income	412	44,2%
	Upper Middle Income	122	13,1%
	Lower Middle Income	370	39.7%
	Low Income	29	3.1%
	Total	933	100.0%

Table 18: Number of MRAs approved by EFMHACA until 19 September 2017 by their application and approval years

Application Year	Approval Year				Total
	2014	2015	2016	2017	
2014	0	39	73	18	130
2015	--	49	266	130	445
2016	--	--	124	156	280
2017	--	--	--	78	78
Total	0	88	463	382	933

5.3.3. Time taken for the Approval of MRAs by the EFMHACA

An exploratory data analysis was conducted to check the assumption of normal distribution in the MRT and see if there are problems in the data such as outliers or problems in coding, missing values, and/ or errors in inputting the data [58].

To test the assumption of normality based on the skewness and kurtosis values, these values were converted to Z scores by dividing the values to their respective standard errors. An absolute value of the score greater than 1.96 or lesser than -1.96 was considered significant at $P < 0.05$ for skewness and normality [58, 59].

As it can be seen from table 19, all of the four Z scores for the skewness of the MRT for the four different application types are not within +/- 1.96 boundaries. Hence, we can conclude that the skewness of the MRT differs significantly from normality for all the four different application types. For kurtosis, the Z score of the kurtosis of the MRT for re-registration applications differs significantly from normality. Overall, we can conclude that our data is not normal with regard skewness and kurtosis.

Table 19: Descriptive statistics of the time (in days) taken for the approval of new SRA, new, re-registration, and fast track applications (N=933)

Application Type	Number of Applications		Statistic	Standard Error	Calculated Z Score
New SRA	201	Skewness	0.575	0.172	3.34
		Kurtosis	-0.367	0.341	-1.08
New	290	Skewness	-0.505	0.143	-3.53
		Kurtosis	-0.005	0.285	-0.02
Re-registration	329	Skewness	0.775	0.134	5.78
		Kurtosis	-0.560	0.268	-2.09
Fast Track	113	Skewness	0.626	0.227	2.76
		Kurtosis	-0.639	0.451	-1.42

Next, normality tests (Kolmogorov-Smirnov test) and a visual inspections of the histograms, normal Q-Q plots and box plots [58-60] of the number of days taken for the approval of the four different application types was conducted and showed that the MRT (in days) was not normally distributed ($p<0.05$) for all application types (Table 20 and Annexes VIII-X).

Table 20:Normality tests of the time (in days) taken for the approval for new SRA, new, re-registration, and fast track type of applications(N=933)

Application Type	Number of Applications	Kolmogorov-Smirnov			Shapiro-Wilk		
		Statistic	Df	Sig.	Statistic	Df	Sig.
New SRA	201	0.101	201	0.000	0.951	201	0.000
New	290	0.062	290	0.010	0.974	290	0.000
Re-registration	329	0.164	329	0.000	0.887	329	0.000
Fast Track	113	0.145	113	0.000	0.927	113	0.000

Hence, comparisons of MRTs between groups was conducted using the nonparametric tests such as Mann-Whitney U-test and Kruskal-Wallis test as this data does not meet the normality assumption for parametric tests. The median and IQR of the MRTs were used as the principal summary statistics in the analysis, although mean times and ranges were also presented to facilitate comparisons with other studies.

The overall median medicines registration time (MMRT) for all types of AMRAs was 359 days (IQR: 152.50-562.00 days) ranging from 185 days (IQR: 84.50-448.50 days) for re-registration applications to 554 days (IQR: 420.75-678.25 days) for new applications (Table 21).

A Kruskal-Wallis test conducted to see if there was a statistically significant difference in the MMRT among the four different application types revealed that there was a statistically significant difference in the MMRT among the four different application types ($X^2(3,N=933)=204.985,P<0.05$). Mann-Whitney *U* test conducted to see the actual difference showed that there was a statistically significant difference in the MMRT between each of the

four different application types($p < 0.05$) except between the new SRA and fast track applications($p=0.745$).

As it can be seen in figure 16 and table 21, the MMRT for all applications decreased from 622.5 days (IQR: 395.75-734.00 days) in 2014 to 89 days (IQR: 58.75-124.50 days) in 2017. The MMRT for each application type submitted from 2014 to 2017 also decreased with time except for New SRA applications submitted in 2015. The highest decrease in the MRT was observed for new applications from 710 days (IQR: 662.00-789.50 days) in 2014 to 74 days (IQR: 35.00-185.25 days) in 2017 while the lowest decrease was for new SRA applications from 345 days (IQR: 198.00-507.00 days) in 2014 to 75 days (IQR: 37.00-151.00 days) in 2017.

Kruskal-Wallis test showed a statistically significant difference in the MMRT among the applications submitted from 2014 to 2017($X^2(3,N=933)=430.753, P<0.05$). Mann-Whitney *U* test revealed a statistically significant difference in the MMRT between the applications submitted from 2014 to 2017 ($p < 0.05$)

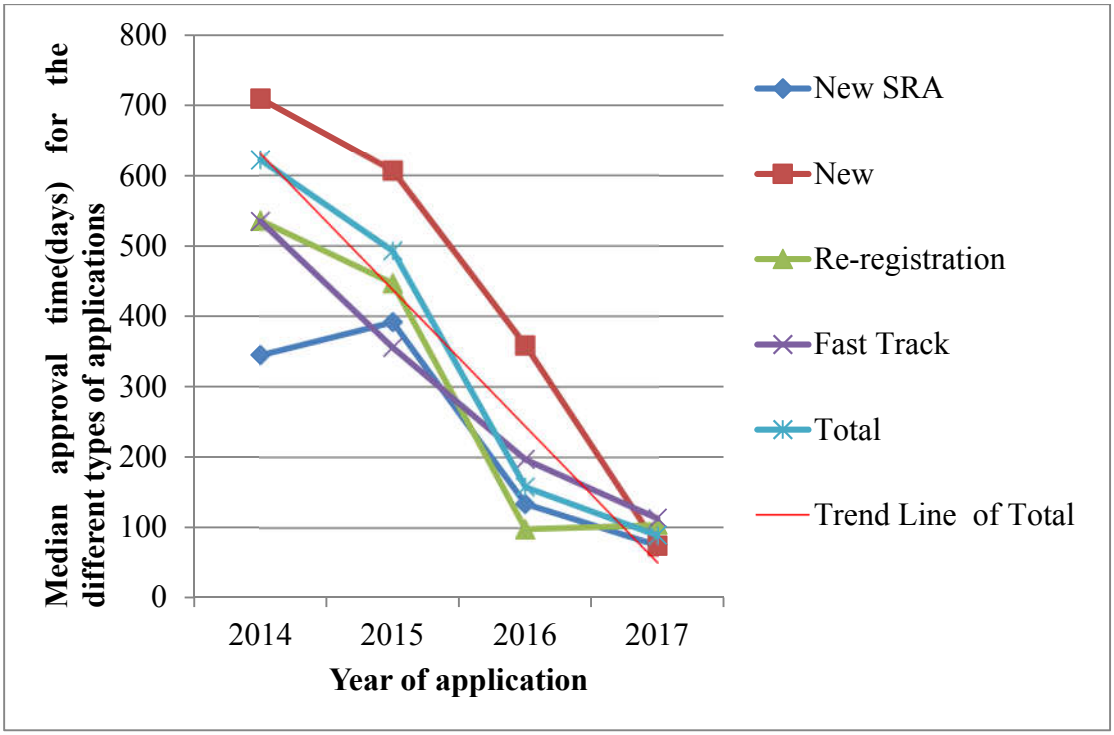

Figure 16: MMRT (in days) taken for the approval of new SRA, new, re-registration, and fast track applications by their year of application(N=933)

The difference in MMRT among the applications submitted from 2014 to 2017 is also statistically significant for each application type ($p<0.05$). Mann-Whitney *U* test conducted to see the actual difference showed that there was a statistically significant difference in the MMRT between the applications submitted in the four different applications years for each application type ($p< 0.05$) except between applications submitted in 2014 and 2016 for the new SRA applications ($p=0.285$) and between applications submitted in 2016 and 2017 for re-registration applications ($p=0.247$).

The MMRT of the applications decreased from 577.50 days (IQR: 354.5-700.5 days) to 248 days (IQR: 109-471 days) after the beginning of the OMRDA and from 441 days (IQR: 236.25-603.75 days) to 75 days (IQR: 53-138.5 days) after the beginning of MRIS by EFMHACA. The MMRT of each of the approved application type also decreased after the beginning of the OMMADA and MRIS by the authority (Table 22). This decrease in the overall MMRT as well as the MMRT of each application type after the beginning of the OMRDA and MRIS was statistically significant as Mann-Whitney *U* test revealed($p<0.05$).

