EVALUATION OF THE RISK MANAGEMENT SYSTEM FOR MEDICINAL PRODUCTS IN KENYA

Wanjiru Wangari Wambu

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Name of student: Wanjiru Wangari Wambu

Registration Number: U51/81403/2015

College: College of Health Sciences

School: Pharmacy

Department: Pharmacology and Pharmacognosy

Course Name: Master of Pharmacy in Pharmacoepidemiology and Pharmacovigilance

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Signature..... Date…….....

Prof. George Osanjo, PhD.

Associate Professor,

Department of Pharmacology and Pharmacognosy,

University of Nairobi

Signature..... Date…….....

Dr.Stanley Ndwigah, PhD.

Senior lecturer

Department of Pharmaceutical Chemistry,

University of Nairobi

Signature..... Date…….....

Dr.Kipruto Sinei, PhD.

Senior lecturer

Department of Pharmacology and Pharmacognosy,

University of Nairobi

DEDICATION

I dedicate this work to my beloved son, Ethan Mwaura Gathiru, and my mum Ann Gathigia Machira. I also dedicate this thesis to Gabriel Gathiru Mwaura, whom, though departed, always urged me to achieve greatness and believed in me.

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LIST OF ABBREVIATIONS AND ACRONYMS

ACT	Artemisinin-based Combination Therapies
ADEs	Adverse Drug Events
ADRs	Adverse Drug Reactions
AIDS	Acquired Immunodeficiency Syndrome
AMPATH	Academic Model Providing Access To Healthcare
ANDAs	Abbreviated New Drug Applications
ASK	Agricultural Society of Kenya
ATC	Anatomical Therapeutic Classification
ATMPs	Advanced Therapy Medicinal Products
BLAs	Biological License Applications
CAPA	Corrective Action Plans
CEM	Cohort Event Monitoring
COMESA	Common Market for Eastern and Southern Africa
COX	Cyclooxygenase
CPMP	Committee for Proprietary Medicinal Products
CTD	Common Technical Document
DHCPs	Dear Healthcare Professionals
DUS	Drug Utilization Studies
EAC	East African Community
EEC	European Economic Community
EMA	European Medicines Agency
ENCePP	European Network of Centres in Pharmacoepidemiology and Pharmacovigilance
ETASU	Elements To Assure Safe Use
EU	European Union

EU-RMP	European Union –Risk Management Plan
FDA	Food and Drugs Administration
FDAAA	Food Drugs Administration Amendment Act
FFDC	Federal Food, Drug and Cosmetics Act
FMEA	Failure Mode Effects Analysis
FTA	Fault Tree Analysis
GIT	Gastrointestinal Tract
GTMPs	Gene Therapy Medicinal Products
HAZOP	Hazard and operability analysis
HCP	Health Care Providers
ICH	International Council on Harmonization
ICSRs	Individual Case Safety Reports
IND	Investigational New Drug
IPAT	International Pharmacovigilance Assessment Tool
ISO	International Organizational on Standardization
KAM	Kenya Association of Manufacturers
KAPI	Kenya Association of Pharmaceutical Industry
KMDU	Kenya Medical practitioners and Dentists union
MAH	Marketing Authorization Holder
MAP	Minimization Action Plan
MOH	Ministry of Health
MRA	Medicines Regulatory Authority
NACADA	National Authority for the Campaign against Alcohol and Drug Abuse
NASCOP	National AIDS and STIs Control Programme
NDAs	New Drug Applications

NSAIDs	Non-Steroidal Anti-inflammatory Drugs
OTC	Over The Counter
PADER	Periodic Adverse Drug Experience Report
PAER	Periodic Adverse Experience Report
PASS	Post Authorization Safety Studies
PBRER	Periodic Benefit Risk Evaluation Report
PIL	Patient Information Leaflet
PMDA	Pharmaceuticals and Medical Devices Agency
PPB	Pharmacy and Poisons Board
PRAC	Pharmacovigilance Risk Assessment committee
PSUR	Periodic Update Safety Report
PV	Pharmacovigilance
QA	Quality Assurance
QPPV	Qualified Person of Pharmacovigilance
REMS	Risk Evaluation and Mitigation Strategies
RMPs	Risk Management Plans
SPC	Summary of Product Characteristics
STIs	Sexually Transmitted Infections
SPS-MSH	Strengthening Pharmaceutical Services: Management Sciences for Health
STMPs	Somatic-Cell Therapy Medicinal Products
TGA	Therapeutic Goods Administration
TEPs	Tissue Engineered Products
UMC	Uppsala Monitoring Centre
USA	United States of America
USAID	United States Agency for International Development

USD	United States Dollars
US-REMS	United States Risk Evaluation and Mitigation Strategies
UK	United Kingdom
WHO	World Health Organization
WWII	World War Two

DEFINITION OF OPERATIONAL TERMS

Biologics: Pharmaceutical products that are derived from biological/natural sources such as human, animal or microorganisms. They include vaccines, blood, blood products, allergens, gene therapies, tissues, recombinant therapeutic proteins and cellular therapies.

Effective risk management: A proactive approach that ensures that the medicinal product is safe by identifying and controlling any risks associated with the product throughout the product's life cycle.

High risk medications: Medicines with increased risk of causing considerable harm or death if used in error.

Law: Rules and guidelines passed by a governing body and which must be followed by everyone**.**

Marketing authorization: Approval granted to a marketing authorization holder to market a medicinal product granted by the relevant health authority.

Marketing authorization holder: The Company in whose name the marketing authorization has been granted.

Medicinal product: Any substance or combination of substances used in treating or preventing disease in human beings, making a medical diagnosis, or used in the restoration, correction or modification of physiological functions.

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

Policy: A document outlining the goals of an agency and activities planned to achieve the stated goal.

Post-marketing surveillance: The identification and collection of information regarding the safety of a pharmaceutical drug or medical device after it has been released on the market.

Regulations: Standards and rules that agencies adopt which dictate how laws will be implemented.

Risk assessment: The process of examining possible causes of harm and necessary measures that need to be put in place to control the risks.

Risk evaluation: The process of assessing the likelihood of a risk happening and the potential impact it might have.

Risk communication: Exchange of information between parties concerning risks.

Risk management: The overall process of identification of potential risks, assessing and taking measures to curb the risks in an effort to protect public health.

Risk management system: A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those interventions.

Serious Adverse Drug Reaction: Any untoward medical occurrence that at any dose; results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or in a congenital anomaly/birth defect.

Summary of Product Characteristics: A document that describes a medicinal product in terms of its properties and conditions for use.

ABSTRACT

Background: All medicinal products have some inherent risks associated with them. Risk management of medicines focuses more on reduction of risks such as Adverse Drug Reactions (ADRs) and Medication Errors (MEs) rather than increasing the benefits. Hence an effective risk management system of medicines tries to ensure that the benefits outweigh the risks in order to protect the patient and target population. The International Conference on Harmonization (ICH) has developed a guideline known as the ICH E2E guideline on pharmacovigilance planning that has been used by developed countries in their risk management approach for medicinal products.

Objective: The main objective of this study was to evaluate the risk management system for medicinal products in Kenya as carried out by the Pharmacy and Poisons Board (PPB) and selected multinational innovator pharmaceutical companies. A comparison was also made between established systems in the European Union (EU), United States of America (USA) and Kenya.

Methodology: The study was divided into two phases. The first phase was a qualitative study aimed at eliciting information on the current risk management practices as carried out by the PPB and by selected multinational innovator pharmaceutical companies. This was achieved by conducting key informant interviews with regulatory affairs and pharmacovigilance experts. An assessment of the pharmacovigilance activities at PPB using the Indicator-based pharmacovigilance Assessment Tool (IPAT) was also done. The second phase was a cross-sectional quantitative study of Periodic Safety Update Reports (PSURs) and Risk Management Plans (RMPs) submitted by Marketing Authorization Holders (MAHs) to the PPB. For instance, data was collected on number and component of PSURs and RMPs and whether they conformed to ICH guidelines. Documentation on regulatory actions taken by PPB and MAHs in 2015 such as recalls of drugs, voluntary withdrawal of products and safety communications were also reviewed. Descriptive data analysis was carried out using Stata® version 13(Stata Corp, USA) with findings being presented as percentages, proportions, graphs and tables.

Results: Ten (10) RMPs and two hundred and forty eight (248) PSURs were submitted between January and December 2015 to PPB. The RMPs were submitted by 2 innovator pharmaceutical companies, while the PSURs were submitted by 13 innovator pharmaceutical companies and 3 generic companies. The relatively few numbers of MAHs who submitted these documents as

well as the low numbers of RMPs and PSURs submitted in 2015 could be attributed to lack of legislation requiring submission of PSURs and RMPs. 47.3% of the PSURs had either an active RMP, Risk Evaluation and Mitigation Strategies (REMS) or both during the reporting period, but none of them had been submitted in 2015. Out of the 9 RMPs that were submitted, 8(88.9%) did not have a corresponding PSUR yet the two go hand in hand in evaluating the benefit-risk profile of a medicinal product.

Conclusion: Kenya has an inadequate risk management system for managing risks associated with medicinal products due to lack of an Act of Parliament enforcing submission of RMPs and PSURs. Unlike the EU and USA whereby there is a legal basis for the submission of PSURs and RMPs, Kenya lacks the relevant policies and regulations, accounting for the low reporting rate. There was also lack of legislation requiring MAHs to conduct postmarketing studies. There were no proper timelines for review and giving feedback to MAHs on the safety documents they submitted**.**

Recommendations: Kenya has a draft Qualified Person for Pharmacovigilance (QPPV) guideline, that if enforced would see MAHs have a QPPV who would be tasked with the overall pharmacovigilance of medicines having marketing authorization, including timely submission of drug safety reports such as RMPs and being the contact person in case safety concerns were to arise with a product. Relevant pharmacovigilance legislation is crucial in strengthening pharmacovigilance, and revision of the Pharmacy and Poisons Act is needed to incorporate the pharmacovigilance legislation. This would among other things, give PPB the power to make it mandatory for pharmaceutical companies to submit RMPs especially for high risk medicines such as thalidomide, for which the same is required by stringent MRAs.

CHAPTER ONE: INTRODUCTION

1.1.Background

Risk management is the process whereby decisions are made to accept a known or assessed risk or the implementation of action to reduce the consequences or the probability of occurrence of an adverse event (1). Medicinal products used in humans and animals have some inherent risks in them pertaining to their quality, safety and efficacy and these risks must be avoided or reduced before consumer use.

The need to have a risk management system for medicinal products worldwide has been necessitated by misfortunes involving their use, primarily, ADRs. According to a study done by Lazarou *et al*, ADRs constituted the fourth and sixth leading cause of death in the US (2). The study also estimated that patients in the US who experienced Adverse Drug Events (ADEs) were hospitalized an average of 8 to 12 days longer than patients who did not suffer from ADEs and their hospitalization cost United States Dollars (USD) 16,000 to USD 24,000 more (2). The socioeconomic impact of ADR has also led to review of pharmacovigilance legislation in the EU in an effort to strengthen the pharmacovigilance system.

Throughout history, there have been documented cases of ADRs that have propelled the necessity for development of a risk management system for medicinal products, policies and stricter regulations by the Medicines Regulation Authorities (MRAs) in the World. In 1937, there were about 700 deaths in more than 11 countries due to diethylene glycol poisoning which led to various responses by MRAs around the world, including the enactment of the Federal Food Drug and Cosmetics Act (FFDCA) in 1938 in the US (3).

In the 1960s, about 10,000 children from mothers who were exposed to thalidomide in Europe and Latin America were born with phocomelia. In 1964, the World Health Organization (WHO) developed the yellow card scheme for voluntary notification of suspected ADRs and it is what is used in the United Kingdom (UK) (4–6). Kenya prohibited the use of the drug as well in 1960. In 2004, there were 140,000 cases of serious heart disease due to Rofecoxib (Vioxx®) use (7). This steered the enactment of the US Food and Drugs Administration Amendment Act (FDAAA) of 2007 which provided the Food and Drugs Administration (FDA) with enhanced statutory authority regarding post-market safety of drugs (8).

Other risks that affect the benefit-risk balance of safe medication use and point to the need of a risk management system include: poor quality products, medication errors, toxicity associated with the product itself or its excipients and unsafe use by prescribers, dispensers and patients. Poor quality products and specifically counterfeit products are a major challenge worldwide and particularly in developing countries.

The greatest impact of counterfeit drugs as well as medication errors is increased morbidity and mortality. Counterfeit antimalarial and tuberculosis medication are reported to cause 700,000 deaths annually in Africa (9). In Bangladesh, about 500 children died after ingesting paracetamol laced with diethylene glycol (10). Medication errors have been said to be more fatal than automobile associated deaths, with about 98,000 deaths in the US being attributed to medication errors(11). Counterfeits and poor quality drugs also lead to false drug resistance reports and reduced medication efficacy, adverse effects from the ingredients used and lost revenue. The East African Community (EAC) loses about US $ 500 million, in unpaid taxes (9). All these have been occasioned by lack of an adequate legislative framework, punitive penalties as well as corruption.

A risk management system for medicinal products is therefore crucial especially when the above safety concerns arise or are anticipated to happen. It provides a detailed description of efforts to prevent, monitor or manage these safety concerns through various strategies in a bid to protect the patient population. For this system to be deemed effective, an evaluation of risks should be done at regular intervals or as more data becomes available. Proposed interventions should be implemented and evaluated for their effectiveness so as to make appropriate adjustments where necessary. If such a system is not available or not efficient, catastrophes involving high risk medicines will continue to happen, leading to increased morbidity and mortality.

