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ASSESSMENT OF FACTORS INFLUENCING MEDICINE MARKET AUTHORIZATION PROCESS IN ETHIOPIA

By:

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June, 2020.

Addis Ababa, Ethiopia.

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A RESEARCH THESIS SUBMITTED TO THE SCHOOL OF PHARMACY, COLLEGE OF HEALTH SCIENCE, ADDIS ABABA UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR DEGREE OF MASTER OF SCIENCE IN MEDICINE REGULATORY AFFAIRS.

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DEPARTMENT OF PHARMACEUTICS AND SOCIAL PHARMACY
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This is to Certify that the thesis prepared by Sefanit Mekonnen T/Mariam, entitled **"*Assessment of Factors Influencing Medicine Market Authorization Process in Ethiopia*"** and submitted in partial fulfillment of the requirements for the degree of Master of Pharmacy in medicine regulatory affairs complies with the regulations of the university and meets the accepted standard with respect to originality and quality.

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Acronyms and abbreviations

APIs	Active Pharmaceutical Ingredients
AMRH	African Medicines Regulatory Harmonization
EFMHACA	Ethiopian Food Medicine Health Care Administration and Control Authority
EFDA	Ethiopian Food and Drug Authority
EMA	European Medicine Agency
EU	European Union
GMP	Good Manufacturing Practice
LRFPIs	Local Representative of Foreign Pharmaceutical Industries
LPIs	Local Pharmaceutical Industries
MA	Market Authorization
MAH	Market Authorization Holders
MRA	Medicine Regulatory Authority
MRIS	Medicine registration information system
NMRA	National Medicine Regulatory Authority
NSRAs	Non Stringent Regulatory Authorities
PIP	Port Import Permit
QC	Quality Control
SIAPS	Systems for Improved Access to Pharmaceuticals and Service
SRAs	Stringent Regulatory Authorities
USAID	United State Agency for International Development
USFDA	United State Food Drug Administration
WHO	World Health Organization

Abstract

Assessment of Factors Influencing Medicine Market Authorization Process in Ethiopia.

Sefanit Mekonnen T/Mariam

Addis Ababa University, 2020

Introduction: To provide safe, quality and effective medicine for the society, medicine has to be registered as per the regulatory requirement of a country. However, there is a reported delay in the market authorization process which has contributed to the shortage of life saving medicines. Therefore, studying those factors that influence medicine market authorization process will have an important role in addressing the problem in depth.

Objective: The aim of this study was to assess the factors influencing medicine market authorization process in Ethiopia.

Methods: A sequential, mixed method study using quantitative and qualitative methods was used. For the quantitative part, retrospective data on applications submitted through Medicine Registration Information System (MRIS) at Ethiopian Food Medicine Health Care Administration and Control Authority (EFMHACA) from July 1, 2016 to Dec 30, 2018 were collected. For the qualitative part, in-depth interviews were held with selected participants from EFMHACA, local representative of foreign pharmaceutical industries (LRFPIs) and local pharmaceutical industries (LPIs) about the challenges they face on the market authorization process. The collected quantitative data was entered to SPSS version 20 for analysis. Bivariate analysis was used to correlate the association between the dependent and independent variables. The qualitative data was analyzed using thematic analysis.

Results: Among 317 new applications submitted through MRIS since 2016, only 18% were approved for Market Authorization (MA); whereas the majority of applications were still in process of registration. The identified factors that hinder MA approval were the limitation of resource, inadequate training and impracticality of regulation by applicants and EFMHACA.

Conclusion and recommendations: MA process takes a long time due to impeding factors from EFMHACA, LRFPIs and LPIs sides.

It is therefore recommended that EFMHACA install sufficient number of qualified personnel; whereas, for LRFPIs and LPIs, building the capacity of their staffs will improve the MA process.

Key Words: Medicine Registration Information System, Market Authorization, Regulatory application.

1. Introduction

1.1 .Background

Medicines are not common goods simply utilized by consumers. This means all stage of their production, from clinical research and development process up to market authorization (MA) approval phase, needs caution as a regulatory perspective to ensure their safety, quality and efficacy. However, in countries where there is a weak regulatory system, implementing equitable medicine polices and strategies within the political and economic context are a challenging task. (Narsai et al., 2012; Suleman et al., 2016).

In this regard,the society's exposure for substandard medicine is more widely spread. Specially, in developing countries, over 25% of medicines available in the market are counterfeited medicines. (Rago et al., 2014). Consequently, 100,000 people die in every year in Africa. As a result, to strengthen the national regulatory framework, the MA process have a significant role to protect society from unsafe use of medicine.(Leon,2014).

So,strong National Medicine Regulatory Authority (NMRA) accordingly international conference on harmonization of technical requirements for registration of pharmaceuticals with collaboration regulatory authority and industrial manufacturer were flourished to set as registration process is a basic requirement for MA.(WHO,2010).Hence, in developing countries applying for registration and obtaining MA approval for safe, effective and quality medicine, distribution factors related with limited resource financial outlay, lack of human power and absence of harmonized system across countries have impact in obtaining MA in reasonable period of time.(Chahal et al.,2016;Roey et al.,2008).

Pertaining on this fact, diseases like malaria, tuberculosis, waterborne diseases and other communicable diseases that need innovation of new medicine still remain in developing countries. And the support of developed countries shows less motivation for development of new treatment and passing through NMRA as per each country's requirement for MA process become discouraging. Consequently, the availability of registered medicine, especially for developing countries in Africa, faces a significant challenge in meeting their mandate. This may open a door for a wide distribution of

unregistered substandard products, which happens to be a current global issue, especially for Africa.

For instance, as WHO studies in 2006 indicate, among 187 antimalarial medicines distributed in the market in Kenya, 42% were not registered. (Clay, 2016)

Also in Nigeria, 2008, surveillance on quality of antimalarial medicines was performed by collecting samples from distributed medicines and it was found that 37% fail to meet the required standard. This shows how counterfeited products are extensively distributed in the market. Following this, the accessibility of registered medicines whose quality, safety and efficacy is assured for public use may become hampered. (Narsaietal, 2012).

However, in 2012, to improve the regulatory capacity of different African countries, WHO provides a technical support for NMRA in product dossier evaluation, good manufacturing practices, information management system and quality data management system. Besides, the goal of harmonization were: to improve the evaluator efficiency with regard of implementation standards, to enhance symmetry management systems, build up systems and process of disseminating information with in regulatory authority and outside with applicants, to harmonize technical document requirements across countries, to improve NMRA assessors capacity by sharing different countries regulatory experience and to improve the time frame for MA approval. (WHO, 2014 : WHO, 2015).

In Ethiopia, Food, Medicine and Health Care Administration and Control Authority (EFMHACA) by proclamation 661/2009 has an authorization for MA process that includes: medicines inclusion in the national medicine list; the manufacturing site has to be certified for compliance with Good Manufacturing Practice(GMP) either by EFMHACA or other recognized stringent regulatory authorities (SRAs); such GMP certified or waived manufacturers have to submit common technical document with content of product dossier; Module 1 – Administrative information and prescribing information ,Module 2 – Dossier Overall Summary of Product, Module 3 – Quality , Module 4 – Nonclinical Study Report and Module 5 – Clinical Study Report with required application fee.

For this purpose, EFMHACA has developed a medicine registration guideline to provide necessary guidance for applicants' dossier preparation and submission through web based system called Medicine Registration Information System (MRIS); Following dossier evaluation completion sample should be submitted for QC (Quality Control) laboratory test. Finally, registration and licensing directorate set decision for MA approval. (EFMHACA, 2014; MRIS, 2016; EFMHACA, Proclamation No.661/2009).

1.2. Statement of the problem

Attaining MA from NMRA is a preliminary requirement to make medicines available for public use. However, registration of medicines is a cumbersome process which requires a significant human, financial, and material resources from NMRA. Due to this reason, acquiring safe, qualified and efficacious medicines that have been registered and marketed for public use has become difficult. As a result, the imbalance of demand and supply of medicine will open the door for counterfeited medicine distribution across the countries, even now. This circumstance is a problem of both developed and developing countries. (Hill and Johnson, 2004; Narsaietal., 2012; Pankajetal., 2013).

In Africa, NMRA has a lot of struggle in facilitating the MA process in regard with lack of human resource, limited infrastructure and having specific regulatory requirement. Also, the capacity of the regulatory authority to implement regulation may vary among countries. Due to this reason, the time frame to complete the MA process and to obtain MA will take up to three years. (Narsaietal., 2012). Also,World Health Organization (WHO) report shows that 50 African countries have different regulatory requirements in the absence integration of information management system for MA application. And the time frame for MA approval is different across countries. (Bellah, 2015 ;Ahonkhai, 2016).

In Ethiopia, FMHACA, collaborating with United States Agency for International Development (USAID) developed System for Improved Access to Pharmaceuticals and Services (SIAPS) program to speed up the MA process. MRIS was developed, which is used for product dossier submission and evaluation. (Tadeg, 2014).

With this trend, from October 2016 to November 2017, among 1422 applications submitted through MRIS system as new application, re-registration and variation applications; 195 (13.71%) products were obtained MA and the remaining products, 471 (33.12%) waiting for prescreening review, 26 (1.83%) in process of prescreening, 174 (12.24%) waiting for dossier evaluation, 282 (19.83%) dossier under evaluation, 115 (8.08%) waiting applicant feedback, 105 (7.38%) complete dossier evaluation and waiting QC laboratory test approval, 41 (2.88%) products in archive (in visible from system because of renewal) and 13 (0.91%) applications rejected.(EFMHACA, 2016; EFMHACA, 2017).

As shown from the above report, even if the system is implemented to facilitate MA process and to shorten the period of MA approval, there are still large number of products that are in process which means they are in screening, assessment, waiting the applicants' feedback and waiting QC result. So MA process has an impact on MA approval. And these results can cause a shortage of medicine in the market and problems on products affordability. Patients have less product choice and the society may be exposed to unsafe, ineffective, and poor quality medicines which causes a serious public health problem associated with increase in mortality and morbidity, provoking of drug resistance, loss of medicine efficacy, loss of confidence in health system and health workers, economic loss for patients, their families, the producers and suppliers. Additionally, it causes wastage of enormous human effort and financial outlay in the development of medicines. (Newton etal., 2010).

With this fact, MA process have an impact to obtain MA and considering the significance study was done in Tanzania focusing on challenges in registration process with involvement of regulatory authority evaluators, manufacturer representatives and pharmacists. However, this study does not include GMP inspectors and QC analysts. (Mkumbwa, 2013).

In Ethiopia, there was no study conducted on factors that influence medicine MA process in regard with implementation of MRIS for product dossier evaluation so this study is timely and important to address those impediments in MA process.

1.3. Significance of study

In MA process for dossier evaluation, even though the MRIS is implemented for electronic dossier submission and evaluation, applications to be screened, service fee to be paid by applicants, assessors to be assigned for dossier evaluation and waiting for QC analysis takes long time. As a result, this has an impact on obtaining MA in reasonable period.

So, the ultimate achievement of this study is to identify those challenges in MA process: GMP inspection, dossier evaluation and QC laboratory test. The findings of this study may help EFMHACA, LRFPIs, and LPIs to formulate strategies to minimize, if possible to avoid those challenges they are facing during MA process, and also to enhance the electronic dossier assessment process.

This may improve smooth and timely registration of medicines, increase the of availability of registered medicines in the market and also grow market competition among registered medicines. Eventually, these lower prices significantly increase the availability and affordability of safe, effective, and quality medicines in the country.

1.4. Literature review

1.4.1. Introduction to market authorization

Medicine regulation is a process that incorporates several activities that are aimed at promoting and protecting the public health. Accordingly, NMRA is committed in monitoring the execution of regulation in any country. Thus, MA process is a basic requirement to control medicines circulating in the market. However, the procedure is generally a very resource-demanding process because medicine's quality, safety and efficacy must be proven by a detailed relevant scientific data about chemistry, manufacturing and control, preclinical and clinical studies. Moreover, prospective risk monitoring and management are increasing within the NMRA 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.. (WHO, 1998;WHO, 2010;Haas, 2015). So MA, which is a legal document, is issued from competent regulatory authority to market safe, quality and effective medicines. (Kumar, 2011; Kashyap et al, 2013).

Applications can be submitted for MA to NMRA as a type of a new drug application if the medicine is discovered for the first time (which is a new medicine), abbreviated new drug application: If the product contains same active ingredients as original medicine apply for MA of generic product and variation: If there is change to existing MA. (WHO; 1998, Pankajet al**.,** 2013).

