A RETROSPECTIVE REVIEW OF PHARMACEUTICAL PRODUCT DOSSIERS SUBMITTED AT THE PHARMACY AND POISONS BOARD BETWEEN 2010 AND 2014

By:

MOKAYA ESTHER GESARE

B. Pharm. (Nairobi)

(U59/69639/2011)

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Department of Pharmaceutical Chemistry

School of Pharmacy

UNIVERSITY OF NAIROBI

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This thesis is my original work and has not been submitted elsewhere for examination, degree or award.

Sign: _____ Date: _____

MOKAYA ESTHER GESARE

U59/69639/2011

This thesis has been submitted for examination with our approval as University supervisors.

Sign: _____ Date: _____

DR. K. O. ABUGA, PhD

Department of Pharmaceutical Chemistry,

School of Pharmacy, University of Nairobi

Sign: _____ Date: _____

DR. B. K. AMUGUNE, PhD

Department of Pharmaceutical Chemistry,

School of Pharmacy, University of Nairobi

DECLARATION OF ORIGINALITY

Name of Student:	Mokaya Esther Gesare
Registration Number:	U59/69639/2011
College:	College of Health Sciences
School:	School of Pharmacy
Department:	Pharmaceutical Chemistry
Course Name:	Master of Pharmacy in Pharmaceutical Analysis
Title of the Work:	A Retrospective Review of Pharmaceutical Product Dossiers Submitted at the Pharmacy and Poisons Board Between 2010 and 2014

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DEDICATION

This work is dedicated to my parents, Mr. John Mokaya and Mrs. Teresa Mokaya for their unwavering love and support throughout my studies and to my son, Jaden, my source of inspiration and motivation.

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ACRONYMS AND ABBREVIATIONS

API	Active Pharmaceutical Ingredient
BC	Before Christ
BTIF	Bioequivalence Trial Information Form
CNS	Central Nervous System
COA	Certificate of Analysis
CPMP	Committee on Proprietory Medicinal Products
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
CVS	Cardiovascular System
DARU	Drug Analysis and Research Unit
DMF	Drug Master File
EAC	East African Community
EAC- MRH	East African Community Medicine Regulatory Harmonization
EC	European Community
EEC	European Economic Community
EFTA	European Free Trade Association
FDA	Food Drug and Administration
FIFO	First In First Out
FPP	Finished Pharmaceutical Product
GC	Gas Chromatography

GMP	Good Manufacturing Practices
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Conference on Harmonization
INN	International Non-proprietary Name
IQR	Inter-quartile Range
LTR	Local Technical Representative
MEDS	Mission for Essential Drugs and Supplies
MRA	Medicines Regulatory Authority
NCD	Non-Communicable Disease
NDA	National Drug Authority
NEPAD	New Partnership for Africa's Development
NQCL	National Quality Control Laboratory
NRA	National Regulatory Authority
OTC	Over the Counter
PIL	Prescriber Information Leaflet
POM	Prescription Only Medicine
PPB	Pharmacy and Poisons Board
QC	Quality Control
QOS	Quality Overall Summary
QOS-PD	Quality Overall Summary-Product Dossier
QPPV	Qualified Person for Pharmacovigilance
SDRA	Stringent Drug Regulatory Authority
SIAMED	WHO Model System for Computer Assisted Drug Registration

SmPC	Summary of Product Characteristics
SPSS	Statistical Package for the Social Sciences
TFDA	Tanzania Food and Drugs Authority
WHO	World Health Organization

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DEFINITION OF TERMS

Drug registration: Is the process undertaken by a national medicine regulatory authority ensure that the pharmaceutical products imported into the specified market meet the required standards of quality, safety and efficacy and it includes pre-marketing evaluation, marketing authorization, and post-marketing review (World Health Organization, 1998).

Medicine Regulatory Authority (MRA): Is an institution in the national government that is responsible for the regulation and protection of public health within its territory, by putting in place measures to ensure that the drugs imported and marketed meet the required standards in terms of quality, safety and efficacy (Lembit and Santoso, 2010)

Marketing authorization (MA): Is a product licence issued by a competent drug regulatory authority, after a satisfactory pre-marketing evaluation process, that allows the applicant to market the product within a specified territory (World Health Organization, 1998)

Marketing Authorisation Holder (MAH): Is the company or person to whom the marketing authorisation is issued, and who has the sole rights to import market and distribute the registered products within the specified territory (World Health Organization, 1998)

Regulatory affairs: Are the processes or activities within an organisation that ensure compliance of an organisation to stipulated regulations and that the products marketed by the organisation meet the standards of quality, safety and efficacy. It involves all activities from product development, product registration, post-market review and post approval maintenance (Praneeth, 2016)

Product dossier: Is a modular set of documents with information on the administrative, quality, nonclinical and clinical aspects of a pharmaceutical product, which is submitted by an applicant to the drug regulatory authority responsible for drug registration and if the information provided is satisfactory, a marketing authorization is issued to the applicant which allows the pharmaceutical product to be imported and marketed within a specified market (Gupta, 2018).

Common Technical Document (CTD): Is modular format for product dossiers, that is widely accepted by most regulatory authorities for registration of medicines. It was originally designed to be used across Europe, Japan and the United States (Gupta, 2018).

ABSTRACT

Background:

Efficient regulation of pharmaceutical products is crucial in ensuring that the medicines within a specified territory meet the stipulated standards of quality, safety and efficacy. The national medicine regulatory authority (MRA) is responsible for drug regulation by ensuring that the products marketed are of the right quality before issuing a marketing authorization, also known as registration certificate or product license. The process of drug registration requires submission of a dossier to the MRA, in Common Technical Dossier (CTD) format which essentially contains all administrative, quality, clinical and non-clinical information about the product. This information has to comply with set WHO guidelines and territory-specific guidelines prior to issuance of a registration certificate. This study is a retrospective review of dossiers submitted at the Pharmacy and Poisons Board, the drug regulatory authority in Kenya, from the period starting January 2014 and ending December 2014.

Objective:

The purpose of this study was to carry out a retrospective review of pharmaceutical product dossiers submitted to the Pharmacy and Poisons in the period starting January 2010 and ending December 2014. Specifically, the study evaluated the turnaround time for new drug approvals and the factors influencing the timelines for drug registration. The study also looked into the therapeutic categories of the pharmaceutical products whose dossiers were submitted in the specified period. A comparative study of Kenya's processes with its neighboring countries, Uganda and Tanzania was also done.

Methodology:

The retrospective review was carried out at the Pharmacy Poisons Board, Lenana Road, Nairobi, Kenya. Data was gathered using a data collection tool and entered into a password protected Microsoft Excel database then exported to STATA version 14.0 software for analysis. Three hundred and forty-seven complete dossiers were reviewed after being stratified based on their respective therapeutic categories. Given that from the data set, only 273 products were registered

at the time of this study, further analysis was restricted to only these products. The time taken to obtain registration is calculated as a difference between the date of submission and the date the product was recommended for registration. A comparative study was done on the regulatory requirements for dossier submissions in Kenya, Uganda and Tanzania based on information obtained from their respective drug registration guidelines retrieved from each of the respective regulatory authority's official website.

Results and discussion

From the sample size of 347 files selected and studied, 78.7% of the products had obtained registration within the specified period. Majority of the products were registered in a period of more than 12 months (47%), and 31% were registered in less than 12 months. About 20% of the products were still pending registration at the time of the study. The median time for registration was 413 days [IQR 283,680] against the stipulated timelines of 12 months, 365 days. Majority of the products submitted for registration were anti-infectives, which constituted 31 % of the total files reviewed. The second highest category was anti-hypertensives (9.2%), followed by gastrointestinal products at 8.1%. Analgesic/ anti-inflammatory medicines were also significant at 7.8% of the files reviewed. Biological products formed the least of products submitted for registration at 0.58 % of the total files. Kenya's regulatory processes and requirements for drug registration were found comparable to those of neighboring countries, Uganda and Tanzania. Pharmaceutical dossiers submitted in each of these countries use the Common Technical Document (CTD) format, and as per the stipulated guidelines. The process of pharmaceutical dossier review forms an important step in drug product lifecycle, as it ensures that the products released into the market meet the required standards of quality, safety and efficacy. This is important because once the product is in the market; it will be very difficult and costly to rectify any quality and safety issues once the product reaches the patient. These issues may have lasting effects on the patient, and some may be fatal. The pharmaceutical dossier should therefore provide adequate and accurate information for the regulator to establish that the product is safe and efficacious for the patient, and that the benefits outweigh the risks.

Conclusion:

The drug registration requirements and practices followed by PPB are comparable to those of NDA, TFDA, and EAC–Compendium. The dossiers are prepared in CTD format, and the language used in the dossiers is English. All the guidelines are based on WHO Guidelines and ICH guidelines on drug registration and the average processing time for the dossiers is 12 months in the guidelines. The average time taken to register a pharmaceutical product in Kenya was approximately 14 months. The major factors affecting turnaround time are the frequency of evaluation meetings at PPB and the time taken by the applicant to adequately respond to the queries raised after initial evaluation. Majority of the products submitted for registration between 2010 and 2014 were anti-infectives, which was in line with Kenya's disease burden at the time.

Recommendations:

The Kenyan MRA, PPB can look into ways to identify gaps and continually improve practices in dossier review. One of the ways would be creating robust systems for dossier monitoring with definite target times for key milestones in the dossier review process. This will allow PPB and stakeholders to plan for outcomes that are more predictable and ensure timely introduction of quality medicines into the market. Risk-based approach for assessment of dossiers or abridged review should be considered to minimize duplication of work and unnecessary delays, especially for products already registered by a stringent regulatory authority.

CHAPTER 1: INTRODUCTION

1.1 Drug Regulation

Drug regulation includes the measures taken by a regulatory authority to ensure that the products marketed and sold to the end user within the territory are of the right quality, and that they are safe and efficacious. This includes the entire process from drug development, approval, manufacturing and marketing of drugs.

It is important to regulate medicines to ensure that only good quality, safe and effective medicine reach the patients. Poor quality and ineffective medicine may lead to therapeutic failures, which in some instances, may be fatal.

The government is mandated to protect its citizens through the use of a National Medicine Regulatory Authority (MRA) whose key role is to effectively control and regulate the manufacture, trade and use of medicines within its territory (Handoo *et al.*, 2012).

As pharmaceutical industries aspire to become competitive at the global level, there is a realization that there is need to have guidelines and systems in place to give assurance that the drug regulatory processes and procedures are under adequate regulation (Kumar *et al.*, 2013).

The need for drug regulation is necessary due to the increase in the prominence of pharmaceuticals as health indicators on international agenda. In addition, with the increase in global trade, the legal and economic issues around pharmaceuticals are becoming more complicated and generating political interest (Management Sciences for Health, 2012a).

The main goal of drug regulation is to protect and promote the safety and health of the population. Although it varies by jurisdiction, in most regions, the therapeutic goods must be registered in the

country from which they are sourced as well as in the target market before they can be imported and marketed.

Drug regulation strengthens governance, regulations and accountability in the pharmaceutical sector, which is key in health systems strengthening. This allow for access and availability of good quality, safe and effective, medicines to patients, while at the same time increasing pharmaceutical sector trade at a regional level which contributes to economic development (Villafana, 2012).

Drug regulation incorporates several activities which include the licensing, inspection and surveillance of manufacturers, control of export, import, distribution, promotion and advertising of medicines, and assessment of medicine to ensure quality and safety standards are met before issuing marketing authorization for individual products. After marketing authorization is granted, regulation involves monitoring and control of the quality and safety of medicines in the market through pharmacovigilance activities and related strategies (Ratanawijitrasin and Wondemagegnehu, 2002)

It is very important that the entire process of introduction of new drugs to the market, including pharmaceutical research and development, is managed effectively in order to meet regulatory requirements. This is the role of drug regulatory affairs in a pharmaceutical company, whose main responsibility is to secure approval of drug submissions from the NRA in the territory and to ensure regulatory compliance of marketed and investigational drugs within the region (Kumar *et al*., 2013).

