A Queuing Analysis of Medicines Registration System Performance in Ethiopian Food and Drug Authority

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This is to certify that the thesis prepared by Abebe Alamneh entitled: *A Queuing Analysis of Medicines Registration System Performance in Ethiopian Food and Drug Authority* and submitted in partial fulfillment of the requirements for the Degree of Master of Science (Regulatory Affairs- Medicine Regulation Track) complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Abstract

A Queuing Analysis of Medicines Registration System Performance in Ethiopian Food and Drug Authority

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Background: The limited number of approved medicines and long waiting time for registration are the major challenges limiting the performance of the regulatory system in Ethiopia. Queue analysis is used for characterizing and estimating the queue process and operating variables of the system to alleviate the challenges related to target timelines.

Objective: To assess the queuing performance of the registration system at the Ethiopian Food and Drug Authority (EFDA).

Methods: A mixed sequential explanatory study design was used for the study. Quantitative data collection involved a review of applications submitted to the EFDA from July 8, 2019 to July 7, 2020. Basic operating characteristics of the registration system performance were executed using single queue multiple server model of the queuing analysis. In-depth interviews with purposively selected registration experts from the EFDA and private organizations were done for the qualitative data collection. Analysis of the interviews involved the thematic analysis approach.

Results: Mean arrival rate of applications to the registration system (λ=10.99 services per day) was 23.74% higher than the mean effective service rate of the system ($c\mu$=8.38 services/day). Basic system performance average operating characteristics of the system could not be estimated indicating that an infinite queue of applications built up over time and was hard to achieve any target timeline in EFDA's current registration system. The qualitative study also showed that the system is being frequently challenged with backlogs.

Conclusion: The study documented weak system performance with lengthy registration process. Appropriate measures to improve mean effective registration service rate should be introduced to meet international standards and the agreed citizen's charter of 2016.

Keywords: *Queue analysis, service rate, arrival rate, utilization factor, system performance characteristics.*

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Acronyms and Abbreviations

ANDA	Abbreviated new drug application
ASEAN	Association of South East Asian Nations
BE	Bioequivalence
CDER	Center for drug evaluation and research (USFDA)
CIS	Common wealth of Independent States
CTD	Common Technical documents
EFDA	Ethiopian food and drug authority
eRIS	Electronic regulatory information system
FIFO	First in First Out
FIR	Further information request
FIRR	Further information request replies
GCC	Gulf Co-operation Council
cGMP	Current Good manufacturing Practice
LATAM	Latin America
LMICs	Low and middle income countries
MA	Market authorization
MRLD	Medicine registration and licensing directorate
NCE	New chemical entity
NMR	New medicine registration
NMRA	National medicine regulatory agency
NRA	National regulatory authority
QC	Quality control
QSIM	Queuing simulation
REN	Renewal application
RSS	Regulatory system strengthening
SF	Substandard and falsified
SRA	Stringent regulatory authority
TRIPS	Trade-related aspects of intellectual property rights
USFDA	United States food and drug administration

1. Introduction

1.1. Background

Any nation's healthcare system must include high-quality pharmaceuticals and healthcare items (Roth et al., 2018). It is also well known that national regulatory authorities (NRAs) have the responsibility of guarding the quality, safety, and efficacy of medical products across the supply chain. According to Khadem Broojerdi et al. (2020), the core NRA responsibilities include market surveillance (product quality monitoring, pharmacovigilance, control of drug promotion and advertising), quality control, and clinical trial oversight. Imports and exports are also controlled, manufacturing facilities are subject to inspection, and import and export licenses are issued.

However, many nations still do not have access to these fundamental components of a functioning healthcare system (Khadem Broojerdi et al., 2020), and as a result, patient care activities and health care financing are suffering from a lack of high-quality drugs and medical products (Lilly et al., 2004).A few of the requirements for a good regulatory performance are the proper coordination of diverse regulatory operations, the availability of financial resources, and an acceptable quantity of human resources with the necessary competency to carry out their duties(Nyika et al., 2022).

Premarket registration of medications that are accessible for sale to the general public is one of the main responsibilities of any organization that regulates pharmaceuticals, such as the Ethiopian Food and Drug Authority (EFDA). The process by which an NRA independently evaluates the safety, effectiveness, and quality of a medical product and then grants consent for lawful marketing in a certain territory is known as medicine registration/marketing authorization.

Timely evaluation and authorization are necessary to provide timely access to medications. The length of time needed for a country's registration procedure is crucial in this regard. (2010) (Bate, Mooney, and Hess). The performance of the registration procedure is, however, poorly documented in many underdeveloped nations, and Ethiopia is no exception. Therefore, the purpose of this study was to close the knowledge gap about the effectiveness of the registration system in Ethiopia.

1.2. Statement of the problem

Understanding how national regulatory agencies (NRAs) are currently functioning gives one a foundation for seeing weaknesses and untapped potential for enhancing regulatory capacity, advancing public health, and advancing the pharmaceutical business (Nyika et al., 2022). On the other hand, a quick and efficient registration procedure is crucial since it affects the company's financial performance as well as the public's access to and cost of necessary medications (Badjatya, 2013).The increasing emphasis on quality, particularly in service-related activities, has made it more crucial to improve regulatory services in terms of waiting times. Customers are increasingly associating quick service with high-quality service when they seek out service providers. Because of this, an increasing number of businesses and service provider organizations are emphasizing waiting time reduction as a crucial part of quality improvement (Bernard W, 2006).

Despite the EFDA's notable advancements over the past few years, the agency continues to face fresh, more difficult problems. Unprecedented shortages of life-saving medications, a dearth of authorized, high-quality medications, and protracted registration wait times are only a few of the difficulties. The pharmaceutical industry's growing need for marketing permission and the public's need for high-quality, secure medications meant that the evaluation of medicines dossiers, cGMP inspections, and quality testing methods could not keep up. In particular, the authority's drug registration section has ongoing challenges due to an ever-growing backlog of new and re-registration applications, post approval variation applications, and additional request answers (EFDA, 2017a).

As a result, there have been ongoing reports of delays in the timeline for the registration procedure, which has delayed the entry of important pharmaceuticals into Ethiopia's market. The real time frame needed to evaluate an application dossier is substantially longer than the goal specified in the EFDA's standard standards. Frequently, applicants had to wait a long period to receive the desired services. Despite the existence of such anecdotal evidence, factors such as the suitability of the assigned human resource, the application queue discipline (the order in which customers are served), the nature of the calling population (where customers come from), the arrival rate (how frequently customers arrive at the queue), the service rate (how quickly customers are served), and the service quality were not studied; consequently, practices are not based on study recommendations.

1.3. Significance of the study

The ultimate goal of this study is to evaluate the queue performance of the registration system and overall registration applications, with a focus on computing operating characteristics like the typical number of customers waiting in line and the typical amount of time a customer must wait in line to receive the desired service. Based on the study's findings, suitable suggestions for attaining steady-state service rates may be identified; enabling the EFDA to reach the aim set out in the citizens' charter (2016) and works toward achieving global best practices. The results of this study will assist management at the EFDA and other nonprofit groups working to enhance the registration system in making choices about the registration system. As a consequence, there will be seamless, organized, and prompt registration of medicines, increased access to high-quality medicines, and a decrease in the number of subpar and fake pharmaceutical items on the market. It helps them to reach a consistent level of service rates with enhanced service quality. As a result, the EFDA will be better able to accomplish its goals and foster long-lasting public confidence and consumer satisfaction.

2. Literature review

2.1. Regulatory performance indicators

As part of its mission to develop regulatory systems, WHO started regulatory benchmarking systems as of 1997. At first, it used a set of indicators meant to assess the regulatory oversight for vaccinations. According to Khadem Broojerdi and colleagues (2020), this was done to answer the urgent question of how to guarantee that vaccinations fulfill the necessary criteria of quality, safety, and efficacy whether they were used domestically in the place of manufacturing or in receiving countries. The WHO created a Global Benchmarking Tool (GBT) to evaluate the strengths and weaknesses in the various regulatory functions and categorize the regulatory systems in terms of maturity levels (ML), that range from1 to 4 (Nyika et al., 2022; Ndomondo-Sigonda et al., 2017), in order to objectively evaluate each NRA and provide an opportunity for further strengthening regulatory systems.

Only 50 of the 194 member nations of the WHO have regulatory agencies that are regarded as mature (Maturity level 3 or 4), whereas 144 have subpar regulatory systems, according to the database of WHO regulatory systems strengthening. According to Khadem Broojerdi et al. (2020), 23% (45 nations) and 51% (99 countries) of the world's countries are at the second-lowest levels of maturity, respectively.

All African nations, with the exception of the Sahrawi Republic, have an NMRA or administrative unit that performs part or all of the duties required of NMRAs at varied stages of development. Based on its own technical evaluations, the WHO classifies NRA performance into four maturity stages (Table 1). Only four NRAs, the Tanzania Food and Drug Authority (TFDA), Ghana Food and Drug Authority (GFDA), Egypt Drug Authority (EDA), and Nigeria National Regulatory Authority (NAFDAC), are working with a WHO Maturity Level 3, and there isn't a single NRA in Africa operating at WHO Maturity Level 4.Egypt and Nigeria have both attained level 3 maturity in the regulation of vaccines (both domestically manufactured and imported). In 2022, the latter two nations will be joined by Tanzania and Ghana as countries with strong regulatory frameworks on the continent of Africa. The Ethiopia Food and Drug Authority (EFDA), like other African authorities, is now being evaluated (WHO website, visited on April, 2021). Tanzania was the first confirmed country in Africa to reach a second-top maturity level regulatory system for medical products in December 2018 (Ndomondo-Sigonda et al., 2019).

As per Indicator MA04 "procedures established and implemented to perform registration and/or marketing authorization" and sub indicator MA04.06 "timelines for the assessment of the applications are defined and an independent mechanism to monitor adherence to the timelines set" the WHO GBT for evaluation of national regulatory systems for medical products registration and marketing authorization clearly stated that target

timelines for application assessment process and mechanisms to follow adherence to the timelines set are required. According to World Health Organization - WHO, 2022, NRAs are expected to implement mechanisms to adhere to the timetables to satisfy the GBT criteria as well as for the quality and predictability of the registration system.

Table 1; WHO global benchmarking tool performance maturity levels. Source: World health Organization.

	WHO GBT Performance Maturity Levels			
ISO 9004	**Maturity Level ①**	**Maturity Level ②**	**Maturity Level ③**	**Maturity Level ④**
	No formal approach	Reactive Approach	Stable Formal system approach	Continual Improvement emphasized
WHO GBT	Some elements of regulatory system exist	Evolving national regulatory system that partially performs essential regulatory functions	Stable, well functioning and integrated regulatory system	Regulatory system operating at advanced level of performance and continuous improvement
	Can be considered as functional if rely on other regulators for some specific functions		Target of WHA Resolution 67.20	Advanced and well resourced regulatory systems

2.2. Factors affecting regulatory performance

In addition to various levels of maturity, NMRAs in Africa also have a broad range of organizational structures, responsibilities, and activities, with some being semi-autonomous and others working under the Ministry of Health (MoH) (Nyika et al., 2022). Some solely control medical items, while others also control food and cosmetics. The MOH ultimately receives reporting from all NMRAs, and the MOH is ultimately in charge (Ndomondo-Sigonda et al., 2017; Keyter et al., 2020). The most prevalent issue affecting the majority of developing nations is the insufficient and unsustainable availability of human resources, which is primarily brought on by low salaries, a lack of training facilities, a shortage of professionals in the pharmaceutical and other essential industries, rigid hiring practices, a lack of career structures and incentives, and the "brain drain" (Nyika et al., 2022). Other difficulties faced by NRAs in developing countries include a lack of political commitment and support, which results in inadequate legislative frameworks and financial resources, inconsistent application procedures, and an inappropriate regulatory culture (Keyter et al., 2018). These issues have a negative impact on the healthcare system.