However, obtaining MA application assessment period is different across countries. For instance, in United State Food Drug Administration (USFDA), the decision time of MA for new drug application will take up to 10 months. But on certain conditions, to expedite the process for those medicines, which are crucial for society, four systems were developed on the bases of the severity of diseases: Accelerated approval pathway- application submitted for medicines used to treat serious diseases condition will be approved in 6 months; Breakthrough therapy designation - for application submitted for enhancement of existing medicine, the approval time will take 60 days; Fast track designation - for application submitted for medicines used to treat life threatening situation, the approval time will take 60 days; Priority review designation - for application submitted for new medicines that provide better outcome than existing medicine, the approval time will take 6 months. (Zeitoun et al., 2015; Wallach et al., 2018).

Also, in European Union (EU), there are four ways of MA approval procedure: As centralized procedure application submitted in one of EU member of state for: Biotechnological medicines, orphan medicines and new active substances having indication for chronic diseases, cancer, HIV and Neurodegenerative disorder medicines and with the approved MA products marketed in all member of state and MA decision takes 7 months. As national procedure applicants apply in one of competent national regulatory authority which is EU member of state for all type of application except as centralized procedure registered products .Or else, as mutual recognition procedure applicants submitted assessment report to one of EU member regulatory authority to get consent withhold MA to market their products in other EU members and decision for MA takes up to 9 months and as decentralized procedure for application which is not previously registered in any member of state used to get different EU Member state MA . So, in such a trend of harmonization, MAH (Market Authorization Holders) possibly market their products with other member countries. (Kumar, 2011).

As the study indicated, there were significant differences in the length of time taken by various drug authorities to evaluate MA applications. 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.(Bate et al, 2010)

In Africa, NMRA have a lot of responsibility in executing MA process with poor facility of QC laboratories, poor regulatory standards, lack of trained personnel and limited financial resources. In regard with this issue, a study shows that in Tanzania challenges that hinder smooth medicines MA process were inadequate number of evaluators as one factor that hinder timely assessment of dossier, lack of continuous expertise training, poor dossier compilation by applicants, unreliable management information system in the regulatory authority and lack of updated reference materials for dossier evaluation results delay of MA process.(Mkumbwa ,2013)

Also, WHO studies shows that in 90% sub-Saharan African countries, NMRA still does not sufficiently perform the required regulatory function. Subsequently, providing safe, quality and effective medicines to the society is a challenging situation.

As a result, there is a shortage of qualified medicine from the market which may open the door for distribution of counterfeited medicines. (Moran et al, 2011; Narsai et al, 2012;Roey et al, 2008).

1.4.2. Medicine registration information system

Countries have different regulatory requirement for medicine registration application. Nevertheless, to enhance the regulatory pathway for MA process and to increase the accessibility of new medicine for society by providing guidance for registration application, there should be standard operating procedure made available for applicants. And using advanced technology such as electronic submission of application and constructing strong collaboration of regulatory agency with applicants enables the decision time for MA to take up to 90 days or less as compared with 6 months of USFDA. And with such trend, countries found in Middle East/North Africa, Eastern Europe, Sub-Saharan African, Latin America and Asia are characterized by using facilitated regulatory pathway.(Libertietal ., 2016).

Correspondingly, in 2009, to enhance the medicine registration process in Africa, New Partnership for Africa's Development and Pan African Parliament held a conference for establishment of African Medicine Regulatory Harmonization (AMRH) which has an important role in building the regulatory framework with objectives: To create harmonization across countries, to establish common technical document (CTD dossier) submission to regulatory body, to rationalize management systems and promote proper use of available resource, to develop MRIS for symmetry flow of regulatory information within and outside countries, to build capacity of evaluators with relation to adherence with regulatory standards.(WHO,2014).

However, WHO report shows that 50 Africa countries still have different national requirements for medicine registration application, the time frame for dossier assessment is not reasonable and the flow of information for MA process is not well organized. (Bellah, 2015).

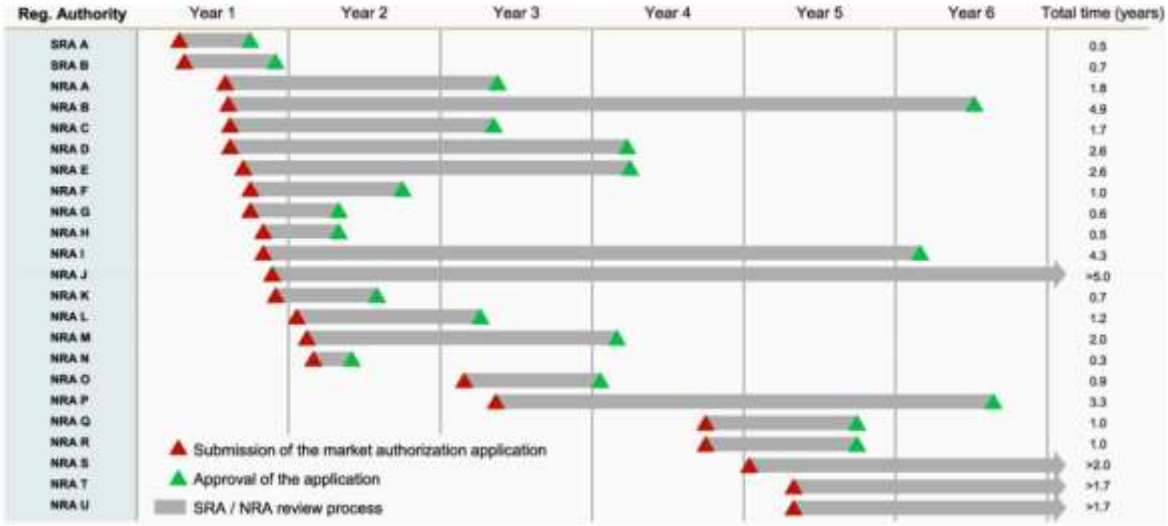

Figure 1:Sub-Saharan Africa countries national regulatory authority time lines for market authorization approval. (Ahonkhai et al., 2016).

As shown in the figure, NMRA took a different time frame starting from application submission to reviewing documents of different countries. In light of these facts, to obtain MA in specified period of time, MA process is the main constraint in Africa. (Ahonkhai et al., 2016).

However, to improve the regulatory function in facilitating MA process, in 2012, Mozambique, USAID developed SIAPS Program to integrate the information flow, to improve the procedure of registration and overall regulatory function through web based system (SIAPS, 2014).Based on these initiated strategies, assessment has been made on implementation of MRIS system for MA application until the approval period.

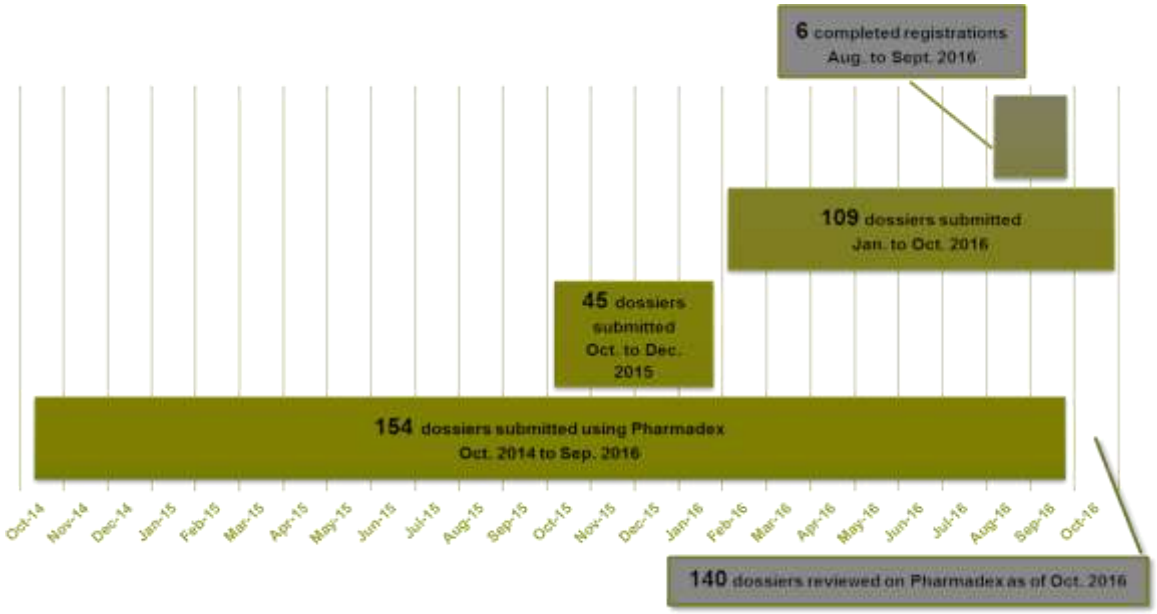

Figure 2: Medicine records handled through pharmadex from October 2014 to September 2016 in Mozambique. (MRIS, 2017).

As studies revealed, from October 2014 to September 2016, 154 dossier applications submitted using MRIS. Among those, 140 dossiers were reviewed and 6 products achieved MA. This indicates that even if the system is implemented to expedite MA process, limitations were still observed in the process. (MRIS, 2017).

In Ethiopia, 2016, MRIS was developed to improve medicine MA process for electronic product dossier submission and evaluation. The strategy was designed to build the capacity of regulatory authority evaluators on bases of set standards for assessment of product dossier, to strengthen and improve regulation, guidelines and standards for medicine registration, to organize pre & post MA approval process starting from application for registration up to market entry to create an apparent way of monitoring system, to build a clear procedure which enable applicants to follow their application status until MA release, to shorten the time frame for MA process & through which system evaluators can notify each other their result of evaluation, to provide well-organized procedure to oversee the MA status for new re-registration and variation applications. (Tadeg, 2014).

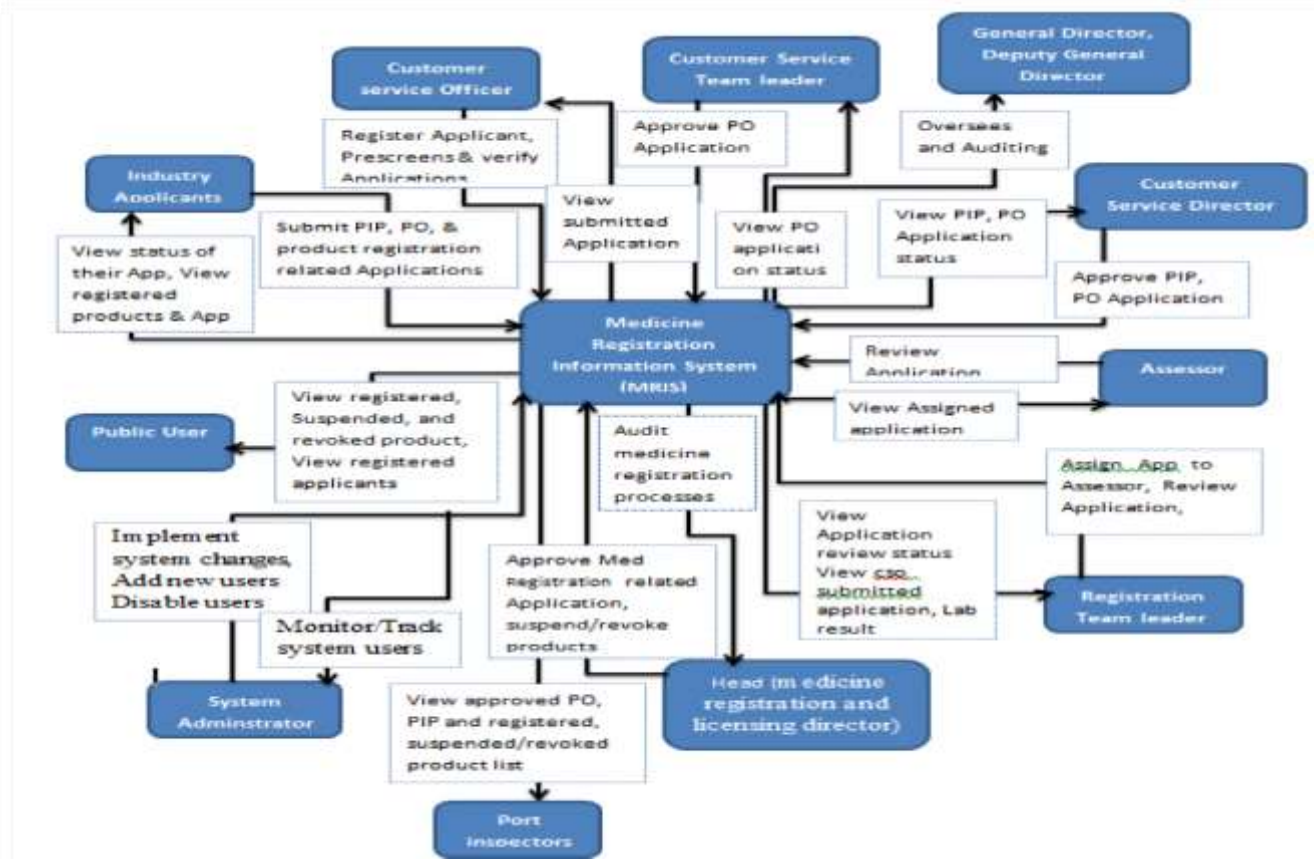

Figure 3: Overall flow of data in Medicine Registration Information system in Ethiopia. (MRIS, 2016).