1. 2 History of drug regulation

The structures of drug regulation have evolved over time to what exists today. This includes laws governing drugs, the drug regulatory authorities, quality control (QC) laboratories, and drug information centers (Ratanawijitrasin and Wondemagegnehu, 2002).

In Europe, it is believed that King of Pontus, Mithridates VI (120 BC), developed a mixture of 41 compounds called "Mithridatium" that was used for almost all ailments until 1780. The

manufacture of medicines including Mithridatium later controlled under the Apothecaries Wares, Drugs and Stuffs Act, which was one of the first measures undertaken by the British government to regulate medicines. This necessitated pharmaceutical inspections of the manufacturing plants and this led to the appointment of inspectors of "Apothecary Wares, Drugs and Stuffs" (Lembit and Santoso, 2008).

The modern medicines regulation started mainly in the 19th century after a scientific breakthrough especially in physiology, chemistry and pharmacology, which set a precedence for drug research and development. However, it is the occurrence of unfortunate events showed the dire need for stringent drug regulation and catalyzed the formulation and implementation of medicines regulatory systems and processes.

One such event occurred in 1937 in the US, when more than a hundred people died after consumption of sulfanilamide elixir, due to diethylene glycol poisoning, which had been used as a solvent without any testing for safety. This incident led to the introduction of the Federal Food, Drug and Cosmetic Act, 1938, which required pre-market notification for any new drugs introduced in US. The second more significant event that catalyzed the need for medicines regulation was the thalidomide catastrophe, that led to an estimate of ten thousand babies being born with phocomelia and related deformities between 1958 and 1960. Thalidomide, at the time, was widely used by expectant women as anti-nausea medicine to relieve symptoms of morning sickness that is common in pregnancy (Lembit and Santoso, 2008).

In 1963, the complete regulatory system was redrafted in United Kingdom and a Committee on the Safety and Drugs was constituted, and subsequently a voluntary adverse drug reaction reporting system (Yellow Card Scheme) in 1964. In the same period, Congress in the United States passed the Drugs Amendments Act of 1962. It mandated the Food and Drug Administration (FDA) to issue approvals for all new drug applications the requisite standards for safety and efficacy were met. The FDA was also tasked with ensuring that manufacturers of drugs complied with Good Manufacturing Practices (cGMP) of drug manufacturers, as well as to register drug establishments. The thalidomide catastrophe also resulted in the introduction of the European Economic Community (EEC) Directive 65/65/EEC which focused primarily on the provisions

relating to the approval of medicinal products (Lembit and Santoso, 2008).

Ten years after the introduction of this directive, there was harmonization in drug regulation initiatives in the European Community (EC) by the introduction of two Council Directives in 1975. The first Directive, 75/318/EEC, focused on the stipulated laws of member states regarding the testing of medicinal products specifically pharmaco-toxicological, analytical and clinical protocols. The second directive 75/319/EEC focused on the laws and regulations surrounding medicinal products. It is this second directive that led to the establishment of an advisory committee to the EC, known as the Committee on Proprietary Medicinal Products (CPMP), and the initiation of the mutual recognition procedure, which is a multi-state procedure that results in a mutually recognized authorization.

The mutual recognition procedure resulted in ease of trade and a created a common market for medicines marketed within the EU, and subsequently, brought about a call for wider harmonization. Preliminary discussions were held between officials from EU, Japan and US at the International Conference of Drug Regulatory Authorities (ICDRA) in Paris, and this led to the formation of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) in 1990. The ICH is a collaborative initiative between the EU, Japan and the United States with observers from WHO, European Free Trade Association (EFTA) and Canada, and whose primary focus is to harmonize the technical requirements for the registration of new medicinal products. Harmonization of pharmaceutical regulatory processes plays a role in enhancing the availability of good quality, safe and effective pharmaceuticals (Lembit Rago, 2008). With increased complexity of technical regulations related to drug safety and efficacy, there have been efforts to harmonize regulatory processes with an aim to increase global trade of pharmaceutical products (Handoo *et al*., 2012).

1.3 Drug Regulation in Emerging Markets

According to a WHO study done in 2004, more than 90% of the medicine regulatory authorities in Africa did not have adequate capacity to effectively regulate and control medicines in their respective territories. The findings have changed over time and a study in 2006 by WHO showed

a substantial progress made by Tanzania and Kenya.

One of the main contributing factors that lead to a regulatory capacity shortfall in Africa is the lack of proper legislative frameworks to allow African medicine regulatory authorities to execute regulatory functions. An estimated 63% of African regulatory authorities lacked adequate resources especially the MRAs financed from government budgets as opposed to regulatory fees (Moran *et al*., 2010).

In 2010, WHO reported an improvement in the structures for medicine regulation that addressed the main regulatory functions but still expressed that the common weakness shared by the African countries assessed was lack of adequate numbers of experienced and qualified staff. It highlighted an urgent need for investment in regulatory capacity building (World Health Organization, 2010).

In addition, the regulatory requirements for dossier submission vary from country to country, and this has made it difficult for pharmaceutical companies to compile a single dossier meets the regulatory requirements for submission in multiple MRAs for registration. It is therefore imperative that the applicant knows in detail the regulatory requirements and practices for each country in which the product is to be registered, and the commercial implications (Handoo *et al*., 2012).

Drug regulation should ensure that all products that have a medical claim have been properly controlled, to protect the public and promote public health. This includes the manufacture, importation, distribution, dispensing and promotion of pharmaceutical products. A multi-country study conducted by WHO showed that for emerging markets, drug regulation did not meet all stipulated requirements for drug registration as compared to the more developed countries. For instance, in Australia, Netherlands and Malaysia, the law requires that traditional or herbal medicines be to be submitted to the regulatory authority for assessment and registration whereas this is not a requirement in Uganda, Zimbabwe or Cyprus. As a result of such differences and gaps in emerging markets, it appears that drug regulation may not cover all the required aspects, thus confers partial protection for public (Ratanawijitrasin and Wondemagegnehu, 2002).

In addition to these findings, the process of assessment of submitted dossiers is a difficult and rigorous task, with increasing difficulty from simple generic drugs to fixed dose combinations and new formulations. The most difficult dossiers to assess are vaccines and novel drugs, which may be more than a thousand pages with plenty of scientific data and information to be evaluated to establish whether they meet standards of quality, safety and efficacy. In some instances, African MRAs may need to rely on prior assessments by regulators such as FDA or EMEA (Ratanawijitrasin and Wondemagegnehu, 2002).

1.4 Drug Registration Process

The process of drug registration includes pre-marketing evaluation, approval and post-marketing review of pharmaceutical products to confirm that they meet the stipulated standards of quality, safety and efficacy as established by the national medicine regulatory authorities. If the outcome of the evaluation is satisfactory, a pharmaceutical product marketing authorization or license is issued (European Medicines Agency, 2018).

Drug regulatory authorities regulate medicinal products that include pharmaceutical products, biologicals, food supplements, herbals and borderline products. This classification is dependent on the active pharmaceutical ingredient and intended medical use. Biological products contain active substances drawn from a biological source produced by cutting edge-technology. This includes insulin, coagulation factors and monoclonal antibodies (European Medicines Agency, 2018). Herbal products contain actives derived from plant sources whereas borderline products are products that cannot be classified as pharmaceutical or cosmetic, but have medical use. The regulatory requirements are different for biologicals, herbals, food supplements and borderline products, depending on the market, but a dossier is not required in most regulatory authorities.

Innovator products and generic products also have different regulatory processes required for registration. Innovator products, also known as the originator products, are products not previously used on humans for medicinal purposes. About 95% of these innovator medicines are from ICH member states; EU, USA and Japan, hence the technical requirements for pharmaceutical submissions are based on ICH technical guidelines. For innovator products, it is

mandatory to submit clinical study reports and related information.

For pharmaceutical dosage forms, the active pharmaceutical ingredient (API) is normally expressed in International Non-Proprietary Name (INN), names derived from WHO guidelines. The INN is unique to a pharmaceutical ingredient, and is globally recognized. International Non-Proprietary Names are also universally available and accessible to the public, hence are normally used to identify pharmaceutical substances without any restriction (Lembit and Santoso, 2008). This process requires submission of a pharmaceutical dossier to the respective national drug regulatory authority.

A pharmaceutical dossier is a file document containing administrative, quality, clinical and nonclinical technical data about a specific pharmaceutical product that is intended for submission to a competent regulatory authority for the assessment and evaluation, after which if found to be satisfactory obtain approval of drug product. The process of reviewing and assessment of the technical information presented in the dossier, and the subsequent issuance of authorization to the applicant by the respective regulatory authority to support the marketing or approval of the product within a specified territory is referred to as marketing approval or product licensing. The document issued by the regulatory authority upon successful evaluation is referred to as a marketing authorization or product license (Swapna *et al*., 2014).

There are different types of dossier formats acceptable in the pharmaceutical industry, including the Common Technical Document (CTD) format, the Asian CTD (aCTD) format, the electronic CTD format (eCTD) format and the country specific registration dossier.

The CTD format is a set of requirements for new application dossiers that is used for product registration and was originally meant to be used across Japan, Europe and the United States. This format that is now widely accepted by most regulatory authorities and has four sections and five modules as depicted in Figure 1 in the following page (Lembit and Santoso, 2008).

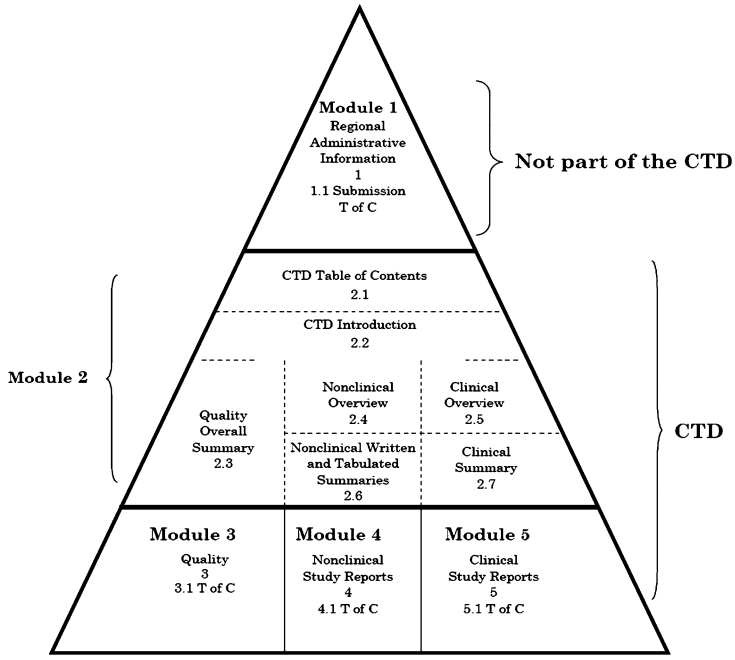

Figure 1: Organization of ICH CTD document (Lembit and Santoso, 2008)

The four sections are mainly the application organization, quality section, safety section and efficacy. Module 1 is region specific, and comprises the administrative and prescribing information for the product. It should contain documents specific to each region such as the respective application form, information about the experts and a cover letter from the applicant. This module also contains product information such as the Summary of Product Characteristics (SmPC), labeling information for the inner and outer packaging, and the patient information leaflet (PIL).

A mandatory requirement for this Module is provision of the Good Manufacturing Practices (GMP) certificate for the finished product manufacturer, and marketing authorization for the product, commonly referred to as Certificate of Pharmaceutical Product (CPP). The regulatory authority in the country of origin issues this document, and shows the marketing status of the drug product at source.