2.3. The impact of poor regulatory performance in the healthcare system

According to Kelesidis et al. (2007), Badjatya (2013), and Ndomondo-Sigonda et al. (2017), the absence of functional NMRAs in any nation exposes the populace to potentially dangerous medical products of variable quality and effectiveness, encourages the spread of substandard, fraudulent, falsely labeled, falsified, and

counterfeit (SSFFC) medical products, and inhibits the rational use of medical products. Recent reports from the WHO state that one-third of the world's population lacks timely access to quality-assured medications, and estimates show that at least 25% of medications in low- and middle-income countries (LMICs) are falsified or substandard (SF), with a yearly cost of about US$31 billion (Kelesidis et al., 2007; Roth et al., 2018).

A significant factor contributing to the poor regulatory performance of NRAs is the lengthy marketing authorization (MA) procedure (Khadem Broojerdi et al., 2020). The amount of time required for the applicant to receive MA has an impact on the product's availability on the market, according to the MA literature that is currently available. Between the first regulatory submission of a new drug authorisation to a well-resourced NMRA and final approval, an unusual delay of 4–7 years has been seen in sub-Saharan Africa (Ahonkhai et al., 2016). One of the reasons why corporations decline to offer pharmaceuticals to some African nations is lengthy registration processes (Ndomondo-Sigonda et al., 2017). Because of these and other related circumstances, NRA-approved medications are not always available, which increases the demand for and usage of unapproved medications to address supply chain gaps (Nyika et al., 2022).

Due to a lack of licensed medications on the market, people could potentially use unregistered medications, which opens the door for the production of substandard and counterfeit medications. A national survey conducted in the USA found a correlation between high rates of medication-related errors and severe adverse reactions and a lack of high-quality medications in acute care hospitals (Lilly et al., 2004; Nyika et al., 2022). As a result, the ability of drug regulatory agencies to oversee pharmaceutical products is always being assessed and improved.

The demands on regulators in developing nations to address the requirement for residents to have access to basic healthcare services and crucial medications for epidemics often have unfavorable effects. Additionally, national regulatory bodies in Africa must proactively plan for and react to pressures connected to regional and global commerce as well as political pressures, such as those associated with the TRIPs agreement and the African Continental Free Trade Area Agreement (AfCFTA), among other things.

Lack of adequate human resources, ineffective legislation that would permit use of international opportunities like the so-called "TRIPs flexibilities," such as compulsory licensing, and insufficient funding for drug regulatory activities are some of the challenges. Other issues include a lack of adequate quality manufacturing capacity, a lack of adequate regulatory capacity to evaluate generic products that may be able to fill the need for essential drugs, and a lack of adequate human resources. It is obvious that in order to solve these issues, a coordinated

national and regional strategy as well as strengthening the national regulatory organizations are advised (Hill and Johnson, 2004; Badjatya, 2013).

2.4. Current medicine registration process and timelines of Ethiopian regulatory system

2.4.1. The Practice in Ethiopia

Premarket registration of medications that are accessible for sale to the general public is one of the main responsibilities of any organization that regulates pharmaceuticals, such as the Ethiopian Food and Drug Authority (EFDA). The process through which an NRA independently evaluates the safety, effectiveness, and quality of a medical product and then grants consent for lawful marketing in a certain region is known as medicine registration/marketing authorization. Preclinical research, clinical trials, and the product information document are the main components; however, smaller agencies might only be able to handle certain of these activities (Bate and Mooney et al.). The EFDA accepts a variety of registration requests, including those for novel chemical entities, abbreviated new drug applications (ANDA), renewal applications, post-approval modifications, etc. In the healthcare system, there are many application streams for new applications depending on the product kind, usage, and demand. Fast track registration, low risk product registration, regular registration, and conditional approval are all available.

Types of application streams in EFDA

Normal standard registration applications

The applications submitted for registration in this application stream will be evaluated chronologically according to the date of submission to the Authority, and the applicant will be informed of the findings through the eRIS system as soon as the assessment is finished. Two assessors will do the evaluation. Internal peer reviews are conducted, i.e., when a submission is evaluated by the primary and secondary assessors in succession. Based on assessment templates, which specify the structure and substance of written reports on scientific evaluations, both assessors evaluate product dossiers. Administrative data, drug substance, drug product, comments on the product label, nonclinical data, clinical data (BE studies), safety and efficacy, good clinical practice aspects, and a list of suggestions to the applicant are all included in this assessment template (EFDA, 2014, no date). Before an MA or more information request letter to the sponsor is given, the final assessment result will be reviewed and authorized by an expert reviewer.

Fast-track registration

Fast track is a procedure created to make it easier to develop and approve medications that address significant medical needs (Levinson, 2008; EFDA, 2017a). Pressure from both the customer and the client on the NRA led to the introduction of a fast-track registration procedure in numerous nations. Consumer advocacy organizations, particularly those focused on HIV/AIDS concerns, have called for the quick approval of medications that have the potential to treat diseases that are now incurable. In order to cut expenses associated with registration delays, the pharmaceutical industry are likewise keen to release new drugs into the market (Wondemagegnehu and Sauwakon, 2002).

According to the 2014 Ethiopian Medicine Registration Guideline, drugs for orphan diseases, vaccines, anti-cancer drugs, anti-tuberculosis drugs, anti-malarial drugs, and anti-retroviral drugs should be given priority for evaluation and registration (EFDA, 2014, 2017a). The evaluation of the additional information reply will proceed normally and result in a delay of the registration procedure, even if the time prioritizing during the first examination of the dossier was taken into mind.

2.4.2. Registration target timelines

Applications for marketing authorization directed towards the Ethiopian pharmaceutical market must be reviewed by the Ethiopian food and drug administration. EFDA established deadlines for evaluating several categories of applications in 2016 and worked to evaluate applications in accordance with the deadlines (Table 2).

Table 2; Registration target timelines of EFDA, citizen's charter, 2016

No		Application type	Target timelines	
			Normal pathway	SRA pathway
1	Domestically manufactured products	New generic application	1.5 month and one hour	NA
		Renewal application	2 days, 1hour and 40 minutes	NA
		Variation applications	1.5 month and one hour	NA
2	Applications from abroad	New generic application	Three months, 5 days and 1 hour	17 days and 1 hour
		Renewal application	2 days, 1hour and 40 minutes	2 days, 1hour and 40 minutes
		Variation application	Three months, 5 days and 1 hour	17 days and 1 hour

However, according to recent studies, the EFDA's registration process for generic products varies from a few months to several years, with an average last decision time of 505 days for new applications under the standard registration pathway and 311 days for SRA applications under the expedited registration pathway (Mekonnen, 2020). This timeframe is a great deal longer than the one it established for itself, the Citizen's Charter, and most other comparable organizations in Africa

The Ghana Food and Drug Authority (GFDA), a regulatory organization with a maturity level of 3 in Africa, was shown to regularly accomplish desired registration timeframes between 2019 and 2021, however the actual registration time of EFDA turned out to be significantly longer. Between 2019 and 2021, the GFDA's median approval time for all products (including both novel active drugs and generics) varied from 137 to 232 calendar days. According to Owusu-Asante et al. (2022) over this time, the median approval times for shortened reviews varied from 84 calendar days in 2019 to 311 calendar days in 2021.

According to Owusu-Asante et al. (2022) the overall decision time for generic products during the 2019–2021 period in the full review pathway was consistent, ranging between 157 calendar days in 2019 (145 generics) and 175 calendar days in 2020 (209 generics), and decreased to 136 calendar days (322 generics) in 2021.

2.4.3. Scientific Assessment timeliness

The registration application will be evaluated in reverse chronological order from the day it was submitted to the authorities. Two assessors, either first and second assessors from inside the medical unit or an external assessor, evaluate scientific evidence submitted in applications in simultaneously for quality, safety, and efficacy. Although there is no set time limit for the scientific evaluation of applications, the system will direct assessors to the second assessor or last reviewer if necessary after they have submitted their initial assessment results. (EFDA, no date; www.efda.gov.et, no date)

Following verification by the reviewers of the assessment results and acceptance by the team leader of the drug registration unit, recommendations or inquiries for more information regarding quality data, clinical data, or administrative information will be given to sponsors. In order to respond to the suggestions, applicants who have received the FIR question letter must do so within 180 days of receiving it (EFDA, 2014). Assessors will consider the applicant's response once more before making a final determination. Two significant contributing causes for market authorization delays are the time it takes for a scientific review of an application and the amount of time it takes manufacturers to react to regulatory inquiries (EFDA, 2014, 2017b).

The International Institute for Regulatory Science's benchmarking research makes a distinction between the time the application spends with the agency and the time it spends with the sponsors within the allocated "company time." The research also suggests that in order to speed up the market authorization process, agencies should shorten both the time needed for the agency's scientific review and the firm to reply to requests for further information (Report, 2005).

For various NRAs across the world, a broad variety of approval periods and registration time constraints were observed. The WHO conducted research on the legal systems of ten nations, and the country reports show that time constraints for the registration process exist in each country with regard to the evaluation and communication of the outcomes of registration applications. Only Australia, Cuba, Cyprus, Estonia, Malaysia, and the Netherlands have time restrictions in their drug laws among the 10 nations covered by the study. Different time restrictions have been established in Australia, Malaysia, and the Netherlands for the registration of various product classes (new chemical entities, generic pharmaceuticals, and fast-track medications). All goods have a single time limit in Cuba, Cyprus, Estonia, and Venezuela. In reality, it typically takes six to 19 months to register a product containing a new chemical entity (NCE) in these nations, two to 18 months to register a generic medication, and two to six months to register a fast-track product (Wondemagegnehu and Sauwakon, 2002). According to Rasheed and Dixit (2015), the MHRA of the UK has 210 days from the day the MA application or dossier was submitted to complete the national procedure.

Registration approval times for generic products ranged from 12 to 24 months for ASEAN nations, 24 to 36 months for GCC nations, 7 days to 24 months for LATAM nations (Peru to Brazil), 6 to 24 months for the CIS (Russia and Belarus), and 8 to 24 months for Asia-Pacific nations other than ASEAN (Badjatya, 2013). According to Narsai and Williams et al. (2012), Badjatya (2013), Badjatya (2014), Badjatya (2015), Badjatya (2016), Badjatya (2017), Keyter et al. (2018), and other sources, the total regulatory median approval time by South African regulatory agency in 2017 was 1411 calendar days.

At the time of the study conducted by the International Institute for Regulatory Science (2004), the mean time from the receipt of the dossier to the beginning of the scientific evaluation was over 200 days for Canada, but just one day for CDER, USFDA. In Canada, applications are processed when resources become available, while in the US, the process allows the validation to be done concurrently with the evaluation and gives applicants 60 days to refuse to submit after receiving comments on their applications. In contrast to the US and Canada, where the outcome letter and marketing permission are interchangeable, there is a definite delay in Switzerland between the announcement of the review's outcome and the issuance of the license to market (Report, 2005).

Recently, both Congress and the media have focused attention on how quickly the USFDA approves generic medications. Original ANDAs must be approved, tentatively approved, or rejected by FDA within 180 days after receipt, according to federal law. The median review period for ANDAs that took more than 180 days to complete

was 217 days. No matter how quickly the other divisions of the US FDA completed their evaluations, Chemistry took longer to examine these initial ANDAs since they all had defects. As a result, FDA took longer to reject them. (Levinson, 2008)

2.4.4. Acceptable Document format

Before marketing medical products, pharmaceutical companies must submit drug registration application dossiers to the EFDA's Medicine Registration and Licensing Directorate (MRLD) online using the electronic registration information system (eRIS) and receive approval (EFDA, 2014, 2017a; Roth et al., 2018).