Table 21:Median, IQR, mean and range (R) of the time (in days) taken for the approval of new SRA, new, re-registration, and fast track applications submitted from 2014 to 2017 (N=933)

Year of Application		Application Type				Total
		New SRA	New	Re-registration	Fast Track	
2014	Median	345(n=27)	710(n=53)	536(n=29)	535(n=21)	622.5(n=130)
	IQR	198.00-507.00	662.00-789.50	328.00-739.00	452.50-723.50	395.75-734.00
	Mean(R)	361.19(169-907)	704.51(365-960)	519.21(86-893)	565.90(178-942)	569.48(86-960)
2015	Median	392(n=114)	607(n=157)	447(n=125)	356(n=49)	493(n=445)
	IQR	246.25-523.00	529.00-664.00	270.00-578.00	175.50-519.00	348.50-620.50
	Mean(R)	399.41(11-851)	596.11(270-874)	422.75(81-783)	351.98(31-749)	470.14(11-874)
2016	Median	134(n=40)	359(n=68)	98(n=140)	197(n=32)	158(n=280)
	IQR	81.00-235..75	262.75-449.00	57.00-173.00	153.25-300.25	70.50-313.00
	Mean(R)	161.30(32-483)	343.81(58-585)	135.40(16-498)	209.31(42-483)	198.16(16-585)
2017	Median	75(n=20)	74(n=12)	104(n=35)	113(n=11)	89(n=78)
	IQR	37.00-151.00	35.00-185.25	63.00-115.00	63.00-161.00	58.75-124.50
	Mean(R)	93.65(36-235)	100.17(7-222)	92.57(32-145)	193.54(17-220)	95.58(7-235)
Total	Median	269(n=201)	554(n=290)	185(n=329)	248(n=113)	359(N=933)
	IQR	141.00-469.00	420.75-678.25	84.50-448.50	157.50-496.00	152.50-562.00
	Mean(R)	316.46(11-907)	536.24(7-960)	273.85(16-893)	327.16(17-942)	371.05(7-960)

The MMRT of medicines in solid, semi-solid, as well as liquid dosage forms was more than 100 days higher than the MMRT of medicines in other dosage forms (inhalational, trans-dermal, and implants). The MMRT of medicines from countries with different levels of income ranges from 257 days (IQR: 114-469 days) for medicines from high income countries to 465 days (IQR:222-625 days) for medicines from countries with lower-middle level of income. The MMRT of medicines from Europe and North America together (Median=228 days, IQR: 110-469 days) was more than 1.8 times lower than the MMRT of medicines from the other continents (Table 23).

Kruskal-Wallis test showed that there was no statistically significant difference in the MMRT among the different dosage forms of the approved medicines ($X^2(3,N=933)=3.225,P=0.358$). However, there was a significant difference in the MMRT among the medicines from countries with different levels income($X^2(3,N=933)=61.627$, $P<0.05$) and among medicines from different continents of the countries of manufacture of the medicines($X^2(2,N=933)=54.824,P<0.05$).

Mann-Whitney *U* test showed that there was a statistically significant difference in the MMRT between the medicines approved from countries with different levels of income($p<00.005$) except between medicines from upper- middle and low income countries($p=0.464$) and between medicines from lower-middle and low income countries($p=0.635$).There was also a statistically significant difference in the MMRT between the medicines approved from the different continents of the countries of manufacture($p<0.005$) except between medicines from African and Asian countries($p=0.787$).

Table 22: Median, IQR, mean and range (R) of the time (in days) taken for the approval of each application type approved before and after the beginning of OMRDA and MRIS by EFMHACA (N=933)

Time of Application			**Type of Application**				**Total**
			New SRA	**New**	**Re-registration**	**Fast Track**	
Before/after OMRDA was started	**Before**	Median	433(n=73)	676(n=123)	486(n=73)	487(n=37)	577.50(n=306)
		IQR	199-589	555-751	328-650	245-648	354.5-700.5
		Mean(R)	413(11-907)	651(270-960)	488(86-893)	448(31-942)	530.73(11-960)
	After	Median	241(n=128)	492(n=167)	138(n=256)	202(n=76)	248(n=627)
		IQR	122-383	355-580	67-330	143-380	109-471
		Mean(R)	261(32-667)	452(7-757)	213(16-722)	269(17-699)	293.11(7-757)
Before/after MRIS was started	**Before**	Median	331(n=172)	565(n=272)	331(n=234)	339(n=94)	441(n=772)
		IQR	198-486	449-688	154-521	187-535	236.25-603.75
		Mean(R)	352(11-907)	563(58-960)	349(16-893)	370(31-942)	427.54(11-960)
	After	Median	80(n=29)	129(n=18)	67(n=95)	113(n=19)	75(n=161)
		IQR	46-142	62-222	53-117	57-162	53-138.5
		Mean(R)	104(32-421)	137(7-286)	89(32-249)	113(17-320)	100.16(7-421)

Table 23: Median, IQR, mean and range (R) of the time (in days) taken for the approved medicines by their dosage form, levels of income of the country of manufacture, and continent of the country of manufacture (N=933)

	Dosage forms of the approved medicines			
	Solid	**Semi-solid**	**Liquid**	**Others**
Median	371(n=576)	309(n=71)	351(n=274)	203(n=12)
IQR	158-562	81-582	145-560	102-379
Mean(R)	376(11-960)	335(36-821)	373(7-920)	289(81-795)
	Levels of income of the country of manufacture of the approved medicines			
	High	**Upper- Middle**	**Lower- Middle**	**Low**
Median	257(n=412)	374(n=122)	465(n=370)	328(n=29)
IQR	114-469	122-589	222-625	196-691
Mean(R)	304(11-907)	385(36-893)	438(7-960)	402(31-757)
	Continent of the country of manufacture of the approved medicines			
	Africa	**Asia**	**Europe and North America**	
Median	421(n=59)	434(n=538)	228(n=336)	
IQR	200-610	193-618	110-469	
Mean(R)	400(31-757)	416(7-960)	293(11-851)	

Others: Inhalational, trans-dermal, and implants

5.4. The Impacts of the Challenges of MR on the Procurement of Essential Medicines by the PFSA

More than three-fourth (80%) of the PFSAPOs said that the agency can not avail all the essential medicines at health facilities. All except one of those think a delay in national MRP is a factor for the delay in procurement and availability of essential medicines in Ethiopia. Most(71.4%) of the PFSAPOs who think the delay in national MRP as a factor for the delay in procurement and availability of essential medicines in Ethiopia rated it as a moderate problem to their procurement activities while the remaining 28,6% rated it as a major problem.

Request for the certificate of registration in the country of origin (85.7%) and procurement of alternative registered medicines ((57.1%) were the two most common ways raised by PFSAPOs to overcome the delay in procurement and availability of essential medicines in Ethiopia (Figure 17).

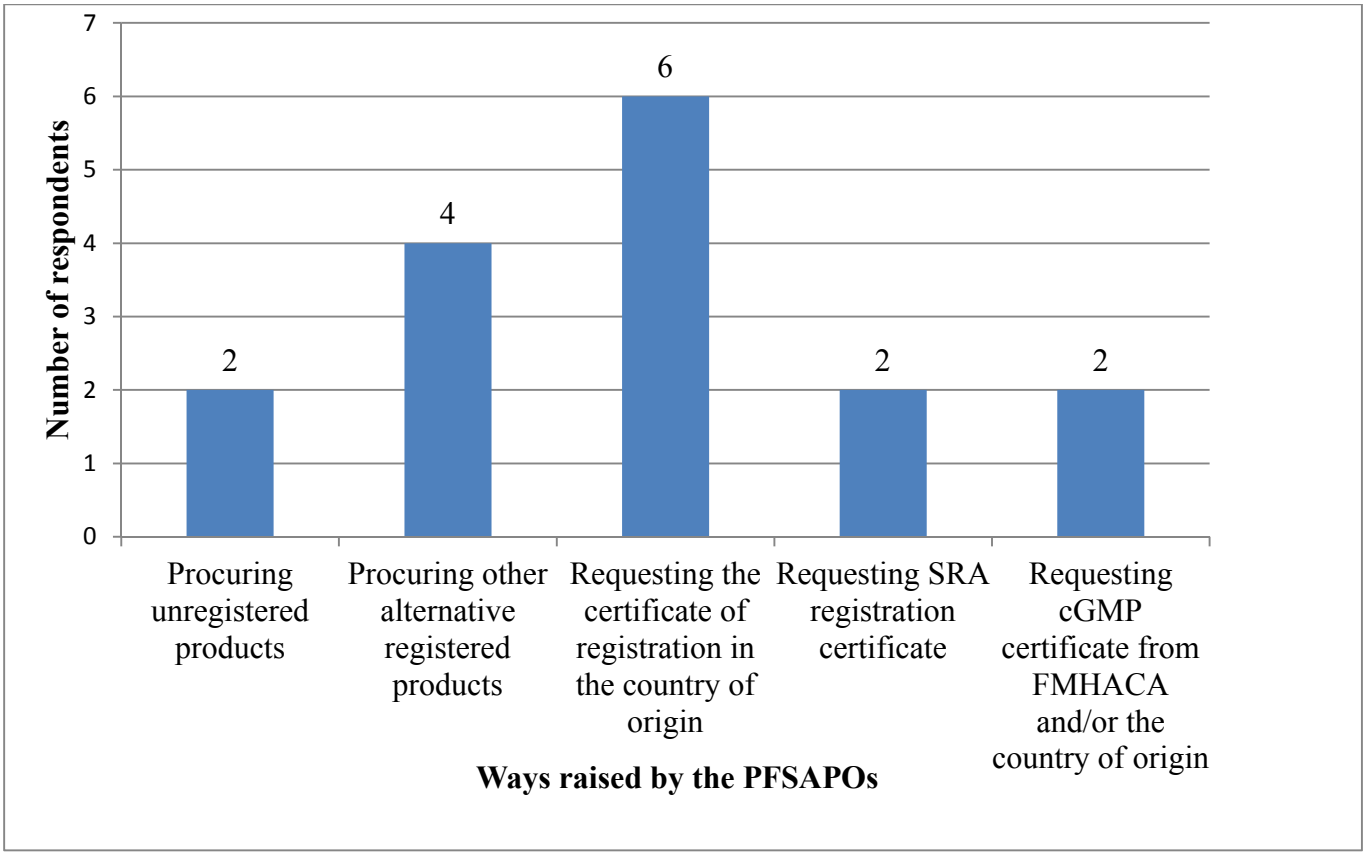

Figure 17: Ways PFSAPOs use to overcome the delay in procurement and availability of essential medicines in Ethiopia

The PFSAPOs said that the delayed national MR is affecting the public health in a number of ways explained in table 24.