Module 2 is composed of summaries of the CTD. The format may differ slightly based on the regulatory authority, but in general, it should contain a brief introduction on the pharmacological class, the mode of action and the intended clinical use of the pharmaceutical product. This module also contains the overall summary of quality, non-clinical and clinical overviews, nonclinical written summaries and tabulated clinical summaries.

Module 3, also known as the quality module, contains in detail all the required information regarding the active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP). This includes formulation development, characterization, manufacturing and quality testing to demonstrate that the medicinal product meets the stipulated quality standards. It has three sections- the table of contents, body data and literature references. The body data section is further divided into four subsections; drug substance, drug product, appendices and regional information.

Module 4 is restricted to new chemical entities. It comprises information on the non-clinical study reports and literature addressing the complete non-clinical testing required for the medicinal product. This module is not applicable to generic products.

Lastly, Module 5 deals with clinical study reports and literature providing information on clinical requirements for the medicinal product (ICH, 2008). For generic products, the applicant needs to demonstrate interchangeability with the reference innovator product. This is through provision of bioequivalence data that compares the bioavailability of the generic product intended for registration and the acceptable reference innovator product. The generic product should have the same rate and extent of absorption as the reference product. Where it is not possible for the applicant to provide bioequivalence study data, comparative dissolution profile data of the generic product with the reference innovator products should be submitted (Randeria *et al.*, 2018).

Each national drug regulatory authority is responsible for setting the standards to ensure that every product submitted for registration is appropriate for that country's population, using appropriate regulations and policies. In general, each regulatory authority has its own set of guidelines, but most are derived from WHO guidelines and use the CTD format for new drug application (Ashok *et al.*, 2017).

The eCTD acts as an interface for pharmaceutical industry and regulatory authority that allows for the transfer of regulatory information throughout the product lifecycle (Moran *et al*., 2010)

The East African Community (EAC) formed in 1999 comprises Tanzania, Kenya, Uganda, Burundi, Zanzibar and Rwanda as the member states. Efforts to bring harmonization in medicine regulation in the region began from as early as 1990. In 2001, EAC national medicine regulatory authorities approved the technical requirements for registration of veterinary immunologicals and these were drawn from the Tanzanian drug registration guidelines(World Health Organization, 2016). In 2012, The East African Community-Medicine Registration Harmonization (EAC-MRH) project was initiated in Tanzania, whose main purpose was to increase access to good quality medicines to the population in member states. The project laid a solid foundation for creation of a framework for joint assessment and approval of medicinal product registration in EAC, as well as joint inspections of manufacturing sites. Approval of the EAC-MRH guidelines took place in the 29th meeting of EAC council ministers in September 2014, and use of the guidelines by member states began on 1st January 2015 (Turner, 2006).

Harmonization of drug regulation in the region is also aimed at facilitating pooled procurement, which in turn would promote growth of the local pharmaceutical industries and ensure sustainable accessibility of essential medicines within the region. It was important to harmonize all the regional drug regulation guidelines before enforcement of patents become mandatory to the least developed countries which may impede supply (Muhairwe, 2008).

In Kenya, the national medicine regulatory authority is the Pharmacy and Poisons Board, established under the Pharmacy and Poisons Act, Chapter 244 of the Laws of Kenya. It regulates the pharmaceutical practice as well as the manufacture and trade of drugs and poisons. It is also responsible for the review and assessment of dossiers submitted , and issuance of marketing authorization upon successful evaluation (Pharmacy and Poisons Board, 2020).

1.5 Study Justification and Problem Statement

The process of pharmaceutical dossier review forms an important step in drug product lifecycle, as it ensures that the products released into the market meet the required standards of quality, safety and efficacy. This is important because once the product is in the market; it will be very difficult and costly to rectify any quality and safety issues at the users' end. These issues may have lasting effects on the patient, and some may be fatal. The pharmaceutical dossier should therefore provide adequate and accurate information for the MRA to establish that the product is safe and efficacious for the patient, and that the benefits outweigh the risks (Patel *et al*., 2019)

The national medicine regulatory authority should implement adequate regulations and procedures that ensure that all the pharmaceutical products circulating within its territory met required standards of quality, safety and efficacy. The authority should also put measures in place to shorten drug registration timelines to minimize unnecessary delays in patients' access to essential medicines (Richardson *et al*., 2018)

In Kenya, the mandate of PPB, through its Drug Registration Department is to receive and review submitted pharmaceutical dossiers for new registration and upon successful evaluation issue a marketing authorization to the applicant. According to the stipulated drug registration guidelines, the dossier processing time should be 12 months after initial submission (Pharmacy and Poisons Board, 2010).

The purpose of this study was therefore to carry out a retrospective review of the processes and procedures followed by the Pharmacy and Poisons Board in dossier processing and registration of pharmaceutical products in Kenya, in the period of 2010 to 2014. Specifically, the study evaluated the time take to obtain registration after initial submission, and the factors influencing the timelines. The study also evaluated the therapeutic categories of the pharmaceutical products whose dossiers were submitted in the specified period. A comparative study of Kenya's processes with its neighboring countries, Uganda and Tanzania was also done to identify any significant differences in drug registration processes, and areas of improvement if any.

1.6 Study Questions

a) Are the drug registration processes and practices followed by PPB comparable to those followed by NDA, TMDA and the EAC-MRH Compendium?
b) What is the turnaround time for pharmaceutical dossier evaluation at PPB and what are the major influencing factors? Is this in line with the processing times as stipulated in the guidelines?
c) What are the profiles of the pharmaceutical products submitted and registered at the PPB?

1.7 Objectives

1.7.1 General Objective

To carry out a retrospective review of the pharmaceutical dossiers submitted at PPB between 2010 and 2014, and the regulatory requirements and practices for drug registration in Kenya.

1.7.2 Specific Objectives

- To compare pharmaceutical dossier review process and requirements followed by PPB to that followed by NDA, TMDA and EAC-MRH Compendium
- To establish the turnaround time for dossier evaluation, and the major influencing factors, for product dossiers submitted at PPB between 2010-2014
- To profile the pharmaceutical products submitted and registered between 2010-2014

CHAPTER 2: LITERATURE REVIEW

2.1 Background

In order to submit a new drug application for marketing authorization to a medicine regulatory authority, the applicant needs to have thorough knowledge of the drug registration process in the specific country. This is important because each country has its own regulatory requirements and procedures to be followed, and these differences will have significant regulatory and commercial implications on the product therefore ideally, this should be done prior to commencing product development (Handoo *et al.*, 2012).

After submission of the pharmaceutical dossier to the respective medicine regulatory authority, the authority is mandated to review the submitted documents, and if the information provided is found satisfactory a marketing authorization is issued to the applicant. Pharmaceutical regulatory authorities experience challenges in performing scientific assessment of the information provided on the dossiers to establish whether the pharmaceutical products are of the required quality, safety and efficacy. It is therefore important for a medicine regulatory authority to regularly review practices and procedures, and assess its performance against established international benchmarks. This will help agencies evaluate and develop strategies to promote timely access of essential medicine to patients in their territories (Hashan *et al.* , 2016)

Globally, there are three types of dossier assessment strategies followed by MRAs. The first type, Type 1 is the verification assessment that avoids duplication of scientific review of data and requires approval of the product by two or more stringent regulatory authorities (SRA). The second type, Type 2 is the abridged assessment, in which the product has to be registered by at least one SRA. Lastly, the third type, Type 3, is the full assessment, which is complete evaluation of scientific data submitted (Mcauslane *et al.*, 2009). Full assessment can be either Type 3A or type 3B. Type 3A requires pre-authorization in another market before finalization of authorization, whereas, Type 3B, pre-registration in another market is considered but not mandatory for finalization of authorization.

In a comparative study done on the regulatory requirements and practices for Saudi Arabia Food Drug Authority (SFDA) with Australia, Canada and Singapore, it was established that the SFDA uses type 3A full assessment whereas Canada and Australia regulatory authorities follow type 3B assessments. The Australian regulatory authority, Therapeutic Goods Administration (TGA), also uses abridged pathways for assessment of dossiers. The Singapore Health Sciences Authority(HSA) uses all routes of assessment, though it mostly utilizes the abridged assessment route for evaluation of its dossiers (Hashan *et al.*, 2016)

The type of assessment followed by the regulatory authority has an effect on the overall registration time, with full assessment taking longer than verification or abridged assessment. This difference in regulatory requirements and duration to get approval will affect introduction of the product into market, and ultimately, when patients will access the new medicines.

Table 1 in the following pages outlines the regulatory requirements for drug registration in Kenya compared to select countries internationally (Handoo *et al*., 2012).

Table 1: Regulatory requirements for Kenya and select countries internationally (Handoo *et al*., 2012)

Registration requirement	Kenya	Tanzania	USA	EU	Brazil (LATAM)	Russia(CIS)	Hong Kong (Asia Pacific)
Manufacturing Site Registration	Yes	Yes	Yes	Yes	Yes	Yes	Yes
GMP Inspection/Approval of FPP manufacturing site	PPB inspection and approval of FPP site	Inspection and approval by TFDA is required	Inspection by US FDA is necessary	Inspection by respective EU authority is necessary	Site needs to be audited by Brazil ANVISA	Site needs to audited by CIS member countries	Authority accepts FDA/PICs/EU approval
Stability Zone for long term stability testing	Zone IV a	Zone IV b	Zone II	Zone II	Zone IVb	Zone I	Zone IVa
Stability Conditions for long term testing	30°± 2°C/ 65%±5% RH	30°C±2°C/ 75%±5% RH	25°C±2°C/ 60%±5% RH	25°C±2°C/ 60%±5% RH	30°C±2°C/ 75%±5% RH	21°C±2°C/ 45%±5% RH	30°± 2°C/ 65%±5% RH
Minimum stability data required during initial submission of application	6 months accelerated; 12 months CRT data	6 months accelerated; 12 months CRT data	3 months accelerated and CRT data	6 months accelerated and CRT data	12 months accelerated and CRT data	6 months accelerated and CRT data	6 months accelerated and CRT data
Stability commitment required while filing	Required	Optional	On 3 commercial batches CRT till shelf life	On 3 commercial batches CRT till 6 months	Optional	Optional	Not required

Dossier format	CTD	CTD	CTD	CTD	CTD	Resembles CTD	Country specific
Registration time	12 months	12 months	24-30 months	9-12months	Varies 7days(Peru) 24 months (Brazil)	6-24 months Russia(18 months)	8-24 months

Key Words: - ANVISA- Agencia Nacional de Vigilancia Sanitaria (National Health Surveillance Agency), CRT-Controlled Room Temperature, RLD-Reference Listed Drug, CTD- Common Technical Document, RH-Relative Humidity, FPP-Finished Pharmaceutical Product, LATAM- Latin America, CIS-Commonwealth of Independent States, BE-Bioequivalence, PIC/S-Pharmaceutical Inspection Co-operation /Scheme

2.1 Drug Registration in Kenya

The practice of Pharmacy in Kenya officially began more than sixty years ago, with the regulation of the quality of medicines commencing in 1977. In this year, the Ministry of Health together with the University of Nairobi formed the Drug Analysis and Research Unit at the University of Nairobi, School of Pharmacy. The first results obtained from analysis of drugs on the market were published in 1982, and it revealed the need to have better control of medicine circulation in the country. These findings led to the formation of the Drug Registration Unit at the Pharmacy and Poisons Board in the same year (Kibwage, 2008).

The Pharmacy and Poisons Board established under the Pharmacy and Poisons Act, Chapter 244 of the Laws of Kenya in 1959, is mandated to regulate the pharmaceutical practice as well as the manufacture and trade in drugs and poisons. From the PPB website, the guidelines for the registration of pharmaceutical products are available and these provide guidance for applicants preparing application dossiers intended for submission to the Pharmacy and Poisons Board (Pharmacy and Poisons Board, 2018).