There are five modules in the CTD. Modules 2, 3, and 4 are meant to be universal for all locations, but Module 1 is region-specific. The CTD format was accepted as a mandatory format for registration submission requirements by the EFDA as a member of WHO in July 2003. The CTD format was also strongly recommended as the format of choice for new drug applications submitted to the FDA in the United States and the EU.

Text and tables must be created in accordance with CTD specifications so that they may be printed on both 8.5 x 11" (U.S.) and A4 (E.U. and Japan) paper. The left-hand border should be wide enough to prevent the binding technique from obscuring any information. According to the EFDA (2014), text and table font sizes should be in a size and style that are easy to read even after photocopying. For narrative material, a 12-point Times New Roman font is advised. The granularity document specifies that each page should be numbered. The first time an acronym or abbreviation is used in a module, it should be specified (European Medicines Agency, 2016).

2.5. Queuing analysis Theory

According to Rosenquist (1987; Bernard W. 2006), queue analysis is a mathematical approach for determining measures of performance for a queuing (waiting line) system based on factors that define the system. The average customer arrival and service time are used as the basis for decisions concerning waiting lines and their management. In queuing formulae, they are used to calculate operational parameters like the typical number of customers waiting in line and the typical length of time a client must wait in line. Depending on the kind of waiting line system being studied, several sets of formulae are employed (M and Palaniammal, 2019; Bernard W, 2006).

Queuing Fundamentals

In a simple queuing system, "customers" come at "servers" and request a service from one of them. It's crucial to realize that a "customer" need not necessarily be a human being; it might be any thing that is waiting for assistance. The "customers" in a "back-office" scenario, such as interpreting radiologic pictures, can be the images that are waiting to be read. In a similar vein, a "server" is any entity that renders a service (Green, 2016).

An elementary queuing system involves "customers" approaching "servers" and asking for a service from one of them. It's important to understand that a "customer" need not always be a human being; it may instead be anything waiting for service. The photos that are awaiting reading might act as the "customers" in a "back-office" situation, such as evaluating radiologic images. In a similar spirit, every entity that provides a service qualifies as a "server" (Green, 2016).

When a customer arrives, they must get in line if all servers are already occupied. While lines of people or objects standing in a queue are common, lineups can sometimes be invisible, as with phone calls or registration forms awaiting the appropriate service. The queue discipline is the policy that governs the sequence in which consumers in a line are served. The well-known first-come, first-served (FCFS) principle is the most prevalent discipline (Bernard W., 2006). In the majority of queuing models, it is assumed that there is an unlimited waiting room and that there is no cap on the number of clients who can be waiting for service. This may be a reasonable assumption if clients do not physically join a line, as in a contact center setting, or if there is a huge waiting area compared to the average volume of customers waiting for service. Even though there is no restriction on the waiting room's capacity, new entrants who perceive a long line may occasionally "balk" and refuse to join it (Bernard W, 2006; Green, 2016).

Finally, queues may be organized in various ways. In most cases, a *single line* that feeds into all servers.

Basic queuing principles and models

The majority of queuing theory is concerned with steady-state system performance. Consequently, most queuing models make the assumption that the system has been in operation for a long enough period of time with the same arrival rate, average service time, and other characteristics that the probabilistic behavior of performance measures like queue length and customer delay is independent of the observational period. (Green, 2016)

Delays, Utilization and System Size

Utilization, which is calculated as the average number of busy servers divided by the total number of servers multiplied by 100, is a crucial metric in queuing theory. Utilization is frequently viewed from a management standpoint as a gauge of production; as a result, a high utilization rate is regarded as desirable. Planning or

assessing capacity in a service system might benefit significantly from understanding basic queuing principles. First, there must be a tight difference between the average demand and the average total capacity, which is determined by multiplying the number of servers by the speed at which each server can serve consumers. In other words, the system will be "unstable" and the queue will keep expanding unless average usage is strictly less than 100% (Bernard W, 2006; Green, 2016).

The Poisson process

We must assume that the arrival and service processes are probabilistic in order to construct a queuing model. Arrivals are typically thought to follow a Poisson process, according to Green (2016). The inter-arrival time of applications or service requests, on the other hand, follows an exponential distribution. The exponential distribution's "memoryless" nature is a key characteristic. This indicates that the time of the following arrival is unrelated to the time of the previous arrival. Additionally, if the arrival process is Poisson, this characteristic results in the fact that the number of arrivals in any given time interval is independent of the number in any other non-overlapping time interval (Bernard W., 2006; Green, 2016). There are four distinct queue models (Rosenquist, 1987), and the multiple server single queue model appears to fit with the Ethiopian registration dossier review process as medicine registration applications are submitted through a single channel (eRIS) to the medicine registration team leader, who then distributes the applications to various assessors chronologically according to their arrival times. The submissions will then be evaluated by a number of assessors, who will submit criticism or recommendations to the team leader for consideration.

2.6. Research questions

The pressures on regulators in developing countries, to respond to the need for access to essential medicines for epidemics and other basic health services to the citizens become detrimental from time to time. In addition, regulators also need to proactively prepare and respond for regional and international trade related and political pressures. However, in the case of EFDA, there was no organized study done based on which to determine the structure and composition of the registration system for the best and effective pre-market assessment of drug products in Ethiopia based on predictable timelines. The present study aimed at answering the following research questions:

1. How well is the Ethiopian registration system functioning as compared to registration target timelines set in the citizens charter?

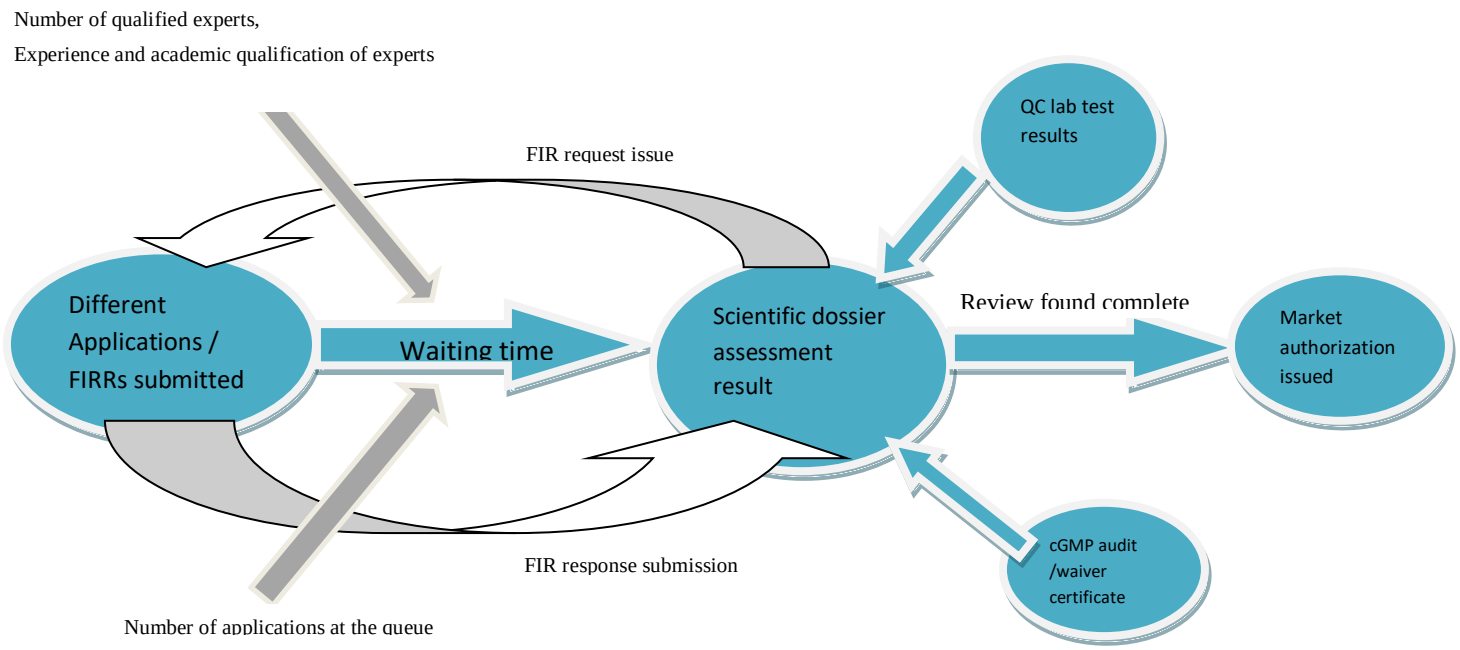
2. What is the average number of customers waiting in line and the average time a customer must wait in line in the queuing system at any specific point in time to get the intended service per customer in medicine unit, registration system?
3. What are the major reasons and impacts of low performance in the registration process?

2.7. Conceptual framework

Overall market authorization process involves three steps: GMP inspection or waiver certificate, QC lab test results and scientific dossier review results with possible repetitive conversations between the authority and sponsors during dossier assessment (Figure 1). From practical experiences, the rate limiting step in the registration process of EFDA is scientific dossier assessment process and hence, the aim of this study is to determine service application queues accumulated and consequently service waiting time by the applicants to get review results in the registration system as shown in figure1 below.

The quality and timeliness of scientific dossier review process will be affected by different factors .i.e. increasing number of applications, number of registration experts, academic qualification and experience of registration experts, documentation and quality of dossiers submitted etc.

Figure 1 market authorization approval process of the EFDA



3. Objective

3.1. General objective

To assess queue system performance of medicine registration process in the EFDA

3.2. Specific objectives

- To assess the current medicines registration system (I-register) of EFDA
- To compute system performance and service delivery operating characteristics of the Ethiopian medicine registration system using queue analysis model
- To evaluate the reasons for and impacts of the medicine registration system performance in EFDA

4. Methodology

4.1. Study setting and period

The study was carried out at EFDA head office; Addis Ababa from July 8, 2019 to July 7, 2020.EFDA is mandated, under the revised Proclamation No1112/2019, to ensure the safety, quality and efficacy of medicines. To this effect, the authority has been working on different regulatory activities. The medicines market authorization system is one of the top priority regulatory functions that have been implemented since the concept of pharmaceutical regulation in Ethiopia. In addition to the dedicated assessors, the authority has been using a national drug advisory committee for the assessment and registration of new medicines. This has evolved over the years to improve the medicine dossier evaluation system(Www.efda.gov.et, 19,4,2021). The authority is comprised of 16 directorates of which eight are administrative and supportive directorates and the rest eight are goal oriented directorates. The study is specifically conducted in the Medicines Registration and Licensing Directorate (MRLD) mandated on registration of medicines, medical devices and cosmetic products applied to get market authorization in Ethiopia. The data collection was done from March 15, 2021 to November 30, 2021

4.2. Study design

A mixed sequential explanatory study design employing quantitative and qualitative methods of data collection was followed for the study. For the quantitative study, an institution-based, cross-sectional review of applications submitted from July 8, 2019 to July 7, 2020 was conducted using single queue multiple server model of queuing analysis method. For the qualitative study, in-depth interviews was conducted with purposively selected registration experts from the authority, regulatory affairs from pharmaceutical importers, multinational company

representative offices and regulatory consultants working as local registration representatives of international companies using a semi-structured interview guide.