Implementing a risk management system for a product can be challenging. Firstly, lack of up-to-date policies and procedures means that there may lack of compliance and adherence to required regulations and standardized practices. For instance, lack of legal framework to enforce pharmacovigilance activities means these activities are not done, thus undermining efforts to protect public health. Health resources in most African countries are limited; hence funding a pharmacovigilance system may not take priority, when compared to other competing interests(12). Tools and techniques in identification and characterization of the risks are necessary, but identifying the appropriate ones to mitigate the risks may be problematic. Even

after appropriate tools have been identified, decisions on suitable options to manage these risks may be difficult. There is also limited expertise in pharmacovigilance. Most of the governments have also not made post marketing surveillance, a key component in risk management, a priority. Stringent MRAs like the European Medicines Agency (EMA) and FDA have legal backing to require MAHs to conduct post marketing authorization safety and efficacy studies, but in African countries, there's lack of regulatory effort, hence limited data for the African population.

Pharmaceutical companies may also have limited resources to carry out pharmacovigilance activities. The pharmaceutical industry in Africa is also plagued by issues of counterfeit and substandard medicines, leading to an increase in the incidence of ADRs, morbidity and mortality. Technological advancements have led to an increase in new products flooding the market, such as biologicals and nano-pharmaceuticals, which are complex in nature and there may be lack of technical know-how on how to deal with safety concerns arising from their use.

A country's or regional MRA primary objective is to ensure that all medicinal products meet set standards of quality, safety and efficacy (13). The MRA must also ensure that pharmacovigilance reports submitted by MAHs are evaluated promptly and regularly and determine whether the benefit –risk balance of medicines remains favourable at both target and individual patient population. It must also ensure there is appropriate, unbiased, correct and regularly updated information to promote safe use of medicines (13). This is achieved by making decisions regarding label changes, variation in marketing authorization, drug safety alerts, and control of unapproved claims, product withdrawal or recalls among other actions. This has also been accomplished by enacting laws, directives, regulations and publishing guidance documents.

Various regulatory agencies have different requirements and guidelines when it comes to risk management systems for medicinal products. This puts a toll on MAHs due to the different approaches in evaluation and presenting safety data across different regions for both domestic and foreign safety information of medicinal products (14). This is both costly and time consuming. Thus, the ICH was developed to bring together regulatory agencies and pharmaceutical industries of Europe, Japan and US to better harmonize technical guidance and requirements (14).

In 1990, the first ICH steering committee decided that it was necessary to harmonize the topics on quality, safety and efficacy, which form the criteria for drug approval of new medicinal products (15). The guideline on quality risk management (Q9) was finalized in 2005 to combat

the risks to the quality of medicinal products. The Q9 guideline provides a systematic approach on principles and tools of quality risk management to enable MRAs and the pharmaceutical industry make "more effective and consistent risk-based decisions" regarding the quality of medicinal products (16). It also reassures MRAs that the pharmaceutical industry has the capacity to deal with safety concerns that are known or might arise with use of the medicinal products. The components of the quality risk management process as pertains to the quality of the medicinal product include; risk assessment, risk control, risk communication and risk review (**see Appendix 1**).

The ICH guideline on Pharmacovigilance planning (E2E) was adopted in 2004 and covers major areas of risk management relating to efficacy concerns with a medicinal product. The E2E pharmacovigilance planning guideline has formed the basis for risk management approach for the EU and Japan (14). In 2005, EMA drafted and published the guideline on risk management systems for medicinal product, based on the E2E guideline. This guideline gave a description of how the pharmaceutical industry can provide details of the risk management system in the form of a European Union-Risk Management Plan (EU-RMP).

Brazil developed guidance documents in 2009 to the pharmacovigilance plan and the risk minimization plan. This guidance is based on the ICH E2E, EMA volume 9A and FDA Risk Minimization Action Plan (MAP) guidelines but its development "is still at an incipient stage"(17). Japan's Pharmaceuticals and Medical Devices Agency (PMDA) published the draft guidance on the risk management plan in August 2011, with the final guidance being published and issued in April 2012 (18).

The other established risk management system in place for medicinal products is REMS by FDA, which came into effect in 2007. Other countries such as Canada, Australia and Switzerland have adopted the EU-RMP and the ICH E2E guideline. China has a 'Risk control plan' while in India, there is no legal requirement for submission of PV reports except for PSUR requirements (14,19).

Kenya's pharmaceutical sector has grown with the pharmaceutical manufacturing industry being the largest in the Common Market for Eastern and Southern Africa (COMESA) region and supplying pharmaceuticals to 50% of the COMESA region (20). However this system is faced with a few challenges. It is estimated that between 10% and 30% of medicines being sold in some regions in Africa, Asia and Latin America are counterfeit (21). In Kenya, a survey

conducted by the National Quality Control Laboratory (NQCL) and PPB found that 30% of the drugs being sold were counterfeit. A joint report by the Kenya Association of Manufacturers (KAM), the judiciary and other players reported that about 40% of antimalarial drugs in the market were counterfeit (22). In yet another study conducted by the Kenya Association of Pharmaceutical industry (KAPI) and the University of Nairobi School of Pharmacy, about 8% of Over The Counter (OTC) medications were unregulated (23,24). The cost of the counterfeit medicines being sold in Kenya per year was estimated to be between USD 65 to 130 million (25).

Pharmacovigilance activities in Kenya began when the department of pharmacovigilance was set up in 2004 at PPB. This department later evolved into the division of medicines information and pharmacovigilance, having 3 sections: medicines information, pharmacovigilance and post market surveillance and clinical trials. Since then, great strides have been made to create awareness on pharmacovigilance and improve on reporting including the formal launch of the national Pharmacovigilance system in 2009 (26). Kenya also became the 98th full member of the WHO programme for International Drug Monitoring in 2010 (27).

One of the challenges facing the pharmacovigilance system in Kenya is lack of legal backing. There is lack of policy and legislation giving PPB the mandate to require the pharmaceutical industry to carry out pharmacovigilance activities, one of the components of a risk management system. In 2010, an assessment of the pharmacovigilance systems in sub-Saharan African countries showed that high risk medicines for which REMS was a requirement in the US for the drug to be marketed were being sold in these countries without a risk management system or implementation of risk management activities as proposed in the REMS. For instance, drugs such as rosiglitazone, alendronate, and budesonide and formoterol inhaler, had approved REMS in the US. However in Kenya and most of the countries evaluated, the study found out that there were neither approved REMS submitted nor were the proposed risk management activities implemented for these medicines. However, the assessment of risk management and communication component of pharmacovigilance showed that among the countries assessed, Kenya was the only country with a mitigation plan for high risk medicines, particularly for opioid analgesics and anticoagulants.

In 2014, Kiogora Gatimbu assessed the structure and process of periodic safety update reporting system in Kenya, a component of risk management of medicines. From the study findings, it was

unclear as to whether there existed an appropriate and comprehensive risk management system for medicinal products. The assessment revealed lack of legislation to mandate MAHs to submit PSURs and one of the recommendations was that PPB should have policies in place to regulate processes of PSURs (28). In 2016, an assessment of the vaccine pharmacovigilance system in Kenya was conducted by Linet Kugo. The assessment identified gaps in the system which included "absence of specific legislation, lack of guidelines and absence of an organizational structure for vaccine safety" (29).

Kenya does not have an established risk management system and heavily borrows from the ICH guideline. There is no legislation mandating MAHs to submit risk management plans (RMPs) and PSURs and therefore only a few of them submit these documents. There is also no legislation giving PPB the authority to require MAHs to submit an RMP. There is no committee mandated to review the few RMPs submitted.

This study compared the risk management system of medicines in Kenya with that in the EU and USA. This is because they have established risk management systems in place while other countries have adopted the EU-RMP model, REMS or both, while incorporating the ICH E2E pharmacovigilance planning and customized their risk management systems in line with their national requirements.

1.2.Statement of the problem

An effective risk management system especially for high risks medicines ensures there are interventions in place to mitigate risks associated with the use of these medicines such as ADRs and MEs so that these medicines are used with caution and are not prematurely withdrawn from the market. For instance, thalidomide (thalomid®) is still available in the market and is indicated for treatment of multiple myeloma in combination with dexamethasone. However, due to its teratogenic property, its distribution is highly restricted. In the US, prescribers and pharmacies must be certified and the patients must be enrolled in the THALOMID REMS® program.

Other drugs such as Isotretinoin, Mifeprostone and Emtricitabine/tenofovir disoproxil fumarate are approved in the US and the MAHs must submit REMS for them. These same products are also marketed in Kenya and although the MAHs may submit REMS for them voluntarily or as required by PPB, the risk minimisation activities set out in these REMS may not be implemented. For instance, there are no REMS programs for any of these products in Kenya. There are no certified prescribers or pharmacies for drugs such as Isotretinoin. Patients are not

compelled to fill the patient agreement forms before initiating treatment with Isotretinoin. Medication guides may be distributed by the MAH to pharmacies and prescribers, but there is no way of knowing whether the patients receive them or whether the patients know their importance and understand the risks associated with the drug.

Furthermore, there is no legal framework for the submission of pharmacovigilance reports and documents since the Pharmacy and Poisons Act CAP 244 does not have a provision for pharmacovigilance. The guideline for the national pharmacovigilance system in Kenya published in 2009 encourages the pharmaceutical industry to share PSURs and data from postmarketing surveillance as well as to conduct pharmacovigilance activities, but there is no specific law mandating them to carry out all these things.

1.3.Study justification

An assessment of the pharmacovigilance systems and their performance in Sub-Saharan countries was conducted in 2011 by the Strengthening Pharmaceutical Systems (SPS) program (25). The assessment showed that the risk management and communication component had the weakest system and performance (25).This was partly due to lack of risk minimization activities for high risk drugs in Africa, though MAHs were required to submit and implement RMPs or REMS for the same medicines by strict MRAs such as EMA and FDA (25). Sharing and communication of emerging safety concerns was also poor (25). This study sought to find out if any significant achievements have been made in Kenya under the risk management component of the pharmacovigilance system since the assessment was completed and recommendations given on improvement.

Other studies have also been conducted in Africa that broadly assessed the pharmacovigilance systems, such as in Nigeria and Ghana, while another study assessed the scope of pharmacovigilance of Artemisinin-based Combination Therapies (ACTs) in Benin. In Kenya, studies have been conducted to evaluate the vaccine pharmacovigilance system (29) as well as the structure and process of the PSUR reporting system (28). However there has been no study in Kenya, and Africa as a whole that has evaluated the risk management system for medicinal products and there is no literature that points to the presence of an established risk management system in place for any African country.

1.4.Research questions

a) What activities are carried out as part to the risk management system of medicinal products in Kenya?

b) How does the risk management system for medicinal products compare with established systems like the FDA-REMS and EMA-RMP?

1.5.Objectives of the study

1.5.1.Broad objective

The overall objective of the study was to evaluate the risk management system of medicinal products in Kenya as carried out by the Pharmacy and Poisons Board and selected multinational innovator pharmaceutical companies in Kenya and how it compared with established systems such as in the EU and USA.

1.5.2.Specific objectives

a) To determine the activities carried out as part of the risk management system of medicines in Kenya by the PPB as well as by the multinational innovator pharmaceutical companies.

b) To compare Kenya's risk management approach for medicinal products with established systems such as in the EU and USA.

CHAPTER TWO: LITERATURE REVIEW

2.1. Literature search strategy

The literature search was conducted by searching various online databases and search engines for articles published in PubMed, Springerlink, ScienceDirect, Mendeley and Google Scholar between January 1987 and December 2017. Author of articles for which the full text was unavailable were contacted. The searches terms that were used included: “risk management”, “risk management plan” “pharmacovigilance” OR “drug safety” OR “medicine safety”, “Risk evaluation and mitigation strategy”, “therapeutic risk management” and “risk minimisation plan”. Combination of search terms was also done, such as: “Pharmacovigilance AND risk management”, “Pharmacovigilance AND Africa”, OR “FDA” OR “EMA”.

The reference lists of the identified articles from the databases and search engines were assessed for any additional relevant studies. Other articles citing the primarily identified studies were also assessed. Information was also obtained from websites of stringent medicines regulatory authorities such as the US-FDA, EMA, Japan’s PMDA, and Australia’s Therapeutic Goods Administration (TGA). Other websites searched included those of the WHO and the ICH. Other sources of literature used included: policy statements, conference proceedings, newsletters, government and non-governmental agency reports, theses and dissertations.

2.2.Concept of risk and risk management

There is no universally accepted definition of risk. Various authors have attempted to describe risk with Tsai M.C. *et al* defining risk as possible events whose unfavourable consequences are difficult to accept or are even unacceptable while Mohammed Mazouni defines risks an intrinsic property of any decision measured by a combination of several factors including severity and occurrence (30,31).All risks are associated with some sort of uncertainty and the International Organization on Standardization (ISO) has incorporated this aspect in its definition of risk as an “effect of uncertainty on objectives” (32).

There are different elements that contribute to the presence of risks and these include: events, consequences, risk sources and likelihood of occurrence. To identify a risk one needs to envisage an event that may or may not occur (the level of uncertainty is characterized by likelihood), due to the presence of risk sources (an element that has the potential to produce a risk), and then foresee its possible consequences. These consequences will in turn have an impact on personal or organizational objectives (33).

Once sources of risks have been identified, attempts are made at managing them. One way is to accept risks and deal with them as they happen, especially when the risks are small and would not have much of an impact. However, if they are deemed to have a potentially large impact, risks can also be avoided. Risks can be transferred and this strategy is used to transfer the impact and management of risks to several other interested parties. Risks can also be exploited especially if they have positive consequences or can be mitigated (34).

Risk management is the process whereby decisions are made to accept a known or assessed risk or the implementation of action to reduce the consequences or the probability of occurrence of an adverse event(1). ISO defines risk management as a coordinated set of activities and methods that is used to direct an organization and to control the many risk that can affect its ability to achieve objectives (32). The concept of risk management for any organization can be rationalized through focusing on the interdependence of the following factors as shown in **figure 1** below.