The drug registration guidelines for the registration of pharmaceutical products describe in detail how to organize applications for submission at PPB. They are based on the World Health Organization (WHO) Guidelines on Submission of Documentation for Prequalification of Multi-source Finished Pharmaceutical Products and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on the CTD (Pharmacy and Poisons Board, 2010).

In Kenya, the process of drug registration started in 1981 after the publication of Pharmacy and Poisons rules and related documents under the provision of the Pharmacy and Poisons CAP 244. These rules stated that before a person or company could import, manufacture for sale or sell any pharmaceutical product in Kenya, registration had to be obtained first from the Pharmacy and Poisons Board (Briggs, 2002)

2.2 Submission of New Drug Applications in Kenya

New drug applications in Kenya are submitted to PPB in CTD format, with the administrative and technical information organized in the five respective modules. Up until 2017, the application was submitted as Module 1 and 2 in MS Word in soft copy and the Modules 3 to 5 in PDF format on a CD-ROM. The application form provided by the PPB has to be filled as well, and was submitted in hard copy, ensuring that the signing of declaration by the applicant. This process has since gone online, where the applicants have to upload the requisite documents onto the PPB portal. The applicant has to submit three sample packs with each application.

Module 1 comprises the administrative particulars of the product. It is in this section where the certificate of analysis (COA) obtained from a WHO pre-qualified lab is attached. The WHO pre-qualified labs allowed in Kenya are Mission for Essential Drugs and Supplies (MEDS) Laboratory and National Quality Control Laboratory (NQCL). The other lab permitted by PPB is the Drug Analysis and Research Unit (DARU), at the University of Nairobi. Another document included in this module is the Certificate of Pharmaceutical (CPP) issued by the exporting country, and it provides the status of the product and the applicant in the respective country of origin. The manufacturing site has also to be inspected by PPB, and if it meets the required standards, a valid GMP certificate of the manufacturing site is provided and included in Module 1 of the dossier.

Module 2 comprises the chemical, pharmaceutical, non-clinical and clinical overviews and summaries of both the Active Pharmaceutical Ingredients (AP1) and the Finished Pharmaceutical Product (FPP). There has to be the Quality Overall Summary (QOS), which outlines and summarizes the information on Module 3. Module 3 is the chemical and pharmaceutical documentation for the API and the FPP. It describes the manufacture, tests, control of the API, excipients, and the FPP in detail. This section relies heavily on the complete and executed Drug Master File (DMF) that has to be included in the section as well. Module 4 comprises the non-clinical study reports and is applicable for new chemical entities only.

Module 5 includes clinical study reports and clinical data references as pertains to the specific pharmaceutical product. It should include the necessary information to demonstrate interchangeability of generic products.

The generic drugs, formulated after the patent of the originator drugs expire, are considered therapeutically interchangeable with the reference innovator product. For the generic product to be considered interchangeable, it must be identical to the reference innovator product in terms of active ingredients, strength, dosage form and route of administration. The two products should be bioequivalent and have the same therapeutic indications. To ensure that the generic product meets the same requirements for purity and quality as the reference innovator product, PPB requires the manufacturer meets GMP standards of the innovator product as well (Pharmacy and Poisons Board, 2010).

The compiled dossier is then submitted to PPB with an accompanying cover letter addressed to "The Registrar PPB", and payment of 1000 USD for foreign manufactured product and 500 USD for locally manufactured product.

2.3 Evaluation of submissions

After the dossier is submitted to PPB, the CTD dossier is screened for completeness and acceptability for filing, and if all is in order, assigned a CTD number, which serves as reference number. This number allows the applicant to follow up on the progress of evaluation, and serves as proof of submission.

The evaluation of submitted dossiers is on First In-First out (FIFO), based on the CTD numbers assigned at the time of submission. If the product meets the fast track criteria, that is, locally manufactured or is a priority medicine, will be given priority over products and be evaluated in a shorter time. A priority medicine is a product indicated for conditions and diseases where no alternative medicine is registered for treatment. If an applicant provides adequate information to demonstrate significant advantages that the product has over the products in the market, in terms of safety and efficacy for treatment and prevention of life threatening diseases, it qualifies for fast track.

The Technical Evaluation Committee composed of PPB, Drug Registration and Evaluation department members, does the evaluation of pharmaceutical product dossiers. Once the preliminary assessment is complete, the primary evaluator compiles an evaluation report which is forwarded to a second evaluator for review, who may make necessary comments and amendments, before finalizing the report. The final report is then archived at PPB for reference purposes, and any queries raised by the evaluators are communicated to the applicant in the form of a query letter.

The query letter is raised and issued to the respective applicant, with a requirement to provide adequate and relevant responses to the queries before a marketing authorization is issued. If the responses provided by the applicant satisfactorily meet the queries raised by the evaluator, the product is recommended for registration. If the responses provided fail to meet the evaluator's expectations, a second query letter is issued to the applicant to provide additional information.

Once the applicant provides satisfactory responses to the queries raised, a conclusion of the application is made. The last step involves presenting the summarized recommendations of evaluation, results from pre-registration analysis and GMP status reports before the Committee on Drug Registration for consideration. After the committee reviews the reports, a decision is made on whether to approve or reject the product for registration. In certain instances, where there are unresolved issues of quality, safety or efficacy of the product, the Committee may delay the issuing approval for the product until the issues are resolved.

The applicant is required to submit to PPB the additional requested information on the query letter within six months, failure to which the product application for registration may be rejected. In case of product is approved for registration by PPB, a registration certificate valid for the year in which the product is registered is issued. Complete applications should be processed within twelve months after initial submission (Pharmacy and Poisons Board, 2010).

There has been a lot of research into pharmaceutical access but little on the regulatory authorities ensuring quality standards of the medicine (Pezzola and Sweet, 2016). However, there are no studies in literature reported on the dossier review process in Kenya. This work therefore will provide important information gap in this area.

CHAPTER 3: METHODOLOGY

3.1 Study Design

A retrospective descriptive study of the pharmaceutical dossiers submitted at PPB over a five-year period (2010 to 2014) was conducted. Data was collected between May and December 2016. Information was collected on the therapeutic categories of the products submitted for registration, average time taken from the time of submission of the dossier to the time of registration and the adequacy of the compiled documents submitted by applicants for registration. The reason for any product dossier that was rejected for registration by the PPB was documented. Further, information was obtained on the major factors that influenced turnaround times for dossier evaluation at PPB. Data was extracted from the selected dossiers using a predesigned data collection sheet (**Appendix 1**). A comparison of the stipulated drug registration guidelines from Kenya (Pharmacy and Poisons Board, 2010), Tanzania (Tanzania Food and Drugs Authority, 2015), Uganda (National Drug Authority, 2018) and EAC-MRH (East African Community-Medicines Regulatory Harmonisation, 2014) was done, and any similarities and differences in the processes were noted.

3.2 Study Area Description

The study was conducted at the Pharmacy and Poisons Board, whose offices are located along Lenana Road, Hurlingham, Nairobi. The Pharmacy and Poisons Board is the Drug Regulatory authority in Kenya established under the Pharmacy and Poisons Act, CAP 244 of the laws of Kenya. The Board regulates the Pharmacy Practice and the manufacture of drugs and poisons. It also implements appropriate regulatory measures to ensure that the products registered in Kenya, meet the standards of quality, safety and efficacy. The PPB, through its Inspectorate division, carries out inspections to ensure that the manufacturing sites for the finished pharmaceutical products marketed in Kenya, both local and foreign, comply to Good Manufacturing Practices(GMP). This division also carries out routine surveillance to ensure that the registered wholesalers and retailers comply with Good Distribution Practices (GDP) for effective, efficient, safe handling, storage and distribution of the medicinal products in the country.

The Drug Registration Department at PPB is responsible for the receipt and evaluations of new drug applications, of both local and foreign products. All the dossiers received, both the soft and hard copies, are kept at the drug registration department registry for a period of five years.

3.3 Study Population

The pharmaceutical dossiers of interest were dossier submissions at the Pharmacy and Poisons Board between 2010 and 2014.

3.3.1 Inclusion Criteria

The dossiers that were included in the study were those that fulfilled the following criteria: They were pharmaceutical product dossiers submitted between 2010 and 2014, products that were pharmaceutical in nature, and that the dossiers were complete with all the required modules.

3.3.2 Exclusion Criteria:

The dossiers that were not included in the study were those that were submitted before 2010 and after 2014, products that were not pharmaceutical in nature that is food supplements, herbal or borderline products, and dossiers that had inadequate information and were incomplete.

3.4 Sample size determination

From SIAMED, the WHO Model System for Computer Assisted Drug Registration used by PPB, it was established from January 2010 to December 2014 a total of 3062 pharmaceutical dossiers were submitted to the Pharmacy and Poisons Board. The data retrieved only contained the brand name of the product, the respective CTD number and the date of submission. To ensure that the sample size obtained was a true representation of the total population, the 3062 products were further classified into their respective therapeutic categories. This was done by quick search of the brand name of the product in the internet, the British National Formulary (British National Formulary, 2012) and Drug-Index.it (Kimotho, 2016). From the INN of the product, the products were classified into their respective therapeutic categories. 330 of the products on the list could

not be classified, as searches for the brand names on the internet and the Drug Index did not yield results; hence, the dossier files that could be used in this study were 2723 files.

The Yamane formula for calculating sample sizes was used to calculate the sample size at 95% confidence level and ***e*** the precision level of 0.05 (Yamane, 1967)

$$n = N/(1 + N(e)^2)$$ .....**Equation 1**

Where ***n*** is the sample size, **N** is the population size, and ***e*** is the level of precision.

n= $2723 \div (1 + 2723(0.05)^2)$

n = $2723 \div (1 + 2723 \times 0.0025)$

n= $2723 \div 7.8075$

n= 348 dossiers

A sample of 347 dossiers was therefore reviewed.

3.5 Sampling Method

Pharmaceutical dossiers are kept in the registry at the Pharmacy and Poisons Board. The first step in sampling involved identifying the dossiers submitted in the period between January 2010 and December 2014 using SIAMED, a WHO Model System for Computer Assisted Drug Registration, which provided the CTD number, trade name and the date of submission. A total of 3062 product files were retrieved from SIAMED for this period.

For the purpose of this study, the products were classified into nineteen different categories: Anti-inflammatory, anti-allergy, antibacterial, anti-diabetic, antifungal, antihypertensive, anti-malarials, anti-neoplastic, anti-protozoal, anti-viral, biologicals, CNS, CVS, gastrointestinal, Intravenous fluids(IV), respiratory, veterinary and some products were broadly classed as others. This included dermatological preparations, wound care products and nutrition and blood products.

Of the 3062 files initially retrieved, 330 product names could not be classified from the desktop review, and these were excluded from the study. Also excluded from the study were vitamins and herbal products. This left a total of 2073 files for the study. From the fourteen categories determined for the products, their respective ratios were established based on the number of files in each class. By use of computer software, 347 files were randomly selected from the 2073 files in their respective strata and ratios.

3.6 Training Procedures and Pilot Study

The principal researcher trained beforehand three research assistants on the data collection procedure. The training took place at outside the registry at the Pharmacy and Poisons Board to check on the ease and suitability of the data collection and process. Data was collected and entered into the appended data collection form to check for its suitability in data collection. Any changes that were noted were incorporated before the main study began.

3.7 Data Collection

Three trained research assistants assisted the principal researcher to extract data from the selected files. The CTD number of the dossier was noted down and counterchecked to avoid duplication. Each form was assigned a unique reference number corresponding to the respective CTD number. A data collection tool (Appendix 1) was used to collect all the necessary information for this research

3.8 Data Collection Instrument

The data collected from the dossiers included the GMP compliance of the manufacturing sites, dosage formulation, legal categorization of the product, stability data availability for the drug substance and the drug product, and the marketing authorization status of the products. Also of interest is availability of comparative dissolution profiles for solid formulations and bioequivalence studies for generic products to show bioequivalence with comparator innovator product.