4.3. Population

4.3.1. Source population

The source population for the quantitative study is all services provided (applications submitted and reviewed) by medicine registration experts in the unit through electronic regulatory information system (eRIS) since the beginning of the current online application system, 2016. For the qualitative study, all medicine registration experts currently working in medicine registration unit of medicine registration and licensing directorate, EFDA, regulatory affairs from pharmaceutical importers, multinational company representative offices and regulatory consultants working as local registration representatives of international companies were included.

4.3.2. Study population

For the quantitative study, all services provided (applications submitted and reviewed) by medicine registration experts in the unit through electronic regulatory information system (eRIS) in every working week from July 8, 2019 to July 7, 2020 (2012 E.C fiscal year). For the qualitative study, all medicine registration experts currently working in medicine registration unit of medicine registration and licensing directorate, EFDA, regulatory affairs from pharmaceutical importers, multinational company representative offices and regulatory consultants working as local registration representatives of international companies were included.

4.3.3. Sample size

For the quantitative study, all services provided (applications submitted and reviewed) by medicine registration experts in the unit through electronic regulatory information system (eRIS) in every working week from July 8, 2019 to July 7, 2020 were collected from weekly reports in MRLD. Applications or service requests received by medicine registration and licensing directorate of EFDA within the study period, July 8, 2019 to July 7, 2020 were included in the study. For the qualitative study, all medicine registration experts working in medicine registration unit of medicine registration and licensing directorate at the time of the interview period, purposively selected regulatory experts from pharmaceutical importers, multinational company representative offices and regulatory consultants working as local registration representatives of international companies were included.

4.4. Inclusion and exclusion criteria

4.4.1. Inclusion criteria

For the quantitative study, all services provided (applications reviewed) by medicine registration experts in the unit through electronic regulatory information system (eRIS) in every working week from July 8, 2019 to July 7, 2020 were included. For the qualitative study, medicine registration experts with over 2 years of experience and currently working in the MRLD, purposively selected regulatory affairs from pharmaceutical importers, multinational company representative offices and regulatory consultants working as local registration representatives of international companies were included.

4.4.2. Exclusion criteria

Quantitative study

Applications reviewed during campaign works in collaboration with external assessors from different universities in the stated study period were excluded in the study.

Qualitative study

Medicine registration experts with less than 2 years practical experience and pharmaceutical importers found outside Addis Ababa were excluded in the study

4.5. Data collection and management

4.5.1. Data collection

Quantitative study

All services requested and provided (applications submitted and reviewed) by medicine registration experts in the unit through electronic regulatory information system (eRIS) in every working week from July 8, 2019 to July 7, 2020 were collected from weekly reports in MRLD through structured data abstracting forms . All applications submitted to the system in the stated study period were generated and collected from eRIS system by an IT manager of the authority to compute application arrival rates.

Qualitative study

In-depth interviews with purposively selected medicine registration experts were made with 12 purposively selected participants from EFDA, pharmaceutical importers, regulatory consultants and representative offices of

multinational companies based in Addis Ababa, by the principal investigator using structured interview guide. The interview guide comprises of demographic data of participants and questions for the general performance and specific strengths and weakness of the medicine registration system in Ethiopia with real time experiences.

The interviews were made at their regular office for the EFDA staff participants and different cafeteria and coffee houses selected as appropriate to conduct the interview and convenience to the participants from private companies. The interviews were recorded both in audio and written notes for few participants who were willing to be recoded and only detailed written notes were taken for participants who were not willing to be audio recorded. The interview was completed based on the saturation of the data after 12 interviews to avoid redundancy.

4.5.2. Data quality control

The data used for the quantitative part of the study was collected from updated electronic regulatory and information system (eRIS) currently being implemented in the registration system of the national regulatory authority of the country. To verify the feasibility of data abstraction tool, pretest was done before the actual data collection for necessary amendment. The interview questions were prepared in consultation with experts in the area and based on literature reviews.

4.6. Data analysis and interpretation

Quantitative study

The characteristics and nature of the queue in medicine registration system resembles and best fits with the multiple-server single queue queuing model with poisson arrival and exponential service times (M/M/S). Hence, excel queue template was used to compute the performance indicating operating characteristics. The queue analysis in excel queue template was carried out by providing the inputs for arrival rate, service rate and number of servers using these values; The performance measurement of a particular model such as Average server utilization (ρ), average number of customers waiting (Lq), average number in system (Ls), average waiting time (Wq), average time in the system (Ws), arobability of zero customers in system (P0), probability of exactly n customers in system (Pn) were executed(Saxena and Sharma, 2013) as illustrated in the results and discussion section.

Different formulae of operating characteristics of single server queuing system are indicated below

$P = \lambda/\mu$

$Ls = \lambda/\mu-\lambda$

$Lq = \lambda^2/\mu(\mu-\lambda)$

$Ws = 1/\mu-\lambda$

$Wq = \lambda/\mu(\mu-\lambda)$

λ = *Arrival rate*

μ = *Service rate*

P = Average server utilization

Lq = Average number of customers in the queue

Ls = Average number of customers in the system

Wq = Average waiting time in the queue

Ws = Average time in the system

There are four type of queuing model, which are single channel single phase system, single channel multiphase system; multiple channel single phase system and multiple channel multiple phase systems (Bernard W, 2006)

In the case of medicine registration system, in medicine registration and licensing directorate (MRLD), customers are registration applicants who may submit new, re-registration, post approval variation applications or FIR response to their application queries. The queue is waiting line of applications that forms to get services by the directorate(Rosenquist, 1987; Mardiah and Basri, 2013) and the system follows multiple server single queue system. Multiple server queuing system is slightly more complex than the single-server queuing system. It is the single waiting line being serviced by more than one server (i.e., multiple servers) (Bernard W, 2006). Multiple server model formulas, like single-server model formulas, have been developed on the assumption of a first-come, first-served queue discipline, Poisson arrivals, exponential service times, and an infinite calling population. The parameters of the multiple-server model are as follows:

λ = *the arrival rate (average number of arrivals per time period)*

μ = *the service rate (average number served per time period) per server (channel)*

c = *the number of servers*

c μ = *the mean effective service rate for the system, which must exceed the arrival rate*

The probability that there are no customers in the system (all servers are idle) is

$$P_n = \frac{1}{c!c^{n-c}}\left(\frac{\lambda}{\mu}\right)^n P_0, \text{ for } n > c;\ P_n = \frac{1}{n}\left(\frac{\lambda}{\mu}\right)^n P_0, \text{ for } n \le c$$

The probability of n customers in the queuing system is

$$P_0 = \frac{1}{\left[\sum_{n=0}^{n=c-1}\frac{1}{n!}\left(\frac{\lambda}{\mu}\right)^n\right] + \frac{1}{c!}\left(\frac{\lambda}{\mu}\right)^c\left(\frac{c\mu}{c\mu-\lambda}\right)}$$

The average number of customers in the queuing system is

$$L = \frac{\lambda\mu(\lambda/\mu)^c}{(c-1)!\,(c\mu-\lambda)^2}P_0 + \frac{\lambda}{\mu}$$

The average time a customer spends in the queuing system (waiting and being served) is

$$W = \frac{L}{\lambda}$$

The average number of customers in the queue is

$$L_q = L - \frac{\lambda}{\mu}$$

The average time a customer spends in the queue, waiting to be served, is

$$W_q = W - \frac{1}{\mu} = \frac{L_q}{\lambda}$$

The probability that a customer arriving in the system must wait for service (i.e. the probability that all the servers are busy).

$$P_w = \frac{1}{c!}\left(\frac{\lambda}{\mu}\right)^c \frac{c\mu}{c\mu-\lambda}P_0$$

Thematic analysis method was deployed for the analysis of qualitative data collected through key informant interviews.

Positionality statement

'The principal investigator of this research, Abebe Alamneh (B.pharm) was an employee of the Ethiopian food and drug Authority (EFDA) during the time of this study. However, it was tried to avoid potential biases using reflexivity with the interviewees explaining the purpose of the interview. On the other hand, the close understanding of the registration process helped the investigator to better understand quantitative data as well as the ideas discussed in the interview.'

4.7. Ethical considerations

Ethical clearance was obtained from the Addis Ababa University, School of pharmacy Ethics Review Committee. An official support letter from School of Pharmacy, Department of Pharmaceutics and Social Pharmacy was written and used to get permission for conducting the research in EFDA.

During data collection, participants were invited to participate voluntarily after explaining the purpose of the study and were informed that withdrawal from the study is possible any time. Participants were also assured that the information they provided will be kept confidential and will neither be transferred to any other third party nor be used for any other purpose other than academic purposes. Written informed consent was signed voluntarily by all participants before the actual data collection.

4.8. Operational definitions

Operating characteristics: are average values for characteristics that describe the performance of a waiting line system.

Service: Assessment of applications of any type submitted to medicines registration unit through the normal communication pathway.

Arrival rate: The frequency at which customers arrive at a waiting line according to a probability distribution

Service rate: The average number of customers who can be served during a time period

Queue: waiting line of applications that forms to get services by the directorate

System performance: A queue system performance of the medicine registration system in relation to achieving target timelines

5. Results

Application arrival rate

There were 668 normal new medicine registration applications(NMR),128 New SRA medicine registration application, 527 medicine re-registration applications(REN),250 post approval variation applications (VAR) and 617 responses for further information requested(FIRR) received in the year 2020 (Table 3).Total number of service requests submitted to the authority in the year was 2190. However, normal new medicine registration applications (NMR) received in the year were counted twice in terms of number of service requests as one new application is assessed by two experts sequentially, primary and secondary assessors at a time, and hence total service requests submitted to the medicine dossier assessment team were 2,858. Applications were assessed in their first come first served order except for SRA applications which has always priority of assessment time as per expedited market authorization strategy 2017

Table 3: Number of registration related request to the EFDA in the year 2020

Type of services	Code	Total number of services	Proportion
New medicine registration application	NMR	668 (serviced two times by 1st and 2nd assessors sequentially)	30.5%
New SRA medicine registration application	SRA	128	5.8%
Medicine re-registration application	REN	527	24.1%
Post approval variation registration application	VAR	250	11.4%
Medicine further information submissions	FIRR	617	28.2%
Total services requested in the year		2,858	

Normal new medicine applications both with and without bioequivalence study were the leading type of applications(30.5%) and SRA route new applications were the smallest number of applications (5.8%) received in the year. Renewal applications (24.1%), post approval variation applications (11.4%) and further information request replies (28.2%) were received.

Total number of services requested within 52 weeks of the year is 2858 and hence the average arrival rate of applications (λ) computed was found to be *10.99* services per day or *54.96* services per week.