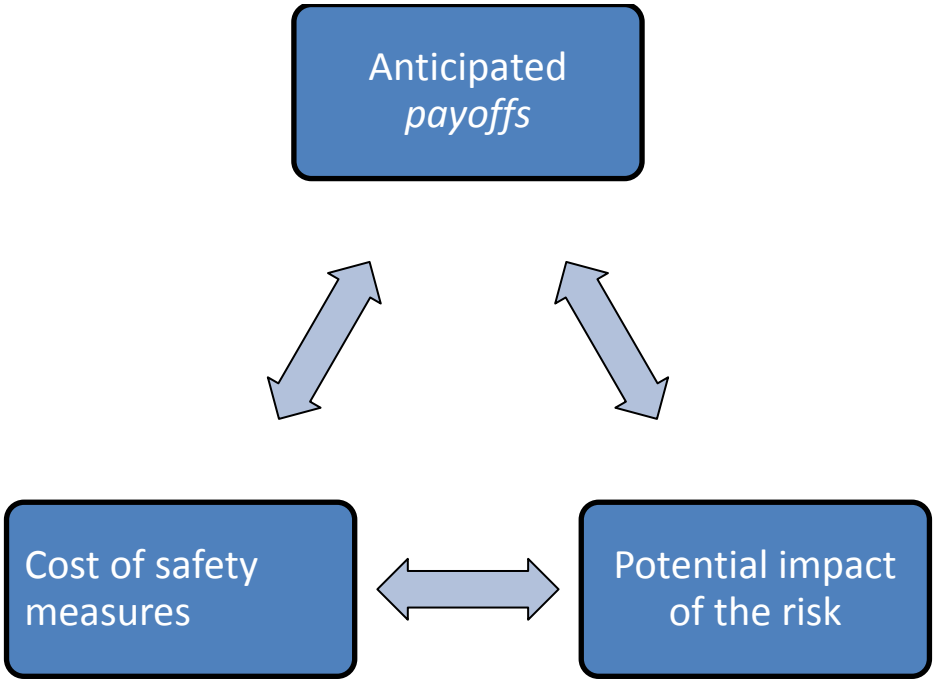


Figure 1: The risk management triangle [19].

The anticipated payoffs in terms of risk management of medicines could be a reduction in serious ADRs, market approval of high risk but crucial medicines for which there are no alternatives and maintenance of benefit–risk balance that ensures maximum benefit of medicinal products. Cost of safety measures applies to risk mitigation strategies that are applied to allow disability, extra costs and possibility of death.

Risk management helps avoid catastrophes and provide safety. If potential risks are known and mitigation strategies are implemented, the magnitudes of the risks are reduced. Risk management also enables one take risks that would otherwise never have been undertaken. In terms of medicinal products, that would otherwise never have gained market approval due to their associated risks are now in the market due to the steps taken to manage their risks. Managing risks does not mean creating a risk-free world, but rather avoiding unnecessary, unexpected and preventable losses (33). Implementing risk management in an organization gives decision makers tools that enable rational choices, taken on the basis of the information available, no matter how limited it may be (33).

2.3.Risks associated with medicinal products

With respect to medicinal products, risks can be broadly categorized into preventable and unpreventable errors. Preventable errors include: known side effects which can either be avoidable and unavoidable, medication errors and medical devise errors and product defects. The unpreventable errors are due to uncertainties arising from unexpected side effects, unstudied uses and populations.

Studies have been conducted to investigate ADRs, medication errors and ADEs-related deaths. Lazarou *et al* in 1998, conducted a meta-analyses of 16 studies on ADRs published between 1964 and 1995 and concluded that over 100 000 deaths per year in the US could be attributed to ADRs (2). According to Juntti-Patinen and Neuvonen's study on 1546 fatal cases occurring during the year 2000 at the university hospital in Helsinki,75 deaths were probably due to drugs (35). Surveys of the Massachusetts General Hospital and Brigham and Women's Hospital in Boston have shown that medication errors are extremely common (36).

2.4.Historical medication mishaps that have catapulted stricter and more effective medicines regulation

In 1937, Sulphanilamide elixir was compounded with diethylene glycol due to an increasing demand for the liquid formulation (3). The tablet and powder formulations had been safely used for treatment of streptococcal infections. The new formulation had not undergone any pharmacological and toxicity studies and resulted in 100 deaths in the US (3). At the time, safety studies were not a requirement. This led to the enactment of the Federal Food, Drug and Cosmetic Act (FFDCA) in 1938 which increased FDA's authority to regulate drugs (3).

Thalidomide was first developed in Germany in 1954 by Chemie Grünenthal, a pharmaceutical company (37). In 1957 it was marketed as an anticonvulsant in epileptic patients and later on, it was marketed as a non-barbiturate sedative at a time when sleeplessness was quite rampant after World War two (WWII) (38). It was claimed to be a completely safe drug that could be used by anyone and in Germany, was sold as an OTC remedy (38).

Dr. William McBride discovered its off-label use in alleviating morning sickness and this practice caught on, with many prescribers prescribing it to pregnant women (38). In 1960, the first few cases of phocomelia were reported and in 1961, there was a dramatic increase in these cases. By the time it was withdrawn, about 10,000 children in Europe and Latin America born to mothers who took it developed phocomelia (39). In reaction to this, the WHO developed the voluntary notification scheme in 1961 (4). A Committee on the Safety of Drugs (CSD) was started in the UK in 1963 and a voluntary adverse drug reaction reporting system (Yellow Card Scheme) was developed in the UK in 1964 (4).

Rofecoxib (Vioxx®) received market approval in the US in May 1999 (25,26). Being a selective Cyclooxygenase two (COX II) inhibitor, it was considered a safer alternative to Non-Steroidal Anti-inflammatory Drugs (NSAID) for the treatment of pain in osteoarthritis. This was due to its "selectivity" in blocking COX II enzymes that were responsible for pain and inflammation and not blocking COX I enzymes that were responsible for protecting the stomach lining. Merck had conducted trials that had shown no increased risks of cardiovascular events when tested against placebo.

The Vioxx Gastrointestinal Outcomes Research study (VIGOR) had been initiated by Merck in January 1999, prior to receiving marketing approval by the US-FDA, to evaluate the safety of Rofecoxib (Vioxx®) on the Gastro-Intestinal Tract (GIT) as compared to an older painkiller, naproxen. The preliminary results in October 1999 had shown that Rofecoxib had fewer episodes of GIT bleeding and ulcers. However, when the focus was shifted to heart problems, the results showed a twofold increase in cardiovascular events due to Rofecoxib use as compared to naproxen (40,41).

In 2004, Merck voluntarily withdrew the product with more than 140,000 cases worldwide of serious heart disease being attributed to it (7). This was after results from the Adematous Polyp Prevention on Vioxx® study (APPROVe) showed that the risk of cardiovascular events due to Rofecoxib became detectable after 18 months of using it as compared to placebo (42,43). Merck

had promoted Rofecoxib's superiority over other NSAIDS in protecting against (GIT) problems but had failed to disclose the relative cardiovascular risks to doctors and the public. Kenya's pharmacovigilance system kicked off in 2004. In 2010, PPB sent out nine safety alerts and recalled various medicinal products due to quality issues. The marketing authorization for rosiglitazone was suspended and medicinal products containing rosiglitazone and sibutramine were withdrawn from the market (25,44). **Table 1** shows other drugs that have been withdrawn worldwide due to their associated ADRs.

Table 1: Drugs withdrawn worldwide due to their associated adverse drug reactions

Year	Drug	Primary indication	Reason for withdrawal
1970	Diethylstilbestrol	Prevent miscarriages and other pregnancy related complications	Rare vaginal tumor in women and girls who had been exposed in utero
1983	Zimelidine (Zelmid®)	Treatment of depression (SSRI)	Risk of Guillain-Barre syndrome, hypersensitivity reaction, hepatotoxicity
1986	Nomifesine (Merital®)	Treatment of depression(Non-sedative)	Haemolyticanemia
1991	Terodiline (Micturin®)	Bladder disorders	Torsade de pointe
1995	Alpidem (Ananxyl®)	Treatment of anxiety	Hepatotoxicity
1998	Terfenadine (Seldane®)	Treatment of allergies, non-sedating	Cardiac arrhythmias
1998	Mibefradil (Posicor®)	Treatment of hypertension	Fatal interactions with at least 25 drugs
2001	Cerivastatin (Baycol®, Lipobay®)	Treatment of high cholesterol	Severe rhabdomyolysis
2005	Bextra ®(Valdecoxib)	Treatment of pain in inflammatory disorders.	Increased cardiovascular risks
2007-2008	Lumiracoxib (Prexige®)	Treatment of osteoarthritis	Liver damage
2010	Propoxyphene (Darvon®)	Treatment of moderate to mild pain	Cardiovascular events
2010	Rosiglitazone (Avandia®)	Treatment of type-2 diabetes mellitus	Cardiovascular events
2011	Drotrecoginalfa (Xigris®)	Antithrombosis, anti-inflammatory	Lack of efficacy

2.5.History of medicine regulation

Medicine regulation can be dated as far back as the 1780s. The king of Potus, Mithridates VI, had prepared "Mithridatium", a concoction that was used in treating most diseases at that time (4). There was no regulation to control for quality or safety of such concoctions at that time, but in 1540, the Apothecaries Wares, Drugs and Stuffs Act was enacted in England, and it required control of medicines via pharmaceutical inspections (4).

Fredrick II was a Roman Emperor and King of Sicily, whose reign was from November 1220 to December 1250. In 1240, he issued a proclamation of the Salerno Medical Edict that saw physicians being forbidden to double up as apothecaries. Also the proclamation stated that all apothecaries were to prepare medications always in the same way-*forma curiae* (4).

These events led to the development of Pharmacopoeias around the 16^{th} Century. The first Pharmacopoeias were developed and used in Spain in 1581 and the rest of Europe followed suit. In 1618, The London Pharmacopoeia detailed standards of preparation of Mithridatium. Thereafter, after WWII and breakthroughs in drug research, modern medicines regulation began.

A series of adverse events influenced the development of medicines regulations. The sulphanilamide elixir tragedy of 1937, which resulted in over 100 deaths in the US, led to a statute that required drug manufacturers to provide evidence on the safety of their drugs before they received marketing approval. Evidence of efficacy was not a requirement then, but this changed after the thalidomide disaster of 1960, when congress passed the Drugs Amendment Act in 1962. The medicines regulatory system underwent significant changes worldwide following these two tragedies. **Table 2** shows a breakdown of the most significant regulations that championed control of medicines as we know it today.

Table 2: History of medicines regulation[4].

Year	Regulation
1938	FDAAA was enacted in the US which introduced a premarket notification requirement for new drugs
1962	The Kefauver-Harris Drug Amendments Act of 1962 was passed by Congress in the US. It gave FDA authority to: approve all new drug applications (NDA), demand evidence on efficacy and safety, require compliance with current Good Manufacturing Practices (cGMP), and to officially register drug establishments.
1964	EEC (European Economic Community) Directive 65/65/EEC aimed at harmonizing approval standards for medicines in the EEC
1968	The Medicines Act in UK established control, promotion and sales of medicines in the UK. It also set up the legislation that, as from 1 September 1971, all medicines already in the UK market had to go through peer review and subsequent approval or be withdrawn.
1975	Directive 75/318/EEC established laws for analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products in member states Directive 75/319/EEC established a Committee on Proprietary Medicinal Products (CPMP) as an advisory committee to the EC and the multistate procedure known now as the Mutual Recognition Procedure.
1989	The first International Conference of Drug Regulatory Authorities (ICDRA) was held in Paris.
1990	Establishment of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use.

2.6.Need for risk management for medicinal products

Clinical trials have various limitations in terms of assessing the long term safety profile of the medicines. The trials are conducted in relatively few subjects in comparison to the intended target population as well as for relatively short periods of time in relation to the period meant for use. Other restrictions include those on co-morbidities, co-medications and conditions of use. As

a result, not all safety issues are addressed during the premarketing face in terms of long latency ADRs, long term side effects and use in populations such as in pediatrics, the elderly and pregnant women.

Advances in Information Technology (IT) have also posed a challenge in terms of how risks for medicines have been managed. While web based tools and data mining have made it easier and simpler to collect and analyze patient data, they have led to generation of false safety signals (45) as well as the risk of information overload leading to serious and unexpected reactions being preceded by less serious phenomena.

The pharmaceutical industry has been rapidly evolving with new advances in Advanced Therapy Medicinal Products (ATMPs) comprising of Gene Therapy Medicinal Products (GTMPs), Somatic-cell Therapy Medicinal Products (STMPs), Therapeutic vaccines and Tissue Engineered Products (TEPs) (46). There is a knowledge gap especially in developing countries by MRAs on how to effectively manage risks associated with biotechnology due to the complexity of these products and limited safety data, with reliance being on actions taken by the developed countries.

"It is often said that regulation follows science; in the case of risk management, regulation has followed not only scientific and technical progress, but growing public expectations that the systems for monitoring the safety of medicines are optimally effective" (47). Emerging drug safety issues test the capability of regulatory systems in determining the risk, evaluating, minimizing or preventing it and sharing information to the public. It has become necessary to manage risks associated with medicines due to the reasons stated above.

In the early years, MRAs put emphasis on collecting safety data on medicines especially after the sulphanilamide and thalidomide tragedies. However, this approach has shifted to establishment of a benefit-risk balance partly due to increased public scrutiny especially when it is thought that the MRAs "collude" with pharmaceutical companies by failing to disclose certain crucial information on perceived risks about a medicinal product, as seen in the Rofecoxib (Vioxx®) scandal.

There are different and overlapping definitions of risk management of medicinal products. The EU defines risk management as "a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those activities and interventions"(47). The FDA's wording is

different but the overall objective is the same. It defines risk management as an iterative process of assessing a product's benefit risk balance, developing and implementing interventions to mitigate these risks, evaluating effectiveness of such interventions and revising them appropriately (47).

Overall, risk management of medicines entails identifying a potential safety risk, assessing the product's benefit–risk balance and implementing risk minimization tools and evaluating success of risk minimization tools. For most products with an established safety profile over years of use, routine pharmacovigilance is sufficient in estimating its benefit risk balance post approval (47). However, some products have unusual safety risks pre or post-approval that necessitates the development of additional risk minimization activities by the MAH to combat the risks (47).