As shown in the process map, the overall activities designed through the MRIS enables the integration of the information system between EFMHACA, LRPFIs and LPIs and public users including the process starting from the application for MA to following the screening status of dossier, the evaluation status of dossier, approval of MA , suspension or revoking of MA will be feasible to LRPFIs, LPIs ,EFMHACA (Director General, Deputy Director General, medicine registration and licensing directorate, registration team leader, assessors, customer service directorate, customer service team leader, customer service officer, port inspectors and system administrator), and public users. (EFMHACA, 2016).

However, even though the system was initiated to improve the regulatory work, due to lack of qualified human resource, incomplete dossier submission to regulatory authority and QC submitted reference standard fail the requirement. This can contribute to the delay of MA process. (Mkumbwa, 2013).

1.4.3. Research question

What is the time frame for approval of medicine market authorization application submitted through MRIS at EFMHACA?

And what are the challenges faced by EFMHACA, LRFPIs and LPIs in medicine market authorization process?

1.5. Conceptual framework

NMRA have a mandate to ensure the safety, efficacy, and quality of medicines. Hence, the regulatory procedure: GMP inspection, dossier evaluation and QC laboratory test. Each country, with its own regulatory requirement, will escalate the complexity of MA process. For instance, lack of symmetrical information flow in facilitating MA process in regulatory agency, weak management system of regulatory agency, missing relevant data to compile dossier by applicants and failure to meet the international standards by manufacturers have impacts on the time span of MA approval. (Mkumbwa, 2013); Moran, 2011; Hill, 2004)

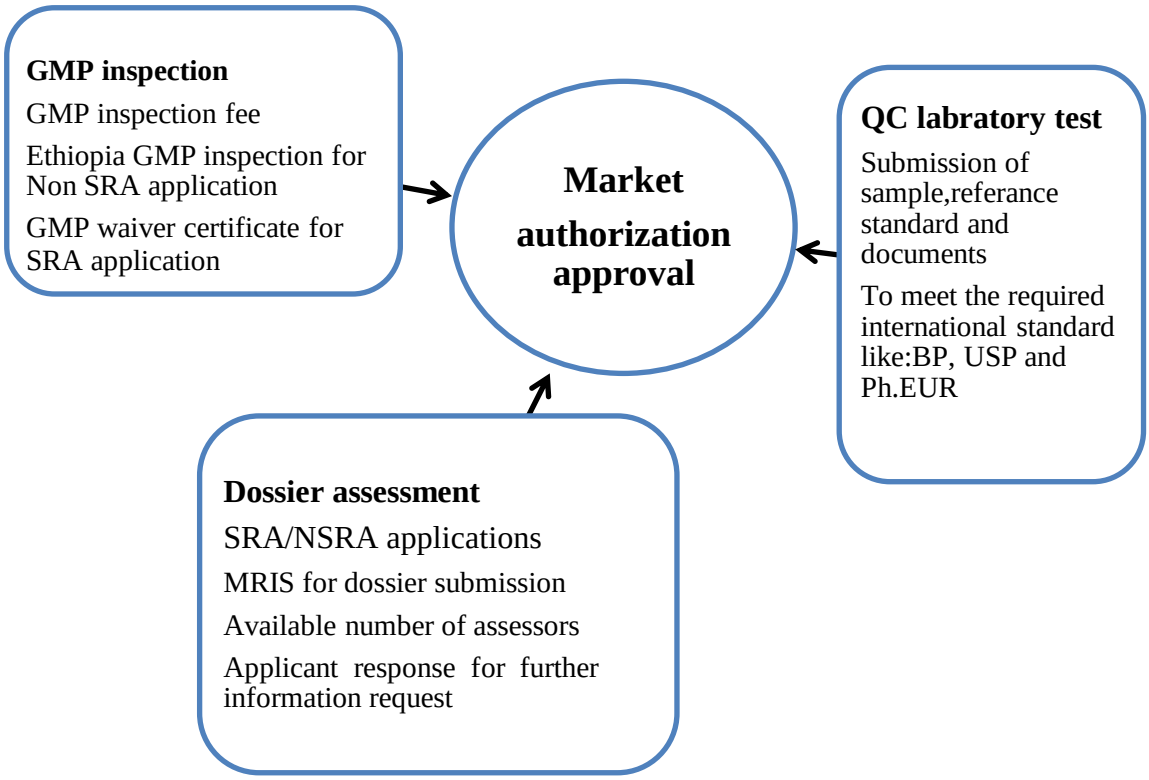

Figure 4: Conceptual framework for factors influencing market authorization process.

2. Objective

2.1. General objective

- To assess the time frame for medicine MA process and associated challenges.

2.2. Specific objectives

- To evaluate the time frame of MA approval for those new applications submitted through MRIS to NMRA.
- To identify challenges associated with MA process.

3. Methods and materials

3.1. Study area and period

The study was conducted in Addis Ababa, the capital city of Ethiopia from April 25, 2019 to May 30, 2019. Addis Ababa hosts the head office of EFMHACA, which is located around Africa Avenue, near Wollo Sefer round about, next to Shoa Shopping Center. The authority has different directorates related to medicines regulation including medicine registration & licensing directorate, medicine facility inspection directorate and medicine quality assessment directorate. As an executive body to regulate medicine by "Proclamation No. 661/2009", the authority has a mandate to give approval of medicine MA by ensuring medicine safety, quality and efficacy.

Addis Ababa also hosts 116 medicine importers which operate as local representatives of foreign pharmaceutical industries (LRFPIs) to import medicines by following national medicine regulation .There are also 11 local pharmaceutical industries (LPIs) which manufacture medicines by complying local regulatory requirements and have MA for their products from EFMHACA.

3.2. Study design

A sequential quantitative and qualitative mixed methods study design was used.

For the quantitative study, application data submitted through MRIS for MA from July 1, 2016 to Dec 30, 2018 was reviewed retrospectively.

For qualitative study, in depth interview data was collected from purposively selected individuals from EFMHACA, LRFPIs and LPIs.

3.3. Sampling procedure

3.3.1. Quantitative study

3.3.1.1. Source population

All new MA applications (product dossier) submitted through MRIS system at EFMHACA.

3.3.1.2. Study population

New MA applications submitted through MRIS to EFMHACA from July 1, 2016 to Dec 30, 2018.

3.3.1.3. Sample size determination

The study identified new applications submitted through MRIS system for MA from July 1, 2016 to Dec 30, 2018.

The supposition used to calculate the actual sample sizes were: 95% level of confidence with 0.05 α value (which yields Z α/2 = 1.96 on the standard normal distribution curve), 5% margin of error, estimated proportion of new application submitted through MRIS (50%). With these assumptions using a single population proportion formula:

$$n = \frac{(Za/2)^2 p(1-p)}{d^2}$$

Where, n = is sample size

z = the value of the standard normal curve score corresponding to the given confidence interval = 1.96

p = estimated proportion of new application MA approved (50%)

d = the permissible margin of error (the required precision) = 5%.

$$n = \frac{(1.96)^2 0.5(1-0.5)}{0.05^2} = 384$$

Since the population is less than 10,000,a correction formula was used. Therefore, using the correction formula:

$$n = \frac{no}{1 + no/N}$$

Where, $n_0$is the initial sample size and N is the total application.

$$n = \frac{384}{1 + 384/1792} = \frac{384}{1.2143} = 317$$

Therefore, the final total sample size included in the study were =317.

3.3.1.4. Sampling technique

Systemic random sampling technique was used. From the total 1792 new applications submitted through MRIS, 317 samples were taken for the study.

To start the selection of application, one of the application numbers was picked randomly from one to six, then systematically from the list in every 6 interval. Sampling was made until the sample size was reached.

3.3.1.5. Inclusion and exclusion criteria

Inclusion criteria

- Medicines MA application submitted through MRIS from July 1, 2016 to Dec 30, 2018.

Exclusion criteria

- MA applications approved before implementation of MRIS system.
- New applications of herbal medicines.
- MA applications that have not completed the prescreening stage.

3.3.1.6. Variables of the study

Independent variables:

- Type of application: SRA and Non SRA application.
- Dossier evaluation status : (Prescreened, Verified , Assigned to Assessors, Submitted to Team Leader, Returned to Assessors, Further Information Requested, FIR Replied, Submitted for Approval)
- Dossier evaluation period: Application submitted date to prescreened date, prescreened to fee attached date, fee attached to verification date, verified to assigned date for assessor, assigned date for assessor to primary assessor date, primary assessor submission date to secondary assessor submission date, primary assessor to team leader decision date, secondary assessor to team leader decision date, 1^{st} further requested date to 1^{st}further reply date, 2^{nd} further requested date to 2^{nd}further reply date and team leader decision to directorate decision.
- Applicant feedback: For deficient document and service fee.

Dependent variables: MA approval.

3.3.2. Qualitative study

3.3.2.1. Sampling and sample size

Purposive sampling method was used for the interview guide questions from EFMHACA, LRFPIs and LPIs interviewees and the selection was made based on the consideration that they are appropriate individuals who could provide rich information needed for the study topic. Sample size was determined based on the sampling criteria as described below and saturation of data, i.e. when additional information cannot be generated.

3.3.2.2. Sampling criteria

The following sampling criteria were used:

Inclusion criteria

- EFMHACA medicine registration and licensing directorate, inspection and licensing director and QC laboratory test directorate experts.
- LRFPIs and LPIs experts who perform medicine MA process, available and volunteer to participate in the study.

Exclusion criteria

- EFMHACA medicine registration and licensing directorate, inspection and licensing director and QC laboratory test directorate, LRFPIs, and LPIs experts who were unavailable during data collection period.
- Unwillingness to participate in the study.

3.4. Data Collection and management

3.4.1. Data collection

For both the quantitative and qualitative parts of the studies, data collection was made by the principal investigator.

3.4.2. Data collection Tool

Quantitative part

Data collection template was used for new applications (SRA and Non SRA applications) by reviewing their status such as prescreen, verify, assigned to assessor, further information request and further reply status were assessed to evaluate the time frame for MA approval as outlined in EFMHACA citizen charter (EFMHACA, 2016&EFMHACA, 2017) (Annex I).

Qualitative part

The in-depth interview assessed participants for their opinion on the time frame for MA approval and perception on implementation of MRIS system for dossier evaluation. Furthermore, the challenges they face during MA process were requested. (Annex III, IV,V&VI). The interview was primarily done by an audio recorder and supplemented by note taking. The interview, which was conducted in the local language (Amharic), took, on average, 30 minutes.

3.4.3. Data quality control

Quantitative study

The feasibility of data abstraction tool was verified by taking 5% (16) new applications which were submitted through MRIS and necessary amendments were made before final data collection. (Annex I)

Qualitative study

The interview guide was piloted to check the questionnaire practicability 5% (6) LRFPIs experts and the interview was conducted in Amharic and translated to English language by the principal investigator. To ensure the reliability of data, multiple data peer review was used. Also, the validity of the translation process (Amharic responses to the English version) was assured by consulting with colleagues to check some proportion of the transcript against the audio recording. (Annex III, IV, V & VI).

3.5. Data analysis and interpretation

Quantitative study

The collected data was entered to SPSS version 20 for analysis. For the descriptive analysis, data was presented as simple frequency and percentage and correlation with bivariate analysis was conducted to explore the association between independent and dependent variables. Then, variables with P-value ≤ 0.05 at 95 % CI were stated with MA approval. Finally, results were presented by using a table.

Qualitative study

The recorded data was transcribed and translated to English language. Then, the data was analyzed using thematic analysis to identify, analyze and report themes. Accordingly, relevant codes were sorted and matched to identify similarities and differences. Then, codes were collated into subthemes, then further into main themes and sorted as factors that influence MA process. Finally, the report was written using the relevant quotes**.**

3.6. Operational definitions

Approval: GMP pass, dossier evaluation completion, QC laboratory test pass to obtain MA.