Table 24: The effects of delayed national MR as of the PFSAPOs

Effects	Frequency	Percent
Decreases the number of alternative medicines on the market potentially leading to poor access to essential medicines	7	100.0%
Increases the price of medicines	6	85.7%
Creates an opportunity for the proliferation of poor quality medicines	6	85.7%
Promotes the irrational use of medicines	1	14.3%
Facilitates the wastage consumer and government resources	1	14.3%
Increases morbidity and/or mortality as a result of poor access and irrational use of medicines	2	28.6%

Delay in procurement due to delay in registration (80%) and lack of sufficient alternative registered medicines (60%) were the two most common MRP related challenges facing the PFSA procurement officers. These and other challenges as well as the PFSAPOs' recommendations to solve these challenges are given in table 25.

Table 25: MRP related challenges facing the PFSAPO**s** and their recommendations to solve these Challenges (N=10)

Challenges	Frequency	Percent	Recommendations	Frequency	Percent
Delay in procurement due to delay in registration	8	80.0%	Facilitate the registration process by minimizing the bureaucracy associated with it	9	90.0%
Reduction in the number of medicines importers and suppliers	3	30.0%	Harmonize the registration process with that of other Sub-Saharan African countries	6	60.0%
Non-competitive medicines price	4	40.0%	Encourage importers and suppliers by facilitating the registration process and other means	4	40.0%
Lack of sufficient alternative registered medicines	6	60.0%	Implement campaign registration	3	30.0%
Forged MR certificates of the country of origin	3	30.0%			

6. Chapter 6: Discussion

All the EFMHACA staff respondents agreed with the shortage of qualified staff in their respective work environment for a number of reasons. This finding agrees with the WHO 10-country study conducted in 2002 that showed shortage of qualified personnel as the major problem facing the NMRAs of the countries involved in the study [15] as well another WHO study conducted between 2002 and 2009 to assess the status of medicine regulation in 26 countries in sub-Saharan Africa that also found the regulatory authorities in most countries did have human resource constraints [61].

Most (83.3%) of the dossier evaluators reported that poor quality of dossiers submitted by the applicants was a challenge in MRP. A study conducted in Tanzania in 2013 also showed that poor dossier arrangement (quality and authenticity of information) was the cause of delay in registration process as reported by 73.8% of the dossier evaluators. Lack of relevant periodic trainings and inadequate time for dossier evaluation were also common challenges facing the dossier evaluators found in this study as well as the study conducted in Tanzania [38].

Most of the EFMHACA staff respondents said they received training while working at EFMHACA and majority of them agreed with the relevance and adequacy of the trainings they received while working at EFMHACA. However, lack of continuing education/training was reported as the main challenge facing the QCL analysts (60%) and GMP inspectors (71.4%). As majority of these respondents were only first degree holders, the lack of continuing education/training can have a significant negative effect on their career activities. So, most of them are in a high need for continuous education/ training.

Majority (64.2%) of the respondents from the LAFPIs said they did not receive any training on dossier pre-screening and compilation for registration purpose. Only 21.1% of the respondents who received training also said that the training has adequately prepared them to pre-screen dossiers for completeness and proper compilation before submission of the dossiers for registration purpose. This shows us that the technical persons in the LAFPIs are in a high need

for training on dossier pre-screening and compilation for registration purpose. These trainings could be provided by the EFMHACA and/ or the foreign PIs they represented.
Most of the respondents from the LAFPIs and the TPLMNPIs said EFMHACA did not register the product/s they requested for registration on time. This finding agrees with other finding in this study that showed only 17(1.8%) of applications approved by the EFMHACA were completed within the expected time.

Delay in MR was reported as the main challenge in MRP by 64.2% of the respondents from the LAFPIs and 84.6% the TPLMNPIs. This finding is also supported by the finding of the study conducted in Tanzania in 2013 as 92.7% of the representatives of medicines manufacturers reported long registration time as main challenge in the MRP in Tanzania [38].

A total of 268 MRAs were submitted to the EFMHACA from 11 April 2014 to 31 December 2014 with an average of around 1.02 applications per day; 1157 applications in 2015 with an average of around 3. 17 applications per day;797 applications in 2016 with an average of around 2.18 applications per day; and 565 applications from 01 January 2017 to 05 September 2017 with an average of around 2.29 applications per day. This indicates that the number of MRAs submitted to EFMHACA is generally increasing from time to time supporting the authority's claim that the number of MRAs submitted to it is increasing from time to time.

However, the highest number of applications was submitted in 2015. The beginning of the OMRDA by EFMHACA in 17 April 2015 may be one possible reason for this high number of submitted applications in 2015.Another potential reason for this is the publication of a document that addresses the investment opportunities in the Pharmaceutical sector of Ethiopia by the Embassy of the Federal Democratic Republic of Ethiopia in New Delhi, India in 2015 [34] as most (41.51% of all the submitted applications and 67.23% of the applications submitted from Asia) were from India.

Out of the 2191 applications (excluding the 596 applications for variation) submitted to the authority between 11 April 2014 and 05 September 2017, only 933(42.58%) applications were approved for MA of medicines in Ethiopia. A similar study conducted in Tanzania in 2013 found

only 170(22.88%) out of the 743 applications submitted to the TFDA in 2010 and 2011 were registered[38]. The difference in the percentage of registered medicines found in this study and the study conducted in Tanzania may be due to the difference in the study period and number of years the studies involved; the potential difference in the registration requirements and resources required for MR between the TFDA and EFMHACA, and the exclusion of variation applications in this study.

The overall MMRT of the AMRAs found in this study was 359 days ranging from 185 days for re-registration applications to 554 days for new applications. The overall MMRT is about 3.74 times longer than the longest timeframe (3 months + 5 days+1 hour for new or variation applications from foreign manufacturers without SRA approval certificate) indicated in the citizen charter for medicines regulation in Ethiopia [37]. However, both the mean and MMRTs for new medicines found in this study (mean=100.17 days, median=554 days) are lower than the MRT found for Ethiopia (730 days) in a study conducted to determine the time taken for registration of new medicines in 192 countries around the world in 2014 [10].

In this study, a statistically significant difference was found between the MMRT of each of the four different application types($p< 0.05$) except between the new SRA and fast track applications($p=0.745$) though the EFMHACA sets different timelines for the approval of new SRA and fast track applications in its citizen charter [37]. Therefore, it is fair to say that new SRA medicines are not being registered quicker than fast track medicines at this time.

The overall MMRT for the applications decreased from 622.5 days for applications submitted in 2014 to 89 days for applications submitted in 2017.This decrease in the overall MMRT was statistically significant($X^2(3, N=933)=430.753, P<0.05$). This shows us that EFMHACA is improving from time to time in terms of the time it takes to register medicines. However, there was a statistically significant increase in MRTs($p<0.001$) for pharmaceutical products approved in Oman from 2006 to 2010 [42].

There was also a statistically significant decrease in the overall MMRT as well as the MMRT of each application types after the beginning of the OMRDA and MRIS. So, it is fair to say that the

beginning of the OMRDA and MRIS by the EFMHACA has decreased the time required for registration of medicines in Ethiopia. However, it does not mean that the beginning of the OMRDA and MRIS are the sole reasons for this decrease in the MRT as the EFMHACA is continuously undertaking various activities that can help it to improve its service.

This study found a statistically significant difference in the overall MMRT among the medicines from the countries with different levels of income($X^2(3, N=933)=61.627, P<0.05$). It ranges from 257 days for medicines from high income countries to 465 days for medicines from countries with lower-middle level of income. The overall MMRT decreased as the level of income increases from lower middle to high income countries. The reason for this may be because countries with higher income may have a stronger NMRA than countries with lower income and hence are more likely to comply with the requirements of NMRAs of their own and other countries.