MRAs require MAHs to submit RMPs and PSURs for medicinal products that have received marketing authorization. This is aided by legislations that give MRAs power to enforce submission of these documents. MRAs come up with the format, content and timelines for submission which are addressed in various guidelines. The EU-EMA and US-FDA have RMPs and REMS respectively as established risk management systems for medicinal products.

2.7.Overlap of pharmacovigilance and risk management

Pharmacovigilance and risk management activities are essential components that are incorporated throughout a product's life cycle and as thus must be regulated. Both aspects must be integrated in any pharmaceutical regulatory system and monitored periodically to ensure their effectiveness (48).

Pharmacovigilance activities are those that identify safety signals derived mainly from post marketing surveillance activities and then assess them to determine if the risk is substantial enough to warrant any further actions. This overlaps with risk management which incorporates these two aspects and manages risks by trying to minimize or prevent risks and reviewing interventions implemented.

Emerging drug safety information obtained from clinical trials, spontaneous ADRs and epidemiological studies has led to MRAs enforcing risk management activities. These include regulatory actions such as withdrawal and recalls of products, issuance of warnings, restrictions on indications and clinical guidance, labelling changes as well as hefty fines being awarded to

pharmaceutical companies (49). Risk management is a responsibility of both the MRAs and MAHs.

2.8. United States versus European Union's risk management system for medicinal products

The EU-RMP and the FDA-REMS are established risk management systems that detail safety information concerning medicinal products during any stage of the products life cycle but most importantly when seeking marketing authorization. A medicinal product's safety information may change depending on data obtained from routine pharmacovigilance activities obtained post marketing and thus the RMP and REMS are updated appropriately. The overall purpose of the RMP and REMS is in minimization of risks by developing and implementing interventions and communicating these risks to HCP as well as patients (48).

2.8.1. Food and Drugs Administration risk management system

FDA's mission is to protect the public health by assuring the safety, efficacy and security of human drugs by having information on a product's benefit-risk balance. Risk management in the US, can be dated as far back as in the 1970s when FDA endorsed distribution of patient package inserts for oral contraceptives (50). Special programs were instituted for Isotretinoin (Accutane®), Clozapine (Clozaril®) and Thalidomide to restrict their access between 1988 and 1998 (50). In the late 1990's it was made mandatory for pharmacists to distribute medication guides with medicines considered to have serious public health risks (50).

In May 2004, FDA came up with 3 risk management draft guidance documents after increased scrutiny due to market withdrawal of various drugs such as Alosterone Hydrochloride (Lotronex®) and Troglitazone (Rezulin®) (50). In March 2005, FDA published the 3 final guidance documents which were the Premarketing Risk Assessment (51), Good Pharmacovigilance Practices (52) and Pharmacoepidemiology Assessment and the Development and use of Risk MAPs (53) to address safety monitoring and interventions.

The three later formed the building blocks for REMS when the FDAAA was signed into law in September 2007.The FDAAA, enacted in March 2008, gave FDA the authority to request for REMS at any time during a product's life cycle (54). The act requires REMS for New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs) and Biological License Applications (BLAs).

REMS are required risk management plans that use risk minimization strategies beyond the professional labelling to ensure that the benefits of certain prescription drugs outweigh their risks (55).The main component of REMS that must be included is a timetable for submission of assessments. For NDAs and BLAs other elements that may be contained include: medication guide, communication plan, Elements To Assure Safe Use (ETASU)-the most extensive part of a REMS and an implementation system, while for ANDAs, the REMS may include the medication guide, ETASU and Implementation systems (**Appendix 2**).

The US-FDA can require REMS when a drug first seeks marketing authorization, or later after approval has been granted, when a new safety concern arises. For instance, there is an approved Mycophenolate (Cellcept®) REMS in the USA. The REMS Elements To Assure Safe Use (ETASU) states that prescribers must be trained and MAHs must maintain a pregnancy registry for women who become pregnant during its use.

Other REMS materials include a patient brochure, a patient-prescriber acknowledgement form, Dear Health Care Provider (DHCPs) communications for prescribers and healthcare centres, a medication guide, Obstetrician / gynaecologist referral letters for contraceptive and pre-conception counselling (56). However, since there is an inadequate risk management system for Mycophenolate in Kenya, some of the above elements are not implemented.

FDA judges the need of REMS by considering various factors; severity of disease, seriousness of known potential ADRs, estimated population size likely to use the product, expected benefit, anticipated treatment duration. After an extensive evaluation process of the REMS by FDA's drug safety and risk management advisory committee, a product may receive marketing authorization. The manufacturer is required to submit routine assessment for all NDAs and BLAs at 18 months, 3years and 7years after receiving marketing authorization, though it may be eliminated after 3 years.

2.8.2.European Union's risk management system

In November 2005, new legislation on risk management of medicinal products came into place which required submission of a risk management system as part of the authorization dossier of innovative medicinal products (45,57,58). This led to the issuance of the "Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use".

In the EU, a risk management system is submitted in the form of an EU-RMP. An EU-RMP is required for all new marketing applications (biologics, chemical entities, generic medicinal product where a safety concern has been identified with the reference medicinal product and it requires additional risk minimization activities), applications with a significant change to an existing marketing authorization (such as a change in indication, new dosage form, new route of administration, change in manufacturing process of biotechnologically-derived product), at the request of the competent authority, when applying for a paediatric-use MA, or when there is a significant change to the benefit–risk profile (59).

The MAH preparing the RMP gives information on the medicinal product's safety profile and measures they have put in place/ propose to put in place in order to minimize the risks associated with the product. The RMP also contains information on additional studies and activities planned to understand the product's safety and efficacy and how they the risk minimization activities will be evaluated to determine if they have been effective (60).

The EU-RMP is comprised of Part I-VI. Part II and III incorporate the ICH E2E notions on safety specification and pharmacovigilance plan. The safety specification sums up the medicinal product's safety profile and summarizes the important identified risks, important potential risks and missing information. These safety concerns arise as a result of the limitations of clinical trials.

The pharmacovigilance plan (Part III), is based on the safety specification (61). It comprises of routine and additional pharmacovigilance activities for the listed safety concerns. The additional pharmacovigilance activities include non-clinical studies such as pharmacokinetic and acute toxicity studies, interventional studies and non-interventional studies such as cohort, case-control and case series studies. Additional pharmacovigilance activities are necessary when the data available is from short term follow-up yet the long term effects are unknown, or when the preclinical data e.g. carcinogenicity is ambiguous (62)

Part IV comprises need for post-authorization efficacy studies to complement the existing evidence on efficacy data. An evaluation of need for risk minimization activities based on the safety specifications beyond the pharmacovigilance actions proposed which leads to the risk minimization plan, and measuring the effectiveness of these measures (61).

The MAH then discusses the proposed routine risk minimization activities such as Summary of Product Characteristics (SPC), labelling and legal status of a medicine. If additional risk minimization activities are required, this is presented in the form of a risk minimization plan, part V (61). These include educational programmes through educational brochures and patient alert cards, controlled access programmes and others such as pregnancy prevention programs and restricted distribution systems. An outline is provided in **Appendix 3**.

An observation that ADRs were responsible for 197,000 deaths per year in the EU, led to a review of safety monitoring (63). Following extensive consultations, new directive and regulations were adopted in 2010 that amended the previous pharmacovigilance laws (64,65). Following withdrawal of Benfluorex (Mediator®) due to the risk of heart valve issues, further amendments were made in 2012 to the pharmacovigilance legislation to allow for "prompt notification and assessment of safety issues" (66–68).

2.9.Risk management of medicines in Africa

There is not much literature on risk management systems for medicinal products in African countries and no study has been done to evaluate such a system if it is already in place, as compared to the EU and US. However the pharmacovigilance system of some African countries has been assessed and the risk management component has been shown to be wanting. For instance in Ghana, a study assessing its pharmacovigilance system in 2010 showed that high risk medicinal products that had already received marketing authorization did not have any strategies to mitigate safety concerns (69).

A study conducted in 2011 by the SPS program assessed the pharmacovigilance system in Sub-Saharan Africa. The assessment of the risk management and communication component found that "there was no formal risk management activity" to mitigate risks associated with medicines (25). In eight out of the nine countries where an in-depth assessment was conducted, there was "no standardised procedure for risk management practices" for marketed high risk medicines in these countries (25). However, some countries like Tanzania, Namibia and Uganda had requested MAHs to submit or implement some form of risk management activities for high risk medicines. For instance in Nigeria, the NMRA requested risk mitigation plans from the MAH for rosiglitazone.

In an effort to strengthen the pharmacovigilance system in African countries, individual NMRAs have published pharmacovigilance guidelines which contain a description of the risk

management system required by the MRA for high risk medicines. Most of the NMRAs have adopted the ICH E2E guideline on pharmacovigilance planning and the EU-RMP. The PPB published the guidelines for the national pharmacovigilance system in Kenya in February 2009, in line with its mission for ensuring safer, efficacious and quality medicines, though there's no mention of a risk management system. In Namibia, the National guideline for medicine safety surveillance was published in November 2011. This guideline spells out that a risk management system should be in form of an RMP and MAHs should discuss the need and content of the RMP with the Namibian Medicines Regulatory Council.

In Egypt, a guideline for MAHs was published in January 2012. Among other things, it describes the requirements of a Qualified Person for Pharmacovigilance (QPPV), a detailed description of the pharmacovigilance system and requirements for risk management systems for medicinal products (70). In August 2014, South Africa's Medicines Control Council (MCC) published a guideline on registration of biosimilar medicines. In this guideline, if a biosimilar has an RMP and some risk management activities are recommended, the MAH should include the south African populace and special groups in these activities (71). Ghana adopted a guideline for safety monitoring of medicines in 2015 whereby, the Food and Drugs Authority in Ghana requires the MAH to provide a Ghana specific annex to the global or EU-RMP (72).

2.10. International Council on Harmonization Harmonized Tripartite Guideline Pharmacovigilance Planning E2E

The ICH was created in 1990 due to the need to harmonize technical requirements for registration of pharmaceuticals for human use. This need to harmonize came up as a result of duplication of work by MAHs when registering medicinal products due to the divergent registration requirements of various countries (14,15) It was established as a joint effort of pharmaceutical companies and regulatory authorities of the EU, US and Japan (14,15).

The ICH has developed guidelines on quality, safety, efficacy and multidisciplinary topics (15). Pharmacovigilance is covered under efficacy guidelines E2A-E2F with guidelines on PSURs and the pharmacovigilance planning being covered under ICH E2C (R2) and ICH E2E respectively (15). The ICH E2E guideline was issued in 2014 and covers most aspects of risk management and has been adopted by the EU and Japan (14).

The ICH E2E guideline focuses on safety specification and the pharmacovigilance plan, which have been incorporated into the EU-RMP. These elements can be presented in the development

of a standalone document for regions that have this requirement or they can be incorporated in the Common Technical Document (CTD) (73).

2.11. Qualified Person for Pharmacovigilance

A QPPV is a person who is responsible for pharmacovigilance of medicinal products that have received marketing authorization (5). The main role of a QPPV is to launch and sustain pharmacovigilance systems for the MAH (5). He/she ensures that evaluation of the benefit-risk profile of a product is continuous and that safety reports: such as PSURs, Individual Case safety Reports (ICSRs), RMPs are submitted to a medicines regulatory authority in a timely manner (6).

The QPPV was established by article 23 of regulation (EC) No 726/2004 in the EU in 2004. It is a requirement that each MAH has a QPPV, who permanently and continuously resides in the EU, and can answer any queries pertaining to a medicinal product for which the MAH has received marketing authorization (61).There is also an EU-QPPV who is tasked with pharmacovigilance activities of all medicinal products in the EU. He also oversees execution and implementation of pharmacovigilance agreements (5,6).

The QPPV acts as a contact point for both the competent authorities as well as for the marketing authorization holders in the EU and should be available on a 24-hour basis in the event that the competent authority has queries (5,6,61). He acts as the MAH's contact person when pharmacovigilance inspections need to be carried out. More detailed roles and responsibilities of the QPPV are found in "Volume 9A of The Rules Governing Medicinal Products in the European Union -Guidelines on Pharmacovigilance for Medicinal Products for Human Use" (61).

2.12. Periodic safety update reports as a risk management tool in the European Union and United States of America

The concept of the PSUR can be traced back to 1992 when the Council for International Organizations of Medical Sciences (CIOMS II) came up with the "International Reporting of Periodic Drug-Safety Update Summaries" (74). This later formed the basis for the ICH E2C guideline on periodic reporting in November 1996. This guideline has been modified since then, with the most recent modification being in 2012.

The ICH E2C guideline was first drafted to enable MAHs summarize and update safety information on the benefit risk profile of new drugs via submission of PSURs (75). This was

implemented in the EU, US and Japan. The name evolved with the second revision from PSUR, to the Periodic Benefit Risk Evaluation Report (PBRER).

PSURs serve as a communication tool between MAHs and MRAs of new safety information derived from a variety of sources as well as providing the benefit-risk profile of the medicinal product (75). The importance of the PSUR is in assessing and evaluating any new safety concerns as well as managing this risk so as to avoid market loss of an invaluable medicinal product (75). PSURs are usually linked to the RMP of a medicinal product, such that the PSUR assesses the risks associated with a medicinal product, while the RMP explains how these risks will be managed. PSURs are not required for the following products which are considered to have low risks; generics, homeopathic medicines, well established products, traditional herbal medicines (76,77).

The EU carries out single assessments of PSURs based on active substances and combinations of active substances in an effort to harmonize and make the benefit-risk assessment stronger. Once the PSUR review is completed, MAHs receive the following documents as part of feedback: initial and an updated single assessment reports by the Pharmacovigilance Risk Assessment committee (PRAC), PRAC recommendation and Committee for Medicinal Products for Human Use (CHMP) opinion.