Assigned to assessor: For dossier evaluation, first and secondary assessors assigned by team leader.

Dossier Evaluator: EFMHACA expert who evaluates the submitted dossier of applicant.

Experts: Qualified employee of EFMHACA/LRFPIs/LPIs assigned for specific purpose.

Further information request: After dossier evaluation, an additional document submission request of EFMHACA to the applicant.

Further reply: Applicant query response to EFMHACA.

GMP inspector: An EFMHACA expert authorized to inspect local and foreign pharmaceutical industries for good manufacturing practice of medicines.

Influence: Are the restrictions related with MA process.

MRIS: Is a web based system used to submit product dossier of applicant to EFMHACA.

New molecule: A medicine which is new for Ethiopian market.

Submitted to team leader: Submission of comments to the coordinator by either primary or secondary assessor after dossier evaluation.

Submitted to approval: Team leader submits the application to the directorate decision for MA approval.

Returned to assessor: The team leader, after reviewing the comment of primary and secondary assessor, returns it back for further clarification.

Rejected: When the submitted application is not acceptable for MA.

Screen: The first stage of dossier evaluation by EFMHACA experts.

Verify: After completion of dossier screen when applicants paid for dossier evaluation.

3.7. Ethical consideration

To conduct the study, ethical clearance was obtained on Ref.No: ERB/SOP/86/04/2019 from Addis Ababa University, School of Pharmacy Ethics Review committee. An official letter from School of Pharmacy, Department of pharmaceutics and social pharmacy was sent to EFMHACA, LRFPIs and LPIs to get consent for research conduct.

For conducting the research, participants were, in prior, informed about the purpose of the study and what is expected from them. Participants' involvement in the study was on a voluntary basis and withdrawal from the study at any time was possible.

The participants were also assured that their answers would remain confidential and only findings were enclosed in the report without the use of personal identifier. Finally, oral informed consent has been taken from each participant. (Annex II).

Any applicant's (LRFPIs and LPIs) application related identifier and EFMHACA assessor's related identifier were not used, while the data collected from the MRIS and the information gathered from EFMHACA were kept confidential. Also the obtained data was only used for the current study.

4. Results

As stated on the sampling procedure, mixed data collection methods using quantitative and qualitative study designs were implemented. For quantitative study, data abstraction tools were used to collect new applications submitted through MRIS system (from July 1, 2016to Dec 30, 2018) to assess the time frame for MA. For qualitative study, key informants from EFMHACA, LRFPIs and LPIs were involved in an interview regarding the factors that influence MA process.

4.1. Quantitative findings

4.1.1. Type of new applications

For the study, 317 new applications which were submitted through MRIS System for MA from July 1, 2016 to Dec 30, 2018) were targeted. Also, these new applications were categorized as Non SRA and SRA type applications. And from those applications, Non SRA applications were 258 (81.4%) and SRA applications were 59 (18.6%).

Furthermore, Non SRA type of application applied as Generic with bio-equivalence 110 (34.7%) and generic without bio-equivalence 139 (43.8%) were the major type of applications which were submitted through MRIS. And the least type of application was applied as NonSRA/new molecule 9(2.8%). (Table 1 below).

Table 1: Non SRA and SRA (with new molecule, with bio-equivalence and without bio-equivalence) applications.

Application type	**N (%)**
Non SRA/new molecule	9 (2.8%)
Non SRA/with bio-equivalence	110 (34.7%)
Non SRA/without bio-equivalence	139 (43.8%)
SRA/new molecule	21 (6.6%)
SRA/with bio-equivalence	16 (5.0%)
SRA/without bio-equivalence	22 (6.9%)

4.1.2. Overall MA status of products

Among 317 new applications which were submitted through MRIS system from July 1, 2016 to Dec 30, 2018, the majority of applications (78%) were still in the process of MA, which means they were in different stage of dossier assessment such as Prescreening, verification, assigned to assessors, submitted to team leader, returned to assessors, further information requested (FIR), FIR replied and submitted for approval stage. From those applications, only 18% attained MA. (Figure 5 below).

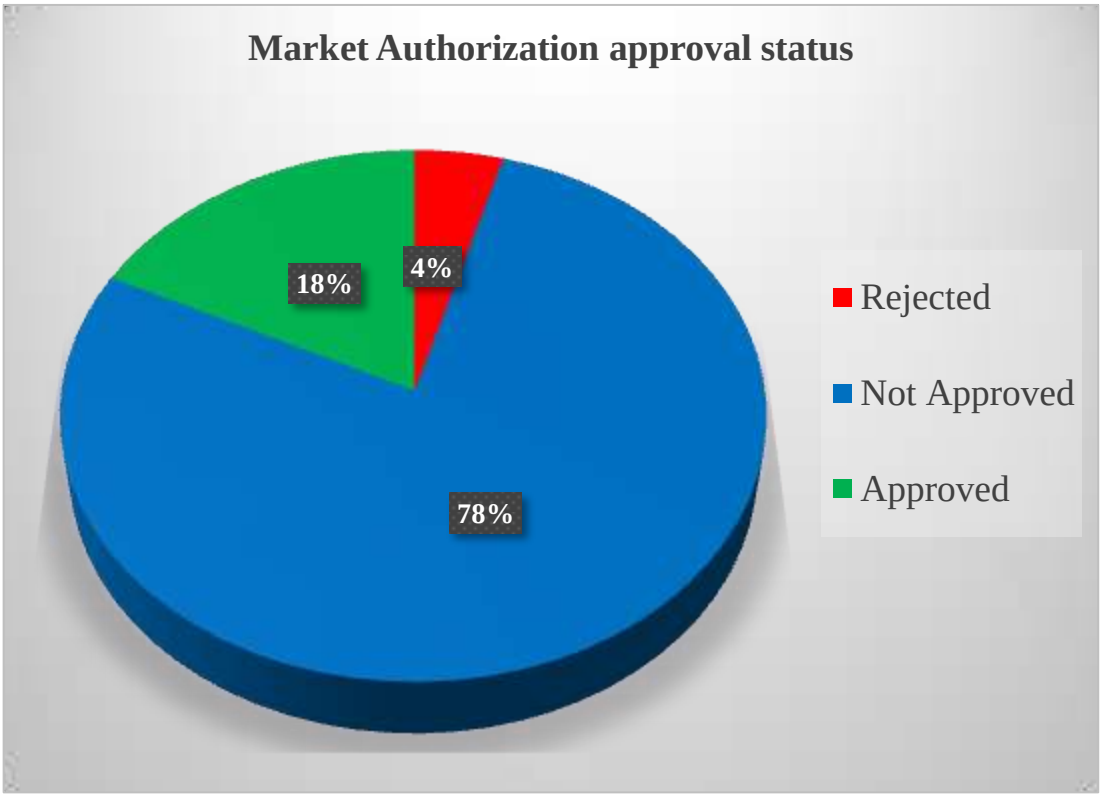

Figure 5: MA status of applications submitted through MRIS system from July 1, 2016 to December 30, 2018.

4.1.3. Current decision days by type of application

All submitted applications through MRIS system had total decision date above 311 days. From these applications, Non-SRA (with bio-equivalence) and Non-SRA (without bio-equivalence) had the highest decision date at above 505 days. The lower decision date was SRA (with bioequivalence) application having a total decision date at around 311 days. (Table 2 below).

Table 2: Current decision days by type of application.

Application types	**Total decision days**	
	Mean	SD
NonSRA/new molecule	358	253.9
NonSRA/with bio-equivalence	521	228.2
NonSRA/without bio-equivalence	505	237.1
SRA/new molecule	343	181.2
SRA/with bio-equivalence	311	165.7
SRA/without bio-equivalence	384	265.6

4.1.4. Total decision days with current MA status of applications

In MA approval process, the applications which were under dossier assessment had a status of: Prescreened, verified, assigned to assessors, submitted to team leader, returned to assessors, further information requested (FIR), FIR replied, submitted for approval, approved and rejected. Among the status which had high decision dates were: Further information requested-575 days, further reply-567 days and submitted for approval-566 days. The least decision date was prescreened date at 340 days. This shows that the majority of applications have taken long decision dates while they were under dossier assessment. (Table 3 below).

Table 3: Total decision days with current MA status of applications.

Market Authorization status	**Total decision days**	
	Mean	SD
Prescreened	340	212.0
Verified	465	363.2
Assigned to assessors	381	230.2
Submitted to Team Leader	475	214.8
Returned to Assessors	431	107.6
Further Information Requested	575	176.2
FIR Replied	567	191.0
Submitted for Approval	566	250.9
Approved	364	226.6
Rejected	453	292.7

4.1.5. **Factors that delay MA approval**

Factors that hinder MA approval were assessed using correlate bivariate analysis to show the association between dependent variable :MA approval with independent variables: Submitted date to prescreened date (p=0.001), Fee attached to verification date (p=0.009), Primary submission date to secondary submission date (p=0.043), Primary assessor date to team leader decision date (p=0.001), 1st further requested date to 1st further reply date (p=0.002), Team leader decision date to directorate decision date (p=<0.001) and application type(p=<0.001) have significant association at 95% confidence interval for delay of MA approval. As shown in table 4 below.

Table 4: Association between MA approval and independent factors.

Variables	Pearson Correlation	Sig. (2-tailed)	Std. Error	MA Approval status	
				95% Confidence Interval	
				Lower	Upper
Submitted date to prescreened date	0.264	0.001*****	0.246	0.171	0.352
Prescreened date to fee attached date	-0.030	0.589	0.036	-0.091	0.054
Fee attached date to verification date	0.146	0.009*	0.142	0.077	0.246
Verified date to assigned for assessor date	-0.064	0.252	0.027	-0.152	0.036
Assigned for assessor date to primary assessor date	0.085	0.130	0.158	-0.023	0.210
Primary assessor submission date to secondary assessor submission date	0.114	0.043*	0.061	0.016	0.224
Primary assessor submission date to team leader decision date	0.187	0.001*	0.068	0.067	0.296
Secondary assessor submission date to team leader decision date	0.096	0.089	0.128	-0.052	0.197
First further requested date to first further reply date	0.170	0.002*	0.058	0.058	0.296
Second further requested date to second further reply date	0.004	0.939	0.135	0.089	0.148
Team leader decision date to Directorate decision date	0.283	<0.001*	0.087	0.054	0.415
Applications type	0.200	<0.001*****	0.075	0.061	0.343

* Correlation is significant at 0.05 level (2-tailed).

4.2. Qualitative findings

The in-depth interview involved 15 participants from EFMHACA, LRFPIs and LPIs. The majority of respondents were from EFMHACA and all the respondents were pharmacists by profession. (Table 5 below).

Table 5: Socio demography characterization of study participant.

Gender	
Male	13
Female	2
Age	35(26-49)
Profession	
Pharmacist	15
Educational level	
Bachelor's degree	9
Master's degree	6
Experience in years	5(2-12)
Place of work	
EFMHACA	9
LRFPIs	4
LPIs	3

4.2.1. Qualitative analysis

The in-depth interview findings on the challenges of the MA process resulted in 285 codes, 16 subthemes and 8 main themes that were identified as factors that influence MA process, which are: Limitation of resources, weak capacity building, MRIS restriction, gaps on implementation of rules, communication barrier, management disruption, commitment breach and lack of transparency.

4.2.2. Limitation of resource

As the majority of respondents claimed, limitation of resources is one of the main constraints that hamper the MA process.