However, the overall MMRT for medicines from countries with low level of income (328 days) was lower than the overall MMRT for medicines from countries with upper-middle and lower middle income countries. This lower overall MMRT may be because most (79.31%) of the applications from low income countries were from Ethiopia as applications from local manufacturers are treated as fast track applications. The MMRT for applications from local manufacturers was 227 days (n=23, IQR: 163-568 days) which was lower than the MMRT for applications from low income countries in general.

This study also found a statistically significant difference in the MMRT among medicines from African, Asian, and European and North American (together) manufacturers ($X^2(2,N=933)=54.824, P<0.05$). The MMRT of medicines from European and North American manufacturers together (Median=228 days, IQR: 110-469 days) was more than 1.8 times lower than the MMRT of medicines from the other continents. This difference can also be explained by the potential difference in the NMRAs among the African, Asian, and European and North American countries.

This study found that a delay in the national MRP was a considerable factor for the delay in procurement and availability of essential medicines in Ethiopia. Thus, we can say the delay in the MR in Ethiopia is negatively affecting the availability of essential medicines in the country.

In general, this study found that the various challenges facing the EFMHACA and the applicant PIs and/ or their local representatives are delaying the MRP decreasing the availability of alternative registered medicines in the country. However, this study did not address the actual quality of the MR dossiers submitted to the authority for sensitivity issues.

7. Chapter Seven: Conclusion and Recommendations

7.1. Conclusion

Shortage of qualified personnel (dossier evaluators, QCL analysts, and GMP inspectors) and poor quality of the submitted dossiers respectively were the major internal and external challenges facing the EFMHACA in carrying out its MR activities. Together with other multifaceted challenges facing the EFMHACA and the applicant PIs and/ or their local representatives, these two major challenges are significantly delaying the MRP in Ethiopia as it was found that only 17(1.8%) of MRAs approved by the EMHACA were completed within the expected time. This delay in the MRP is decreasing the availability of alternative registered medicines on the market potentially leading to poor access to essential medicines in the country. However, it is important mentioning the significant improvement EFMHACA has achieved the past four years in decreasing the delay in the MR in the presence of the previously mentioned challenges and the increasing number of MRAs being submitted to the authority.

7.2. Recommendations

Based on the findings of this study, the following recommendations were given for the improvement of the MRP in Ethiopia.

7.2.1. Recommendations for EFMHACA

To improve the MRP in Ethiopia; the authority should also consider the various recommendations of the respondents involved in this study as there could be new ideas the authority did not consider yet in the implementation of different initiatives for expedited MR.

The authority should also set the timeline required for the completion each of the steps in the MRP as the timeline required for MR is the sum of the time required for the reception and validation of the application; queuing for scientific review; scientific review; question to company and company response; and MR procedure.

There is also a gap in the documentation of activities in the authority. For example, it was difficult to find the dates of submission and approval of variation applications; the dates further information requests/queries were sent to the applicant PIs; the dates the applicant PIs responded for these request/queries, the dates of sample reception and completion of the analysis of the sample; and the dates of notification to the applicants. So, the authority should work to improve its documentation process.

EFMHACA should also work on the ways to conduct other scientific studies on the MRP without disclosing the applicant PIs' data. The sensitivity of this should not blindly become an obstacle for further scientific studies.

7.2.2. Recommendations for Academic Institutions

Some universities in Ethiopia already started post graduate programs in pharmaceutical regulatory affairs. However, this is not enough as the country's demand for pharmaceutical regulatory affairs professionals will increase due to the rapidly developing pharmaceutical sector in the country. Hence, the academic institutions in collaboration with Ministry of education and EFMHACA as well as other stakeholders, should review and include regulatory affairs in their pharmacy training curriculum for undergraduate students in Ethiopia.

7.2.3. Recommendations for the Ministries of Health and Civil Service

The Ministries of health and civil service should work together to solve the shortage of qualified personnel at EFMHACA. This could be achieved by creating more training opportunities for the existing staff; employing additional qualified personnel; creating attractive career structure and incentives at EFMHACA; etc.

7.2.4. Recommendations for Further Research

Although poor quality of the submitted dossiers was reported as the major problem facing the dossier evaluators at EFMHACA, this study did not address the actual quality of the medicines registration dossiers submitted to the authority for sensitivity issues. So, a study can be conducted to assess the quality of the submitted dossiers after communicating on sensitivity issue with EFMHACA.

As the ultimate purpose of this study is to improve patients' access to safe, effective, and quality essential medicines in Ethiopia, the findings of this study are meaningful only if other studies are conducted on the factors after MR that can influence patients' access to safe, effective, and quality essential medicines in the country such as the medicines supply management and price.

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Annexes:

Annex I: Questionnaire for Dossier Evaluators

Dear Madam/Sir

My name is Haylay Araya. Currently, I am a Masters graduating student in Pharmaceutical Quality Assurance and Regulatory Affairs at the school of pharmacy, Faculty of Health Science, Institute of Health, Jimma University. I am conducting a study entitled as **Medicines registration process in Ethiopia: Its challenges and their impacts on the timely approval and procurement of essential medicines in the country**.

The ultimate purpose of this study is to promote the constant availability of affordable medicines of assured quality, safety and efficacy by collecting information on the challenges facing the national medicines regulatory authority, local pharmaceutical industries and registered local agents of pharmaceutical industries during medicines registration in our country as the results of the survey could be used as an input for the improvement of the drug registration systems.

Thinking about its main objective, your response is indispensible for the successful accomplishment of this study. Consequently, you are kindly requested to give your genuine response that will offer a big value for me. Your information will be kept strictly confidential and you don't need to write your name or any special identification that might disclose who you are. Your participation is voluntary.

Thanking you for your willingness to participate in this study, I politely ask you to encircle your answer and for the parts that need writing, to write your answer neatly and shortly as possible.

Section I: General Information

1. Gender a. Male b. Female
2. Age(Years)_____
3. Your Profession a. Pharmacist b. Medical Doctor c. Others Specify_____
4. Educational Level a. Diploma b. First Degree c. Master's Degree
5. Field of Specialization(If available)_____
6. Experience as medicine registration dossier evaluator a.0-1 year b.2-4 years c.5-7 years d. 8 years and above

Section II: Questions related to the challenges of medicines registration process of our country (For questions you think they have more than one answer, you can encircle all the possible answers)

1. Have you received any training on medicines registration dossier evaluation/assessment?
   a. Yes b. No

   If your answer to question number 1 is "No", please skip questions number 2, 3 & 4.
2. How much training (on average) do you receive per a year?
   a. 1-2 b. 3-4 c. 5-6 d. 7 and above
3. How do you rate the adequacy of the number of the trainings you got?
   a. Very Adequate b. Adequate c. Undecided d. Inadequate e. Very Inadequate
4. How do you rate the relevance of the trainings you got? a. Very Relevant b. Relevant c. Undecided d. Irrelevant e. Very Irrelevant
5. How do you rate the comprehensiveness of the medicines registration dossiers the applicant companies submit with respect to the registration guideline?
   a. Excellent b. Good c. Satisfactory d. Poor e. No Experience
6. Do you think the currently available number of dossier evaluators in your organization is sufficient? a. Yes b. No

If your answer to question number 6 is "Yes", please skip questions number 7.1 & 7.2

7. What do you think is the reason for this?
   7.1. The organization didn't initially hire enough number of evaluators? a. Yes b. No
   If "Yes", this is because?
   a. There is a shortage of qualified and skilled personnel on the market
   b. It is difficult to attract qualified personnel on the market for financial and other resource and incentive related reasons
   c. The organization believes the currently available number of evaluators is enough
   d. Others Specify_____
   7.2. There is high turnover of evaluators? a. Yes b. No **If "Yes", this is because of?**

a. Low Salary b. Lack of attractive career structure and incentives c. Poor retention mechanisms d. Others Specify_____

8. Do you have reliable information technology facilities and services in your work environment?
   a. Yes b. No

   If your answer to question number 8 is "Yes", please skip question number 9

9. If your answer is "NO", what do you think is /are the reason/s for this?
   a. Lack of qualified ICT staff
   b. Lack of commitment by the institutional management
   c. Erratic power supply
   d. financial problem
   e. Others Specify_____

10. Do you think you have all the necessary guidelines, standard Operating Procedures/SOPs, and templates for dossier evaluation in your work environment? a. Yes b. No
11. Generally, to what extent is the limitation of resource in your organization a problem to your activities?
    a. Major b. Moderate c. Minor d. Not a Problem
12. How do you describe the support you get from the management?
    a. Excellent b. Good c. Satisfactory d. Poor e. No Experience
13. How much are you satisfied with your work in the organization?
    a. Very Satisfied b. Satisfied c. Undecided d. Dissatisfied e. Very Dissatisfied
14. What are the most common challenges you face during medicine registration dossier evaluation?
    i. _____
    _____
    ii. _____
    _____
    iii. _____
    _____
    iv. _____
    _____

15. Your recommendation/s to solve these challenges

i. _____-

_____

ii. _____

_____

iii. _____

_____

iv. _____

_____

Thank You for Your Participation

Annex II: Questionnaire for QC Lab Analysts

Dear Madam/Sir

My name is Haylay Araya. Currently, I am a Masters graduating student in Pharmaceutical Quality Assurance and Regulatory Affairs at the school of pharmacy, Faculty of Health Science, Institute of Health, Jimma University. I am conducting a study entitled as **Medicines registration process in Ethiopia: Its challenges and their impacts on the timely approval and procurement of essential medicines in the country**.