In the USA, MAHs were initially required to submit periodic safety reports in the form of Periodic Adverse Drug Experience Report (PADER) and Periodic Adverse Experience Report (PAER) for medicinal products approved under NDAs, BLAs and generic products. However, with the new guideline that came into place in 2016, MAHs can submit PBRERs in place of the PADER, PAER and PSUR (78).

2.13. Risk communication as an integral component of risk management of medicinal products

Pharmaceutical risk communication entails communication of risks associated with medicines by regulators, pharmaceutical companies, healthcare workers and patients themselves. This communication can be: general communication which includes communication to the public through press releases, safety notices/alerts and via newsletters or targeted communication which involves tailor making the message to suit a specific population (79). This communication should be tailored to the audience, up-to-date, timely, unbiased, and evidence-based and of good quality (80).

FDA communicates pharmaceutical risks via various avenues. One is by use of safety alerts. A survey done by Pharmaceutical Research and Manufacturers of America (PhMRA), on FDA's safety alerts showed that most patients felt more secure knowing that FDA was evaluating the medicines and had more confidence in the drug safety system (81). FDA also communicates on new safety information identified from the Adverse Events Reporting System (AERS) via its website, as well as publishing a newsletter quarterly to raise awareness on reported ADRs and AEs(81). They also provide an index to drug specific safety information (81).

Tools that have been used in pharmaceutical risk communication include the traditional labelling tools: the SPCs/ Product Information, Patient Information Leaflets/ Patient Leaflets (PILs/PLs) and the carton (82,83). In the USA, medication guides, drug facts labels, package inserts and patient information sheets (84) are the main modes of communicating pharmaceutical risks, while the EU uses the SPCs and PIL. The pharmaceutical companies are required by MRAs to use various templates when communicating risks, and these templates have sometimes restricted the way the risks are communicated to the physicians and patients, who are the intended targets (82,83).

The SPC is crucial as it provides a description of the properties of the medicine, how the medicine will be used in accordance with what it is being used to treat/prevent (82,85). The SPC is intended mainly for the healthcare professionals as a point of reference and used in the development of the PIL which is the reference document for patients.

However, though the SPC acts as a valuable risk communication tool, it doesn't necessarily have all the information and should be augmented with use of other tools. A study by Arguello et al assessing the adequacy of SPCs in relaying information on pregnancy and breastfeeding, showed that there were vague recommendations for use in pregnancy and lactation in almost 60% and 20% of SPCs, respectively (86).

The European Commission in 2009, made revisions to some areas in the SmPC, and issued the "Guideline on Summary of Product Characteristics (SPC) Revision 2" (87). Among the key changes included: inclusion of information on pharmacogenomics, if known, expansion of information on special patient populations and description of specific risk minimization measures under special warnings and precautions (87).

Dear Healthcare Professional (DHCP) letters present another form of communication between the MAHs and the healthcare professionals. They are used in communicating new emerging or updating information about a medicinal product. The DHCP letters can either be initiated by the MAH or the MRA can ask the MAH to draft and disseminate the letters when there is a safety concern. According to a study by Mazor *et al* in 2005, there is a correlation between the format and content of these letters (88). Various MRAs such as the US-FDA and South Africa's Medicines Control Council (MCC) have come up with guidance on DHCP letters, to allow effective communication.

Other than the format and content of DHCP letters, the timelines of sending the letters is considered important as well. Various court cases have been filed by the public against MAHs who claimed that the MAHs had not sent DHCP letters in a timely manner to healthcare professionals thus resulting in ADRs associated with the medicinal products. The plaintiffs won the cases and were awarded settlements. Such cases include: the *Tietz vs. Abbott Laboratories, Incorporation* (89,90), *Rutz vs. Novartis Pharmaceutical Corporation* (90), *Winters and Balding vs. Novartis Pharmaceutical Corporation* (91) and the *Medtronic multidistrict litigation (MDL)* case (90). It can be seen that the DHCPs, would serve as a measure to protect MAHs from litigations if done timely and correctly.

2.14. Postmarketing surveillance in risk assessment and evaluation

Postmarketing surveillance is essential in pharmacovigilance as it enables: identification of previously unknown ADRs, understanding of known drug-related ADRs, identification of high risk groups, and long term effects of drugs as well as evaluation of irrational use of medication (92,93). This is achieved primarily through spontaneous reporting, post marketing studies and active surveillance (92,93).

Studies, such as drug utilization reviews are used in providing denominator data to determine rates and economic burden of ADRs (94). An assessment of incidence and causes of medication errors can lead to interventions that will lead to reduction in preventable ADRs. Active surveillance is used in addressing safety concerns that have arisen post-authorization.

Risk communication via labelling alone is now deemed insufficient (95).Postmarketing surveillance is necessary in characterizing the safety profile of a drug, investigating various safety concerns with a medicinal product, as well as evaluating risks when a medicinal product is used in populations that were not studied before authorization was granted. These studies can

either be voluntarily initiated by MAHs, imposed by the MRA prior to granting marketing authorization or after marketing authorization has been granted especially when safety concerns have arisen or they can be agreed upon with the MAH (96).

In the US, the FDA modernization Act of 2007 requires MAHs to furnish the FDA with annual reports on post marketing studies they are conducting, either as postmarketing requirements (imposed studies) or postmarketing commitments (agreed upon studies) (95,97). Section 506(B) requires FDA to track these studies and report them annually in a federal register.

The FDAAA of 2007, section 505(o) gave authority to the FDA to require MAHs to conduct certain post-marketing studies and clinical trials when seeking approval or after having received marketing authorization (97,98). Guidance was released in 2011, informing the pharmaceutical industry the requirements for the postmarketing studies and types of studies that are required and agreed upon (99). FDA also provides basic information on the status of these studies to the public on its website (97).

Regulation (EC) No 1235/2010 and Directive 2010/84/ EC in the EU, require MAHs to conduct Post Authorization Safety Studies (PASS) while applying for marketing authorization or after post-authorization. Guidance is released for MAHs to use on the format and content of study protocols as well as final study reports for non-interventional studies as outlined in "Commission Implementing Regulation No 520/2012 of 19 June 2012" (100). The public are able to review protocols and abstracts of final study reports of these studies in the EU post-authorization study register; E-Register of studies, that is available on the European Network of Centres in Pharmacoepidemiology and Pharmacovigilance (ENCePP) website (101).

These studies can be either interventional studies, comparative observational studies: cohort studies, case-control studies, cross-sectional studies, active surveillance studies: cohort event monitoring, registries, sentinel site surveillance or other studies such as drug utilization reviews (73).Assessment of these postmarketing studies is done by the PRAC in the EU and by the FDA in the USA. Postmarketing studies are important in evaluation of safety concerns, provided that the appropriate study design is tailored for the medicinal products and safety concerns and a comprehensive study protocol is in place (95).

CHAPTER THREE: METHODOLOGY

This study was divided into two phases. The first phase was a qualitative study aimed at eliciting information on the current practices with regards to risk management of medicinal products. The second phase was a quantitative phase that entailed review of Risk Management Plans (RMPs) and Periodic Safety Update Reports (PSURs) as well as documentary evidence of regulatory actions taken by the Pharmacy and Poisons Board (PPB) in 2015.

3.1 Qualitative phase

3.1.1.Study design

This was a descriptive cross-sectional study entailing in-depth interviews of key informants in order to have a better understanding of what the current practices are in risk management of medicinal products in Kenya.

3.1.2.Study Site

The study was conducted at the premises of the PPB as well as in selected multinational innovator pharmaceutical companies such as Hoffman La-Roche, Pfizer, AstraZeneca, and Sanofi Aventis.

The Pharmacy and Poisons Board is the medicines regulatory agency (MRA) in Kenya that was established under the Pharmacy and Poisons Act, Chapter 244 of the laws of Kenya. The board is empowered to make rules under which medicines may be imported, manufactured for sale or sold in Kenya and if all the set requirements are met, the products are then registered to be used in the market.

Hoffman-La Roche is one of the leading pharmaceutical companies in diagnostics as well as in pharmaceuticals such as anti-malarial, antibiotics and cancer medications. The headquarters of the Roche group is based in Basel, Switzerland and has companies located in over 100 countries.

Pfizer is an American based innovator pharmaceutical company that produces medicines and vaccines in disciplines such as immunology, oncology, cardiology, diabetology and neurology. In East Africa, Pfizer has carried out a variety of programs such as running anti-malarial campaigns, providing financial support to Academic Model Providing Access To Healthcare (AMPATH), donating growth hormone medication to Gertrude's Children Hospital as well as providing treatment for Acquired Immunodeficiency Syndrome (AIDS) related fungal infections.

AstraZeneca is a British-Sweden pharmaceutical company which manufactures and distributes a variety of drugs for cancer, cardiovascular diseases, respiratory and gastrointestinal infections, neuroscience and inflammation. In Africa, AstraZeneca launched the Healthy Heart Africa program to tackle an increasing burden of cardiovascular disease. In Kenya, it is located on Argwings Kodhek road at Chaka place, 2nd floor.

Sanofi Aventis is a French pharmaceutical company with its headquarters in Gentilly France. It covers major therapeutic areas such as oncology, diabetes, vaccines, central nervous system, cardiovascular, internal medicines and consumer healthcare products. Sanofi partners with the Kenya association for the welfare of people with epilepsy to train healthcare professionals, community healthcare workers and conduct awareness campaigns. Sanofi is located at Kenya Medical Association (KMA) centre 6th floor Mara road.

3.1.3.Key informant selection

The key informants included in the study were pharmacovigilance and regulatory affairs experts in PPB as well as in selected multinational innovator pharmaceutical companies working in Kenya in 2017.

3.1.4.Inclusion criteria

Key informants were included in the study if they met all of the following criteria:

a) Had to be regulatory affairs or pharmacovigilance practitioners
b) Had to have been working at the PPB or in a multinational innovator pharmaceutical company for at least 1 year
c) Had to give informed consent to participate in the study.

3.1.5.Exclusion criteria

Key informants were excluded from the study if they did not meet any of the above criteria.

3.1.6.Determination of number of key informants to be interviewed

Since this study had a qualitative phase, principles of sampling for qualitative studies as described by Sandelowski were applied (102). According to these principles, a minimum sample size of 4 is sufficient for a key informant interview. Therefore, in each of the multinational innovator pharmaceutical companies, 1 key informant was interviewed, while in PPB, 5 key informants were interviewed.

3.1.7.Recruitment of Key informants

Purposive sampling was used in recruitment of the interviewees. This type of sampling was advocated for as it focused on identification of persons that met a certain criterion. The potential participants were identified by paying a visit to each of the study site premises and a request was made to meet the individuals tasked with regulatory affairs or pharmacovigilance roles.

The individuals were approached in their offices and via telephone calls and informed about the study. They were requested to suggest a time and venue that was convenient for them. The appended informed consent form (**Appendix 4**) was provided to the interviewees and it was a prerequisite for them to sign it before the interview was conducted.

3.1.8.Research Instruments

The WHO Pharmacovigilance indicator tool was used to formulate some of the questions in the key informant questionnaires. The indicators measure the existence and performance of pharmacovigilance structures and processes and identify the strengths and weaknesses (103). They also reveal the achievements, growth or lack of growth of the pharmacovigilance systems (103).

Only aspects relating to the risk management process within the pharmacovigilance setting were used. The indicators used included C02, P10, P11 and P12. A value was signed for each indicator that had been fulfilled. (**See Appendix 5**)

Complimentary to this tool is the Indicator-Based Pharmacovigilance Assessment tool (IPAT) which acts as a comprehensive performance metric for pharmacovigilance and medicine safety systems (104). IPAT was used in this study in evaluating the current state of the pharmacovigilance system. Only aspects pertaining to risk management were evaluated (**See Appendix 6**).

IPAT is a collaborative project of the Management Sciences for Health's Strengthening Pharmaceutical Systems (MSH/SPS), the Delphi group and the University of Washington as well as consultations from Namibia and South Africa(104). It was then pilot-tested in Rwanda and field-tested in South Africa with improvements being made to the initial draft before the final version was published in 2015 (104).

The IPAT tool assesses the pharmacovigilance and medicines safety system of a country using 26 core and 17 supplementary indicators (104).A country is said to have a functional

pharmacovigilance system when all the core indicators have been achieved. Once the core indicators have been achieved, a country can proceed in developing plans for achieving the supplementary indicators (104). The findings are then presented in form of radar charts or a pharmacovigilance capacity-building framework format (104).

IPAT has been used in various countries to assess their pharmacovigilance activities. In Africa, a survey and in-depth assessment was conducted by MSH in the following sub-Saharan countries: Burkina Faso, Ghana, Democratic Republic of Congo, Kenya, Senegal, South Africa, Nigeria, Tanzania and Uganda. Outside Africa, IPAT has also assessed the pharmacovigilance system and its performance in the Philippines, Ukraine and in five Asian countries.

3.1.9.Data collection

Interviews were conducted by one individual who posed the questions, took detailed notes and observed for any reactions with the aid of the appended interview guides (**Appendices 7 & 8**). The interview guides were designed to obtain information on the existing risk management strategies and the effectiveness and capacity of the multinational innovator pharmaceutical companies and PPB to adequately conduct risk management of medicinal products.

This interview guide for PPB (**Appendix 8**) was adapted from the Indicator-Based Pharmacovigilance Assessment tool. In order to improve validity of responses from the pharmaceutical industry, prior research was done on the medicinal product profile of the pharmaceutical company and products requiring risk management strategies. Websites of the EU and FDA were reviewed to get more information about products requiring RMPs and REMS respectively. In addition, key informants were asked for any supporting documents to support the information they provided. Within 24 hours after the interview, all written notes were transcribed and destroyed shortly after the transcribing process.