Human resource limitation

The inadequate number of qualified experts who perform GMP inspection, dossier assessment and QC laboratory tests are not sufficient to perform the regulatory work efficiently. For instance, to inspect a specific product line, there is a lack of qualified inspectors also to assess dossier. Especially, after the review of primary assessor, the secondary assessors available to evaluate the review are very few as compared to the number applications to be assessed. Regarding this matter, the respondents said:

"During dossier evaluation as campaign, there are many primary assessors but internally those available secondary assessors are seven in number. Suppose 185 primary assessors took one month each to complete the evaluation of one dossier Due to this, assessing the dossiers to be reviewed with those seven assessors will be difficult to accomplish within a reasonable time and secondary assessor time have taken long duration." (EFMHACA respondent 6)

"In our organization, for new registration, re-registration and post marketing surveillance, many samples were submitted for analysis and the analysis has been made by experts. But the experts could also be assigned for another job like maintenance of machine while the applicants wait for the sample analysis" (EFMHACA respondent 7)

Equipment limitation

The available equipment's which were used for QC analysis are old fashioned and need frequent maintenance. Also, using the functional equipment waiting the completion of processed analysis was compulsory before starting new analysis. Following this circumstance, advanced technology equipment with other laboratory

facilities are required to perform the analysis in well-organized laboratory. Regarding this matter, the respondents said:

"Those available machines are not enough to conduct the work. Also, we have to wait the line to use the available machines meaning we should wait for the other analyst to finish what he was doing."(EFMHACA respondent 7)

"*The available equipment's are old version. Nowadays, there are many sophisticated (modern) machines available globally which are better and help to simplify each work. Many of the equipment don't work properly because it has been used for many years. They just pay money for maintenance rather than buying a new and modern machine."(EFMHACA respondent 8)*

4.2.3. Weak capacity building

As the majority of respondents agreed, capacity building work should be strengthened for GMP inspectors, dossier evaluators and QC analysts and regulatory experts who facilitate MA process because having an opportunity to train only for a short period is not sufficient to help them perform on their delegated job efficiently.

Inadequate training

For GMP inspection, due to lack of qualified experts, the inspectors can mistakenly pass a company that failed or fail a company that should have passed .In addition, those primary assessors are external assessors, like from higher education center so they don't get easily familiar with the regulatory function. And, obviously, a difference in technical skill among the assessors can be seen. For example, if the same dossier was evaluated by the primary assessor and the review comment was further information request in perspective of secondary assessor, it may become recommended for MA.So,to reconcile the comment from the two assessors, the team leader may make a decision, meaning either the dossier should be evaluated once more or an assessor's change might be made. In such instance, the evaluation period may become long. Regarding this matter, the respondents said:

"*There are some problems like a wrongly made pass decision when the company was supposed to fail. For instance, even the local companies that passed by our standards might fail on inspection of USFDA or Europe. So, if we were qualified enough they also made same decision like our inspectors made." (EFMHACA respondent 3)*

"Experts should acquire a specific training product-wise to be qualified enough. But there is a lack of training on new emerging technologies for dossier assessment so it's difficult to evaluate safety, quality and efficacy of medicine and to cope up with scientific jargons. Also, nowadays, we have made absence of risk based approach for dossier assessment."(EFMHACA respondent 5)

On other hand, to run MA process by being aware of the regulatory requirements, applicant's regulatory personnel faced challenges at the beginning because they didn't get the chance to get training by those hiring companies. Even though there was chance for basic dossier assessment training, which was given by EFMHACA, getting the opportunity was very rare. So facilitating the regulatory work by understanding medicine guidelines such as compiling dossier as CTD format and understanding the requested documents by those experts and making it clear for foreign applicants was challenging. Along with experts, self-effort was compulsory to the system. Asking experienced regulatory experts, evaluating those registered product dossier to acquire knowledge on those documents enclosed in the dossier and reviewing the dossier checklist to compile dossier are some of the ways of familiarizing with regulatory work. In relation to this, respondents said:

"*To be best suit with the situation by understand the trend what they want to ask also, I know the commonly requested questions and revolving area. Additionally, I have reviewed a complete dossier which was prepared beforehand, and then I realized that which documents were required." ((LPIs respondent 1)*

"I didn't get any training but by reviewing the guideline and checklist myself, I compiled the dossier."(LRFPIs respondent 1)

Inadequate regulatory expertise

Applicant's regulatory personnel may lack regulatory knowledge. As a result, failure to fulfill the regulatory requirements was a clearly noticed problem. This is because the personnel that's experienced in facilitating the MA process may resign from the company and the new personnel who will be assigned by the company may not have regulatory knowledge. Not only this, but the assigned personnel doesn't have adequate pharmaceutical knowledge to even to contact the EFMHACA experts regarding on the regulatory issue.

In addition, there was a level of uncertainty observed on the regulatory experts of foreign applicants. Because of incomplete and misarranged dossier submitted to

EFMHACA which deviates from medicine registration guideline, even if there's awareness of the requested further information to prepare the query response, gaps were observed. And this situation can have an impact on the smooth facilitation of MA. In regard to this, respondents said:

"Regarding document compilation, I don't know whether it's a lack of knowhow or negligence but when the document arrives, it'll either become mixed with other product documents or it'll be arranged in descending order starting from module 5 to module 1. And this problem happens in both sides of foreign applicants and agents."(EFMHACA respondent 4).

"The reason they make a delay to give a further reply might be because they're not seeing it as priority; or not. I don't know. I don't even know how strong the regulatory department is. I don't know anything."(LRFPIs respondent 2)

4.2.4 .MRIS restriction

The implementation of MRIS improves the facilitation of the MA process. On the other hand, there are also gaps raised in the system utilization by EFMHACA, LRFPIs and LPIs experts.

Impediment of MRIS

The documents that were submitted though the system were lost following this circumstance. EFMHACA request the applicants for further information to submit the missed documents. As a result, an unnecessary redundant document exchange occurred between EFMHACA and applicants. Also, due to the system's moderate capacity, file size reduction is compulsory when submitting documents through the system. For instance, large file size documents such as bioequivalence report, batch manufacturing record and validation report submission were difficult. So solving the mentioned problems, considering that the system is new, requires checking the performance and making improvements.

"Due to the MRIS software error, there are some conditions that took five up to six times in correspondence of further information. But, since they understood the problem with their software, they tolerated even the fifth and sixth request for further information correspondence. Because the questions were not about why you didn't submit the document but about the system conveying that it's not attached to the MRIS." (LRFPIs respondent 4)

"Large file sizes are not to be attached through the system. Once the document is attached and the process starts to run, editing is impossible. All this convinces us to use the system suitably."(LPIs respondent 2)

Gaps on MRIS utilization

At the beginning, applicants were terrified to use MRIS. They weren't even willing to accept the system. So both hard copy and soft copy dossier were submitted to EFMHACA while few documents were attached through the system. Additionally, the system needs good internet connection to have access everywhere. But, because of power outages, if the server's off on EFMHACA side then, the users will not able to reach the system even if the power is available at user's end. Also, due to the lack of information technology to properly utilize the MRIS, gaps were noticed by applicant regulatory experts. Due to this reason, inappropriate filling of documents and incomplete documents were submitted through the system. Even on MRIS, when the trained regulatory experts resign from the company, the newly hired experts won't be familiar with the system. As a result, EFMHACA experts faced problems on the applied documents. In regard to this, the respondents said:

"The implementation of MRIS system brings good progress in terms of speeding up MA process. But, due to difficulties in updating the system, unrecognized problems were observed through time."(EFMHACA respondent 4)

"Due to lack of knowledge on information technology, they uploaded incomplete documents through the system. Sometimes, due to the resignation of trained experts, the newly hired experts who replaced them will not even be familiar with the system." (EFMHACA respondent 6)

"One of the problems in accessing the MRIS was internet connection. There might be power outage at any time and then I won't be able to access the system. For instance, the server at EFMHACA could be down, and if I try to attach the softcopy, I won't be able to reach the system nor be able to respond online. And this results in delay of cases to the user" (LRFPIs respondent 3)

4.2.5. Gaps on implementation of rules

To attain MA approval as per the time frame indorsed by a regulatory body the citizen charter rules must be implemented practically in the major regulatory functions:-GMP inspection, dossier evaluation and QC laboratory test. Hence, constraints that occur in either of these procedures hinder the approval of MA in accordance with the recommended date.

Deviation from set standards by regulators

Once the GMP inspection of foreign pharmaceutical industries is performed, the report should be released in one month. But each inspector's report takes a long time until it's reviewed by GMP task force. Also, evaluation of dossier and the release of further information might be prolonged due to different internal reasons such as a prolonged waiting time for prescreening of dossier, delay of payment for dossier evaluation by applicants and lengthy period of time in assigning assessors/after assignment of assessors/when assessors get changed. So, as a result, the dossier evaluation period becomes long. In regard to this matter, the respondent's replies were:

"*Notification for GMP report based on standard operating procedure should be within two weeks. Hence, practically, after the inspectors send their reports for a review of from GMP inspection committee, it may take up to three months until the release of report to the applicants."(EFMHACA respondent 3)*

"For real! Policy is a different thing. In the current scenario to register medicine electronically…I submitted my application on August 2018,then I got feedback in January 2019 as a screened and verified status."(LPIs respondent 1)

Gap on implementation of rules by applicants

If the assessor gets insufficient material on the submitted dossier after the dossier evaluation, applicants will be requested to submit further information. But applicant don't keep the time frame set by EFMHACA when provide the reply.

Apart from this, there's a lack of API information on the applicant side. For instance, local manufacturers who manufacture finished pharmaceutical products import raw materials such as Active pharmaceutical ingredients (APIs) from China and India and also the API documents, which are confidential and come from the API suppliers. But due to the lack of API information, applicants use their convenient time to

submit the query reply to EFMHACA. As a result, the dossier evaluation period may become long. Furthermore, applicants have a responsibility to submit the required sample, reference standard and working standard to EFMHACA either from their manufacturing plant or by purchasing from official monograph like USP, BP and Ph.EUR pharmacopeia. But they took a long time to submit the required reference standard and working standard due to the unavailability of reference standard, price issue and until the arrangement the procurement of reference standard. This circumstance results in the delay of QC analysis. In relation to this, the respondents said that:

"The time frame in which I got a feedback for further information from my company isn't well-known; it depends on their convenience. So I just wait for their response."(LRFPIs respondent 2)

"QC directorate requests for reference standard submission, But it was challenging because, sometimes, when the companies were asked to procure the reference standard, they couldn't find it since it's a single reference standard, which means they going to buy; and that will be expensive so they complain about it. So I suggest that EFMHACA manage reference standards by themselves, and then applicants will pay the service fee."(LRFPIs respondent 3)

"We can get the open part of the document (the finished product document) but getting the closed part of document (API document) is very difficult. EFMHACA doesn't understand this challenge. As a result, there are products that are not yet registered."(LPIs respondent 1)

4.2.6. Communication barrier

EFMHACA experts may get into a conflict of ideas while doing their job. Also, when the regulatory experts of applicants get in contact with EFMHACA experts, a misunderstanding/variance on the requested documents can happen.

Misunderstanding among regulators

One of the GMP inspectors decision on the findings of the inspection may differ from the other inspectors. For instance, if one of the inspectors categorizes the deficiency observed during a plant inspection as a critical deficiency, then the other inspector may consider it as major deficiency. So, clearly, a difference in skill and work experience was observed among the inspectors. So, naturally, there might be an argument during their discussion on their GMP inspection on their ideas. So, to

resolve such kind of problem, each inspector's findings will be submitted to the GMP task force. Then after evaluation of each inspector's findings, the committee will have a discussion with the inspectors and make a decision on the inspection report.

Similarly, in dossier assessment, the primary assessor's evaluation comment might be different from the secondary assessor's comment. For example, if the primary assessor's comment on dossier evaluation were on further information request, then on the secondary assessing, it becomes recommended for MA. During this time, the team leader will review the comments of both the assessors and forward his evaluation comment or return back the comments of both assessors to be reviewed again. In such cases, in the process of clarifying the reasons for the comments, there might be gloomy moments with the team leader. And these circumstances can have an impact on the smoothness of the regulatory work process. Regarding this matter, respondents said:

"There might be a conflict of ideas among experts while they're doing their job. For instance, after the assessor's evaluation, the team leader also reviews the evaluation comment of the assessor. And if the team leader asked justification for those comments, then instead of clarifying the reasons, the assessor may fiercely complain. So, in such cases, if the team leader has a suspicion on the evaluation findings, then he will decide to assign another assessor."(LPIs respondent 2)

"Of course! Conflict of ideas has occurred between the inspectors because it's science. However, the report findings may be disseminated to the GMP task force so, after evaluation of each inspector's reports, they will decide to choose one side."(EFMHACA respondent 3)

Misunderstanding of the regulatory requirement by applicants

During the MA process, misinterpretation may occur between regulatory authorities and foreign pharmaceutical manufacturers because of the lack of elaboration/clarification for the required document and sample by the regulatory experts. For instance, for QC, actual product sample submissions criteria are different depending on the type of dosage form. For sterile products and ophthalmic products, for example, actual product sample submissions with reference standards are compulsory for analysis. But due to the lack of ability by the assigned regulatory experts to clearly inform the required samples to the manufacture, the manufacturer may not submit the appropriate sample for analysis. As a result, during QC sample submission, the authority may not be compelled to accept it because of the incomplete sample submission. This interruption will lead to a further time delay until the actual product sample prepared and sent to the authority. In addition, countries that have a language barrier like China have poor documentation in the preparation process of dossier. So,to resolve this situation, agents should intervene to make the set of medicine regulation of Ethiopia clear. However, gaps were observed in this scenario as well. Besides, assessors faced problems in the process understanding the submitted document. In regard to this matter, respondents said:

"In my experience, I've seen a problem in the sample submission status. I think there has been a misunderstanding between import regulatory experts and foreign pharmaceutical manufactures on the matter of clarifying things to the foreign manufacturers and the submission of the required sample to the regulatory authority."(EFMHACA respondent 7)

"Agents should inform our country's regulation to their applicants so that they would submit based on the set standards. In such cases, Chinese companies have a slight problem understanding the English language. So, to make sure that everyone is clear with the guideline, the agent's regulatory person should clarify such things. In the meantime, they should forward an email appropriately and in detail about the requirements. Sometimes, we even find documents written in Chinese. As long as it's an international company, an international language should be used. So this is a big problem we are facing."(EFMHACA respondent 4).