The ultimate purpose of this study is to promote the constant availability of affordable medicines of assured quality, safety and efficacy by collecting information on the challenges facing the national medicines regulatory authority, local pharmaceutical industries and registered local agents of pharmaceutical industries during medicines registration in our country as the results of the survey could be used as an input for the improvement of the drug registration systems.

Thinking about its main objective, your response is indispensible for the successful accomplishment of this study. Consequently, you are kindly requested to give your genuine response that will offer a big value for me. Your information will be kept strictly confidential and you don't need to write your name or any special identification that might disclose who you are. Your participation is voluntary.

Thanking you for your willingness to participate in this study, I politely ask you to encircle your answer and for the parts that need writing, to write your answer neatly and shortly as possible.

Section I: General Information

1. Gender a. Male b. Female
2. Age(Years)_____
3. Your Professional Qualification a. Technician b. Graduate(BSC) c. Postgraduate(MSC) d. Others Specify_____
4. Field of Specialization (If available)_____
5. Experience as QC lab analyst a.0-1 year b.2-4 years c.5-7 years d. 8 years and above

Section II: Questions related to the challenges of medicines registration process of our country (For questions you think they have more than one answer, you can encircle all the possible answers)

1. Have you received any training on QC lab analysis after you start working in this organization?
   a. Yes b. No

   If your answer to question number 1 is "No", please skip questions number 2, 3 & 4.

2. How much training (on average) do you receive per a year?

   b. 1-2 b. 3-4 c. 5-6 d. 7 and above

3. How do you rate the adequacy of the number of the trainings you got?

   a. Very Adequate b. Adequate c. Undecided d. Inadequate e. Very Inadequate

4. How do you rate the relevance of the trainings you got? a. Very Relevant b. Relevant c. Undecided d. Irrelevant e. Very Irrelevant

5. Do you think the currently available number of QC lab analysts in your organization is enough?

   a Yes b. No

If your answer to question number 5 is "Yes", please skip questions number 6.1 & 6.2

6. If not enough, what do you think is the reason for this?

   6.1. The organization didn't initially hire enough number of staff? a. Yes b. No **If "Yes", this is because?**

   a. There is a shortage of qualified and skilled personnel on the market
   b. It is difficult to attract qualified personnel on the market for financial and other resource and incentive related reasons
   c. The organization believes the currently available number of evaluators is enough
   d. Others Specify_____

   6.2. There is high turnover of staff? a. Yes b. No **If "Yes", this is because of?**

   a. Low Salary
   b. Lack of attractive career structure and incentives
   c. Poor retention mechanisms
   d. Others Specify_____

7. Do you think there are reliable information technology facilities and services in your work environment? a. Yes b. No

If your answer to question number 7 is "Yes", please skip question number 8

8. If your answer is "No", what do you think is /are the reason/s for this?

   a. Lack of qualified ICT staff
   b. Lack of commitment by the institutional management
   c. Erratic power supply
   d. financial problem
   e. Others Specify_____

9. Do you think you have all the necessary guidelines and standard Operating Procedures/SOPs in your work environment? a. Yes b. No
10. How often do you encounter samples that fail the QC analysis tests?
    a. Didn't Encounter b. Rarely c. Moderately d. Very Often
11. In general, to what extent is the limitation of resource in your organization a problem to your activities?
    a. Major b. Moderate c. Minor d. Not a Problem
12. How do you describe the support you get from the management?
    a. Excellent b. Good c. Satisfactory d. Poor e. No Experience
13. How much are you satisfied with your work in the organization?
    a. Very Satisfied b. Satisfied c. Undecided d. Dissatisfied e. Very Dissatisfied
14. What are the most common challenges you are facing in conducting the various tests/assays in the lab?
    a. Financial Constraints(Low Budget)
    b. Limited Numbers of Qualified Professionals
    c. Lack of Continuing education/Training
    d. Limited Quantity of Functional Lab Equipments/Instruments
    e. Unavailability of Certain Reference Standards/Substances
    f. Unavailability of Pharmacopeial/Specifications
    g. Unavailability of Certain Reagents, Solvents and Indicators
    h. OthersSpecify_____
    _____
15. Your recommendation/s to solve these challenges?
    i. _____
    ii. _____
    iii. _____
    iv. _____

Thank You for Your Participation

Annex III: Questionnaire for GMP Inspectors

Dear Madam/Sir

My name is Haylay Araya. Currently, I am a Masters graduating student in Pharmaceutical Quality Assurance and Regulatory Affairs at the school of pharmacy, Faculty of Health Science, Institute of Health, Jimma University. I am conducting a study entitled as **Medicines registration process in Ethiopia: Its challenges and their impacts on the timely approval and procurement of essential medicines in the country**.

The ultimate purpose of this study is to promote the constant availability of affordable medicines of assured quality, safety and efficacy by collecting information on the challenges facing the national medicines regulatory authority, local pharmaceutical industries and registered local agents of pharmaceutical industries during medicines registration in our country as the results of the survey could be used as an input for the improvement of the drug registration systems.

Thinking about its main objective, your response is indispensible for the successful accomplishment of this study. Consequently, you are kindly requested to give your genuine response that will offer a big value for me. Your information will be kept strictly confidential and you don't need to write your name or any special identification that might disclose who you are. Your participation is voluntary.

Thanking you for your willingness to participate in this study, I politely ask you to encircle your answer and for the parts that need writing, to write your answer neatly and shortly as possible.

Section I: General Information

1. Gender a. Male b. Female
2. Age(Years)_____
3. Your Profession_____
4. Educational Level a. First Degree b. Master's Degree c. Others Specify_____
5. Field of Specialization(If available)_____
6. Experience as GMP Inspector? a. 0-1 year b.2-4 years c.5-7 years d. 8 years and above

Section II: Questions related to the challenges of medicines registration process of our country (For questions you think they have more than one answer, you can encircle all the possible answers)

1. Have you received any training on GMP inspection? a. Yes b. No

   If your answer to question number 1 is "No', please skip questions number 2, 3 & 4
2. How much training (on average) do you receive per a year? a. 1-2 b. 3-4 c. 5-6 d. 7 and above
3. How do you rate the adequacy of the number of the trainings you got? a. Very Adequate b. Adequate c. Undecided d. Inadequate e. Very Inadequate
4. How do you rate the relevance of the trainings you got? a. Very Relevant b. Relevant c. Undecided d. Irrelevant e. Very Irrelevant
5. Do you think the currently available number of GMP inspectors in your organization is sufficient? a. Yes b. No

   If your answer to question number 5 is "Yes", please skip questions number 6, 6.1, & 6.1
6. What do you think is the reason for this?

   6.1.The organization didn't initially hire enough number of evaluators? a. Yes b. No

   If "Yes", this is because?

   a. There is a shortage of qualified and skilled personnel on the market
   b. It is difficult to attract qualified personnel on the market for financial and other resource and incentive related reasons
   c. The organization believes the currently available number of evaluators is enough
   d. Others Specify_____

   6.1.There is high turnover of evaluators? a. Yes b. No **If "Yes", this is because of?**

   a. Low Salary
   b. Lack of attractive career structure and incentives
   c. Poor retention mechanisms
   d. Others Specify_____
7. Do you have reliable information technology facilities and services in your work environment?

   a. Yes b. No

   If your answer to question number 7 is "Yes", please skip question number 8

8. If your answer is "No", what do you think is /are the reason/s for this?
    a. Lack of qualified ICT staff
    b. Lack of commitment by the institutional management
    c. Erratic power supply
    d. financial problem
    e. Others Specify_____
9. Do you think you have all the necessary guidelines, standard Operating Procedures/SOPs, and templates in your work environment? a. Yes b. No
10. Generally, to what extent is the limitation of resource in your organization a problem to your activities?
    a. Major b. Moderate c. Minor d. Not a Problem
11. How do you describe the support you get from the management?
    a. Excellent b. Good c. Satisfactory d. Undecided e. Poor
12. How much are you satisfied with your work in the organization?

    a. Very Satisfied b. Satisfied c. Undecided d. Dissatisfied e. Very Dissatisfied

13. From experience, how do you rate the compliance of the PIs you inspected for GMP?

Location of GMP Inspected Companies	
14.1.**Local**	**14.2.Foreign**
a. Excellent	a. Excellent
b. Good	b. Good
c. Satisfactory	c. Satisfactory
d. Poor	d. Poor
e. No Experience	e. No Experience

15. What are the most common challenges you face in carrying out inspection services?
    a. Financial Constraints(Low Budget)
    b. Limited Numbers of Qualified Professionals
    c. Lack of Continuing education/Training
    d. Lack of SOPs or guidelines
    e. Limited access to relevant information on inspection

f. Others Specify_____

16. Your recommendation/s to solve these challenges

i. _____

ii. _____

iii. _____

iv. _____

Thank You for Your Participation

Annex IV: Questionnaire for the Local Agents of Foreign Pharmaceutical Industries

Dear Madam/Sir

My name is Haylay Araya. Currently, I am a Masters graduating student in Pharmaceutical Quality Assurance and Regulatory Affairs at the school of pharmacy, Faculty of Health Science, Institute of Health, Jimma University. I am conducting a study entitled as **Medicines registration process in Ethiopia: Its challenges and their impacts on the timely approval and procurement of essential medicines in the country**.