3.1.10. Data analysis

Grounded theory approach was used in analysing the responses from the interviews. It is an inductive methodology used in generation of theories from data systematically collected and analyzed and was first developed by Glaser and Straus in 1967 (105,106). In the grounded theory approach, data is gathered either through participant observation, interviews or collection of artefacts (106). This approach involves constant comparative analysis whereby the data is collected and is simultaneously analysed using different techniques until a theory is developed which offers an explanation about an area of interest and how any concerns arising have been

resolved. In this study, a theory was developed by using constant comparative analysis, theoretical sampling and theoretical coding. Data collection and analysis continued until a point of theoretical saturation was achieved.

In the assessment of pharmacovigilance activities at PPB using the IPAT tool, various core and supplementary indicators pertaining to: policy, law and regulation, systems, structures and stakeholder coordination, risk assessment and evaluation and risk management and communication were used. These included indicators: 1.4, 2.1, 4.1, 4.2, 4.3, 4.5, 5.1, 5.3, 5.5, 5.6 and 5.9. For every core and supplementary indicator that was achieved, a score of 2 and 1 was assigned respectively. A score of 0 was assigned if the indicator was not fulfilled.

3.2.Quantitative phase

3.2.1.Study design

This entailed a cross-sectional review of documents submitted to the PPB by the multinational innovator pharmaceutical companies as part of the risk management practice for medicinal products as well as documents in the pharmacovigilance department in PPB that detailed regulatory actions that had been taken by both PPB and the pharmaceutical companies.

3.2.2.Study site

The study site for this quantitative phase was the PPB as it is the MRA in Kenya and is in charge of giving marketing authorization in Kenya for medicinal products and ensuring the documents submitted by the Marketing Authorization Holder (MAH) conform to the International Council on Harmonization (ICH) E2E Pharmacovigilance planning standards as well as to local requirements.

3.2.3.Documents reviewed

The study population included RMPs and PSURs submitted to PPB by the multinational innovator pharmaceutical companies detailing risk management practices. The risk management practices that were identified in these documents included mention of patient alert cards, educational programs, prospective registry and epidemiological studies undertaken for the various medicinal products.

Regulatory actions taken by the PPB in 2015 were determined by searching for these actions in the PPB website as well as documents found at the pharmacovigilance department. The regulatory actions included: product recalls, withdrawals, safety communications to healthcare

professionals, the general public and other organizations as well as initiation of post marketing surveillance.

3.2.4.Document inclusion

Documents were reviewed if they fulfilled the following criteria:

a) Documents that were submitted as PSURs and RMPs.
b) Documents that were available in the archive of PPB in 2017
c) Documents that were submitted from January 2015 to December 2015.
d) Documents that detailed regulatory actions initiated by either PPB or by the pharmaceutical companies.

3.2.5.Document exclusion

Incomplete, illegible documents and those that did not meet the above criteria were excluded from the study.

3.2.6.Sample size and sampling technique

The entire population of PSURs and RMPs submitted from January to December 2015 were reviewed as they detailed risk management practices by the MAHs. A total of 248 PSURs and 10 RMPs were submitted by MAHs during the study period. Universal sampling was deployed in identification of documents for review since not all medicinal products required an RMP or REMS and Kenya has not enforced submission of these documents.

3.2.7.Data collection

The data collection documents were PSURs and RMPs which were evaluated for risk management components under the risk management section of the document as submitted by the MAH to PPB. The components evaluated in the documents included mention of the following: patient alert cards/ medication guides, provider communication plan/educational programs, provider information sheet/ SPC, monitoring of patients receiving medications in terms of registry studies, epidemiological studies, specifications of distribution, dispensing monitoring of distribution and any additional data analysis/study data.

3.2.8.Data analysis

Dummy tables were created to help in developing the analysis plan **(See Appendix 9)**. The dummy tables were developed to summarize the documents reviewed, the type of risk management components in the documents reviewed, and conformity of the risk management

documents to internationally established requirements. From the filled dummy tables, descriptive data analysis was carried out using Stata® version 13(Stata Corp, USA). First, data was entered into an Excel spreadsheet and later the findings were transformed quantitatively.

3.3.Privacy and Confidentiality

To ensure confidentiality, any information that directly linked the documents submitted to their respective MAH was not recorded, but rather codes were used as identifiers. All information collected was kept under a password protected file.

3.4.Ethical considerations

One aspect of the study involved human participants taking part in key informant interviews and hence approval for the study was sought from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH-UoN-ERC) before carrying out the study **(Appendix 10),** reference number KNH-ERC/A/31.) Approval was also granted from the Pharmacy and Poisons Board to review documents and conduct key informant interviews. (**Appendix 11**, reference number PPB/MIP/PMS/LET/183/16.)

3.5.Credibility

To ensure that the data obtained gave a meaningful and valid insight of the risk management system in Kenya, methodological triangulation was used. This incorporated interviews with key informants at the PPB and multinational innovator pharmaceutical companies as well as documentation analysis of PSURs, RMPs, memos and circulars at the PPB and information on the PPB website. The different methods used were meant to add value to each other and give a robust comprehensive overview of the study topic.

The data collection tools were pretested before the actual interviews were undertaken and any necessary corrections were made. The study participants were contacted after the interview to get any clarification on the responses given during the interview.

CONCEPTUAL FRAMEWORK

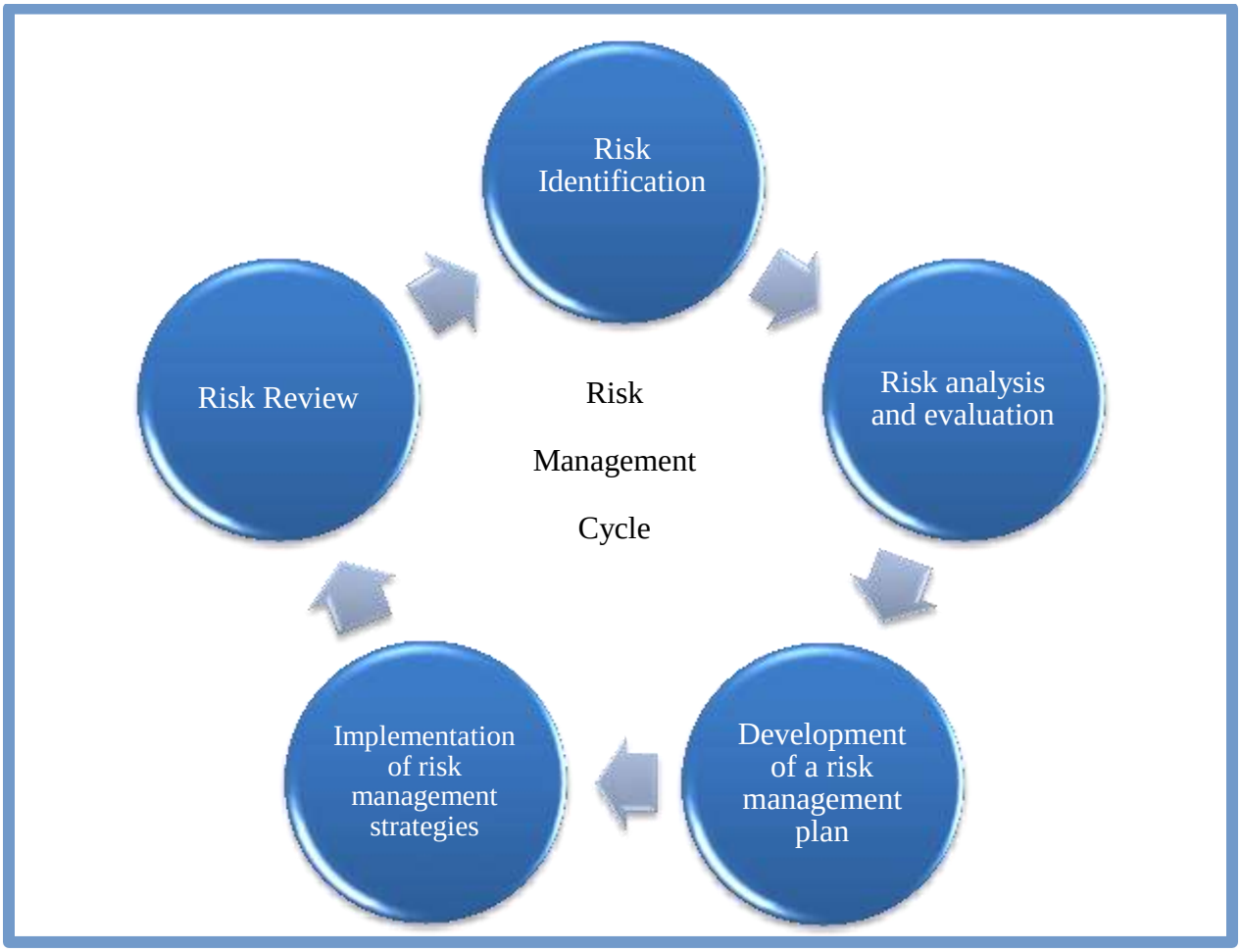


Figure 2: Conceptual Framework of Risk Management Process [(107)].

Risk identification

In risk identification, systematic processes are used in identifying risks, causes of the risks, estimating the magnitude of the consequences of the risks, and the likelihood that the outcomes will occur as well as level of control of these risks. Tools that can be used in identifying risks include brainstorming, check sheets, flowcharting, process mapping and fishbone diagrams (108).

Risk analysis

For a medicinal product to be approved for use in humans, a benefit risk analysis is done to ensure the benefits outweigh the risks. This involves use of quantitative methods in estimating the risks, qualitative methods to describe risks as “high”, “medium” and “low” and/or a combination of them. This involves the following types of analysis Failure Modes Effects

Analysis (FMEA), Event Tree Analysis(ETA), Hazard Checklists(HCI),Hazard and Operability (HAZOP), Fault Tree Analysis(FTA) etc (109).

Risk evaluation

Risk evaluation considers the strength of evidence of the identified risk, what the probability of the risk is and what the likely outcome of the risks are and assignment of priority on what risks to deal with urgently and more frequently. By using strength of evidence from epidemiological studies such as case-control studies, randomized clinical trials and meta-analyses, decisions are made to either retain or withdraw marketing authorization (49).

Development of a risk management plan

A risk management plan is a document that details the risk management strategy to be used by an organization. It entails methods and tools of identifying the possible risks and analysing their impact and the mitigation strategies to be used in case the risks arise. When managing risks, it's important to consider the anticipated financial costs, expectations of stakeholders as well as the balance between the measures taken and costs (110).

Implementation of risk management strategies

This involves the process of controlling the risks. In terms of medicinal products, this can be done by communicating risks to patients and healthcare workers through labelling, implementing additional measures such as educational programs for healthcare professionals, restricted distribution of high risk medicines as well as having post-marketing studies.

Risk review

Review of the appropriateness of interventions is done in each component of the risk management system and their impact on the overall minimization of risks is assessed. It identifies if new risks have arisen and whether there is need to prioritize other risks.

CHAPTER FOUR: RESULTS

Risk Management Plans (RMPs) and Periodic Safety Update Reports (PSURs) are key components of risk management of medicinal products. Their routine submission forms part of the International Council on Harmonization (ICH) E2E pharmacovigilance planning and E2C (R2) guidelines respectively.

The results are presented in six different sections. A review of the RMPs and PSURs submitted in 2015 is described in the first two sections, 4.1 and 4.2. The third section, 4.3, consists of a description of regulatory actions taken by both Authorization Holders (MAHs) and the Pharmacy and Poisons Board (PPB).

Section 4.4 is the findings of a qualitative interview that aimed at identifying risk management practices as conducted by both PPB and the MAHs, while section, 4.5, is an appraisal of pharmacovigilance activities at PPB using an indicator-based pharmacovigilance assessment tool. The last section, 4.6, is a comparison of the risk management practices amongst USA, EU and Kenya.

4.1.ASSESSMENT OF RISK MANAGEMENT PLANS

In 2015, ten (10) RMPs were submitted to the PPB by MAHs. However only 9 (90%) of the submitted ones were available for review since the soft copy of one of the RMPs could not be traced and there were no manual copies. None of the local pharmaceutical companies submitted RMPs.

4.1.1 Characteristics of drugs for which a Risk Management Plans were submitted

The RMPs were submitted by only 2 pharmaceutical companies. Out of the 9 RMPs, 2 RMPs each were submitted for Tenofovir, Emtricitabine/Tenofovir and Vildagliptin/Vildagliptin-metformin, while 1 RMP each was submitted for Zolendronic acid, Everolimus and Deferasirox.

The RMPs submitted included 8 (88.9%) chemical entities, and only 1 (11.1%) biologic therapy-Everolimus. All the 8 RMPs were submitted by multinational innovator pharmaceutical companies. **Table 3** presents the classification of the RMPs submitted.

Table 3: Classification of drugs for which risk management plans were submitted in 2015

Anatomical classification	Therapeutic classification	N
Antiinfectives for systemic use	Antivirals for systemic use	4
Alimentary canal and metabolism	Drugs used in diabetes	2
Antineoplastics and immunomodulating agents	Antineoplastic agents	1
Musculoskeletal system	Drugs for treatment of bone diseases	1
Various	All other therapeutic products	1

The methodology that was used in classifying the drugs was obtained from the WHO collaborating Centre for Drug Statistics Methodology (111). Using this methodology, the drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system (level 1 and 2). The first level was the anatomical classification and the second was the therapeutic classification **(Table 3)**. Antivirals, a subgroup of antiifectives for systemic use (44.4%) and drugs used in diabetes, a sub group of drugs used in the alimentary canal and metabolism (22.2%) accounted for the highest proportion of RMPs submitted.

4.1.2 Specific risk management strategies identified in risk management plans

The risk management strategies were classified into two; routine risk minimization activities and additional risk minimization activities. Routine risk minimization activities are those expected for all drugs, while the additional risk minimization activities are put into place when routine risk minimization activities are deemed insufficient. These activities are summarized in **table 4.**

Table 4: Risk management strategies identified in the risk management plans

	n (%)		
	Chemical entities	**Biologics**	**Total**
Routine Risk minimization activities			
SPC Special Warnings and special precautions	8 (100)	1(100)	9(100)
SPC contraindications	8 (100)	1(100)	9(100)
SPC Undesirable effects	8 (100)	1(100)	9(100)
Additional Risk minimization activities			
Educational program	4 (50)	-	4(44.4)
Educational brochure	4 (50)	-	4(44.4)
Patient reminder card	1(12.5)	-	1(11.1)
DHCP letters	1 (12.5)	-	1(11.1)

Key: SPC refers to Summary of Product Characteristics, DHCPs refers to Dear Healthcare Professional letters

Routine risk minimization measures for all the drugs in the RMPs included communication of safety concerns in the SPC sections: special warnings and precautions, contraindications and undesirable effects.