Service rate determination

One full year weekly performance reports of the medicine dossier assessment team archived in the directorate were used as a data source to determine the average service rate of the team and the team members (servers). Customized tabulated data extracting tool designed for the purpose was used to collect data from 52 weekly performance reports of the 2020 fiscal year. There were 14 assessors working in the medicine assessment team in the fiscal year. Number of services reported by all assessors (servers) in the week, number of active servers in the week (assessors who reported non-zero number of services in the report are considered active in the week), number of idle days in the week and average weekly and monthly service rates per individual assessors were computed for each week, month and for the year accordingly *(Table 4)*

Table 4 Average weekly, monthly and yearly service rates per individual/day

Month	Number of working weeks	Date	Number of services provided in the week	Number of active servers in the week	Number of idle days in the week (Holidays, meetings,)	Average weekly service rate / individual/day	Average monthly service rate/individual/ day
July	Week 1	1/11/2011 to 5/11/2011	18	4	0	0.9	0.958
	Week 2	8/11/2011-12/11/2011	9	3	0	0.6	
	Week 3	15/11/2011 - 19/11/2011	48	7	0	1.37	
	Week 4	22/11/2011- 26/11/2011	43	9	0	0.96	
August	Week 5	29/11/2011- 03/12/2011	42	6	0	1.4	1.858
	Week 6	06/12/2011- 11/12/2011	70	4	0	3.5	
	Week 7	13/12/2011- 17/12/2011	28	5	0	1.12	
	Week 8	20/12/2011- 24/11/2011	44	6	0	1.47	
	Week 9	27/12/2011-1/13/2011	73	8	0	1.8	
Septe	Week 10	4/13/2011-2/1/2012	12	7	1	0.4	0.578

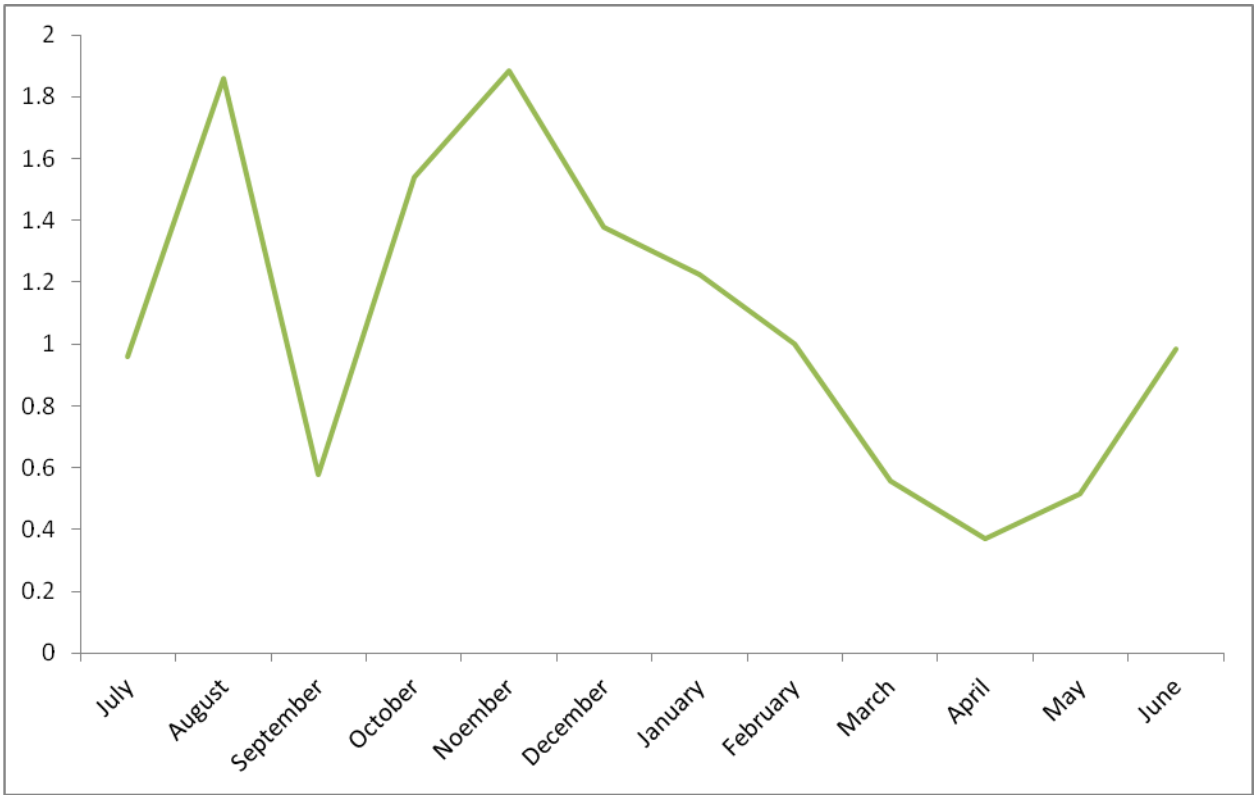
mber	Week 11	5/1/2012-9/1/2012	18	7	0	0.51	
	Week 12	12/1/2012-16/1/2012	21	4	0	1.1	
	Week 13	19/1/2012-23/1/2012	17	6	0	0.57	
	Week 14	26/1/2012-30/1/2012	11	7	0	0.31	
Octobe	Week 15	3/2/2012-7/2/2012	30	8	0	0.75	1.538
r	Week 16	10/2/2012-14/2/2012	50	8	0	1.25	
	Week 17	17-21/02/2012	77	7	1	2.75	
	Week 18	24-28/02/2012	49	7	0	1.4	
Nove	Week 19	1-5/03/2012	32	4	0	1.6	1.885
mber	Week 20	8-12/03/2012	106	10	0	2.12	
	Week 21	15-19/03/2012	61	7	0	1.74	
	Week 22	22-26/03/2012	94	9	0	2.08	
Decem	Week 23	29/03/2012-3/4/2012	39	8	0	0.98	1.378
ber	Week 24	6-10/4/2012	55	6	0	1.83	
	Week 25	13-17/4/2012	17	4	0	0.85	
	Week 26	20-24/4/2012	82	8	0	2.05	
	Week 27	27/4-01/05/2012	53	9	0	1.18	
Januar	Week 28	4-8/5/2012	37	7	0	1.06	1.225
y	Week 29	11-15/5/2012	54	8	0	1.35	
	Week 30	18-22/5/2012	57	10	0	1.14	
	Week 31	25-29/5/2012	54	8	0	1.35	
Februa	Week 32	2-6/6/2012	35	7	0	1	1
ry	Week 33	9-13/6/2012	42	10	0	0.84	
	Week 34	16-20/6/2012	25	9	0	1.16	
	Week 35	23-27/6/2012		Campaign works	1		
March	Week 36	30/6-04/7/2012	29	5	0	1.16	0.555
	Week 37	7-11/7/2012	17	6	0	0.57	
	Week 38	14-18/7/2012	9	7	0	0.26	
	Week 39	21-25/7/2012	8	7	0	0.23	
April	Week 40	28/7-02/8/2012	15	9	0	0.33	0.372
	Week 40	5-9/8/2012	15	12	0	0.25	
	Week 41	12-16/8/2012	20	12	0	0.33	
	Week 42	19-23/8/2012	22	12	0	0.37	
	Week 43	26-30/8/2012	35	12	0	0.58	
May	Week 44	3-7/9/2012	26	12	0	0.44	0.515
	Week 45	10-14/9/2012	36	12	0	0.6	
	Week 46	17-21/9/2012	32	13	0	0.5	
	Week 47	24-28/9/2012	37	14	0	0.52	
June	Week 48	1-5/10/2012	49	12	0	0.82	0.983
	Week 49	8-12/10/2012	88	13	0	1.36	

	Week 50	15-19/10/2012	80	13	0	1.24	
	Week 51	22-26/10/2012	27	11	0	0.51	
	Week 52		No services				
	Averages /Total		2039	8.3		1.01	1.01

Number of active servers in the week ranges from the minimum of three (21.4%) experts in the 2nd week and 14 (100%) experts at work in the 47th week of the year were identified. The average number of active servers in the year was found to be 8.3 (59.3%) experts out of 14 experts assigned permanently for the medicine dossier assessment team. The average service rate (μ) was found to be 1.01 services per day/individual and when multiplied by average number of active servers (c), the mean effective service rate of the medicine registration team (cμ) was 8.38 services per day. Hence, the medicine registration team was serving at the rate of 8.38 services per day while applications were arrived to the system and build a queue at the rate of (λ) 10.99 service requests per day

The service rate also showed significant seasonal variation as depicted in the *Figure2* below. The lowest service rate was recorded in April (0.372) while the highest service rate was recorded in November 2020 (1.885).

Figure 2: Monthly service rates of the registration system from July 8-2019 to June 7-2020



5.1 Data Computation, Analysis & Interpretation

5.1.1. Application of the Single-Queue Multiple Server Queue Formulae

Based on the above findings on the average arrival rate, queue length, mean effective service time and queue discipline, the analysis of the queuing system was executed as follows using **single-queue multiple servers model (M/M/8)**

λ = 54.96 services per week (10.99 applications per day)

μ = 5.05 services per week (1.01 services/day)/individual

c = 8.3 servers (functional servers on average)

$c\mu$ =41.91 services per week (8.38 services/day)

As computed above, the mean arrival rate (λ) of the system was found to be 10.99 services per day or 54.96 services per week and the mean effective service rate ($c\mu$) of the system was computed as 8.38 services/day or 41.91 services per week. Based on these basic operating characteristics the above queue performance characteristics were supposed to be computed easily using software called ***Microsoft Excel Queue Template M|M|c***. However, according to Queue Analysis theory, the mean effective service rate ($c\mu$) must be greater than mean arrival rate (λ) of the system for the system to be functional and manageable. That means, customers must be served faster than they arrive, or an infinitely large queue will build up and the system will go unmanageable as a result.

> In other words *"the ratio of the arrival rate to the service rate must be less than one for the system to be functional and manageable based on the queuing theory assumptions. The server must be able to serve customers faster than they come into the service center in the long run, or the waiting line will grow to an infinite size, and the system will never reach a steady state."*(Bernard W, 2006)

However, in our case the computed mean effective service rate ($c\mu$) (8.38 services/day or 42.91 services per week) is much less than mean arrival rate (λ)(10.99 services per day or 54.96 services per week). The results of the stated operating characteristics showed that mean arrival rate of the registration system is 23.74% higher than the mean effective service rate of the system and hence, the queue performance characteristics can never be estimated using the above formulae or Microsoft Excel Queue Template M|M|c. According to the interpretation in the queue analysis theory, it means the system is not well functioning and/or unmanageable to provide services as predicted and steady state service timelines and other steady state average performance characteristics could not be achieved.

5.2 Results of the Qualitative Study

5.2.1 Characteristics of participants

Twelve participants participated in the interviews out of whom four were from pharmaceutical importers, two from health regulatory consultant offices, two from local representative offices of the multinational pharmaceutical manufacturer companies, four were medicine registration directorate, EFDA. Ten participants were male, all participants have first degree in pharmacy and two had additional master's degree level education in business administration (MBA). In terms of professional background, all were pharmacist's at-least in their first degree and currently working as regulatory expert at their respective organizations. The average period of participants who stayed on their position at time of interview was six years that ranges from 4 to 9 years.

Table 5: Demographic characteristics of participants in the key informant interview

Characteristics		Number
Sex	Female	2
	Male	10
Age (in Years)	25-35	5
	Above 35	7
Highest academic degree completed	First Degree	10
	Second Degree and above	2
Profession	Pharmacist	12
	Other	0
Place of work (Organization)	Pharmaceutical importers	4
	Regulatory consultant offices	2
	Ethiopian food and drug authority	4
	Representative office of multinational company (Ethiopian regulatory representative for Ethiopia)	1
	Representative office of multinational company (regulatory representative for East Africa	1
Role/position in the	Junior	3

organization	Senior	9
Length of service in current role/position	1-5	3
	>6	9

5.2.2 Major themes identified in the analysis

The analysis identified four major themes in the areas of registration target timeline achievement and competency, contributing factors for long registration timeliness, registration impact on the current healthcare system and product shortage in the market and view of national and international pharmaceutical companies to the registration system and their level of satisfaction.