The data initially extracted from SIAMED provided the respective dates of submission for the product. For each dossier, information on the outcome of evaluation and the dates the products were recommended for registration was obtained from the minutes of evaluation that could only be accessed by an authorized PPB staff.

3.9. Variables

Independent variables included the administrative particulars of the product such as the therapeutic class of the product, the GMP status of the manufacturing site, Certificate of Pharmaceutical Product, pre-registration analysis of the product and the summary of product characteristics.
Dependent variables included product specifications, method of analysis and variation, dossier evaluation time, and recommendation for registration certificate.

3.10 Quality Assurance Procedures

The data collection forms were pretested before use. Any inadequacies or inconsistencies noted from the pilot study, and the necessary modifications were made. After the data collection was completed, the data entry was done which was followed by data cleaning before data analysis.

3.11 Data management and Analysis

Data was collected using the data collection tool and entered into a password protected Microsoft Access database, as well as MS Excel before being exported to STATA 14 for analysis. The hard copy data forms were stored in a lockable cabinet in the PPB registry during collection. These were moved to a lockable cabinet in the statistician's office during data entry and analysis. Upon completion of data entry, the hard copy forms were compared with the entered data to identify errors and corrections made appropriately.

The time taken to obtain registration was calculated as a difference between the date of submission and the date the product was recommended for registration. Given that from the data set, only 271 products were registered at the time of this study, further analysis was restricted was restricted to

these products.

The Shapiro-Wilk test was used to determine whether continuous variables were normally distributed. Histograms of continuous data were used to determine data distribution. Variables that were not normally distributed were summarized as the median and the inter-quartile range (IQR). Variables that were normally distributed were summarized as the mean and standard deviation (SD) of the mean.

A comparative study was done on the PPB, NDA, TFDA and EAC-MER Compendium guidelines. These guidelines were retrieved from each of the respective regulatory authority's official website.

CHAPTER 4: RESULTS AND DISCUSSION

4.1 Introduction

In this chapter, data is presented from the study in line with the research objectives. First, a comparison between pharmaceutical dossier evaluation in Kenya and regional guidelines is presented. This highlights the key similarities and differences in the dossier requirements, as well as the processes and procedures followed by the regulatory authority before a marketing authorization is granted. The time taken to obtain registration for the selected products is discussed, with a discussion on the key factors that influence turnaround time for products submitted. Lastly, the profile of products submitted and registered between 2010 and 2014 is discussed, in terms of therapeutic class, country of origin, dosage formulation, shelf-life and storage conditions and the legal category.

4.2 Comparison of PPB drug registration guidelines with regional guidelines

A comparison was done on drug registration guidelines from PPB (Kenya), National Drug Authority (NDA) from Uganda, Tanzania Food and Drugs Authority (TFDA) from Tanzania, and the EAC-MRH Guidelines. This was done to assess similarities and differences in regulatory practices in drug registration.

It is important for a medicine regulatory authority to regularly review practices and procedures, and assess its performance against established international qualitative and quantitative benchmarks. This will help agencies evaluate and develop strategies to promote timely access of essential medicine to patients in their territories (Hashan *et al.*, 2016)

From the guidelines studied, the dossiers in the respective countries have to be prepared in the CTD format, with the requisite five modules. Module 1 of the dossier is country specific, and documents are compiled in accordance to the stipulated guidelines in each country. The key differences and similarities in the information to be provided in the dossiers, as per the guidelines studied are presented in Table 2 in the following page.

Table 2: Comparison of PPB guidelines, with NDA, TFDA and EAC-MRH compendium guidelines

	PPB GUIDELINES (KENYA)	NDA GUIDELINES (UGANDA)	TFDA GUIDELINES (TANZANIA)	EAC-MER Compendium
Dossier format	CTD format	CTD format	CTD format	CTD format
Dossier language	Language used for dossiers-English	Language used for dossiers -English	Language used for dossiers should be English	Language for dossiers-English
Product information language	Product information, Language English/Kiswahili	Product information must be presented at least in English; any other language may be used in addition provided it does not affect readability.	Product information, Language used should be English or Kiswahili	Product information-Language requirement is English and French
GMP certificate	PPB GMP Certificate is mandatory/Evidence of application for GMP	NDA GMP required/ evidence of application for GMP	TFDA GMP certificate/application for GMP required	GMP- for EAC-NMRA and/or SRA is sufficient
Requirement of Certificate of Pharmaceutical Product (CPP)	Required	Required	Required	Required
Pre-registration analysis requirement	Pre-registration analysis is a requirement	Pre-registration analysis is not mandatory	Not a requirement	Pre-registration analysis is not required
Requirement of information about the experts	Info about the experts not a requirement	Info about the experts is required; a signed declaration form is in the ascribed format.	Info about the experts is required, with signed declaration form	Information about the experts is required
Evidence of WHO prequalification	Not a requirement	Not required	Required	Evidence of WHO Prequalification required
Regulatory status in SRA	Not a requirement	Regulatory status in SRA is required	Required	Regulatory status in SRA

Appointment of Local Technical Representative(LTR)	LTR is mandatory	LTR letter is required	LOA not mandatory	LTR not a requirement
Appointment of person responsible for pharmacovigilance(PV)	Person responsible for PV Not a requirement	This is a requirement	Not a requirement	Person responsible for PV required(1.18)
Options for registration	Registration in per PD route	PD route	PD route	4 options for registration; 1. CEP 2. EAC-APIMF 3. PD 4. Recognition of WHO PQ Products
Processing time	Processing within 12 months	Processing within 12 months	Processing FIFO-12 months	Processing-FIFO within 12 months
Container Labelling	Is general (for primary and secondary packaging labeling). Control of labeling is as per variations guidelines	More defined and specific (For primary and secondary packaging). Needs to conform to the summary of Product characteristics	More defined and specific (For primary and secondary packaging). Needs to conform to the summary of Product characteristics.	Labelling requirements are more refined in the EAC compared to the PPB. It also includes other requirements for individual EAC states (and small volume containers).
Outer Packaging	Site of Manufacturing is a must on secondary (Site responsible for release)	Physical site responsible for release of the product required	Physical site responsible for release of the product required	Physical site responsible for release of the product required
	The name and physical address of the manufacturing site is mandatory (A logo maybe included	The name and physical address of the manufacturing site-or a logo maybe included	The name and physical address of the manufacturing site-or a logo maybe included	The name and physical address of the manufacturing site-or a logo maybe included

	Not a requirement for Kenya	Directions for use is included on blister pack	Directions for use included for blister pack	Direction for use is included in blister pack
	Batch number, Manufacturing date and expiry date is mandatory	Batch number and expiry date included. Manufacturing date only added if space is enough(for small containers)	Batch number and expiry date included. Manufacturing date only added if space is enough.(For small containers)	Batch number & expiry date is mandatory. Manufacturing date is optional (if space is available)
	The name and address of MAH is a requirement (Not been practiced)	The name and address of MAH is a requirement	The name and address of MAH is a requirement	The name and address of the Marketing Authorization Holder is a requirement
	Proprietary name/strength & Expiry date in Braille in addition (not a requirement)	Proprietary name, strength and expiry date in Braille(Marburg Medium)	Proprietary name/strength & Expiry date in Braille in addition	Proprietary name/strength & Expiry date in Braille in addition
	Not a requirement	The word "sterile" if the product is sterile	The word "sterile" if the product is sterile	The word "sterile" if the product is sterile
	Not a requirement	Registration number issued by NDA	The registration number issued by TFDA	Not specified
Ascribed format for Quality Overall Summary in Module 2 (QOS-PD)	Section 2.3 No requirement of QOS-PD(Annex IV)	Section 2.3 QOS-PD in ascribed format required.	Section 2.3 QOS-PD in ascribed format required.	Requirement to complete Annex IV(QOS-PD)
Batch analysis for API	Sec 3.2.S.4.4 (Sec 3.2.1.4.4): Batch analysis is not provided for in PPB guidelines. However, it is provided for in PPB application form.	Sec 3.2.S.4.4 (Sec 3.2.1.4.4): Batch analysis is provided for in NDA Guidelines	Sec 3.2.S.4.4 (Sec 3.2.1.4.4): Batch analysis is provided for in TFDA Guidelines	Sec 3.2.S.4.4 (Sec 3.2.1.4.4): Batch analysis is provided for in EAC MER guidelines

Stability data for API	Stability data is for PD route	Stability data is for PD route	Sec 3.2.S.7 stability data: provide documents for: •option 2-CEP, •option 3-API prequalified WHO •Option 4- APIMF	Sec 3.2.S.7 stability data: provide documents for: •option 2-CEP, •option 3-API prequalified WHO •Option 4- EAC APIMF
Interchangeability of generic drugs-Module 5	Outlined in sec 5.2 on interchangeability	Identical to PPB Guidelines	Identical to PPB Guidelines	Guidelines on Biopharmaceutics and Bio waiver is separate from drug registration guidelines

Key:- API- Active Pharmaceutical Ingredient, CEP-Certificate of Suitability, CTD-Common Technical Document, CPP-Certificate of Pharmaceutical Product, EAC-East African Community, EAC-APIMF(East African Community-Active Pharmaceutical Ingredient Master File), EAC-NMRA(East African Community-National Medicine Regulatory Authority), FIFO-First In First Out, GMP-Good Manufacturing Practice, LOA- Letter of Appointment, MAH- Marketing Authorization Holder, PD-Product Dossier, PQ-Prequalification, PV-Pharmacovigilance, SRA-Stringent Regulatory Authority, WHO-World Health Organization

The process of drug registration in Kenya was found to be comparable to the process that is followed in Uganda, Tanzania and by the EAC-Compendium. For all the NMRA studied, the dossier is to be prepared in CTD format, with five modules and the language to be used is English. The first module, Module 1, is country specific and prepared in accordance to the stipulated guidelines issued by the respective MRA. Most of the regulatory requirements and procedures are similar for Kenya, Uganda, Tanzania and EAC-Compendium. All the regulatory bodies require provision of provide a CPP (Certificate of Pharmaceutical Product) and Manufacturing authorization for the FPP manufacturer to confirm that the product is licensed and marketed in the country of origin. There is a requirement to provide a valid GMP certificate for the FPP manufacturer to ensure that the products are manufactured in an approved site, to maintain the required standards of quality, safety and efficacy (Yano *et al*., 2016).

All the guidelines studied require provision of product information, that is, the Summary of product characteristics (SmPC), Labelling (primary and secondary packaging) mockups, and the information leaflet. Kenya requires the provision of a Prescriber Information Leaflet intended for the qualified healthcare professional, whereas for Uganda and TFDA Patient Information Leaflet is sufficient. The packaging should have one of the languages as English and any other language, in most instances Kiswahili (Pharmacy and Poisons Board, 2010).

According to the guidelines for TFDA, NDA and PPB, the processing time for the dossier upon submission to MRA is stated as 12 months. For PPB, once a product dossier is assessed, the applicant is issued with a query letter, and is required to provide appropriate and sufficient information upon issuance of a query letter from NMRA within 6 months. For EAC-Compendium, the processing time and approval of the product should be within 12 months.

There are a few differences in regulatory requirements for the regulatory bodies studied. For instance, in order to submit the dossier to PPB and NDA, the applicant needs to have appointed a local technical representative (LTR), with registered offices in the respective territory who should be responsible for all matters technical and commercial in the specified country, as well as submit the dossier on the applicant's behalf. The power of attorney appointing the LTR should be provided in Module 1 of the dossier. This is not mandatory in for TFDA or the EAC-Compendium. In

addition, there is also a requirement by NDA Uganda to the applicant states the qualified person responsible for pharmacovigilance (QPPV), who will be responsible for handling pharmacovigilance on behalf of the applicant, for the product to be registered. This is not required for Kenya, Tanzania or EAC-Compendium.