The additional risk minimization measures employed included: educational programs for healthcare professionals, educational brochures for prescribers, a patient reminder card and Dear Healthcare Professional letters. As presented in **table 4**, additional risk minimization measures were proposed in 6 out of the 9 RMPs submitted.

The proposed educational programs and educational brochures were recommended for Emtricitabine/Tenofovir and Tenofovir. The educational programme was targeted at clinicians and was aimed at communicating risks of renal complications and appropriate management. The proposed management included assessing creatinine clearance before and during treatment and appropriate dose adjustments in patient with renal impairment that were on these drugs. Educational brochures were targeted at healthcare professionals and they advised on renal function management and dose adjustments.

For Deferasirox, a DHCP letter was disseminated to healthcare professionals communicating that a new formulation was available under a new trade name. A patient reminder card was implemented for Zolendronic acid to remind patients on precautionary measures to take to reduce the risk of osteonecrosis of the jaw. However, this was only implemented in the EU.

4.1.3 Types of indicators that were used to evaluate the effectiveness of risk minimization measures

Indicators are used to assess whether the interventions that were proposed were effective or not. The types of indicators that were used are presented in **table 5.**

Table 5: Indicators used to measure effectiveness of risk minimization measures

Effectiveness of risk minimization measures	Chemical entities n (%)	Biologics n (%)	Total n (%)
Process indicators			
Physicians Surveys	4 (50)	-	4(44.4)
DUS studies to assess clinical actions	2 (25)	-	2(22.2)
Outcome indicators			
Routine PV and assessment of new data in PSURs	1(12.5)	1(100)	2(22.2)

Key: DUS refers to drug utilization studies, PSURs refers to Periodic Safety Update Reports, PV refers to pharmacovigilance

Process indicators measure the extent of implementation of the risk minimization interventions as planned while outcome indicators measure the extent to which the proposed interventions of risk minimization were met. Effectiveness of additional risk minimization measures was evaluated in all the RMPs that had additional risk minimization measures.

Physician surveys were used as process indicators and evaluated physicians' knowledge and understanding of educational materials disseminated to physicians in the RMPs for Emtricitabine/Tenofovir and Tenofovir **(Table 5)**. The Tenofovir RMP included a drug utilization study to verify physicians' understanding of prescribing Tenofovir to paediatric patients after implementation of educational programs and whether they were following the recommendations set out in the Tenofovir SPC. There were no reported process indicators in the RMP for Everolimus, the biologic therapy.

As an outcome indicator, routine pharmacovigilance and assessment of new data in PSURs was proposed in measuring the effectiveness of the DHCP as an additional risk minimization measure for Deferasirox and for measuring routine risk minimization measures proposed for the biologic therapy Everolimus.

4.1.4 Additional pharmacovigilance activities

Additional pharmacovigilance activities reinforce routine pharmacovigilance activities and include non-clinical studies, interventional studies/clinical trials and non-interventional studies. The additional pharmacovigilance activities that were conducted in the RMPs included: 7 clinical trials, 9 epidemiological studies and 7 registries as presented in **table 6**. In 2 of the 9 RMPs submitted, 4 studies were conducted in Africa, specifically in Egypt and South Africa.

Table 6: Additional pharmacovigilance activities conducted in the risk management plans

Additional Pharmacovigilance activities	n (%)		
	Chemical entities	**Biologics**	**Total**
Clinical Trials	6 (75)	1(100)	7(77.8)
Epidemiological studies	8 (100)	1(100)	9(100)
Registries	6 (75)	1(100)	7(77.8)
African inclusion in the studies	1 (12.5)	1 (100)	2 (22.2)
Additional trial and study data	5 (62.5)	-	5(55.6)
Additional data analysis	1 (12.5)	-	1(11.1)
Non-intervention study to capture off label use	3 (37.5)	-	3(33.3)

Five additional trials, one additional data analysis as well as three non-interventional trials to capture off-label use were reported, but only in the RMP for chemical entities.

4.1.5 Compliance of risk management plans with International Council on Harmonization requirements

All nine (9) RMPs complied with the ICH harmonized tripartite guideline on pharmacovigilance planning, ICH E2E. They all had the major components that were provided in the guideline, i.e. the product overview, safety specification and pharmacovigilance plan, and risk minimization

measures. Differences between them were the addition of two parts: plans for post-authorization efficacy studies and summary of the risk management plan by product in four out of the nine risk management plans. This is outlined in **table 7.**

Table 7: Compliance of risk management plans with International Council on Harmonization requirements

Compliance with risk management plan format	n (%)
Part I: Product Overview	9 (100)
Part II : Safety specification	9 (100)
Part III: Pharmacovigilance plan	9 (100)
Part IV: Plans for post-authorization efficacy studies	4 (44.4)
Part V: Risk minimization measures	9 (100)
Part VI: Summary of the risk management plan by product	4 (44.4)
Part VII: Annexes	9(100)

4.2. PERIODIC SAFETY UPDATE REPORTS SUBMITTED IN 2015

Two hundred and forty eight (248) PSURs were submitted in the year 2015. However 25 (10.08%) were not available for review due to the reasons stated in **table 8.**

Table 8: Reasons for exclusion of periodic safety update reports

Reasons for exclusion of PSURs	n (%)
Soft and manual copies missing	14 (5.6)
Softcopy damaged while manual copy was an executive summary	2(0.8)
Softcopy submitted was blank	2(0.8)
No soft copy available, while manual copy was a cover letter	1(0.4)
Labelled as PSUR but documents were labelling safety updates	4(1.6)
Labelled as PSUR but documents were PSUR reporting requirements	1(0.4)
Softcopy was password protected	1(0.4)

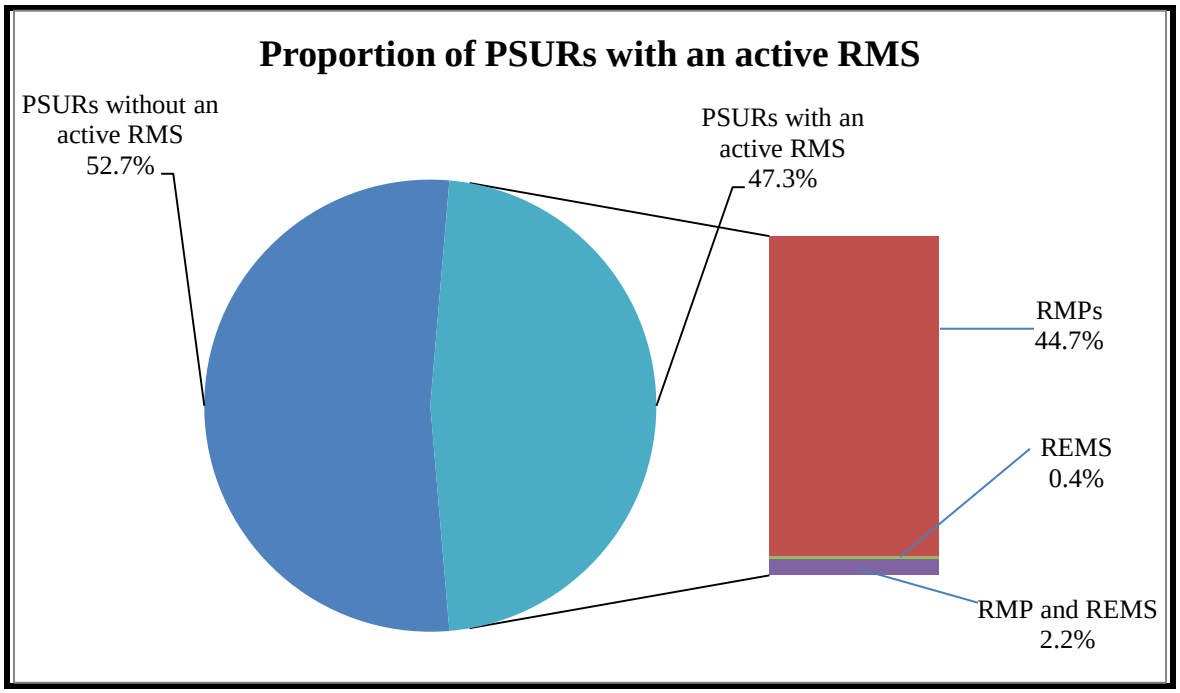
Key: PSUR refers to Periodic Safety Update Reports

Three (3) of the PSURs covered multiple formulations of the drugs (single and combination formulations) and thus were reviewed as separate entities, making the total periodic safety update reports under review to be 226 (91.1%).

4.2.1 Proportion of periodic safety update reports with an active risk management system

There is currently no database of products with an RMP, thus a medicinal product was determined to have one if there was mention of it in the document. The FDA website was also used to determine the medicinal products that had an active Risk Evaluation and Mitigation Strategies (REMS) during the reporting period of the PSUR.

One hundred and seven (47.3%) of the PSURs submitted had an RMP, REMS or both. Of the 107, One hundred and one (44.7%) had an RMP, 5 (2.2%) had both an RMP and REMS, while 1 (0.4%) had only REMS and no mention of an RMP **(Figure 3)**. Out of the 16 pharmaceutical companies that had submitted the PSURs, 14 (87.5%) of the companies had medicinal products with an RMP, a REMS or both.



Key: REMS refers to Risk Evaluation and Mitigation Strategies, RMP refers to Risk Management Plan, RMS refers to Risk Management System

Figure 3: Periodic safety update reports with a risk management system

4.2.2 Pharmaceutical companies that submitted periodic safety update reports

A total of 177 (78.3%) PSURs were submitted by 13 innovator pharmaceutical companies with the largest proportion being submitted by company C (75, 33.2%), B (28, 12.4%) and D (25, 11.1%) as shown in **figure 4**.

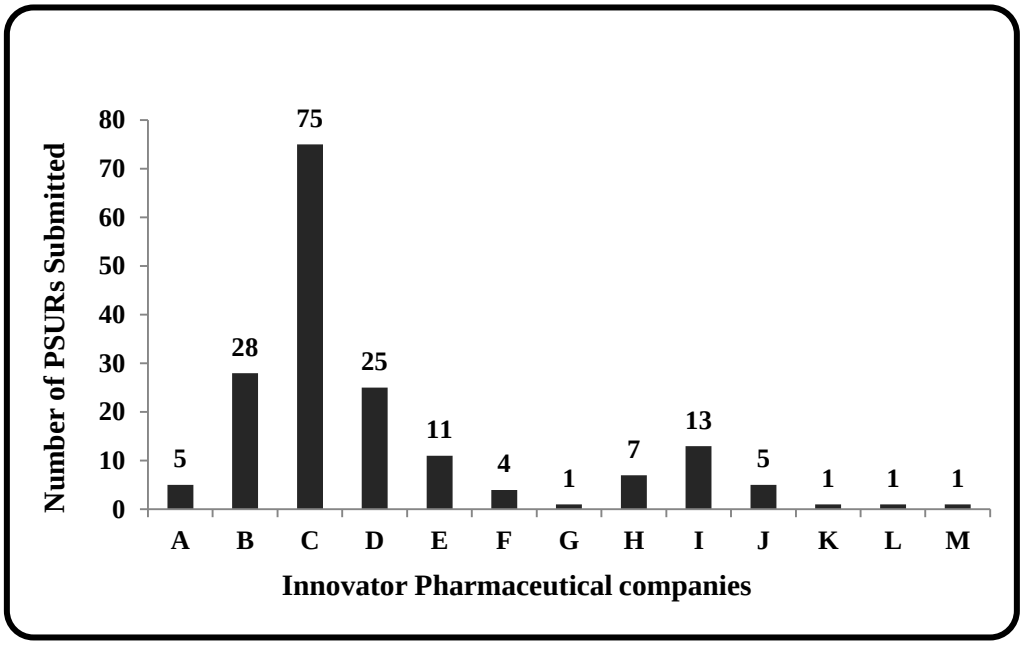


Figure 4: Innovator pharmaceutical companies that submitted periodic safety update reports

Only 3 generic pharmaceutical companies submitted PSURs in 2015.Of the 49 (21.7%) PSURs, majority were submitted by company N (35, 15.5%) as displayed in **figure 5.**

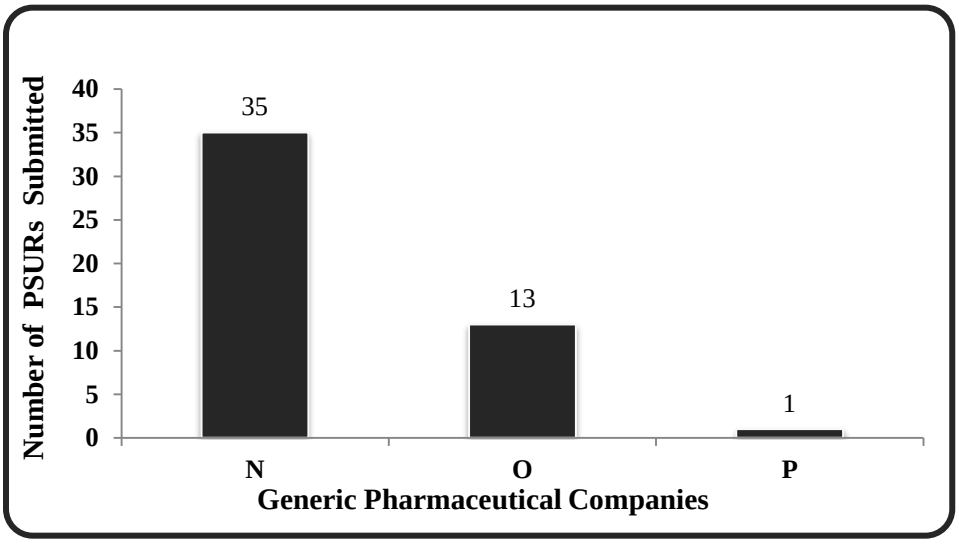


Figure 5: Generic pharmaceutical companies that submitted periodic safety update reports

4.2.3 The period covered by the periodic safety update reports

One hundred and nine (48.2%) of the PSURs submitted covered 12-23 months, followed by 50(22.1%) and 49(21.7%) covering < 1 year and 3-4 years respectively **(figure 6)**. In Kenya, there are no set guidelines as to when PSURs are submitted, hence the differences noted in the submission periods.