5.2.2.1 Registration target timeline achievement and competency

Overall, there was consensus among participants about current context of the registration system and its impact and value in the pharmaceutical supply chain and healthcare system of Ethiopia. Almost all participants reflected that the registration system is passing through rigorous and promising improvement as compared to the previous practices, especially after the introduction of the online application portal, electronic information and regulatory system (eRIS). Recent strategies to expedite registration process like SRA pathway and registration of low risk medicines were appreciated by the participants mentioning that it is a wise move by most regulatory authorities to cascade applications according to its risk level. However, according to participants, the system is still suffering from significant consistency problems, not only in the registration timeline but also in decision making. Respondents' from the applicant side stressed that the registration system is hardly predictable about its registration timeline and that even affects their trust to the employer. Moreover, though participants appreciated the initiative, they practically mentioned serious gaps in the implementation of the recognized SRA pathway mentioning that they are facing challenges in communications with experts as the authority has many requirements yet not aligned with the recognized countries procedures. For example, according to a respondent from a multinational pharmaceutical company for east Africa, European countries have no procedure for renewal of MA unless there is post approval variation from the approved product detail. They rather put a strong post market vigilance system to follow it in the market. EFDA; however, requests renewed market authorization certificate from SRA country to waive the GMP certificate and due such inconveniencies, the country is missing opportunities that could improve access and availability of essential medicines.

"…. The MA issued from most of EU countries may have no validity date and renewal is required if only there is some variation on the approved product. EFDA requested me to bring renewed MA just because MA was issued before 5 years and rejected my application" [regulatory representative for a multinational pharmaceutical company for East Africa]

Participants argued that there are also unnecessary rejections currently due to nontechnical assessment results and incompleteness of the application. For example, in appropriate rout of application could have been corrected in the system itself than rejecting the application as it causes unnecessary extension of the approval process. The following quotes depict participants' opinions about the situation of the current registration in Ethiopia.

"……For example, from my three applications of similar product with different strengths submitted at the same time, two of them were approved in two months time while the rest one took me two years to complete and get it approved"[senior regulatory expert from a multinational pharmaceutical company]

"……Most of the time, companies request us to give them expected approval timeline and registration plan in the contract agreement or prior discussion. However, due to the EFDA registration system is highly unpredictable and inconsistent; it's a big challenge for us to give them the registration timeline"[Senior regulatory consultant from a private regulatory consultant firm]

"….most of the time we couldn't get it registered in the timeline we promised and companies will take it as our limitation on follow up and execution problems" [Registration expert from a multinational pharmaceutical company]

Respondents from medicine registration and licensing directorate of EFDA also agree on the long timeliness of the registration system. In addition, participants noted that the short assessment time allocated for a single application is highly affecting the assessment quality and that in turn is a challenge in achieving the authority's mission and objectives.

"……but the time allocated for each assessor to assess applications is too short to make well informed and scientifically sound evidence based decision" [senior medicine dossier assessor from EFDA]

5.2.2.2 Contributing factors for the long registration timelines

The recurrent idea that was identified under this theme was extensive workload and huge backlog of applications as the main reason for the registration system being unable to deliver services as per established target timelines

on the citizen charter of EFDA, 2016.All respondents, irrespective of where they are working, agree that there is workload over the capacity of the registration team under normal circumstances. However, participants have varied views towards the reason to the workload and backlog in the system. Participants from medicine registration and licensing directorate, EFDA emphasized that the reason for the extensive workload in the current registration system is shortage of manpower in the medicine registration team. It was indicated that medicine registration team comprises of 14 full time medicine dossier assessors at the time of this interview. Most of respondents from the applicant side, on the other hand, have a different view for the reason of the registration workload and backlog. They rather believe that the workload and backlog accumulation mainly arises from the limitation of the registration system itself. They divided reasons for the delay of assessment and backlog in to two broad categories as reasons from the authority side and reasons from the applicant side.

A. Reasons from the authority side

According to participants, the problem starts from the registration directorate itself as registration experts do not spend their full time on dossier assessment due to different meetings, trainings, GMP audit and other domestic and international travels etc; hence, backlogs will be accumulated as a result. Moreover, there is wide variation in execution rate between dossier assessors in the registration and licensing directorate due to negligence and personal limitation on technical capability and decision-making process.

The other reason they mentioned was unnecessary further information requests and irrelevant conversations thereof. Majority of participants agree that sometimes, irrelevant further information and documentations which have less significance or no value to the decision making process are requested by the authority repeatedly. When these further information requests were replied by the applicant, it will be automatically submitted to the assessor for another round assessment and these similar conversations continue with the applicant, the registration system will get overwhelmed with repeated review for a single application. Respondent quotes supporting these are as follows.

> *"...Yes, we frequently face with huge backlog of application accumulations and that's why we call for campaign dossier assessments two or three times a year in collaboration with different universities."*[Senior dossier assessor at MRLD, EFDA]

> *" ... Application flow is generally decreased since 2018 due to the policy change of limited agents to unlimited agents by EFDA and the Covid-19 global pandemic in 2019. But still the registration timeline*

couldn't be met as per the target timeline set."[Former registration team leader and dossier assessor at MRLD, EFDA]

"….The interpersonal difference of assessors also matters most. Few assessors deliver rapidly while others forget it for long" [Technical manager and regulatory expert from a local pharmaceuticals importer]

"*….I saw few of my applications took one months and more on the "Under Review" status. This shows there is lack of follow up to the assigned assessors by the director or team leaders"*[regulatory expert from a local representative office of multinational company]

"*…The other reason for the workload is too many registration requirements for all medicines and irrelevant, sometimes editorial and unrelated further information and documentation requests, just as a formality,."* [Regulatory expert from a Pharmaceutical importer]

".... I was wondering that, the further information requested were significantly different for the same product differs only in strength" [senior regulatory expert from a multinational pharmaceutical company]

Moreover, significant number of respondents depicted that they don't share the letter generated and issued from EFDA directly to their company (international manufacturer), they rather send email message of what is requested, transcribing into meaningful and sometimes polite sentences. According to participants, this is because; EFDA has no standard for the way of communication and request letters may contain aggressive words (sometimes near to insults), warnings while the cases are simple to manage and poorly organized sentences transferring vague messages etc.And this frustrates and sometimes disappoints international applicants they represent. Unlike others, some respondents told that they directly download and send the generated further information request letter but faced bad reactions from their international companies and even some companies ignore the application as a result than replying to the request. Hence, many products fail to be approved and that in turn, causes shortage of product options in the market against the objective of the authority.

"I have received a further information request letter saying 'you have been submitting creepy dossiers for the last twenty products… so authority will take measure…"" [Regulatory expert from a pharmaceutical importer]

"...Companies having vast global experience in the area, few companies don't even expect such communication from a country's national regulatory agency. Even don't believe if the letter is really from

the authority. Some say its 'disrespectful'."[Owner and senior regulatory expert from a regulatory consultant firm]

As a result, most of the time, the direct regulatory-industry communication is interrupted by the local representatives and getting to be indirect with transcription. This, in turn has a negative impact in full understanding of the regulatory requests by the industry regulatory affairs experts who are preparing replies and may end up with misguided and unrelated replies which may lead to another round of further explanation request.

B. Reasons from the applicants side

Applicants have also significant contribution to the unnecessary and unreasonable workload over the authority registration system. According to participants, one of the major reasons for the 'further information requests' by the authority is product dossier incompleteness which were supposed to be prescreened by the applicants regulatory experts before submission. Incomplete or low quality dossiers will be the first reason for the repetitive further information requests by the assessors. This, in turn leads to numbers of unnecessary request-reply cycles of the same product causing high workload.

The other reason is negligence and lack of technical skills in using the application submission portal, the electronic and regulatory information system (eRIS). A significant number of simple, most of the time editorial further information requests are caused by this issue but still accounts significant contribution for the delays in application approvals and creating artificial workload over the registration system. According to participants, this comes from less understanding and priority given to the regulatory activities by importers representing international manufacturers for the registration of products and less attention given to the gap by EFDA itself. It is commonly seen that non-healthcare professionals including those in IT, Accounting, Law etc are working as a regulatory representatives of importers and are processing submission of applications, further information requested replies (FIRR) and other in person communications with the experts.

"…there is less understanding of the regulatory laws, process and documentation by local representatives. Due to this, there is usually long and redundant further information request-reply cycle. I have come across application with up to five request and replies conversation" [Regulatory expert from a pharmaceutical importer]

"....But as of me, not only non-health related professionals but also pharmacists can't do it unless they took additional training regarding regulatory processes or have no industry experience"[Technical manager and regulatory expert from pharmaceutical importer]

"...I remember an occasion where the registration pre-screener annoyingly told the representative to go to her office and come back with well educated professional" [Regulatory expert from a pharmaceutical importer]

5.2.2.3. Impact of the registration system on access, availability and public confidence to the products

All respondents agreed and appreciated the significant impact of registration in assuring availability of quality medicines in the market. The current registration process by EFDA, including the GMP manufacturing site audit and sample quality testing is trusted by majority of the respondents to assure availability of quality medicines in the healthcare system but practically, they have reservations with the idea they witnessed. When respondents reply to the question for the criteria of drug selection for their personal or close family use, almost all participants, irrespective of where they work, responded that they do not consider registration approval as the only criteria to use. They rather see the manufacturer profile, country of origin, brand names and so forth to select products for personal use among many registered options.

"...I always prefer drugs manufactured by my own company abroad whom I represented as I know how careful they are for quality. If no, I prefer taking European brands for my own and family use" [Regulatory representative from a multinational pharmaceutical company]

"...to be honest my preference criteria is not registration only both for myself, my children and other family members. I see brands, country of origin as additional criteria. Especially for my children, I care most"[senior medicines dossier assessor from MRLD, EFDA]

Even though there are different strategies being implemented by EFDA to mitigate the impact of registration time on the shortage of medicines in the market, majority of participants agreed that long registration approval time has its own impact on the product shortage in the market. According to respondents, even though long registration time for all application types contributes for the shortage, majority of them emphasized that the impact on products familiar in the market causes a devastating effect as products are already have high demand in the market. In this regard, renewal applications and post approval variation applications were repeatedly mentioned to cause panic and serious market disturbances even when disappeared for a short period Participants from the

applicant side depicted that they usually receive calls from aggressively searching prescribers, chronic patients and caregivers when their products get out of market at the time of renewal and variation applications as suppliers couldn't market the product before getting approval certificates in the country and even the eRIS system sacks the product from the registered products database so that importers can't get purchase order approval as a result.

> *"...In my opinion, renewal registration process is the most unnecessary process as the product is already approved by EFDA. It's better to strengthen post market surveillance system and put strong system to track variations"*[Owner and technical manager of regulatory consultant firm]

> *"Re-registration is just time wasting. For example in Tanzania, as soon as you pay the retention fee and submit the documents to the system, you can sale your product and TFDA may evaluate the documents in its own convenient time"*[regulatory representative from a multinational pharmaceutical company for east Africa]

> *"....I had a variation application which took 2 years to get approved. I urge the authority to give similar priority as renewal to variation applications as well*. [Senior regulatory representative from a multinational company for Ethiopia]

5.2.2.4 Perspectives and level of satisfaction of local and international companies on the registration

Participants from the applicant side were asked two questions regarding their attitude towards the current EFDA registration system and general view and satisfaction of their clients (international pharmaceutical manufacturers) towards the registration process. Respondents were open enough to tell that majority of the international companies think that EFDA is highly bureaucratic in its registration system and requirements. This is due to relatively stringent requirements as compared to most of other African countries, unreasonably long assessment timeline and long further information-reply cycles with sometimes illogical queries.

Unlike the international manufacturers view, participants from local representatives want EFDA to improve the inconsistencies stated and also stressed that the agency need to be stringent and careful in the registration system as it is a public health security issue. Participants complained that, EFDA has a problem of considering them (importers and registration local representatives) as applicants citing that they are a partner and stakeholder in the pharmaceutical regulation sector sharing responsibilities in assuring quality of medicines in the market.