The ultimate purpose of this study is to promote the constant availability of affordable medicines of assured quality, safety and efficacy by collecting information on the challenges facing the national medicines regulatory authority, local pharmaceutical industries and registered local agents of pharmaceutical industries during medicines registration in our country as the results of the survey could be used as an input for the improvement of the drug registration systems.

Thinking about its main objective, your response is indispensible for the successful accomplishment of this study. Consequently, you are kindly requested to give your genuine response that will offer a big value for me. Your information will be kept strictly confidential and you don't need to write your name or any special identification that might disclose who you are. Your participation is voluntary.

Thanking you for your willingness to participate in this study, I politely ask you to encircle your answer and for the parts that need writing, to write your answer neatly and shortly as possible.

Section I: General Information

1. Gender a. Male b. Female
2. Age(Years)_____
3. Your Profession a. Pharmacist b. Medical Doctor c. Others Specify_____
4. Educational Level a. Diploma b. First Degree c. Master's Degree
5. Field of Specialization(If available)_____
6. What is your position in this organization?_____
7. How long have been working on the same position?

    c. 0-1 year b. 2-5 years c.6-10 years d. above 10 years

Section II: Questions related to the challenges of medicines registration process of our country (For questions you think they have more than one answer, you can encircle all the possible answers)

1. Have you received any training on medicines dossier pre-screening and compilation for registration purpose? a. Yes b. No

   If your answer to question number 1 is "No", please skip question number 2

2. Do you think the training you got has **adequately prepared you** for the pre-screening and compilation of medicines dossiers for registration purpose? a. Yes b. No
3. Based on your experience, did FMHACA register the product/s you requested for registration **on time?** a. Yes b. No

   If your answer to question number 3 is "Yes", please skip question number 4

4. If your answer to Q4 is "NO", what do you think is /are the main reason/s for this?

   a .FMHACA's failure to notify the results of the evaluation of the dossier to the applicant within the specified time (30 days).

   b. Companies Problems to fully comply to in the registration requirements of country/authority
   c. Companies Problems to respond to requested queries to the authority within the specified time(6 months)
   d. OthersSpecify_____

   _____

6. Do you think the timeline for medicines registration could be shortened? a. Yes b. No

   If Yes, how?_____
7. Do you think certain aspects of the medicines registration procedures could be simplified?

   a. Yes b. No **If Yes, which aspect?**_____
8. Do you think the current guidelines for medicines registration should be updated?

   a. Yes b. No **If yes, which section/requirement?**_____
9. Do you think current requirements of the medicines registration guidelines are?

   a. Easy to Understand b. Not always clear c. Generally Unclear

10. How do you rate the medicines registration fee of our country in comparison with the registration fee the nearby countries ask

For **local companies**	For **foreign companies**
a. Reasonable b. Too Low c. Too High d. No Experience	b. Reasonable c. Too Low d. Too High e. No Experience

11. In general, how do you rate the quality of the FMHACA's scientific opinions provided after evaluation of the medicines registration dossier and /or laboratory analysis of the sample?

    a. Excellent b. Good c. Satisfactory d. Poor

12. What are the most common challenges you face during medicine registration process?

    i. _____

    ii. _____

    iii. _____

    iv. _____

13. Your recommendation/s to solve these challenges

    i. _____

    ii. _____

    iii. _____

    iv. _____

Thank You for Your Participation

Annex V: Questionnaire for the Technical Persons of Local and Multi-national Pharmaceutical Industries

Dear Madam/Sir

My name is Haylay Araya. Currently, I am a Masters graduating student in Pharmaceutical Quality Assurance and Regulatory Affairs at the school of pharmacy, Faculty of Health Science, Institute of Health, Jimma University. I am conducting a study entitled **Medicines registration process in Ethiopia: Its challenges and their impacts on the timely approval and procurement of essential medicines in the country**.

The ultimate purpose of this study is to promote the constant availability of affordable medicines of assured quality, safety and efficacy by collecting information on the challenges facing the national medicines regulatory authority, local pharmaceutical industries and registered local agents of pharmaceutical industries during medicines registration in our country as the results of the survey could be used as an input for the improvement of the drug registration systems.

Thinking about its main objective, your response is indispensible for the successful accomplishment of this study. Consequently, you are kindly requested to give your genuine response that will offer a big value for me. Your information will be kept strictly confidential and you don't need to write your name or any special identification that might disclose who you are. Your participation is voluntary.

Thanking you for your willingness to participate in this study, I politely ask you to encircle your answer and for the parts that need writing, to write your answer neatly and shortly as possible.

Section I: General Information

1. Gender a. Male b. Female
2. Age(Years)_____
3. Your Profession a. Pharmacist b. Medical Doctor c. Others Specify_____
4. Educational Level a. Diploma b. First Degree **c.** Master's Degree
5. Field of Specialization(If available)_____
6. Type of your organization? a. Local b. Multi-national

7. For how many years have you worked in this organization?
   a. 1 – 3 b. 4 – 7 c. 8 – 11 d. 12 - 15 d. 16 and above
8. What is your position in this organization?_____
9. How long have been working on the same position?
   a. 0-1 year b. 2-5 years c.6-10 years d. above 10 years

Section II: Questions related to the challenges of medicines registration process of our country (For questions you think they have more than one answer, you can encircle all the possible answers)

1. Have you received any training on dossier preparation and compilation for registration purpose? a. Yes b. No

If your answer to question number 1 is "No", please skip question number 2

2. Do you think the training you got has **adequately prepared you** for the preparation and compilation of medicines dossiers for registration purpose? a. Yes b. No
3. Based on your experience, did FMHACA register the product/s you requested for registration **on time?** a. Yes b. No

If your answer to question number 3 is "Yes", please skip question number 4

4. If your answer to Q4 is "NO", what do you think is /are the main reason/s for this?
   a. FMHACA's failure to notify the results of the evaluation of the dossier to the applicant within the specified time (30 days).
   b. Companies Problems to fully comply to in the registration requirements of country/authority
   c. Companies Problems to respond to requested queries to the authority within the specified time(6 months)
   d. Others Specify_____
      _____

5.Do you think the timeline for medicines registration could be shortened? a.Yes b.No

If Yes, how?_____
_____

6. Do you think certain aspects of the medicines registration procedures could be simplified?

a..Yes b. No

If Yes, which aspect? _____

7. Do you think the current guidelines for medicines registration should be updated?

a. Yes b. No

If yes, which section/requirement?_____

8. Do you think current requirements of the medicines registration guidelines are?

a. Easy to Understand b. Not always clear c. Generally Unclear

9. How do you rate the medicines registration fee of our country in comparison with the registration fee of

10.1. **Nearby** Countries		10.2.Other **Developing countries Africa**	
Fees they ask for **local Companies**	Fees they ask for **foreign companies**	Fees they ask for **local Companies**	Fees they ask for **foreign Companies**
a. Reasonable b. Too Low **c. Too High** d. No Experience	a. Reasonable b. Too Low **c. Too High** d. No Experience	**a. Reasonable** b. Too Low c. Too High d. No Experience	a. Reasonable b. Too Low c. Too High **d. No Experience**

10. In general, how do you rate the quality of the FMHACA's scientific opinions provided after evaluation of the medicines registration dossier and /or laboratory analysis of the sample?

a. Excellent b.Good c. Satisfactory d. Poor

11. What are the most common challenges you face during medicine registration process?

i. _____

ii._____

iii. _____

iv._____

12. Your recommendation/s to solve these challenges

i. _____

ii._____

iii. _____

iv._____

Thank You for Your Participation

Annex VI: Questionnaire for PFSA Procurement Officers

Dear Madam/Sir

My name is Haylay Araya. Currently, I am a Masters graduating student in Pharmaceutical Quality Assurance and Regulatory Affairs at the school of pharmacy, Faculty of Health Science, Institute of Health, Jimma University. I am conducting a study entitled as **Medicines registration process in Ethiopia: Its challenges and their impacts on the timely approval and procurement of essential medicines in the country**.

The ultimate purpose of this study is to promote the constant availability of affordable medicines of assured quality, safety and efficacy by collecting information on the challenges facing the national medicines regulatory authority, local Pharmaceutical Industries and registered local agents of pharmaceutical industries during medicines registration in our country as the results of the survey could be used as an input for the improvement of the drug registration systems.

Thinking about its main objective, your response is indispensible for the successful accomplishment of this study. Consequently, you are kindly requested to give your genuine response that will offer a big value for me. Your information will be kept strictly confidential and you don't need to write your name or any special identification that might disclose who you are. Your participation is voluntary.

Thanking you for your willingness to participate in this study, I politely ask you to encircle your answer and for the parts that need writing, to write your answer neatly and shortly as possible.