4.2.7. Management disruption

Efficient regulatory function and coordination among different directorates can have a crucial positive impact. However, some gaps, which were observed in different directorates, may also hinder the MA process.

Administrative gap on decision making

In GMP inspection, if the applicants apply for plant inspection, the schedule might not be prepared in the specified period of time due to reasons like the arrangement of competent inspectors through the evaluation examination and or the time delay until they get foreign currency permission for travel cost. Following this circumstance, applicants may complain on delay of schedule. In relation with this, respondents said:
"GMP inspection schedule for foreign companies don't have a regular schedule. It doesn't even depend on the number of applicant's application. Sometimes the application schedule might be arranged for 20 companies. Or sometimes up to 100companies application can wait in line."(EFMHACA respondent 3)
"As a result of many factors like waiting to get foreign currency permission and preparing those competent experts, the inspection might be delayed rather than commencing on the scheduled date."(EFMHACA respondent 1)

Gaps in organizing the regulatory work

For different type of applications (new, re-registration and variation application), there is no division of experts, the same experts make the assessment of new application, re-registration and variation application. Accordingly, until the experts assigned for a different type of application finish their delegated job, the time line for dossier assessment becomes too long. Moreover, unintended chemicals were procured for QC analysis purpose rather than the required ones. As a result, the analysis could not be made till the required chemicals are procured. In regard to this matter, the respondents said:
"The document review is done online nowadays, but there is no division of experts for different types of applications, either new, re- registration and variation application. For instance, if it's a minor variation application, it is possible complete it within two days if the experts were assigned separately for variation applications."(LPIs respondent2)

"If we plan to print chromatogram and need paper, we must follow the procurement procedure of government. Also, if we require materials for the analysis, we must wait until it is procured. So we may not get in time and the analysis would be incomplete because the chemicals suppliers are from China, India and other countries. The purchased chemicals are not brought as required. It's an irrational way of a purchasing trend."(EFMHACA respondent 7)

4.2.8. Commitment breach

Commitment of experts and higher management are necessary preconditions GMP inspection, dossier assessment and QC control laboratory test and the overall MA approval process. But some gaps were observed in expert delegation.

Dedication gap by regulators

After GMP inspection, payment applicants wait for inspection for a long time because of the preconditions that has to be fulfilled for GMP inspection such as: selection of competent inspectors based on the authority`s criteria, getting abroad travel permit and getting foreign currency permission from relevant government institutions for inspection trip. On other hand, in process of dossier assessment, problems that include the loss of the submitted soft copy dossier and omission of dossier assignment to assessors were observed. As a result, without evaluation, the submitted dossier will be held for long time while the applicants wait for a response from the authorities. In regard to this matter, respondents said:

"The commitment of assessors was a debatable issue, considering how sometimes the submitted soft copy dossier was lost. Even the dossier assigning may be skipped."(LRFPIs respondent 4)

"There's a lack of commitment by the higher managers; they don't see GMP inspection as a serious work, they just consider it as source of benefit. But once we pay the service fee, there should not be any reason for not getting the appropriate service."(LPIs respondent 2)

Dedication gap by applicants

The regulatory experts who facilitate MA process were negligent and weren't able to perform their delegated job efficiently, like, for instance, proving the documents before submission, inattention giving to compile dossier as CTD format by foreign applicants. Furthermore, when the agent's regulatory experts receive those documents, they don't arrange the documents properly; or they don't check the missed documents before applying for registration.

Besides, foreign applicants should check their method of analysis before planning procurement of reference standard for QC analysis along with official monograph like USP, BP and Ph.EUR pharmacopeia. However, there is no such trend on the applicant's side. Relatedly, respondents said:

"Apparently, there is less attention for proper compilation of documents. It's also misarranged. Plus, the company documents were not complied as per CTD format of the guideline; and these problems were from both applicant and agent side. As a result, the evaluation period becomes long."(EFMHACA respondent 4)

"For instance, let's say the product is metronidazole and it's prepared as per British pharmacopeia. Then, they should understand the method of pharmacopeia as well as their own method of analysis. But there is no such kind of trend practiced on the manufacturer's side." (EFMHACA respondent 7).

4.2.9. Lack of transparency

Clear information flow from top management to the end user is a basic requirement to expedite MA process of GMP inspection, dossier assessment and QC laboratory test by linking all processes through a system. However, in the process of MA, a lack of symmetrical information flow from EFMHACA to the applicant side was observed.

Gap on symmetry flow of information in EFMHACA

MRIS was developed to have symmetrical information flow for dossier assessment procedure. However, the system is only limited for evaluation process, whereas GMP inspection and QC analysis process were not included in the system. Due to this reason, gaps were observed in QC analysis from the sample receiving stage to registering the received sample like: Physicochemical analysis sample coded, status sample of distribution. Moreover, the QC result registered on database was made by

those analysts manually. In addition, the QC result was sent to registration & licensing directorate by hard copy and in person. The same manner goes for GMP inspection process beginning from GMP schedule notification up to the release of GMP report. There is no symmetry of information flow so applicants communicate with the inspection directorate in person to follow the GMP schedule and receive the GMP report by hard copy. In regard to this matter, the respondent's replies were:

"*MRIS is only for dossier evaluation whereas QC sample status is not enclosed in the system. But, if it's included, it will be helpful to identify who submits what kind of sample. So, information flow should be systematic as in a software should be developed that introduces an entrance code into the system, after which all experts could get access to the sample status." (EFMHACA respondent 7)*

"*MRIS is for medicine registration, but the inspection report has been made by hard copy. Similarly, the result is also sent by hardcopy to the registration and licensing department.So, it will be good if the GMP approved companies, with their reports attached to the system, become accessible for applicants and registration department as well." (EFMHACA respondent 3)*

Discernment to process MA by applicants

Nowadays, the attention of agents has shifted to the business sector rather than passing through MA process .This is because instead of facing the hassle of MA, they prefer to procure registered products from foreign industrial manufacturers who pass Ethiopian GMP and get MA from EFMHACA. As a result, a lack of caution for document preparation is a clearly noticed problem. For instance, incomplete document submission without reviewing the content of dossier, less focus in preparation of requested further reply and unnecessary exchange of documents between regulatory authority and applicants can be cited among the consequences of a lack of attention on MA process. This results in a wrong perception for running MA process, which is a basic precondition for ensuring the quality, safety and efficacy of medicines for public use. So, if it's business orientated, even essential medicines on public demand may not be registered in a timely manner due to lack of interest in running the MA process. Additionally, the flawed perception of foreign applicants for regulatory authorities of developing countries like Africa has caused them to submit a low quality reference standard for QC analysis. This also brings an

inconvenience between the regulatory authorities and applicants by affecting the smooth process of MA. Regarding this matter, respondents replied:

"Nowadays, the system is open. Though, in the future, I am skeptical about finding an agent who will register products because once the product is registered, why would they face a hassle? They simply want to continue with the business. So the only way you will get agents to register products is by imploring them. This is because registration is a costly and tedious process.." (EFMHACA respondent 4)

"The wrong perception of foreign applicants for the regulatory authority of developing countries like Africa compelled them to make their own decision. They will say it's enough without requesting the consent of authority; they will simply procure lower quality of products and they will try to send it for EFMHACA rather than procuring as per the official pharmacopeia like: USP, BP and Ph.EUR pharmacopeia." (EFMHACArespondent 7)

5. Discussion

The study revealed that, from 317 new applications which were submitted through MRIS for MA, majority of the applications were Non-SRA. 78% of the applications were under dossier evaluation this is because from application submission date to directorate decision date taking long decision days. As a result, only 18% of the total applications got MA approval. Also, according to the respondents, the hindrances for the remaining applications under different stages of dossier assessment for MA approval were: limitation of regulatory experts, weak capacity building, impracticality of rules and management disruption by applicants and EFMHACA.

For the regulatory authority to perform the regulatory work efficiently there should be adequate number of qualified experts. Hence, the findings from both the quantitative and qualitative study associate delays in MA approval to limitation of dossier assessors, especially pertaining to the low number of secondary assessors in EFMHACA. Similar findings from other studies also reported the lack of experts as one reason that leads to the delay in MA. (Bate et al., 2010; WHO, 2010; Mkumbwa, 2013).

Enhancing the technical skill of experts also has an importance in reducing the unnecessary time taken for dossier assessments and to minimize back log. However, a majority of respondents claimed, that weak capacity building efforts were made to support the assessors. Due to this reason, for the same dossier evaluation, inconsistencies on decision making were observed among the assessors. This might lead to holding of the documents by the team leader until the final decision is made.

In addition, due to lack of training on specific product line inspection like, biological products, the assigned inspector might make a wrong pass or fail decision. As a result, the company may complain on those findings by being confident and giving justification on the inspection report and such kind of instance leads to arguable decision. So, improving the experts' competency with different trainings is important to make experts capable enough to perform their jobs efficiently. A related (Wolde et al., 2017) study showed that, in Namibia, the regulatory agency has a constraint of qualified experts. And these problems increase the number of unassessed dossiers and eventually registered medicines to the society.

Ultimately, the development of SIAPS program assisted the regulatory agency experts by providing capacity building trainings in dossier evaluation, GMP inspection and QC laboratory test of medicines. Following these strategies, those dossiers were submitted through a web-based system for HIV/AIDS and TB and vaccines.

The average number of days taken to review and approve the applications for MA were decreased. The amount of backlog dossiers presented, as compared to new dossiers received, also declined. Thus, the percentage of dossiers processed within the same period increased. Moreover, as report (Kamwanja et al., 2011) showed that, to resolve the constraint in qualified staff, harmonization of regulatory authorities is important for resource and information sharing, in order to expedite the MA process. Accordingly, Economic Community of West African States (ECOWAS) which is a harmonization of countries namely :Burkina Faso, Gambia, Ghana, Liberia, Mali, Niger, Nigeria, Republic of Guinea, Senegal and Togo have funding support from the European Union to strengthen the regulatory authorities for efficient implementation of regulation. This is done by providing continuous training for their Staffs like: Training of online courses and training for pharmacy inspectors. In the same manner, EFMHACA which is now Ethiopian Food and Drug Authority (EFDA) should strengthen continual professional development programs by collaborating with other regulatory agencies.

Furthermore, as per the GMP directive the inspectors report and submit to the GMP task force within 14 days after completion of inspection. Then, within 30 calendar days the inspection report is sent to the inspected facility but if the report review is incomplete and other internal problems occur, the release of GMP report to the applicants may take up to three months or so. To implement set standards practical gaps were noticed. As a result, obtaining MA at the recommended date of citizen charter becomes challenging. (EFMHACA, 2017)

The set time frame for MA based on citizen charter for the Non-SRA application was found to be 95 days and 17 days for the SRA application. To implement the set standards and to expedite the MA process; the majority of respondents in Ethiopia claimed that, the only regulatory procedures to expedite the MA process for new medicine applications was fast track registration for local manufacturers, product

application ,public health programs, medications like: ART drugs, anti-malaria drugs ,TB drugs and contraceptives and SRA applications. These methods are ways of facilitating dossier assessment even if the dossier assessment approach is not a risk based approach. Accordingly, EFDA recently start to implement a risk based approach, in which medicines will be categorized based on the risk they impose on patients, as low risk and high risk medicines, and these approaches will enhance the dossier assessment period. (EFMHACA, 2016; EFMHACA, 2017)

Related with, (Leyens et al., 2015) a study revealed that in the USFDA and EMA, different regulatory procedure are applicable based on risk and benefit evaluation to expedite the MA process for new medicine applications. Accordingly, based on the risk based approach, Conditional approval (CA) in the EMA is allowed for medication to be approved for life threatening situations, emergency situations and rare diseases in small populations. Accelerated approval (AA) in the USFDA is allowed for medication to be approved for serious illnesses if it offers a benefit over the available treatments. Based on those approaches, most of the approval is made for oncology, anti-infective ,nervous system and inborn genetic disorder medication. So, EFDA currently by applying different regulatory approaches for different categories of medication will improve the MA approval period.