"….when we informally discuss, companies say that your regulatory authority is too stringent and bureaucratic" [Regulatory representative from a pharmaceutical importer]

"… mostly not satisfied in the registration process. Even sometimes, they (manufacturers) tell us in diplomatic words that the authority is very stringent and the registration process is too long" [senior regulatory expert from a pharmaceutical importer]

6. Discussion

The study has integrated findings from both quantitative and qualitative analysis for more complete understanding of the system and adequately addresses the research questions. Results from the queuing analysis of the EFDA application flow to the registration team and current registration process service rates were interpreted based on the queue analysis theory that aimed to answer the major research objectives. The in-depth interviews with key informants offered to further elaborate the findings from the quantitative study.

The results found in this study could be interpreted based on queue analysis theory as, in the current registration system of EFDA, the queue of applications will never reach a steady state. This means, the waiting line grows to an infinite size as time goes on and this is a characteristic of unmanageable queuing system. Hence, the system is not well functioning to provide services in the predictable steady state service timelines and other steady state average performance characteristics could not be achieved unless measures are taken accordingly to correct the registration system in different strategies. Moreover, the authority will hardly be able to achieve any target timeline set consistently in the citizen's charter in its current registration system.

The fact in this finding agrees with the practical observations seen in the registration system and previous similar studies done in the area. The registration time for generic products in EFDA fluctuates from few months to years with average last decision time of 505 days for new application in normal registration pathway and 311 days for expedited registration pathway of SRA applications(Mekonnen, 2020).These average timelines show that the EFDA timeline is significantly higher than its own target value on citizens charter of 17 days for SRA to 3 months for new standard applications(EFDA, 2016). The findings are also higher compared to the timeline of the MHRA, United Kingdom accounting for 210 days from the date of submission of the MA application or dossier(Rasheed and Dixit, 2015) and for Belarus with 180 working days(Badjatya, 2013).

However, the averages approximately agree with registration timeframe for generic products registration approval for ASEAN countries 12-24 months, GCC countries24-36 months, LATAM countries varies from 7 days in Peru

to 24 months in Brazil, CIS 6-24 months, Russia 18 months, Asia pacific except ASEAN 8-24 months (Badjatya, 2013).

Results of the qualitative study also supported that the current registration system is rarely achieving the target timelines promised on the 2016citizen's charter of EFDA leading to application queue built up repeatedly. As a result, EFDA frequently calls for campaign product dossier assessment programs by out sourcing to different universities in the country aiming to clear accumulated queue of registration applications as part of the *zero backlog flagship initiative*. Though this in turn, is believed to pose another challenge on product dossier assessment quality as most of the time new pharmacists are employed as an external assessor after getting induction training on basic dossier assessment.

It was also revealed that applications spend majority of the time waiting for their turn to be assessed rather than in the actual assessment practice due to the system insufficiency to uphold the current service flow to EFDA registration system. Previous studies showed that, many stringent regulatory authorities have passed through similar challenges previously and gradually become who they are now. The study done 20 years back in Canada showed the mean delay from receipt of the dossier to start of the scientific assessment was almost 200 days for Canada, at the time of the study done by international institute for regulatory science (2004). But the reason for this is different as in Canada; applications are picked up when resources become available. In the US, only a single day is spent before assessment for CDER, USFDA and the procedure lets the validation be carried out in parallel with the assessment, and allows 60 days for a refusal to file after application validation feedback was issued(Report, 2005).

The findings of the present study revealed that weak performance of the registration system with respect to the target timelines is multi-factorial in which the factors can generally be categorized in to two broad categories. As discussed above, participants from the medicine registration and licensing directorate, EFDA, depicted that the reason for the extensive workload in the current registration system is shortage of skilled manpower in the medicine registration team. It is known that medicine registration team comprises of 14 full time medicine dossier assessors at the time of this study. However, according to most of participants from the applicants, the workload over the system is likely to be artificial created due to the internal and external factors in the registration system.

Key informants from importers and other applicants rather believe that the workload and backlog mainly arises from the limitation of the registration system itself. Participating in other parallel regulatory functions, field visits

and travels, and personal negligence of the experts were mentioned in the reason for not spending full time on dossier assessment by experts as the first reason for accumulation of backlogs. The other agreeably mentioned reason by the applicant side participants that has a significant contribution for the workload and backlog was unnecessary and irrelevant further information requests, substandard and poor communication practices with the applicants and irrelevant conversations thereof. These findings were also supported by the quantitative finding as the average service rates showed high seasonal fluctuations (F*igure 2*) and the annual average active servers in the year was 8.3 out of 14 experts. This means, on average, only 59.3% of the total medicine full time assessors were found at their regular dossier assessment work throughout the working weeks of the year. Repetitive further information request-reply cycles and inconsistent and disorganized query request letter communications were found to have equivalent contribution in creating the workload (*Figure 2*). Due to non-standard words in communication letters, majority of the respondents revealed that they are unlikely to share further information request letters directly to the company they represented rather and are often forced to send a transcription email of the requested information. Such indirect communication of EFDA with the manufactures, in turn may have a negative impact in full understanding of the regulatory requests by the industry regulatory affairs experts who are preparing replies and may end up with misguided and unrelated replies which may lead to another round of explanation request.

The recent improvements made by EFDA to expedite the registration process; facilitated regulatory pathway for low risk medicines and reliance based assessments for SRA approved products were well appreciated by the participants. However, non-aligned requirements of the reliance pathway with the individual national procedures of the recognized agencies are still causing significant challenge in the registration process. Moreover, due to such inconveniencies, essential medicines are missing or lagging to enter into the local market.

Applicants have also significant role to cause the system busy. Incomplete or low quality dossiers are the primary reason for the repetitive further information requests by the assessors, according to in-depth interview findings. In addition, negligence and lack of technical skills in use of the application submission portal, the electronic regulatory information system (eRIS) by the applicants causes a significant number of simple and editorial further information requests. This, in turn leads to numbers of unnecessary request-reply cycles of the same product. It was also reported that non-healthcare professionals without adequate training are working as a regulatory representatives for importers and are processing submission of applications, further information requested replies (FIRR) and other in person communications with the experts. Further, long approval time in the registration

process has been associated with the long replies time [company time] taken by the applicants to submit the requested documents. The time frame of EFDA registration system, elucidated by previous study shows, those query responses were submitted by applicants after 567 days on average, implying that after further information released applicants took a long time(Mekonnen, 2020).

Respondents agreed and appreciated the significant impact of registration in assuring availability of quality medicines in the market. The current registration process by EFDA, including the GMP manufacturing site audit and sample quality testing is trusted by majority of the respondents to assure availability of quality medicines in the healthcare system. However, even though, there are different mitigation strategies being implemented by EFDA to mitigate the impact of registration time on the shortage of medicines in the market, majority of participants agreed that long registration approval time has its own impact on product shortage in the market. Majority of participants emphasized that the impact of registration time on the product familiar in the market causes a devastating effect on the market as products are already in higher demand. In this regard, renewal applications and post approval variation applications were repeatedly mentioned to cause panic and serious market disturbances even when disappeared for short period in the market.

Other countries experience showed that the insufficiency to provide services in the promised timelines and non-consistent service provisions may end up with low customer satisfaction, complaint and sometimes, legal subjugation for different service standards. USFDA's timeliness in approving generic drugs has recently been a topic of scrutiny by both Congress and the media. Federal law requires that FDA approve, tentatively approve, or disapprove original ANDAs within 180 days of receipt(Levinson, 2008).

7. Limitations of the study

This study applied multiple server single queue model of queuing analysis for the medicine dossier scientific review process in the registration process of EFDA assuming that queue of applications follows an infinite calling population, a first-come-first-served queue discipline and followed poisson distribution arrival rate, exponential service times as that of the assumptions of queue analysis method. However, EFDA has few cases where application queues are not served exactly in first-come-first-served queuing discipline for the cases of expedited registration procedures as explained in the Ethiopian medicine registration guideline(EFDA, 2014).

In addition, Ethiopia and the world general situation and business environment was overwhelmed by the Covid-19 pandemic in the study period, July 8, 2019 to July 7, 2020 of the research. The application flow, hence, may be affected and have some deviation resulting in some level of limitation to the

8. Conclusion

The results from this study showed that EFDA is generally facing significant challenges to meet registration timelines set in the agreed citizen's charter of 2016. Moreover, the system has relatively longer and unpredictable registration time as compared to the international best practices by agencies operating with and above the WHO maturity level 3 regulatory standards. In-depth interviews indicated that the long and unpredictable registration time might have a significant contribution in affecting the availability and affordability of essential medicines in the market, especially when coupled with a potential decrease in registration applications for fear of the long waiting time and complex process.

9. Recommendation and Policy Implications

Based on the findings in this research, the following recommendations are drawn for system strengthening and addressing existing limitation of the regulatory authority:

For EFDA:

A) Internal system strengthening:

It's recommended to improve service rate as an important variable to focus on in this case, and can be managed through appropriate system strengthening measures in the three major pillars of the system:

i) People;

- Allocating sufficient trained manpower in the registration system based on appropriate researches and assessments to successfully uphold the flow of applications.
- Address the training and continuing education needs of assessors to continually improve the review and ensure that assessors acquire international updated technical expertise.
- Initiate and enforce appropriate legislations for the applicants to hire well trained regulatory experts enabling appropriate submission of applications.

ii) Process

- Avoiding unnecessary and irrelevant further information request-reply cycles and artificial workloads created thereof through standardizing the assessment release procedures,
- Standardizing direct letter communications with standardized formats, templates and review schemes before released to applicants and avoid intermediate communication chains, unnecessary translations in the communication channels through agents having competing market interests
- Expanding trust based facilitated regulatory pathways and risk based assessments to expedite the assessment rate and registration process in general and aligning documentation requirements with the standard process flow, certification schemes, publications and documents disclosure policies of respective recognized stringent regulatory (SRA) agencies.
- Avoiding repetitive assessments of the same API for different formulations via developing approved national API database

iii) Technology

- Continually updating the submission portal, eRIS to accommodate varying nature of applications, assessment templates and decision making process.

B) **Advocacy and collaboration in the sector**

The regulatory system should play its pivotal role in enhancing local production of pharmaceuticals; create favorable regulatory landscape to enhance the attractiveness of the pharmaceutical market in the country via;

- Strong advocation and strengthening collaboration with regional and international agencies towards regulatory reliance and harmonization
- Proactive review of the upcoming global trade related initiatives and making necessary arrangements and regulatory preparedness accordingly for the best use of associated opportunities to enhance the country's pharmaceutical market.

Applicants

Applicants who submit registration applications seeking marketing authorization should also contribute in the system strengthening process of Ethiopian regulatory system by allocating appropriately trained regulatory affairs professionals as a regulatory focal person. Appropriate follow up of applications, timely and clear responses submission and proper understanding and communication to regulatory queries are few responsibilities.

References

Ahonkhai, V. et al. (2016) 'Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries : A Case for Change and a Framework for Optimized Product Market Authorization'. *Plos one* 11 (11):, pp. 1–12. Available at: https://doi.org/10.1371/journal.pone.0166515.

Badjatya, J.K. (2013) 'Overview of Drug Registration Requirements for Pharmaceuticals in Emerging Market', *Journal of Drug Delivery and Therapeutics*, 3(2). Available at: https://doi.org/10.22270/jddt.v3i2.466.

Bate, R., Mooney, L. and Hess, K. (2010) 'Medicine registration and medicine quality : a preliminary analysis of key cities in emerging markets'. *Research and Reports in Tropical Medicine*: pp. 89–93. Available at: https://doi.org/10.2147/RRTM.S15199.

Zaidi, S. M. JunaidIII, B. W. Taylor (2006) Introduction to Management Science. *The Journal of the Operational Research Society* ; Prentice Hall: P 174

Ethiopia food and drug Authority (2014) guideline for registration of medicine. Third edit. Addis Ababa, Ethiopia: EFDA.