Section I: General Information

1. Gender a. Male b. Female
2. Age(Years)_____
3. Your Profession _____
4. Educational Level a. Diploma b. First Degree c. Master's Degree d. Others Specify_____
5. Experience as procurement officer
    a. 0-1 year b.2-4 years c.5-7 years d. 8 years and above

Section II: Questions related to the challenges of medicines registration process of our country (For questions you think they have more than one answer, you can encircle all the possible answers)

1. Can your agency avail all the essential medicines required at health facilities **on time**? a. Yes b. No

   If your answer to question number 1 is "Yes", please skip questions number 2 to 5.

2. If your answer to question number 1 is "No", do you think **a delay in national medicines registration process** is factor for the delay in procurement and availability of essential medicines? a. Yes b. No

   If your answer to question number 2 is "No", please skip questions number 3, 4&5

3. If your answer to question number 2 is "Yes", how do you overcome the problem?
   a. By procuring unregistered products
   b. By requesting the medicines registration authority to speed up the registration process of the medicine/s for procurement
   c. By requesting the certificate of registration of the medicine in the country of origin
   d. Others(PleaseSpecify)_____
      _____

4. Generally, to what extent is the **delay in national medicines registration** a problem to your procurement activities?
   a. Major b. Moderate c. Undecided d. Minor

5. What do you think are the effects of this delay in national medicines registration
   _____
   _____
   _____

6. What are the most common **medicines registration process related challenges** you face in carrying out your work?

   i. _____
   ii. _____
   iii. _____
   iv. _____

7. Your recommendation/s to solve these challenges

i. _____

ii. _____

iii. _____

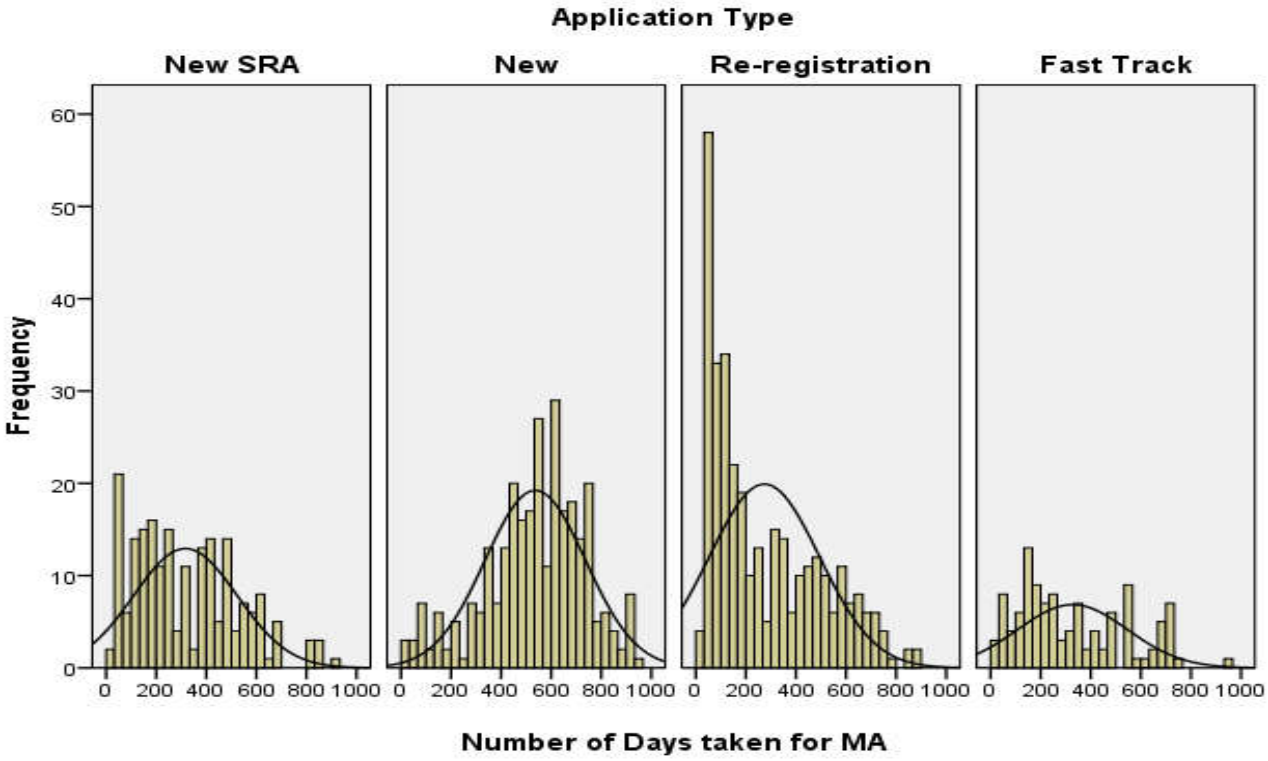
iv. _____

Thank You for Your Participation

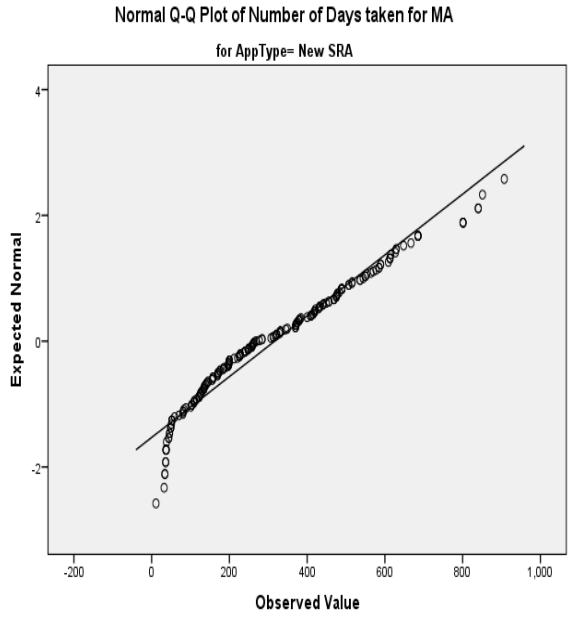
Annex VII: Data collection tool for approved medicines registration applications submitted to the EFMHACA 11 April 2014 to 05 September 2017

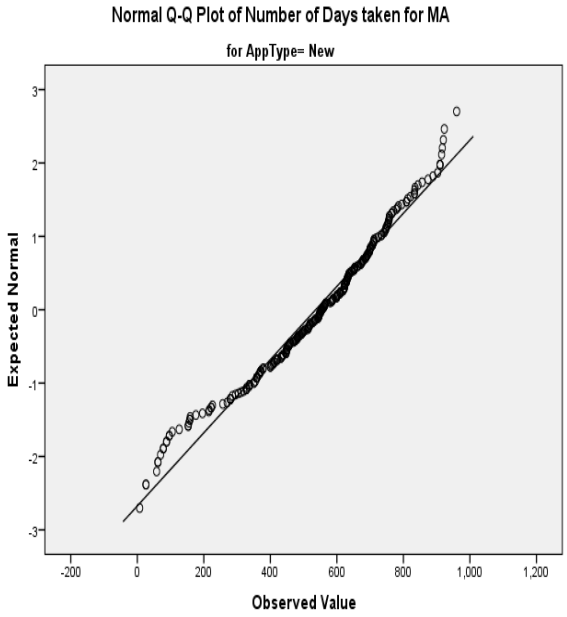
File No.	Application type	Product dosage form	Country of applicant company	Date of application	Date of market authorization	Number of days taken for market authorization

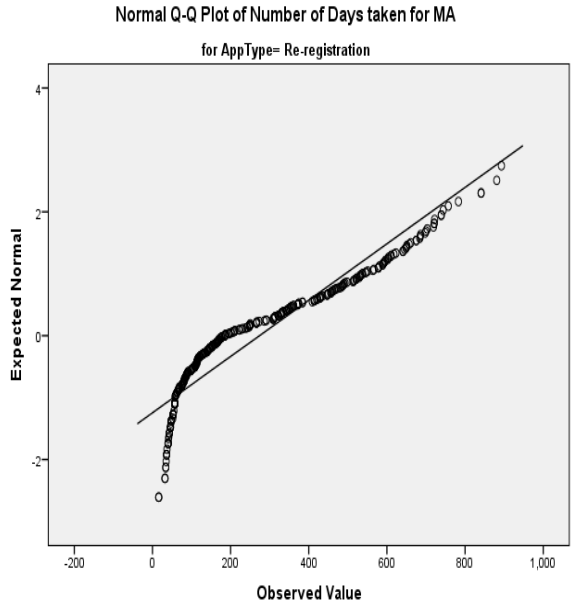
Annex VIII: Histograms of the time (in days) taken for the approval of new SRA, new, re-registration, and fast track applications