There is also a requirement for product pre-registration analysis is a requirement in Kenya. This is where the applicant is required to submit sufficient samples to accredited labs, that is, Drug Analysis and Research Unit (DARU), at the University of Nairobi, Mission for Essential Drugs and Supplies (MEDS) Laboratory, and National Quality Control Laboratory (NQCL) for pre-registration analysis to confirm that the product to be registered meets the specified quality standards. The acknowledgement of submission of samples to the lab that is, the signed laboratory request form or the respective Certificate of Analysis (CoA) if available is then included in Module 1 of the dossier. Whereas this is a mandatory requirement for new applications in Kenya, this is not a requirement for Uganda or for Tanzania (Tanzania Food and Drugs Authority, 2015).

For Uganda, Tanzania, and EAC, there is a requirement to provide information about the experts in Module 1. The experts must provide detailed reports of technical information provided in Modules 3, 4 and 5. The reports have to be the experts' independent assessment of the information provided in the dossier, and any additional references must be provided (East African Community-Medicines Regulatory Harmonisation, 2014) In essence, the signed reports or declarations should be from the quality expert, non-clinical expert and clinical expert. The experts are also required to provide their curriculum vitae (CV), to provide information on the educational background, training and professional experience. Information on the experts is not required in Kenya. Depending on the applicant's organization structure, and the products of interest, these may not be readily available and could affect completeness of the documents submitted in the affected countries. Further, this may affect processing times if requested by the authority and is not readily available.

In the Module 2 of the dossier, the applicant is required to provide chemical, pharmaceutical, non-clinical and clinical overviews and summaries. This module includes a section, Quality Overall Summary(QOS), which follows the scope and outline for Module 3, the Quality Module. For

Tanzania, Uganda, and EAC there is an ascribed format in which to provide information for the QOS, known as the Quality Overall Summary-Product Dossier (QOS-PD). There is no ascribed format for the QOS in Kenya, provided the information is sufficient. In Uganda, in addition to the QOS-PD, there is a requirement to provide a Quality Information Summary (QIS) and Bioequivalence Trial Information Form (BTIF) as separate MS-Word file whereas this is not a requirement in Kenya, nor Tanzania. The QIS is a condensed summary of key quality information in the QOS-PD, whereas the BTIF provides information on any bioavailability or bioequivalence studies performed (National Drug Authority, 2018). The information on the QOS-PD, QIS and BTIF is to be provided in ascribed templates provided in the respective guidelines. In Kenya, this information is provided as part of the CTD.

Modules 3 to 5 are similar for the dossiers submitted to PPB, NDA, TFDA and to the EAC dossiers. Module 4 is non-clinical study reports is applicable for new chemical entities only, and is not required for generic products. Module 5 is for providing clinical study reports. The information to be provided in these sections is the same for all the respective authorities, and prepared in accordance to CTD format and stipulated guidelines.

From the comparison of the guidelines, it is evident that PPB guidelines are comparable to those of NDA, TFDA and the EAC-Compendium guidelines, and those regulatory requirements and practices are similar. This makes it easier for harmonization initiatives, and for collaboration of member states (New Partnership for Africa's Development and World Health Organization, 2009)

4.3 Time taken to Obtain Registration

The time taken to obtain registration was calculated as the difference between the date of submission and the date recommended for registration A total of 347 dossiers were studied, out of which 271 had obtained registration at the time of this study which was between May 2016 to June December 2016. The categorized time taken to obtain registration is presented in Table 3 in the following page.

Table 3: Status and time taken for registration

Status and Time Taken for Registration	n	%
Registered in less than 12 months	110	31.7
Registered in more than 12 months	163	47
Pending registration	72	20.7
Rejected	2	0.6
Total	347	100

A total of 347 files were studied, and 78.7 % of the products obtained registration. Of these, majority of the products were registered in a period of more than 12 months (47 %), while 31 % were registered in less than 12 months (365days). About 20.7 % products were still pending registration at the time of the study. Given that from the data set, only 271 products (78.7 %) of the total files studied had been registered at the time of study, further analysis was only restricted to these products.

The Shapiro-Wilk test was conducted to determine if the variable time taken to obtain registration was normally distributed. The p-value was 0.000. This indicated the variable was not normally distributed. Therefore, all the data was summarized using the median and interquartile range as 413 days [IQR 283,640] as the average time for registration. This is depicted Figure 2 in the following page.

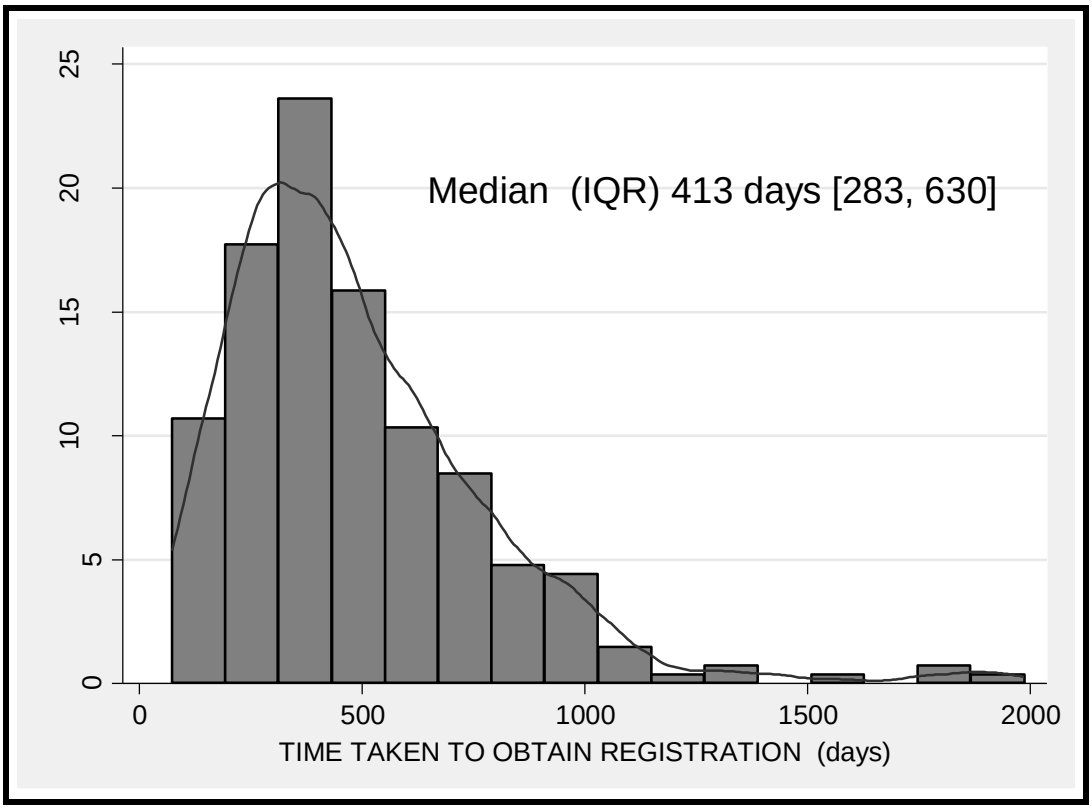

Figure 2: Time taken to Obtain Registration in Days

The PPB drug registration guidelines state that new product applications should be processed within 12 months after submission, and the applicant is required to submit adequate responses to the queries raised within 6 months upon receipt of the query letter. Should the applicant need more time to compile and provide the additional information requested, a formal letter should be made to PPB.

Locally manufactured products and priority medicine are considered for fast track registration, and complete applications are to be processed within 90 days after submission, according to the PPB Guidelines (Pharmacy and Poisons Board, 2010). Priority medicines are those that are considered to meet urgent healthcare needs in the population, and for which there is no suitable alternative available in the market (Ministry of Health, 2015). These products need to be fast-tracked to ensure steady supply and timely access of the products, to meet the urgent healthcare needs of the target population.

In a report done by NEPAD in 2010, the average registration time was assessed for the EAC countries studied. In Kenya, it was found that the average registration time was nine months in 2010, six months in 2008 and four months in 2009. In Tanzania, for the period 2007-2009, the average time taken for registration was 18 months (Kamwanja *et al.*, 2010). From the study, the average time for registration between 2010 and 2014 was 413 days, about 14 months. This is ten months more than the turnaround time in 2009. This may be attributed to the adoption of the CTD format for new applications by PPB in 2010, as it would require time for setting up adequate systems and capacity building. Despite this, the average turnaround time of 14 months is acceptable as per the stipulated total processing time in the PPB guidelines.

There were two files that were rejected for registration, which accounted for about 0.6% of the total files studied. For one of the products, the reason for rejection was that the manufacturing site of the finished pharmaceutical product failed GMP inspection by PPB. The other pharmaceutical product was rejected for registration because the product repeatedly failed pre-registration analysis, at the designated quality control laboratory.

It is important for the regulatory authority to strive to meet stipulated target times for product approval, as well as within the dossier review process, as this allows agencies and stakeholders to plan for more predictable outcomes and identify areas of improvement (Hashan *et al.*, 2016). This will also minimize delays and ensure timely access to quality, safe and efficacious medicines (Richardson *et al.*, 2018).

4.4 Factors affecting turnaround time

At the time of the study, 72 files were still pending registration, which accounted for 20.7 % of the total files study. Majority of the products had been registered in a period longer than the stipulated 12 months (40.7 %).

The major factors that affect registration timelines at the PPB are number of evaluation sittings held in a year and the time the applicant takes to adequately provide responses to the queries raised by the PPB, upon the issuance of a query letter. It is estimated and at any evaluation sitting held by PPB, an approximate of 100 dossiers are evaluated. From this, it is evident that, the number of evaluation sittings ultimately would affect registration timelines. The more sittings there are in a

year, the more dossiers are evaluated and ultimately shorter evaluation times. Upon the issuance of a query letter after initial evaluation is done by PPB, the applicant is required to provide satisfactory response to queries within six months. The faster the applicant is able to provide satisfactory response to the authority, the shorter the overall turnaround time is likely to be.

One major query that would affect the registration timeline is the requirement to provide current GMP certificate as issued by the PPB. For a first time inspection, the applicant is required to make a formal application to PPB to have the manufacturing site of the finished drug product to be inspected. Once the application is received, PPB inspectorate then plans a schedule to visit and inspect the manufacturing plants. After a successful audit of the plant by PPB, a GMP certificate is issued to the applicant that is valid for three years.

The time taken before PPB schedules an inspection to a specified plant is dependent on the location of the plant and the number of inspections planned for that specific region. This may at times take longer than anticipated. If one of the queries raised to an applicant is provision of a valid GMP, and the GMP certificate is yet to be issued, the process would be delayed until the applicant receives the certificate even when all the other queries have been addressed.

Another query that leads to delays is the requirement to provide bioequivalence study reports for some products. Bioequivalence study reports may be required for some generic pharmaceutical products to confirm that the product is therapeutically equivalent and interchangeable with the innovator reference product (Tamboli *et al*., 2010) . Bioequivalence testing has to be performed in internationally acceptable bioequivalence centers, of which most are not available in East Africa. Pharmaceutical companies have to rely on overseas institutions that charge an estimated average of USD 50,000 to USD 200,000 per drug which is too expensive for most companies (Federal Ministry for Economic Cooperation and Development(BMZ), 1997). It also takes substantial amount of time to meet the study requirements and generating the study report. Therefore, if an applicant receives a query from PPB to provide BE study report, it may lead to delays in providing the response to queries.

PPB also requires that the applicant provide COA for the product samples submitted at a local WHO prequalified lab. Given that, a COA is mandatory before the MA is granted, if laboratory has yet to provide the COA or the applicant has had to do repeat analysis. As per the guidelines,

after a query letter is issued, the applicant is given six months by PPB to provide satisfactory response. This does not happen in practice, as some applicants take more time to adequately respond to the queries raised.