Ethiopia Food and Drug Authority ; EFMHACA Citizens charter (2016). Addis Ababa, Ethiopia.

Food, Medicine and Health Care Administration and Control Authority of Ethiopia (2017) 'Expediting Medicine Market Authorization Strategy'.

Ethiopia Food and Drug Authority application submission portal 'Electronic regulatory information system (eRIS) (accessed on 16 may 2021). Available at: www.eris.efda.gov.et.

European Medicines Agency (2016) 'EMA/CPMP/ICH/2887/1999 - ICH guideline M4 (R4) on common technical document (CTD) for the registration of pharmaceuticals for human use-organisation of CTD', 4(June 2016). Available at: www.ema.europa.eu/contact.

Green, L. V. (2016) Queueing theory and modeling, Handbook of Healthcare Delivery Systems. *Graduate School*

of Business,Columbia University,New York; P 1-16. Available at: https://doi.org/10.1201/b10447-20.

Hill, S. and Johnson, K. (2004) 'Emerging Challenges and Opportunities in Drug Registration and Regulation in Developing Countries', *Access to Medicines*, (May), p. 47.

International Conference for Harmonization (ICH) official website . Available at: https://www.ich.org/page/ctd (Accessed: 12 January 2023).

Kelesidis, T. et al. (2007) 'Counterfeit or substandard antimicrobial drugs: A review of the scientific evidence', Journal of Antimicrobial Chemotherapy, 60(2), pp. 214–236. Available at: https://doi.org/10.1093/jac/dkm109.

Keyter, A. et al. (2018) 'The Regulatory Review Process in South Africa : Challenges and Opportunities for a New Improved System', 52(4), pp. 449–458. Available at: https://doi.org/10.1177/2168479018776649.

Keyter, A. et al. (2020) 'Implementation of a Framework for an Abridged Review Using Good Reliance Practices: Optimising the Medicine Regulatory Review Process in South Africa', *Therapeutic Innovation and Regulatory Science*, 54(5), pp. 1199–1207. Available at: https://doi.org/10.1007/s43441-020-00144-0.

Khadem Broojerdi, A. et al. (2020) 'The World Health Organization Global Benchmarking Tool an Instrument to Strengthen Medical Products Regulation and Promote Universal Health Coverage', *Frontiers in Medicine*, 7(August), pp. 1–7. Available at: https://doi.org/10.3389/fmed.2020.00457.

Levinson, D.R. (2008) 'Department of Health and Human Services inspector general t he food and drug administration ' s g eneric d rug r eview p rocess', (June).

Lilly, E. et al. (2004) 'National survey of the impact of drug shortages', *Am J Health-Syst Pharm*. 61, pp. 2015–2023.

M, S.S. and Palaniammal, S. (2019) 'An Ann Simulation of Single Server with Infinite Capacity Queuing System', *International Journal of Innovative Technology and Exploring Engineering*, (12), pp. 4067–4071. Available at: https://doi.org/10.35940/ijitee.

Mardiah, F.P. and Basri, M.H. (2013) 'The Analysis of Appointment System to Reduce Outpatient Waiting Time at Indonesia ' s Public Hospital', *Advances in Mathematics: Scientific Journa*l. 3(1), pp. 27–33. Available at: https://doi.org/10.5923/j.hrmr.20130301.06.

Mekonnen, S. (2020) 'Assessment of factors influencing medicine market authorization process in Ethiopia', Addis Ababa University, pp. 1–9.

Narsai, K., Williams, A. and Mantel-Teeuwisse, A.K. (2012) 'Impact of regulatory requirements on medicine registration in African countries - perceptions and experiences of pharmaceutical companies in South Africa.', *Southern med review*, 5(1), pp. 31–7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23093897%0A http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3471191.

Ndomondo-Sigonda, M. et al. (2017) 'Medicines Regulation in Africa: Current State and Opportunities', *Pharmaceutical Medicine*, 31(6), pp. 383–397. Available at: https://doi.org/10.1007/s40290-017-0210-x.

Nyika, A. et al. (2022) 'Importation and distribution of unregistered medicines in the public sector: similarities, differences, and shared challenges among Southern African Development Community (SADC) countries', *BMC Health Services Research*, 22(1), pp. 1–7. Available at: https://doi.org/10.1186/s12913-022-07995-3.

Owusu-Asante, M. et al. (2022) 'Evaluation of the Food and Drugs Authority, Ghana Regulatory Review Process: Challenges and Opportunities', *Therapeutic Innovation & Regulatory Science*. Available at: https://doi.org/10.1007/s43441-022-00478-x.

Rasheed, A. and Dixit, M. (2015) 'Regulatory requirements and different pathways for registration of drug products in united kingdam', *Der Pharmacia Lettre*, 7(3), pp. 188–195.

Cone, M., & Walker, S. (2004). *Beyond Benchmarking: What are the key metrics that agencies and companies should use to measure performance? WORKSHOP REPORT Institute for Regulatory Science*.

Rosenquist, C.J. (1987) 'Queueing Analysis : A Useful Planning and Management Technique for Radiology',

Journal of Medical Systems. 11(6), pp. 413–419.

Roth, L. et al. (2018) 'Expanding global access to essential medicines : investment priorities for sustainably strengthening medical product regulatory systems', *Globalization and Health.* 14(1) pp. 1–12.

Saxena, P. and Sharma, L. (2013) 'Simulation Tool for Queuing Models : QSIM Academic Discipline And Sub-Disciplines', 5(2), pp. 74–79.

WHO website (29 -10- 2022). Available at: https://www.who.int/news/item/30-03-2022-egypt-and-nigeria-medicines-regulators-achieve-high-maturity-level-in-who-classification-and-who-launches-list-of-regulatory-authorities-that-meet-international-standards (Accessed: 29 October 2022).

Wondemagegnehu, E. and Sauwakon, R. (2002) Effective drug regulation A multicountry study, *WHO Library Cataloguing-in-Publication Data* (2002) 1-202

World Health Organization - WHO (2022) 'WHO Global Benchmarking Tool Plus Medical Devices (GBT+Medical Devices) for Evaluation of National Regulatory System of Medical Products. Registration and Marketing Authorization (MA): Indicators and Fact Sheets', (November), pp. 1–68. Available at: https://cdn.who.int/media/docs/default-source/medicines/regulatory-systems/gbt-medical-devices/02_gbt-md_rev_vi-md_ver_1_ma_20220301_clean.pdf?sfvrsn=60cf824c_3&download=true.

Ethiopia food and drug authority (EFDA) official website (6-6-2021) ; EFDA home. Available at: http://www.fmhaca.gov.et/.

Annexure 1: Data abstracting tool from electronic registration and information system (eRIS) weekly report of the medicine registration unit to determine average service rate from July 8, 2019 to July 7, 2020

Working weeks in 2012 E.C fiscal year	Number of services provided in the week	Number of active servers in the week	Number of idle days in the week (Holidays, meetings,)	Average service rate of the week
Week 1				
Week 2				
Week 3				
Week 4				
Week 5				
Week 6				
Week 7				
Week 8				
Week 9				
Week 10				
Week 11				
Week 12				
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Week 49				
Week 50				
Week 51				
Week 52				

Annex2: Key informant interview guide for qualitative study, English version

Guide for key informant interview

A Queuing Analysis of Medicines Registration System Performance in Ethiopian Food and Drug Authority

I. Background Information of Key Informants

Participant Identification Code:	
Sex	
Age (in Years)	
Highest academic degree you have completed	
Profession	
Place of work (Organization)	
Role/position in the organization	
Length of service in current role/position	
Total work experience in the sector	

II. Interview guide

1. How do you assess the situation of medicine registration process in Ethiopia?

1.1. What is your opinion on the current performance of medicine registration system as compared to EFDA objectives?

2. Do you think EFDA achieved service timeliness promised on citizen's charter or medicine registration, particularly dossier assessment timelines currently? (note: explain citizen charter target timelines if needed)

2.1. If the answer is no, how do you evaluate the differences of the timelines in the current practice and the target timelines in the citizen charter?

2.2. What do you think are the contributing factors for failing to meet the timeline as promised?

How do you describe the level of satisfaction of medicine registration applicants about the services and performance of the directorate?

3. How do you explain the contribution and/or impact of the registration process for the availability of quality medicines in the Ethiopian healthcare system? (Probe; what is your thought on the contributions of the

registration system on the availability quality medicines in the healthcare system? Please share with us your thoughts on the quality and safety of the registered items by EFDA?)

3.1. How do you describe the influence of the registration process on medicine shortage in the country?

4. How do you assess the competency of medicine product dossier assessment in Ethiopia as compared to international best practices;

   Probe: Please evaluate the situation in the areas of Technical capacity; Assessment quality; Service timelines

5. What best intervention strategies do you recommend for EFDA to improve its competency in the medicine registration system?
6. We tried to estimate the average analysis time based on the service rate of EFDA and application arrival rate for medicine registration in EFDA in the 2020 data on eRIS. However, the result we got showed that it's difficult to get steady state queue of application in the current system and service timelines fluctuates too much and got unpredictable. How do you see this result of analysis? Do you think it explains the current registration system?
7. From your point of view, are there any relevant aspects or questions that you feel should be addressed, but weren´t mentioned thus far?

Thank you very much for your time and cooperation!!!

Annex3: Key informant interview guide for qualitative study, Amharic version

Guide for key informant interview

A Queuing Analysis of Medicines Registration System Performance in Ethiopian Food and Drug Authority

Background Information of Key Informants

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Annexure 3: Written informed consent to in-depth interview participants

Informed Consent Form	
Study Title: A Queuing Analysis of Medicines Registration System Performance in Ethiopian Food and Drug Authority	
Introduction and study objective	
Dear participant, My name is _____, and I am contacting you on behalf of the study team. We are conducting a research on "**A Queuing Analysis of Medicines Registration System Performance in Ethiopian Food and Drug Authority**" for the partial fulfillment of MSc in regulatory affairs (medicine truck) program, School of Pharmacy, Addis Ababa university. We are, hence, pleased to get your opinions on medicine registration system in the country in this interview. Your responses will be strictly confidential and your name or any personalized information will not be used or appear in any documents, communications, or analysis related to these data. Participation is completely voluntary, and you do not have to answer all questions you do not wish to. You can opt to withdraw consent at any time. Your responses will be integrated with many others in EFDA and other stakeholders in the country to ensure a broader understanding on the issue. There is no guarantee of immediate benefit from your participation, yet, the results will help the research team and other indirect users of the research findings to review and improve their systems as appropriate. While participating, you are requested to: 1) Collaborate with our data collectors to respond to questions linked to key medicine registration processes in Ethiopia. 2) authorize the use of these data while maintaining anonymity	
Confidentiality	
Our study team will maintain complete confidentiality during the interview. The other members of the assessment or advisory team or viewers of the report will NOT be told your name or any other personally identifiable information.	
Benefits	
The benefit of your participation in this exercise is that the data arising from this assessment will be used to improve medicine registration system in Ethiopia and this in turn, to help sustainable access to safe, effective, quality assured and affordable essential medicines and medicine-related pharmaceutical services.	
Who to contact	
If you decide to participate in this exercise and you have additional doubts or questions, you can communicate with Ato Abebe Alamneh, the principal investigator at 0947 80 17 05.	
Verbal consent and agreement	
If you would like to participate, please confirm that you understood everything I have told you about this exercise. Do you have any questions?	
Agrees to participate	
Does NOT agree to participate	
Name:	

Signature:	Day/Month/Year
Person Obtaining Consent:	
Name:	
Signature:	Day/Month/Year