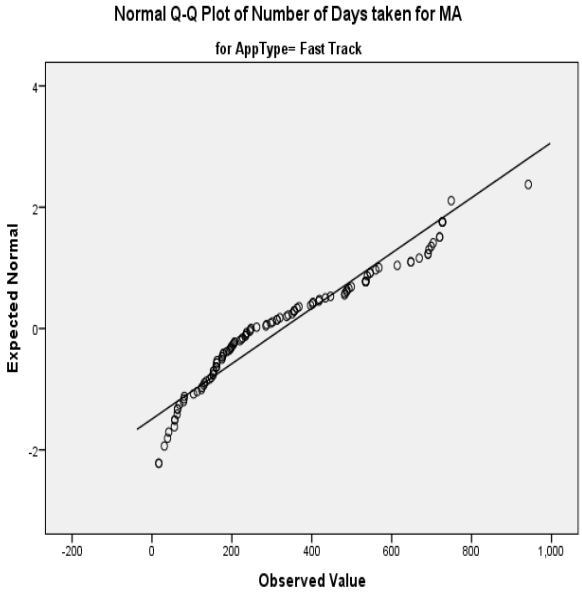


Annex IX: Normal Q-Q plots of the time (in days) taken for the approval of new SRA, new, re-registration, and fast track applications

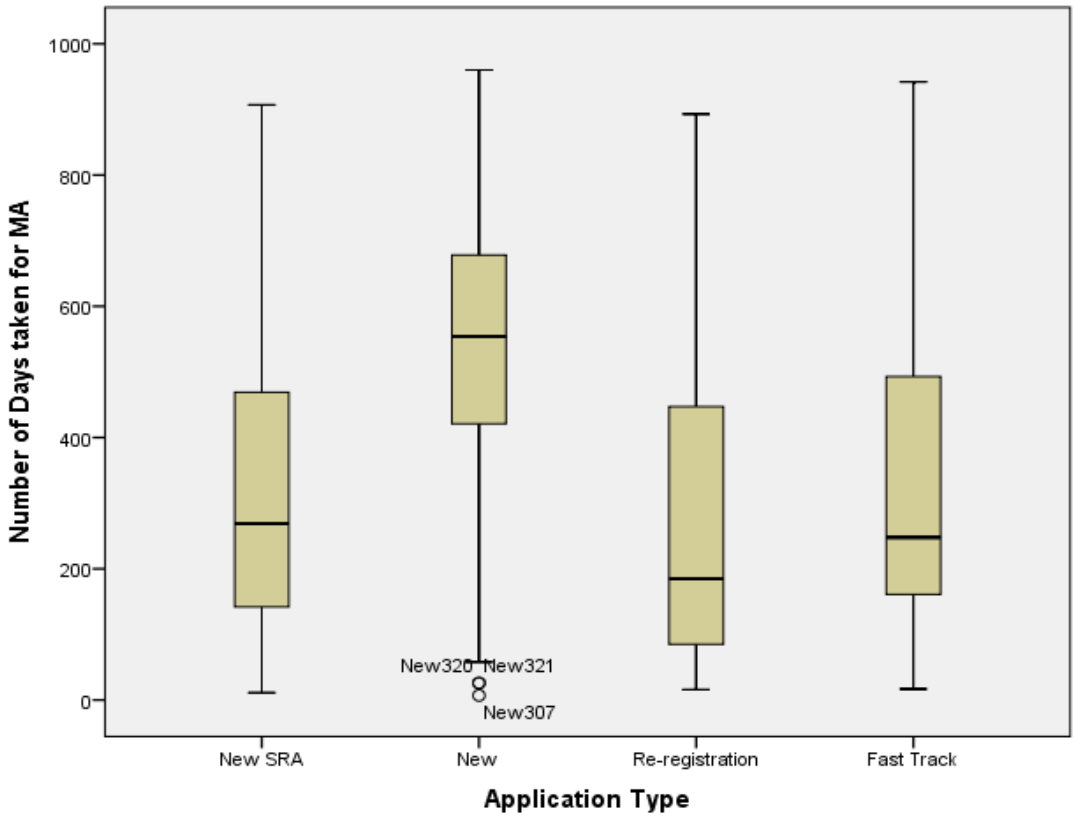








Annex X: Box plots of the time (in days) taken for the approval of new SRA, new, re-registration, and fast track applications



Annex XI: List of Local Representatives of Foreign Pharmaceutical Industries, Local and Multi-National Pharmaceutical Industries Involved in the Study

List of Local Agents of Foreign Pharmaceutical Industries	
S.No	**Name**
1	Afro Germen Human Medicine and medical supplies importer and wholesaler
2	Alo Vera Pharmaceuticals and Medical Equipments Importer and Wholesaler
3	Amba Human Medicine and Medical Supplies Importer and Wholesale
4	Ametco Export and Import PLC human medicine and medical supplies importer
5	Atma Import & Export PLC
6	Badreg Human Drug and Medical supplies importer and wholesaler
7	Bahar Human Medicine and Medical Supplies Importer and Wholesaler
8	Beker Human Medicine and Medical Supplies Importer and Wholesaler
9	Birole Pharmaceuticals Importer and Wholesaler
10	Bishaw General Trading Pharmaceuticals and Medical Supplies Importer and Distributer
11	Caretinea Pharma International Plc
12	Caroga Pharma Drug and Medical Supplies Importer and Wholesaler
13	Dat Intrnational Trading Human Medicine and Medical Supplies Importer and Wholesaler
14	Dkt Ethiopia
15	ELPIS Human Medicine and Medical Supplies Importer and Wholesaler
16	Equatorial Business Group PLC
17	Estro Human Medicine and Medical Supplies Importer and Distributor
18	Etab Intermedica Human Medicine and Medical Supplies Importer and Wholesaler
19	Etmedix Human Medicine and Medical Supplies Importer and Wholesaler
20	Eyasu Human Drugs and Medical Supplies Importer And Distributor
21	Fekere Trading PLC
22	General Chemicals And Trading Human and Medical Supplies Importer and Wholesaler
23	Gez Chemicals And Pharmaceuticals Human Medicine And Medical Supplies Importor And Distributor
24	Grace Trading PLC
25	Hosam Pharmaceuticals Trading Human Medicine and Medical Supplies Importer and Wholesaler

26	Kare Human Medicine and Medical Supplies Importer and Wholesaler
27	Kefyalew Pharmaceuticals & Medical Supplies Import & Distribution Enterprise
28	LB Pharmaceuticals PLC Human Medicines and Medical Supplies Importer and Wholesaler
29	Lewi Import and Export PLC
30	MDX International Pharmaceutical Human Medicine and Medical Supplies Importer and Distributor
31	Meditech Human Medicine and Medical Supplies Importer and Wholesaler
32	Medix Human Medicine and Medical Supplies Importer and Wholesaler
33	Meruna Import And Export PLC
34	Mesroy International PLC
35	Momentum Pharmaceutical PLC
36	Nared Human Medicine Medicine And Medical Supplies Wholesaler
37	Pharma Birbir P.L.C Drug and Medical Supplies Wholesaler
38	Remkaln General Trading Human Drug and Medical Supplies Importer and Wholesaler
39	Pharma Selam Medicines and medical supplies importer and wholesaler
40	Tadba Human Medicine and Medical Supplies Importer and Wholesaler
41	Tripharma Trading PLC
42	Universal Investors Drug and Medical Supplies Importer and Wholesaler
43	Venus Human Medicine and Medical Supplies Importer and Distributer
44	Vital Pharmaceutical Human Medicine and Medical Equipment Importer and Wholesaler
45	V-Tag Inrernational Trading PLC Human medicine and medical supplies Importer and wholesaler
46	Washa Human Medicine & Medical Supplies Importer and Distributor
47	Wecare Pharmaceutical & Medical Suplply Wholesaler
48	West Pharma Human and Vet Drugs and Medical Supplies Importer and Distributer
49	Wise Team Human Medicines and Medical Supplies Importer and Wholesaler
50	Woyn Chemicals, Human Medicines and Medical Supplies Importer and Wholesaler
51	Yoha Pharmaceuticals Medicines and medical supplies importer and wholesaler
52	Zaf Pharmaceuticals Drug and Medical Supplies Importer and Wholesaler
53	ZE-EL. Trading Human Medicine and Medical Supplies Importer and Wholesaler
List of Local and Multi-national Pharmaceutical Industries	

S.No	Name
1	Addis Pharmaceuticals Factory S.C
2	Bayer Trading Representative Office Ethiopia
3	Brawn Laboratories PLC
4	Cadila Pharmaceuticals (Ethiopia) Plc
5	East African Pharmaceuticals PLC
6	Ethiopian Pharmaceuticals Manufacturing Sh.Co
7	Fewes Pharmaceuticals Plc
8	Glaxosmithkline Pharmaceutical Ethiopia
9	Julphar Pharmaceutical Plc
10	MSD Ltd Ethiopia
11	Novartis Pharma Ethiopia
12	Sandoz Ethiopia
13	Sanofi Ethiopia

ASSURANCE OF PRINCIPAL INVESTIGATOR

The undersigned agrees to accept responsibility for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the Faculty of Health Science, Institute of Health, Jimma University in effect at the time of grant is forwarded as the result of this application.

Name of the student: _____

Date._____ Signature _____

APPROVAL OF THE FIRST ADVISOR

Name of the first advisor:_____

Date._____ Signature _____

APPROVAL OF THE SECOND ADVISOR

Name of the second advisor:_____

Date._____ Signature _____