4.5 Profiles of the Products Submitted and Registered:

4.5.1 Therapeutic Categories:

The products were classified into their respective therapeutic categories. In total, there were 19 designated categories that were: anti-inflammatory, anti-allergy, antibacterial, anti-diabetic, antifungal, antihypertensive, anti-malarial, anti-neoplastic, anti-protozoal, anti-viral, biological, central nervous system (CNS), gastrointestinal, cardiovascular system (CVS), intravenous fluids (IV), respiratory, veterinary and some products were broadly classed as 'others'. This included dermatological preparations, wound care products and nutrition and blood products. The distribution of the products in the various categories is illustrated in Figure 3 below.

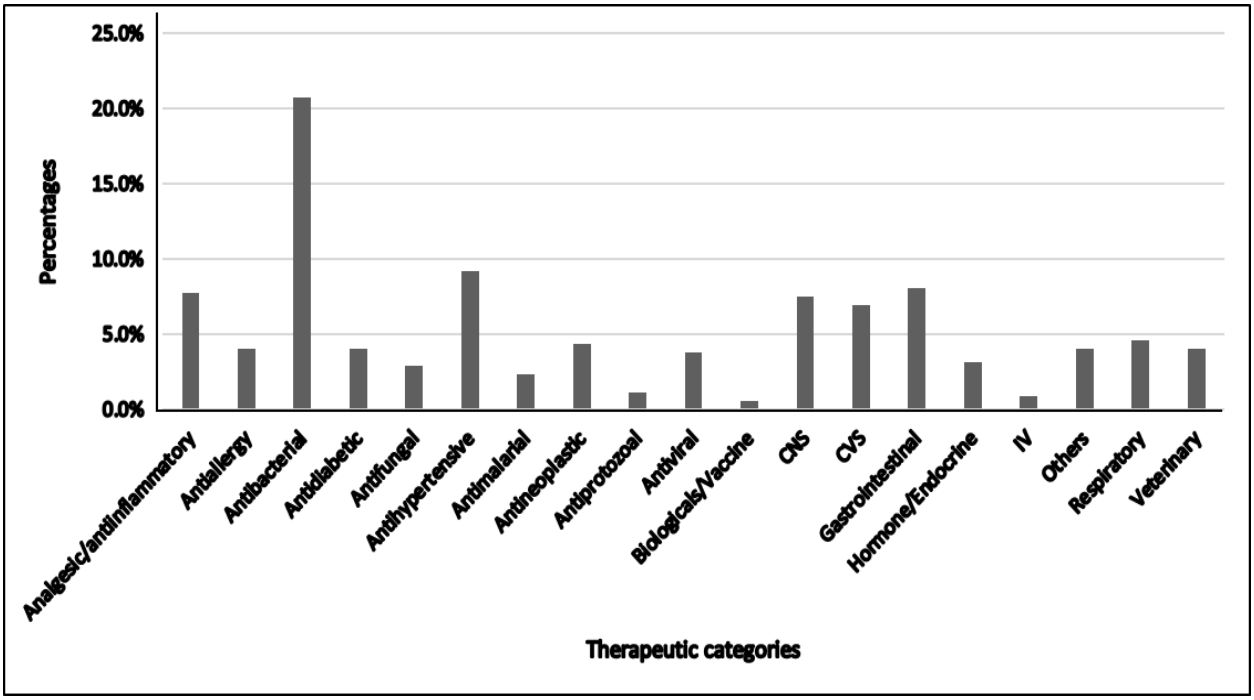

Figure 3: Therapeutic categories as a percentage of the total files studied

About 31 % of the products submitted for registration were found to be anti-infectives comprising antibacterial, antifungal, antiprotozoal, antimalarial and antiviral agents. Of these, the majority were antibacterial agents accounting for 20.8% of the total files studied time of this study.

The second and third highest categories were anti-hypertensives and gastrointestinal products, at 9.2% and 8.1% of the total products respectively. Analgesic and anti-inflammatory agents were also significantly high in number at 7.8% of the files studied. The therapeutic category with the least number of products submitted for registration, was biologicals at 0.6% of the total files studied. Biological products include but not limited to, vaccines, recombinant proteins, gene cell therapies, antibodies, blood products and components. At the time of this study, the draft guideline for biologicals was still underway. The guideline for registration of biological products has since been developed by PPB.

This trend of the therapeutic categories for the products submitted for registration seems to be in line with the disease burden in the country at the time. According to the Ministry of Health, Human Resource Strategy 2014-2018, communicable and non-communicable diseases (NCD) and violence or injuries contributed to highly to disease burden and mortality in the country. In 2012, pneumonia was the leading cause of death, followed by malaria and thirdly cancer that has been on the increase.

Non-communicable diseases (NCDs) have been on the increase in the recent years, and this attributable to the rise in the middle income class with changes in lifestyle that is physical inactivity, dietary changes and increase in alcohol consumption and smoking (Ministry of Medical Services and Ministry of Public Health and Sanitation, 2009). This may explain the high numbers of anti-infectives and anti-hypertensives in an effort to adequately meet the healthcare needs of the population.

4.5.2 Dosage Form Distribution

Drug substances are rarely administered to the patient as active ingredients, but instead are given as part of a formulation that includes one or more non-medicinal agents commonly known as excipients. These excipients serve varied and specialized pharmaceutical functions. The

combination of the drug substance and the excipient produces various types of dosage forms, with each form being unique in pharmaceutical and chemical characteristics.

Regardless of the dosage form, there needs to be compatibility between the drug substance and the excipients to ensure that the drug product produced is stable, safe, efficacious, attractive and easy to administer (Allen *et al*., 2005).

For this study, the products were divided into 11 dosage forms, which were tablets, injectable, capsules, suspensions, syrups, crèmes, ointments, and solutions for injection, solutions, eye/ear drop and other dosage forms. Other dosage forms included suppositories, pessaries, patches and inhalers. The different types of dosage forms are as shown in Table 4 below.

Table 4: Dosage forms

Formulation	n	%
Tablets	171	49.3
Injectables	57	16.4
Capsules	37	10.7
Suspensions	18	5.2
Syrups	15	4.3
Creams	4	1.2
Ointments	2	0.6
Solutions for injection	6	1.7
Solutions	9	2.6
Eye/ear drops	8	2.3
Other dosage forms	16	4.6

The most frequently submitted dosage form was tablets at 49.3 %, followed by injectables at 16.4 % and thirdly capsules at 10.7 %.

Tablets are the most widely distributed form, with 70 % of the total medicines marketed being in the tablet form. The tablet dosage form offers greater dosage precision and least content variability. It is suitable for large-scale production as it is associated with low cost of production, which would mean higher returns for the manufacturer. In terms of stability, it offers great chemical and microbial stability over other thus ensuring quality of the product is maintained throughout the product life cycle (Manimaran, 2012).

The second most submitted dosage form is injectable which offers several advantages over other dosage forms especially in hospitals. This is because they offer immediate physiological action in case of emergency and are useful for uncooperative patients. Parenteral form is also used for drugs that are not readily absorbed after oral administration (Krupadanam *et al*, 2001).

Creams and ointments were the least submitted for registration (1.2 % and 0.6 %, respectively). This may be attributed to the fact that ointments may not be popular with the patients of the target market, as ointments are generally greasy and difficult to wash off from skin. There have been problems with drug release especially if the product has limited solubility and ointment base. Creams and ointments also have low chemical and microbial stability (Damodharan, 2016)

4.5.3 Shelf-life of the products:

The shelf-life of a product is the length of time that a drug product is expected to remain within its registered specifications when stored under stipulated conditions, from the manufacturing date (Puglielli, 2014).

Most of the products submitted for registration at PPB during the study period had an assigned shelf life of 2-3 years, and collectively 94 % of the products were found to be within this range. The products that had shelf life of less than two years included some antibiotics and biologicals, which were highly unstable (Table 5).

The factors that determine the degree and rate of degradation can either be divided into environmental (moisture, heat and light) or product related such as the physico-chemical properties of the active substance and excipients, dosage form and packaging.

Products marketed within a specified territory should remain stable under a wide range of conditions of temperature and humidity to ensure satisfactory shelf life. Ideally, the shelf life

should allow sufficient time for manufacture of the pharmaceutical product, transportation, storage and finally sale to the patient. For oral solid dosage forms, minimum acceptable shelf life is 24 months (World Health Organization, 1997) .

Table 5: Shelf-life of products

Shelf-life (months)	n	%
6	1	0.3
12	2	0.6
18	5	1.4
24	196	56.5
30	4	1.2
36	133	38.3
48	6	1.7

4.5.4 Storage conditions:

The storage condition of a product is important to ensure the pharmaceutical product remains stable throughout its shelf life. Kenya is in climatic Zone IVa according to ICH stability zones which means long term stability data has to be provided at temperatures of 30°C ±2°C and humidity of 65 % ± 5% RH (World Health Organization, 2016).

As part of the requirements for registration, most of the pharmaceutical products have to submit stability data at these conditions and have specific storage instructions on the pack for store below 30 °C. For this study, six possible storage conditions were used for the submitted products. Table 6 below provides a summary:

Table 6: Storage conditions

Storage conditions	n	%
Does not require special storage conditions	4	1.2
Store at 20°C-25°C	5	1.4
Store below 25°C	75	21.6

Store below 30°C	218	62.8
Store in a fridge 2°C-8°C	11	3.17
Store in a cool dry place	34	9.8

The stability data submitted by the applicant must demonstrate to the regulatory authority the product will remain stable throughout its assigned shelf life in the target market, under the respective climatic conditions (International Conference on Harmonisation, 2008)

From the dossiers studied, it was established that 62.8 % of the products had assigned storage conditions, of "Store below 30°C", and 21.6 % at "Store below 25 °C". This demonstrates that most of the applications complied with the specified storage conditions as per the stipulated PPB guidelines on drug registration(Pharmacy and Poisons Board, 2010). There may be exceptions for some products to have labelled storage conditions of "Store below 25 °C", if sufficient justification is provided by the applicant and there is demonstrable need for the product in the market.

4.5.5 Legal category:

The legal category of the product refers to its scheduling, which is a national classification system of medical products based on benefits and safety risk profile, that controls and regulates how medicines are to be made available to the public(Therapeutic Goods Administration, 2010).

In Kenya, scheduling of medicine is one of the core elements in the Pharmacy and Poisons Act. Drugs are classified into various categories based on the institution and professional level at which the drug may be prescribed and dispensed. They are broadly divided into Part I and Part II Poisons. Part I poisons are only to be dispensed to the patient by a registered pharmacist, and this comprises Schedule I (Prescription Only Medicine) and Schedule II (Pharmacy Only Medicine). Prescription Only Medicine (POM) can only be sold to the patient through a valid prescription from a medical doctor, dentist or veterinary doctor. Pharmacy Only Medicine is a small group of medicine that can be obtained from pharmacy without prescription but are not available for self-selection.

Part II Poisons can be dispensed by registered pharmacist and any other authorized personnel. This includes Schedule III medicine can be dispensed by registered pharmacist or pharmaceutical technologist by an authorized prescriber. It also includes Schedule IV medicine which is Over-the-

Counter (OTC) that is sold in authorized pharmacies without a prescription (Ministry of Health, 1994). A new scheduling policy in Kenya is currently underway.

For this study, the legal categories were derived from PPB Guideline on New Applications (Pharmacy and Poisons Board, 2010). These were: general sales, over-the-counter medicine (OTC), pharmacy only medicine and prescription only Medicine (POM). General Sales medicines are those that are available off the shelf and can be dispensed by individuals with no pharmacy training. They can be sold in supermarkets (Aronson, 2009).

The legal categories for the products submitted in the study period are shown in Table 7.