Likewise, a clear work description for each expert was also necessary to oversee their activities and detect the gap in the regulatory authority .Hence, in EFMHACA, the available experts are assigned for different kinds operation. For instance, as a respondent claimed that one expert who performs the QC analysis may be delegated to the maintenance of equipment which is not a part of their professional skill and due to this, they might not do the analysis that is part of their professional skill until the assigned job is finished. In the same way, one assessor may perform different kinds of jobs like assessing new applications, re-registration of applications, other various applications and MA preparation. As a result, due to the heavy work load on the experts, it may took 575 days to review one type of a dossier application and to release further information to the applicant, so it becomes difficult to accomplish the assigned job in a specified period of time .

The study made by (Roey et al.,2008) states that, regulatory authorities of developing countries lack a clear and organized work procedure .Additionally, as a study

(WHO,2010) shows that out of 26 sub-Saharan countries, the job description for an expert was absent in the regulatory authority of five countries and assignment of the job for experts was unclear in four other countries. For instance, one regulatory authority directorate may participate in another directorate's work and as a result an unmanageable workload is faced by the experts. So, EFDA nowadays, should employ additional experts to facilitate the regulatory work and strengthen the retention mechanism for those available experts.

On other hand, applicants should adhere to the national regulatory requirement by preparing the required documents within a set time frame.

However, as the time frame shows, those query responses were submitted by applicants after 567 days implying that after further information released applicants took a long time.

Regarding this, respondents claimed that, the applicants had not prepared the requested documents or were not aware of the regulatory requirement and they used unspecified period of time for the preparation of the documents. Hence, if the applicants didn't submit the query responses within specified period and it results in a delay of MA approval within the recommended date. Related with a study (Ahonkhai et al., 2016) showed that, the applicants took a long time to prepare and submit the appropriate query response to the regulatory authority due to the lack of prioritization given and incompetency constraints from the applicant's side. As result, the authority prolonged the approval time for MA.

Also, as respondents claimed that, the regulatory personnel who are assigned by the applicants are not knowledgeable about the regulatory requirement and this results in the misunderstanding between the regulatory authority experts and the applicants which might bring about improperly arranged and mixed documents which belong to other products. Incomplete documents were submitted to EFMHACA due to this reason, the unnecessary exchange of information between applicants and EFMHACA may occur repeatedly until the problem is resolved.

A (Mkumbwa ,2013) study shows that, the overall knowledge of pharmacists in-charge of medicine MA process was found to be low and only a few of them knew the information required for the preparation of the dossier. So, applicant's regulatory

personnel should have training opportunities from those hiring companies or should get formal education opportunities in regulatory affairs.

In addition, applicant's perception on MA process should changed, applicant's main focus should not just be to market their products quickly, rather they should cautiously prepare the registration document before submitting it to the regulatory authority for successful completion of MA. Also, as the respondents claimed ,without EFMHACA's consent, the applicants procure unacceptable reference standard. However, Until the appropriate reference standard is procured and submitted for analysis, the time will be prolonged and this circumstance may have an impact for MA approval period.

Similarly, the study which was carried out by (Hill et al., 2004) stated that, MA process should not be seen as a stumbling block, it needs to be seen as a critical step to ensure safety, quality and efficacious medicine access to the society. So, applicants must prioritize the fulfillment of the compulsory regulatory requirements for successful completion of MA. Also, EFDA collaborating with applicants and by implementing proclamation 1112/ 2019 possibly will address those hindering factors of MA process to enhance the regulatory framework.

6. Limitation of study

During data collection from MRIS system, the applications that have the same date for: submission date, prescreening date, fee attached date and verified date were enclosed. When the system started earlier. Only a partial part of the dossier was submitted through the system and the whole part of dossier was submitted by hard and soft copy. As a result, unable to estimate the decision date difference within each stage.

Local manufacturer's applications which is considered as a fast track registration can't be identified from those normal procedure applications which means it's only identified by assessors view. So, it's not possible to determine their total decision date for MA separately.

7. Conclusion

As the study revealed, the MA process takes a lengthy time in Ethiopia, as compared to the MA time frame which has been stipulated in the authority`s Citizen Charter. An application as Non-SRA and SRA taking long decision days while under different stage of dossier evaluation had impact for MA approval in a reasonable period. Also, as respondents claimed, the main contributing factors in case of EFMHACA were limitation of resource and weak capacity building. In the case of LRFPIs and LPIs, there were limitations that involved inadequate training and gaps on the implementation of rules by applicants. So,a limited number of qualified GMP inspectors, dossier assessors and QC analysts and a lack of sufficient knowledge regarding the regulatory work carried out by applicants regulatory personnel have a negative inducement on the implementation of the set regulation for MA approval.

8. Recommendation

This study puts forward a number of recommendations that aim to improve the medicine MA process in Ethiopia. They are categorized into resource approach, regulatory approach, capacity building approach and researcher approach.

Resource approach

- Professionalsshould be specialized in different expertise for dossier evaluation;quality assessors should be specialized in pharmaceutics, pharmaceutical analysis, and medicinal chemistry; non-clinical assessors should be specialized in pharmacology, biochemistry, and pharmacognosy; clinical assessors should be specialized in clinical pharmacology, clinical pharmacy, biopharmaceutical sciences, also chemist, enviromental science, biomedical engineers for GMP inspection and QC laboratory test EFMHACA should employ based on the flow of applicants' dossier applications, GMP appilcants and submitted QC samples.
- The government should becooperating with financial aid organizations like USAID. If advanced technology equipments are planted for analysis, then the QC result problem that arises because of inefficient equipmentwill be resolved.
- EFMHACA should encourge and strengthen the invovment of higher education students for dossier evaluation, especially to support the limited personnel ofsecondary assessors.

Regulatory Approach

- EFMHACA should revise the regulatory procedure. That means dossier assessment based GMP inpsection will improve GMP inspection system.
- EFMHACA should design a system for dossier evaluation including abbreviated procedure for SRA applications, expedited assessment which includes conditional approval, collaborative approach for products prequalified by WHO and for non-SRA applications; new, re-registration and variation applications assigning different assessors. This is because non-SRA types of applications take a longer evaluation period than SRA application. As a result, dossier assessment period will be enhanced.

- EFMHACA should collaborate with other regulatory agency like USFDA, EMA, Health Canada, Japan and New Zealand. It should also collaborate with the East African Community Medicines Regulatory Harmonization (EAC-MRH) program including Burundi, Kenya, Rwanda, Uganda and Tanzania. Then applying mutual regulatory procedure will extend the existing MA to other countries, which will expedite the MA process.
- Enhancing the regulatory data management system will also improve the accessibility of regulatory information such as GMP inspection schedule, GMP report, sample for analysis, reference standard and QC documents for EFMHACA and applicant experts. And as a supplement for these subjects, developing a system like MRIS will form clear information flow. Additionally, strengthening MRIS performance will solve the restraints which were observed in the system utilization.
- Strengthening the regional regulatory office involvement in the execution of MA process.

Capacity building approach

- The government should collabrate with WHO and other SRA regulatory bodies like USFDA, EMA, Health Canada & Japan and make arrangements for training programs and experience sharing sessions on specific product dossier evaluation, GMP inspection and QC laboratory test to enhance the skill of the experts at an international level.
- Create a system for capacity building program for EFMHACA and applicants' experts and strengthen formal education opportunity in regulatory affairs.

Researcher approach

- Updated proclamation 1112/2019 for EFDA was not enclosed in the study, because my research was conducted based on proclamation 661/2009, to use those implemented regulation 299/2013, medicine guideline 2014, GMP inspection guideline 2014, GMP directive 2017 and citizen charter 2016. Therefore, in future I recommend a researcher to address proclamation1112/2019 to forecast those factors that influence medicine market authorization process.

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Annexes

Annex I: Data abstracting tool for number of new applications submitted through MRIS System for market authorization approval from July 1, 2016 to Dec 30, 2018.

Application .No	Type of application	Current status	Submitted date	Prescreened date	prescreened to fee attached date	Fee attached date to verification	Verified to assigned date for assessors	Assigned date to primary assessor date	primary submission date to secondary submission date	secondary submission to team leader decision date	Further requested date to Further reply date	Team leader decision date to Directorate decision date	Total decision date

Annex: II

In-Depth Interview

Addis Ababa University

College of health sciences

School of pharmacy

Department of pharmaceutics and social pharmacy

Consent form for in-depth interview

Introduction

This questionnaire is prepared for an in-depth interview to assess of factors influencing medicines market authorization process in Ethiopia. I am a postgraduate pharmacy student conducting a study on the above mentioned research topic. The study has an importance in enhancing the availability of quality, safety and efficacy of medicines for the society by addressing the obstacles that affect market authorization approval in relation with MA process.

To obtain the necessary information for this purpose, I am conducting a self-structured interview guide. The interview will take up to 30 minutes of your time and the interview will be done at your convenient location. Your participation is based on your full consent and the information you provide will be strictly confidential. Audio recorder will be used during the interview and direct quotes might be taken from your response to be used in the research without disclosing who you are and the collective responses from different respondents will only be identified by using codes.

Considering the objective of study, your response has a crucial impact on the successful completion my work. With this in mind, you are kindly requested to give your indisputable response to the questions without hesitating to further explain yourself.

Are you willing to respond to the questions? Yes/No.

መጠይቅ 2

አዲስ አበባ ዩንቨርስቲ

የጤና ሣይንስ ኮሌጅ

የፋርማሲ ት/ቤት

የሶሻል ፋርማሲ እና ፋርማሲቲዉክስ ዲፓርትመንት

የቃለ-መጠይቅፎርም

መግበቢያ

ይህ መጠይቅ የተዘጋጀው ጠለቅ ብሎ በተደረገ ቃለመጠይቅ ሲሆን፣ጥናቱም በኢትዮጲያ የመድሃኒት የገበያ ፈቃድ ለማግኘት ያሉትን ችግሮች የሚያሣይ ነው።እኔ ሰፋኒት መኮንን የድህረ ምረቃ በሪጉላቶሪ አፌርስ በመድሀኒት ትራክ ላይ ተማሪ ስሆን ከላይ በተጠቀሰው እርዕስ ጥናቴን አርጊያለው።የዚህም ጥናት አላማ ጥራቱን፣ደህንነቱን እና ፈዋሽነቱን የጠበቀ መድሀኒት ለህብረተሰቡ ለማስገኘት ሲሆን ከዚሁም ጋር ተያይዞ ከመድሀኒትም ዝገባ ሂደት ጋር ያለውን ችግሮች በመለየት ሂደቱን እንዲጎለብት ለማድረግ ይረዳናል።ስለዚህም ይህን አርዕስ በተመለከተ መረጃ ለመሰብሰብ ይጠቅም ዘንድ ከታች የተዘጀውን ቃለ - መጠይቅ አዘጋጅቻለው። በጥናቱ ለመሳተፍ ሙሉ ለሙሉ የእርስዎን ፈቃድ የሚጠይቅ ሲሆን ከእርስዎ የሚገኘውም መረጃ በሚስጥር የሚያዝ ሲሆን የሚሰበሰበውም መረጃ ሙሉ ለሙሉ ለመሰብሰብ በቃለ - መጠይቁ ግዜ የድምፅ የመቅጃ መሳሪያ ተጠቅሚያለሁ።

ነገር ግን የእርሰዎ ሀቀኛ የሆነ መረጃ መስጠት የምርምራ ስራዬን ትክክለኛ አላማውን ለማሳካት በከፍተኛ ሁኔታ ያግዘኛል። ስለዚህም የቀና ትብብሮን እንድትሰጡኝ በትህትና እጠይቃለው። ቃለመጠይቁም እስከ 30 ደቂቃ የሚወስድ ሲሆን እርስዎም በመረጡት ቦታ እና ሰአት ይካሄዳል።

በመቀጠልም ጥያቄያን ለመጀመር ዝግጁ ነዎት? አዎ ☐ *አይደለሁም* ☐

Annex III: Interview guide for GMP inspectors

Section I: Socio-demographic characteristic of respondents

1. Gender - Male ☐ Female ☐
2. Age_____
3. Profession _____
4. Educational level _____
5. Experience (years) _____

Section II: Questions based on research topic.