Table 7: Legal categories

Legal category	n	%
General sales	3	0.9
OTC	6	1.7
Pharmacy Only	6	1.7
Prescription only medicine	332	95.7

Almost all of the products submitted for registration were Prescription only medicine (POM) 95.7%. Only 0.9 % of the products were general sales and OTC medicine was at 1.7 %.

When medicine first is introduced into the market, it is by default scheduled as prescription only medicine (POM). This is to promote rational drug use and to ensure the quality, safety and efficacy of the product is maintained, until eventual dispensing to the patient. The medicine may later be rescheduled to non-prescription schedules by regulatory authority based on criteria such as low potential for misuse and abuse, efficacy of medicine, low potential for harm, and ability of consumer to diagnose and manage minor ailments (Aronson, 2009) .

4.5.6 Origin of the Drug Product:

The origin of the pharmaceutical product was studied. For this purpose, the products were broadly divided into eight broad categories, which could be either a region or a country. These categories were Kenya, East Africa, South Africa, Middle East, India, Asia, America and Europe.

This is shown in Table 8 in the below.

Table 8: Country or Region of Origin

Region/Country	n	%
Kenya	45	13.0
East Africa	3	0.9
South Africa	3	0.9
Middle East	10	2.9
India	199	57.4
Asia	35	10.1
America	6	1.7
Europe	46	13.3

More than half of the products submitted for registration come from India, and Asia region (67.5 % collectively). 13.3 % of the products registered at the time of the study were from Europe and only 1.8 % was from African countries collectively. Locally produced products submitted were 13% of the total files studied.

India is among the highest generic pharmaceutical product producers worldwide and contributes an estimated 20% of global generic product exports. Among the compelling reasons for the rise in India's pharmaceutical stature include inexpensive labor, lower production costs, strong government support and lower research and development costs. It is estimated that the production costs are 60 % cheaper than the US and 50 % cheaper than UK (Van, 2016) .

It is interesting to note that a high number of pharmaceutical products submitted for registration (13.3 %) originated from Europe. This can be attributed to the rise in middle-income class in developing countries, Kenya included, who are able to afford essential health care from private institutions and have access to medical insurance. With this greater purchasing power and improved market access, there is continuous infiltration and growth of innovative products in these markets(Howard, 2015)

Locally produced products formed 13.0 % of the product dossiers studied. According to the Kenya National Drug Policy, to encourage local production of pharmaceutical products both for local and export markets, the local pharmaceutical manufacturers should be given support and incentives such as duty remissions (Ministry of Health, 1994). This coupled with the reduced registration times and lower fees for registration, encourages growth of local pharmaceutical and products in the market(Pharmacy and Poisons Board, 2010). Despite this, the local pharmaceutical manufacturers face stiff competition from their imported counterparts. This could be attributed to competitive pricing of imported generic products, lack of the technical capacity to manufacture some products such as vaccines and economies of scale (Management Sciences for Health, 2012b)

CHAPTER 5: CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

The drug registration requirements and practices followed by PPB are comparable to those of NDA, TFDA, and EAC–Compendium. The dossiers are prepared in CTD format, and the language used in the dossiers is English. All the guidelines are based on WHO Guidelines and ICH guidelines on drug registration. The average processing time for the dossiers by PPB as per the stipulated guidelines should be 12 months comparable guidelines by NDA and TFDA. The EAC-Compendium guidelines clearly state that the processing time and approval should not take more than 12 months.

The average time taken in the study period for a product to obtain registration after initial submission to PPB was approximately 14 months. According to the PPB guidelines on drug registration, the processing time for dossiers after initial submission is 12 months, and the queries raised from the evaluation are sent to the applicant. The applicant is given 6 months to adequately respond to the queries raised after which a marketing authorization may be issued.

The major factors that determine turnaround time are the number of evaluation meetings held by the PPB to assess and review the dossiers submitted, and the time taken applicant takes to adequately respond to the queries as per the query letter issued by PPB.

The most common therapeutic class of products submitted for registration were anti-infectives (31 %) that included antibacterial, antifungal, antiprotozoal, antimalarial and antivirals. This was in line with the burden of infectious diseases in Kenya between 2010 and 2014.

5.2 Recommendations and Future Work

PPB can look into ways to identify gaps and continually improve practices in dossier review. One of the ways would be creating robust systems for dossier monitoring with definite target times for key milestones in the dossier review process. This will allow PPB and stakeholders to plan for

more predictable outcomes, which will in turn ensure timely introduction of medicines into the market.

PPB can also consider risk-based approach for assessment of dossiers or take up abridged review. This may help minimize duplication of work and unnecessary delays, especially for products that are already registered by a stringent regulatory authority.

5.3 Study Limitations

The study relied on the information in the dossiers as submitted by the applicant at the time of initial application. There was no access to the queries raised after evaluation of the dossiers, or the respective query responses submitted by the applicant as these are considered highly classified. This information was extracted from SIAMED and minutes of PPB evaluation committee, which could only by accessed by authorized PPB staff. It was therefore difficult to accurately establish the specific factors that caused delay in the turnaround times for the products that were pending registration.

Secondly, of the 347 files randomly selected only 273 of the product had been recommended for registration at the time of study so further analysis was limited to only the files that had completed the registration process.

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APPENDIX 1:

For the study "A Retrospective Review of the Pharmaceutical Dossiers Submitted at Pharmacy and Poisons Board between 2010 and 2014"

General information

1. Date of data collection:…….
2. Product identification number:……
3. Date of dossier submission:……
4. Therapeutic Classification: …….
5. Product recommended for Certificate?☐Yes ☐No
6. If Yes, Date of recommendation:……..
   Is it within twelve months post submission? ☐Yes ☐No

   If No, Give reasons:
   - ☐ Delay in obtaining COA from pre-qualified lab
   - ☐ Delay in obtaining GMP
   - ☐ Delayed in response to queries by applicant
   - ☐ Delay in evaluation post submission and resubmission
   - ☐ Others (specify):……..

7. If Product was not approved for registration, give reason for rejection:
   - ☐ Failed to comply with analytical standards
   - ☐ Failed GMP compliance
   - ☐ Lack of COPP
   - ☐ Others (specify)

8. Did the applicant appeal the decision (if rejected):?

   Outcome of Appeal:

Module 1: Administrative Particulars

1. International non-proprietary name (INN) of API:

   …….

2. Strength of API per Unit dosage:

   …….

3. Dosage form: *Tick as appropriate*
   - ☐ Tablet
   - ☐ Syrup
   - ☐ Suspension
   - ☐ Injection
   - ☐ Ointment
   - ☐ Crème
   - ☐ Oral powder
   - ☐ Others(Specify)
4. Proposed shelf life:
   - ☐ Less than 24months
   - ☐ 24 months
   - ☐ 30 months
   - ☐ 36 months
   - ☐ Others(specify)
5. Preferred storage conditions:
   - ☐ Store in a refrigerator 2-8ºC
   - ☐ Store below 25º C
   - ☐ Store below 30ºC
   - ☐ Does not require special storage conditions
   - ☐ Others(Specify)
6. Pharmacotherapeutic group:
   - ☐ Antibacterial
   - ☐ Antiprotozoal
   - ☐ Antiviral

- ☐ Analgesic/Anti-inflammatory
- ☐ Antihypertensive
- ☐ Anti-diabetic
- ☐ Hormone/Endocrine medicine/ and Contraceptives
- ☐ Gastrointestinal
- ☐ Antineoplastic and immunosuppressive agents
- ☐ Medicine for respiratory disorders
- ☐ Blood products of Human Origin& Plasma substitutes
- ☐ Biological e.g. Vaccines, Immunoglobulins
- ☐ Other(specify):

7. Legal category:
   - ☐ Controlled medicine
   - ☐ Pharmacy only
   - ☐ Prescription only
   - ☐ Over the counter(OTC)
   - ☐ General sales product
8. Country of origin or release: ……...
9. Certificate of Pharmaceutical Product(COPP) available? ☐Yes ☐No
10. Good Manufacturing Practice (GMP) status of the manufacturer (s) of the finished product(FPP)
    - ☐ Applied for (Receipt of payment attached)
    - ☐ Complied
    - ☐ Not complied
    - ☐ Others (specify):…….
11. Has the product been submitted to WHO prequalified lab? ☐Yes☐No

Name of laboratory:

- ☐ Mission for Essential Drugs and Supplies(MEDS)
- ☐ Drug Research and Analysis Unit(DARU)
- ☐ National Quality Control Laboratory(NQCL)
- ☐ Other (specify):……..

Certificate of Analysis available? ☐Yes ☐No

Outcome of pre-registration analysis:☐Complies ☐Failed to comply

☐Other(specify):……

12. Is the Summary of Product Characteristics available? ☐Yes ☐No

Module 2: Chemical, Pharmaceutical, Non-clinical and Clinical Overviews and Summaries.

1. Manufacturer of API (Country of Origin): …….
2. Description of manufacturing process available?☐Yes ☐No
3. Control of materials used in manufacture of API available?:☐Yes ☐No
4. Critical steps and intermediates available?☐Yes ☐No
5. Process validation and evaluation available?☐Yes ☐No
6. Manufacturing process and development available? ☐Yes ☐No
7. Characterization of the API:
   - ☐ Physiochemical Properties (e.g. gravimetry, Color changes)
   - ☐ Chromatography (e.g. HPLC, TLC, GC)
   - ☐ Spectroscopy (e.g. UV, IR)
   - ☐ Others (specify): …….
8. Container closure system details available? ☐Yes ☐No
9. Stability: Is stability data available?☐Yes ☐No

Storage condition		Storage time (months)								
	Tick appropriate	0	3	6	12	18	24	36	48	60
Accelerated: 40±2°C/75±5 % RH		*	*	*						
Long term: 30±2°C/65±5 % RH		*	*	*	*	*	*	*	*	*
Long term (2): 25±2°C/60±5 % RH		Conducted if API is not stable at 30°C								

OVERVIEW OF THE FINISHED PHARMACEUTICAL PRODUCT/DRUG PRODUCT

1. Description

   .....

2. Composition of the FPP(S) …….

   ……..

   ……..

   ……..

3. Batch size and composition formulae available?☐Yes ☐No
4. Pharmaceutical development of FPP available?☐Yes ☐No
5. Manufacturer of FPP (Country of Origin): ……
6. Signed and stamped certificate of analysis for excipients used available?☐Yes ☐No
7. Container closure system for the FPP available?☐Yes ☐No
8. Stability of the FPP(s): Is stability data available?☐Yes ☐No

Storage condition		Storage time (months)								
	Tick appropriate	0	3	6	12	18	24	36	48	60
Accelerated: 40±2°C/75±5 % RH		*	*	*						
Long term: 30±2°C/65±5 % RH		*	*	*	*	*	*	*	*	*
Long term (2): 25±2°C/60±5 % RH		Conducted if FPP is not stable at 30°C								

Module 3: Chemical and Pharmaceutical documentation:

1. Is the complete and executed DMF available?☐Yes ☐No.
2. Specifications for the Raw Materials available?☐Yes ☐No
3. Analytical procedures for the Drug substance:

   Identification: …….

Assay: …….

Determination of related substance: ……

4. Batch analysis done?☐Yes ☐No

   COAs available?☐Yes ☐No

5. Stability data available?☐Yes ☐No

Module 4: Non-clinical study reports for New Chemical Entities

1. Is it a new chemical entity?☐Yes ☐No
2. If new chemical entity;

   Summary of studies done available?☐Yes ☐No:

   Literature references available?☐Yes ☐No

Module 5: Clinical Study Reports:

1. Is it a New Drug Entity?☐Yes ☐No
2. If New:

   Tabular Listing of Clinical Studies done available?☐Yes ☐No

   Study reports available?☐Yes ☐No

   Literature references enclosed?☐Yes ☐No

   Interchangeability of Generic Drugs:

   Bioequivalence studies performed?☐Yes ☐No