1. Can you share with me your training experience as GMP inspector ?

_____

_____

2. Do you think currently available number of GMP inspectors are sufficient to perform inspection?

_____

_____

_____

3.Can you share with me the procedure for inspection of manufacturer's site?

_____

_____

_____

4. Do you think the available guidelines/SOP in your organization are satisfactory for GMP inspection?

_____

_____

5. How do you describe the pharmaceutical manufacturer's compliance with Ethiopian GMP?

_____

_____

_____

6. What are the common problems face in GMP inspection?

_____

_____

_____

_____

7. Your recommendation/s to solve these challenges?

_____

_____

_____

Thank You for Your Participation!!

መጠይቅ 3

ከመልካም አመራረት ፈታሾች ጋር የተደረገ ቃለመጠይቅ

ክፍል 1 አጠቃላይ መረጃ

1. *ፆታ - ወንድ ☐ ሴት ☐*
2. *እድሜ_____*
3. *የስራ ዘርፍ_____*
4. *የትምህርት ደረጃ_____*
5. *የስራ ልምድ_____*

ክፍል 2 በጥናቱ አርዕስ ላይ መሰረት ያደረገ ጥያቄ

1. *በመልካም አመራረት ፈታሽነት የወሰዱትን ስልጠና ልታካፍሉኝ ትችላለህ/ሽ?*
   _____
   _____
2. *በመልካም አመራረት ስራ ያሉት ባለሙያዎች በቂ ናቸዉ ብለክ/ሽ ታስባለክ/ሽ?*
   _____
3. *የመድሀኒት ፋብሪካ ፍተሻ ሂደት ምን ይመስላል?*
   _____
   _____
4. *አሁን በመስሪያ ቤታችሁ ያሉ ጋይድላይን እና ኤስ ኦ ፒ የመልካም አመራረት ፍተሻ ለማካሄድ በቂ ነዉ ብለክ/ሽ ታስባለክ/ሽ?*
   _____
   _____
5. *የመድሀኒት አምራቾች የኢትዮጵያን የመልካም አመራረት ፍተሻ የማለፍ ሁኔታቸዉ እንዴት ትገልፀዋለክ/ሽ?*
   _____
   _____
6. *በተደጋጋሚ በስራ ላይ የነጠሙህ/ሽ ችግሮች ምንድን ናቸው?*
   _____
7. *ይህን ችግር ለመቅረፍ ያለዎት ሀሣብ ምንድን ነው?*
   _____
   _____

ስለ ተሳትፎዎ እናመሰግናለን::

Annex IV: Interview guide for dossier evaluators

Section I: Socio - demographic characteristic of respondents

1. Gender- Male ☐ Female ☐
2. Age_____

3.Profession _____

4.Educational level _____

5.Experience (years) _____

Section II: Questions based on research topic

1. Can you share with me your training experience as dossier evaluator?

   _____

   _____

   _____

2. How is the procedure for dossier assessment?
   - Different medicine dossier applications; New, Re-registration and variation applications and for those applications what are the mechanism to dossier evaluation?

_____

_____

_____

3. How do you explain the applicant adherence with medicine registration guideline?

_____

_____

_____

4.How do you describe your communication with applicants in MA process?

_____

_____

_____

5. How do you see the implementation of MRIS system for dossier evaluation?

_____

_____

_____

6. What are common challenges face in MA process that hinder market authorization approval?

_____

_____

_____

_____

7. Your recommendation/s to solve these challenges?

_____

_____

_____

Thank You for Your Participation!!

መጠይቅ 4

ከመድሀኒት ሰነድ ገምጋሚ ጋር የተደረገ ቃለመጠይቅ

ክፍል 1 አጠቃላይ መረጃ

1. *ፆታ - ወንድ* ☐ *ሴት* ☐
2. *እድሜ*_____
3. *የስራ ዘርፍ*_____
4. *የትምህርት ደረጃ*_____
5. *የስራ ልምድ*_____

ክፍል 2 በጥናቱ አርዕስ ላይ መሰረት ያደረገ ጥያቄ

1. *ለመድሀኒት ሰነድ ግምገማ የወሰዱትን ስልጠና ልትነግሪኝ/ረኝትችያለሽ/ህ?*

_____
_____

2. *በሰነድ መገምገም ያለው ሂደት ምን ይመስላል፣ ለአዲስ ምዝገባ፣ለነባር ምዝገባ እና ለሰነድ ለዉጥ?*

_____
_____

3. *አመልካቾች በምዝገባ ሂደት ዉስጥ ከመድሀኒት ከመመሪያ ደንቡ ጋር ያላቸዉ መግባባት እንዴት ትገልፀዋለክ /ትገልጭዋለሽ?*

_____
_____

4. *በመድሀኒት ማስመዝገብ ሂደት ዉስጥ ካመልካቾች ጋር ያለዎትን መግባባት እንዴት ትገልጭዋለሽ/ህ?*

_____

5. *ለመድሀኒት ሰነድ ግምገማ የኤም አር አይ ኤስ ትግበራን እንዴት ታየዋለህ/ሽ?*

_____
_____

6. *በተደጋጋሚ በስራ ላይ የገጠመህ/ሽ ችግሮች ምንድን ናቸው?*

_____

7. *ይህን ችግር ለመቅረፍ ያለዎት ሀሣብ ምንድን ነው ?*

_____
_____

ስለተሳትፎዎእናመሰግናለን::

Annex V: Interview guide for QC analysts

Section I: Socio -demographic characteristic of respondents

1. Gender- Male ☐ Female ☐
2. Age_____
3. Profession _____
4. Educational level _____
5. Experience (years) _____

Section II: Questions based on research topic

1. Do you think the currently available number of QC experts is sufficient to perform analysis?

_____

_____

_____

2. How do you describe the available standard operating procedure for your work environment?

_____

_____

_____

3. Do you think the available facilities & resources found in your organization are enough for QC analysis?

_____

_____

_____

4. How do you explain the submitted products fulfillment with set standards?

_____

_____

_____

5. What are the most common challenges you face in your work?

_____

_____

_____

_____

6. Your recommendation/s to solve these challenges.

_____

_____

_____

,

Thank You for Your Participation!!

መጠይቅ 5

ከመድሀኒት ኳሊቲ ኮንትሮል አናሊስት ጋር የተደረገ ቃለመጠይቅ

ክፍል 1 አጠቃላይ መረጃ

1. *ፆታ- ወንድ ☐ ሴት ☐*
2. *እድሜ_____*
3. *የስራ ዘርፍ_____*
4. *የትምህርት ደረጃ_____*
5. *የስራ ልምድ_____*

ክፍል 2 በጥናቱ አርዕስ ላይ መሰረት ያደረገ ጥያቄ

1. *በመድሀኒት ኳሊቲ ኮንትሮል የወሰዱትን ስልጠና ልትነግሪኝ/ልትነግረኝ ትችያለሽ/ህ ?*

_____
_____

2. *ለኳሊቲ ኮንትሮል ሰራ ያሉት ባለሙያዎች በቂ ናቸዉ ብለክ/ብለሽ ታስባለክ/ሽ ?*

_____
_____

3. *በስራዎት ኢንቫይሮመንት ዉስጥ ያለዉ እስታንዳርድ ኦፕሬቲንግ ፕሮሲጀር እንዴት ትገልፀዋለክ/ሽ?*

_____
_____

4. *በድርጅቱ ውስጥ ያለው አቅርቦት ለኳሊቲ ኮንትሮል ምርምር በቂ ነው ብለክ/ሽ ታምናለህ/ሽ ?*

_____
_____

በኳሊቲ ኮንትሮል ምርመራ ጊዜ የተቀመጠዉን እስታንዳርድ የማሟላት ሁኔታ እንዴት ታየዋለክ/ሽ?

_____
_____

5. *በተደጋጋሚ በስራ ላይ የገጠመህ/ሽ ችግሮች ምንድን ናቸው ?*

_____
_____

6. *ይህን ችግር ለመቅረፍ ያለዎት ሀሣብ ምንድን ነው?*

_____
_____

ስለ ተሳትፎዎ እናመሰግናለን::

Annex VI: Interview guide for LRFPIs & LPIs experts

Section I: Socio-demographic characteristic of respondents

1. Gender - Male ☐ Female ☐
2. Age_____
3. Profession _____
4. Educational level _____
5. Experience (years) _____

Section II: Questions based on research topic

1. How many Pharmaceutical companies represent to facilitate medicine MA process?
   - How many medicines registered since you start working at your company?

_____

2. Can you share with me your training experience to pre-screen dossiers for proper compilation before submission for registration purpose?
   - Have you received any training on dossier preparation and compilation for registration purpose?

_____

_____

_____

3. Based on your experience, how do you see MA process for market authorization approval at EFMHACA ?
   - How do you see the GMP inspection schedule?
   - How do you explain the time frame for dossier evaluation?
   - How do you see quality control laboratory test process?

_____

_____

_____

4. Do you think the implementation of MRIS system fill the gap in MA process?
   - How do you describe the system performance?

_____
_____
_____
_____

5. What are the common challenges in MA process?

_____
_____
_____
_____

6. Your recommendation/s to solve these challenges?

_____
_____
_____

Thank You for Your Participation!!

መጠይቅ 6

ከመድሀኒት አስመጪዎች እና ከሀገር ዉስጥ የመድሀኒት አምራቾች የተደረገ ቃለመጠይቅ ጋር

ክፍል 1 አጠቃላይ መጠይቅ

1. *ፆታ - ወንድ ☐ ሴት ☐*
2. *እድሜ_____*
3. *የስራ ዘርፍ_____*
4. *የትምህርት ደረጃ_____*
5. *የስራ ልምድ_____*

ክፍል 2 በጥናቱ አርዕስ ላይ መሰረት ያደረገ ጥያቄ

1. *ለምን ያህል የመድሀኒት አምራቾች የመድሀኒት የገበያ ፈቃድ ሂደት ታከናውናለክ/ሽ?*

_____

- *አሁን ላለህበት/ሽበት ካምፓኒ ምን ያህል መድሀኒት አስመዝግበሀል/ሻል?*

_____
_____

2. *ለመድሀሂት የገበያ ፍቃዴ ሂደት በትክክል ወይም በአግባብ የመድሀኒት ሰነድ ለማቀናጀት የወሰድካቸው ሰልጠና ወይም ልምድ ብታካፍለኝ/ብታካፈይኝ?-_____*
   - *የመድሀኒት ሰነድ ለማቀናጀት የወሰድከዉ/የወሰድሽዉልምድአለ?*

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3. *ከልምድህ የመድሀኒት የማስመዝገብ ሂደት ምን ይመስላል?*

_____

- *የመልካም አመራረት ፍተሻው እስኬጁል ምን ይመስላል?*

_____

- *የመድሀኒት ሰነድ ለመገምገም የጊዜ ሁኔታን እንዴት ትገልፀዋለክ /እንዴት ትገልጭዋለሽ?*

_____

- *የመድሀኒትጥራትፍተሻሂደቱንእንዴትታየዋለህ/ሽ ?*

_____

4.ኤም አር አይ ኤስ ትግበራ ለገቢያ ፈቃድ ሂደት ውስጥ ያሉት ክፍተቶች ምልቶታል ብለህ ታስባለህ/ሽ?

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- *የሲስተሙን ብቃት እንዴት ትገልፅዋለክ /ትገሊጪዋለሽ ?*

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5.ተደጋጋሚ በስራ ላይ የገጠመህ/ሽ ችግሮች ምንድን ናቸው?

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6.ተደጋጋሚ በስራ ላይ የገጠመህ/ሽ ችግሮች ምንድን ናቸው ?

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ስለተሳትፎዎእናመሰግናለን።

አዲስ አበባ ዩኒቨርሲቲ
በ ፋርማሲ ትምህርት ቤት
Addis Ababa University
School of Pharmacy
የኢቲካል ሪቪው ቦርድ
Ethical Review Board

ቀን Date: April 24, 2019

ቁጥር Ref. No.: ERB/SOP/86/04/2019

To: **Sefanit mekonnen**

School of Pharmacy

Re: Ethical Clearance

It is to be recalled that you submitted a study proposal entitled ***"Assessment on factors influencing medicine market authorization process in Ethiopia"*** for ethical approval by the School's Ethical Review Board (ERB). The Board thoroughly reviewed the proposal based on its operational guidelines and found it to fulfill all ethical requirements stipulated in the guidelines. This is, therefore, to inform you that the proposal is ethically approved for implementation.

With best regards,

Arebu Issa

Chairperson, ERB

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