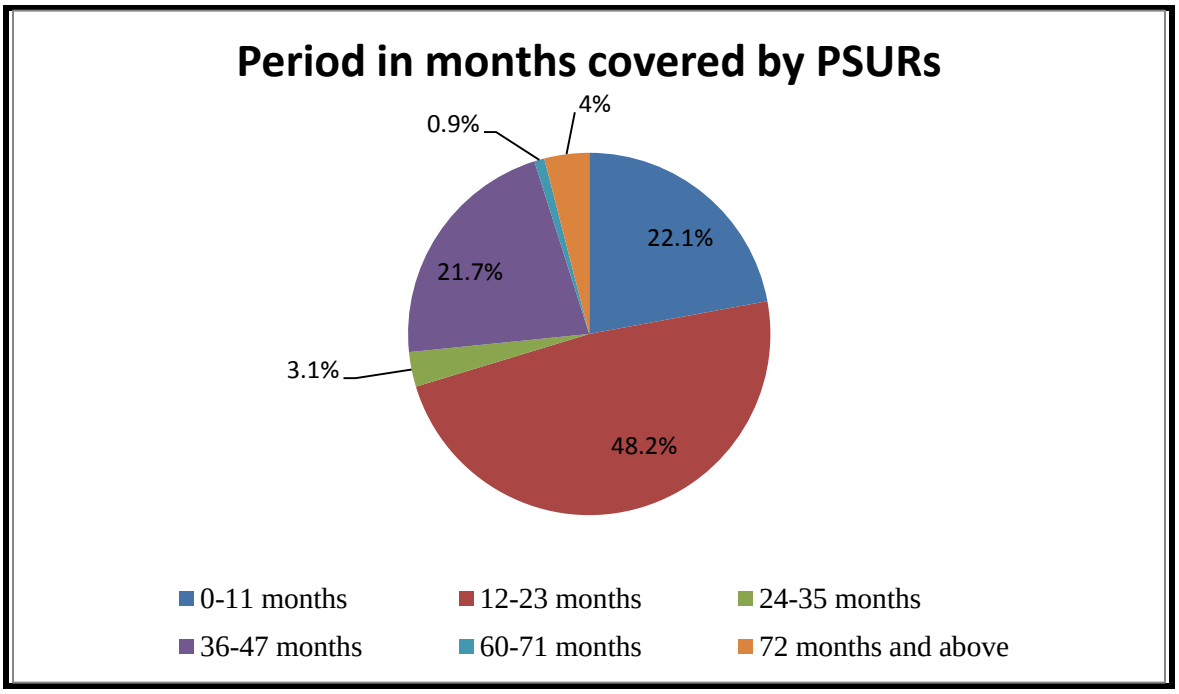


Figure 6: Period covered by the periodic safety update reports

4.2.4 Pharmacological classification of periodic safety update reports

Of the 226 PSURs submitted, 178 (78.8%) of them were for chemical entities, while 48 (21.2%) were for biologics. The WHO collaborating Centre for Drug Statistics Methodology was used in classifying the drugs according to the Anatomical Therapeutic Chemical (ATC) classification system (level 1) (111).

Table 9: Pharmacological classification of Periodic safety update reports

Classification	%	Classification	%
Vaccines	14.6%	Sex hormones and modulators	2.7%
Agents acting on renin angiotensin system	7.1%	Antibiotics and chemotherapeutics for dermatological use	2.7%
Antivirals for systemic use	6.6%	Drugs for acid related disorders	2.7%
Analgesics	5.8%	Antithrombotic agents	2.2%
Antibacterials for systemic use	5.3%	Beta blocking agents	2.2%
Drugs used in diabetes	4.0%	Ophthalmologicals	2.2%
Drugs for obstructive airway diseases	3.5%	Endocrine therapy	2.2%
Antineoplastic agents	3.1%	Others	<2%
Psycholeptics	3.1%		

Key: Others include: Anaesthetics, Antidiarrheal/intestinal inflammatory/antiifectives, Antianaemic preparations, Antiemetics and antinauseants, Antihemorrhagics, Antiprotozoals, Antipsoriatics, Antiepileptics, All other therapeutic products, Antihistamines for systemic use, Anti-acne preparations, Antifungals for dermatological use, Anti-parkinsonism drugs, Antiobesity preparations excluding diet preparations, Beta blocking agents, Calcium Channel Blockers, Cardiac therapy, Contrast media, Corticosteroids, Cough and cold preparations. Drugs for functional gastrointestinal disorders, Drugs for bone disease, Drugs for constipation, Immunosuppresants, Immunostimulants, Lipid modifying agents, Muscle relaxants, Nasal preparations, Psychoanaleptics, Stomatological preparations, Urologicals.

Most of the medicinal products belonged to the ATC groups of vaccines (33, 14.6%), agents acting on the renin angiotensin system (16, 7.1%) and antivirals for systemic use (15, 6.6%) as shown in **table 9.**

4.2.5 Specific risk management strategies identified in periodic safety update reports

The risk management strategies were classified into two; routine risk minimization activities and additional risk minimization activities. Routine risk minimization activities are those expected for all drugs, while the additional risk minimization activities are put into place when routine risk minimization activities are insufficient.

As part of routine risk minimization, more biologics included SPC contraindications, special warnings and precautions and undesirable effects (100% vs. 71%) as compared to chemical entities.

More educational materials for healthcare professionals (12.8% vs. 7.8%) and Dear Healthcare Professional communications (6.4% vs. 1.7%) were proposed for biologics as compared to chemical entities. More educational materials for patients (2.8% vs. 2.1%) were proposed for chemical entities as compared to biologics **(table 10)**. An educational material for the biologic was a patient alert card implemented as a postmarketing commitment and was meant to be distributed to the patients after the drug was administered. An educational outreach was implemented to increase awareness about the association between a gadolinium-based contrasting agent and a rare disease. Some biologics required media campaigns (3, 6.4%) and training of healthcare professionals (3, 6.4%).

Manufacturing restrictions used as risk minimization measures included sticky labels for gadobutrol to identify the product and dose administered, while changes in the external packaging, limitation in package size and limitation of dose were proposed for fluticasone propionate's use in children. There was also a new product design for the rotavirus vaccine and fentanyl patch **(table 10).**

Table 10: Specific risk management strategies identified in periodic safety update reports

Routine risk minimization measures	n (%)	
	Chemical entities	**Biologics**
SPC special warnings and precautions	127(71.3%)	47(100)
SPC contraindications	127(71.3%)	47(100)
SPC undesirable effects	127(71.3%)	47 (100)
Additional risk minimization measures		
Educational materials for healthcare professionals	14 (7.8)	6 (12.8)
Educational material for patients	5 (2.8)	1 (2.1)
Educational outreaches	1 (0.6)	-
DHCP letters	3(1.7)	3(6.4)
Training for healthcare professionals	-	3(6.4)
Media campaigns	-	3(6.4)
Manufacturing restriction		
Product design	1 (0.6)	1 (2.1)
Sticky labels	1 (0.6)	-
External packaging &limitation on dose and pack size	1 (0.6)	-
Others		
Pregnancy Prevention Program	1 (0.6)	-
Risk management module	1 (0.6)	1 (2.1)
Free testing	1 (0.6)	1 (2.1)
Use of explicit labelling language	1 (0.6)	-

Key: SPC refers to Summary of Products Characteristics; DHCP refers to Dear Healthcare Professional

Other additional risk minimization measures included a risk management module and adverse event-antibody testing which were proposed for methoxy polyethylene glycol-epoetin beta and epoetin beta. A pregnancy prevention program was implemented for mycophenolate while explicit labelling language around paediatric use was implemented for fluticasone propionate **(table 10).**

4.2.6 Measures to assess the effectiveness of risk minimization measures

Process indicators measure the extent to which planned additional risk minimization activities are implemented. More of the process indicators to measure the effectiveness of risk minimization measures were proposed for biologics as compared to chemical entities as presented in **table 11.**

Table 11: Indicators used to measure effectiveness of risk minimization measures

	n (%)	
Effectiveness of risk minimization measures	**Chemical entities**	**Biologics**
Process indicators		
Questionnaires	-	1(2.1)
Evaluation studies	-	1(2.1)
User acceptance testing	-	1(2.1)
Physicians Surveys	4(2.2)	-
Cognitive/ reader testing	1(0.6)	1(2.1)
Drug utilization studies	2(1.1)	-
Outcome indicators		
Annual review of reported ADR cases	3(1.7)	-
Published literature on extent of inappropriate use of drugs	1(0.6)	-
Frequency of A.E reports through ongoing PV activities	3(1.7)	1(2.1)
Number of free tests initiated,	1(0.6)	1(2.1)
Reduced number of complaints from implemented new design,	-	3(6.4)
Number of medication errors reports	2(1.1)	-
Comparison data of before and after implementation of pregnancy prevention programme.	1(0.6)	-

Key: ADR refers to Adverse Drug Effects, A.E refers to Adverse Events, and PV refers to Pharmacovigilance

The process indicators included a questionnaire to determine whether the patient alert card had reached the patient and an evaluation study to determine extent of use of the patient alert card for the biologic therapy, rituximab.

A survey to gauge physicians' knowledge and understanding were implemented for the following chemical entities: Everolimus, Ticagrelor, Rivaroxaban and Fentanyl. Drug utilization studies to evaluate clinical actions after educational materials were distributed to physicians were implemented for Cyproterone acetate and rivaroxaban. Cognitive reader /acceptance testing of educational materials provided to physicians and patients to determine whether they understood the materials provided was implemented for methoxy polyethylene glycol-epoetin beta and planned for rituximab **(table 11).**

Outcome indicators are safety outcomes that measure the frequency of adverse events that a risk minimization measure intends to prevent. More specific safety outcomes to determine whether the additional risk minimization activities were effective were proposed for chemical entities as opposed to biologics. These included annual review of adverse event reports, published literature on inappropriate use of medicines, comparison of pre-and post-pregnancy prevention programme data as well as review of medication errors reports.

For methoxy polyethylene glycol-epoetin beta and epoetin beta, the MAH offered free adverse event-antibody testing as an additional risk minimization measure as indicated on the educational material. Thus the number of free tests initiated by the physician was assessed as an outcome indicator to assess this risk minimization measure. For the biologic rotavirus vaccine, revision of the instructions and an educational program were implemented to reduce complaints associated with the new product design, and thus, a reduction in number of these complaints was used to evaluate the effectiveness of this risk minimization measure **(table 11).**

4.2.7 Additional pharmacovigilance activities

More additional pharmacovigilance activities: clinical trials (19.2% vs. 14%), epidemiological studies (29.8% vs. 27.5%) and registries (21.3% vs. 5.0%) were conducted for biologics as compared to chemical entities as presented in **table 12.**

Table 12: Studies that were reported in the Periodic Safety Update Reports

Additional pharmacovigilance activities	n (%)	
	Chemical entities	Biologics
Clinical trials	25 (14)	9(19.2)
Epidemiological studies	40 (27.5)	14(29.8)
Registries	9 (5.0)	10(21.3)
African inclusion in the studies	8 (4.5)	5(10.6)

More studies were conducted in Africa for biologics (5, 10.6%) as compared to those for chemical entities (8, 4.5%). The African countries where the studies were reported to have been completed / still ongoing included: Egypt, South Africa, Algeria, Tunisia, Kenya and Libya.

4.2.8 Risk evaluation and mitigation strategies components

PSURs for 2 chemical entities had the following REMS components: medication guide, communication plan and an assessment report submission. A medication guide was appended in the PSUR for Omeprazole-Sodium bicarbonate combination and a communication plan for Fluticasone propionate was stated as having been implemented in various countries. However it could not be established whether the medication guide and communication plan were implemented in Kenya. This is shown in **table 13**.

Table 13: Risk evaluation and mitigation strategies components in periodic safety update reports

Risk evaluation and mitigation strategies components	n (%)		
	Chemical entities	Biologics	Total
Medication guide	2 (1.1)	-	0.9
Communication plan	2 (1.1)	-	0.9
Additional risk minimization activities			
REMS approval and reports submission	2 (1.1)	-	0.9

Key: REMS refers to Risk Evaluation and Mitigation Strategies

4.3.TYPES OF REGULATORY ACTIONS TAKEN BY THE PHARMACY AND POISONS BOARD AND MARKETING AUTHORIZATION HOLDERS IN 2015

Risk control, an aspect of risk management, tries to minimize risks and is a responsibility of both the MRA as well as the MAHs. In terms of medicinal products, this can be done by detecting and stopping distribution of illegal or substandard products, withdrawing or recalling drugs, suspending or revoking a marketing authorization as well as communicating the risk to various stakeholders.

There were a total of 29 regulatory actions recorded in a file found in the pharmacovigilance department of the PPB in the year 2015. Twenty one (21) of these actions were initiated by PPB while 8 were by MAHs. The 21 actions initiated by PPB included: quarantine of drugs (5, 23.8%), lifting up of regulatory actions (2, 9.5%), safety communications to various stakeholders (12, 57.1%), a product quality survey (1, 4.8%) and a request to carry out tests in a laboratory outside Kenya (1, 4.8%) as shown in **figure7.**

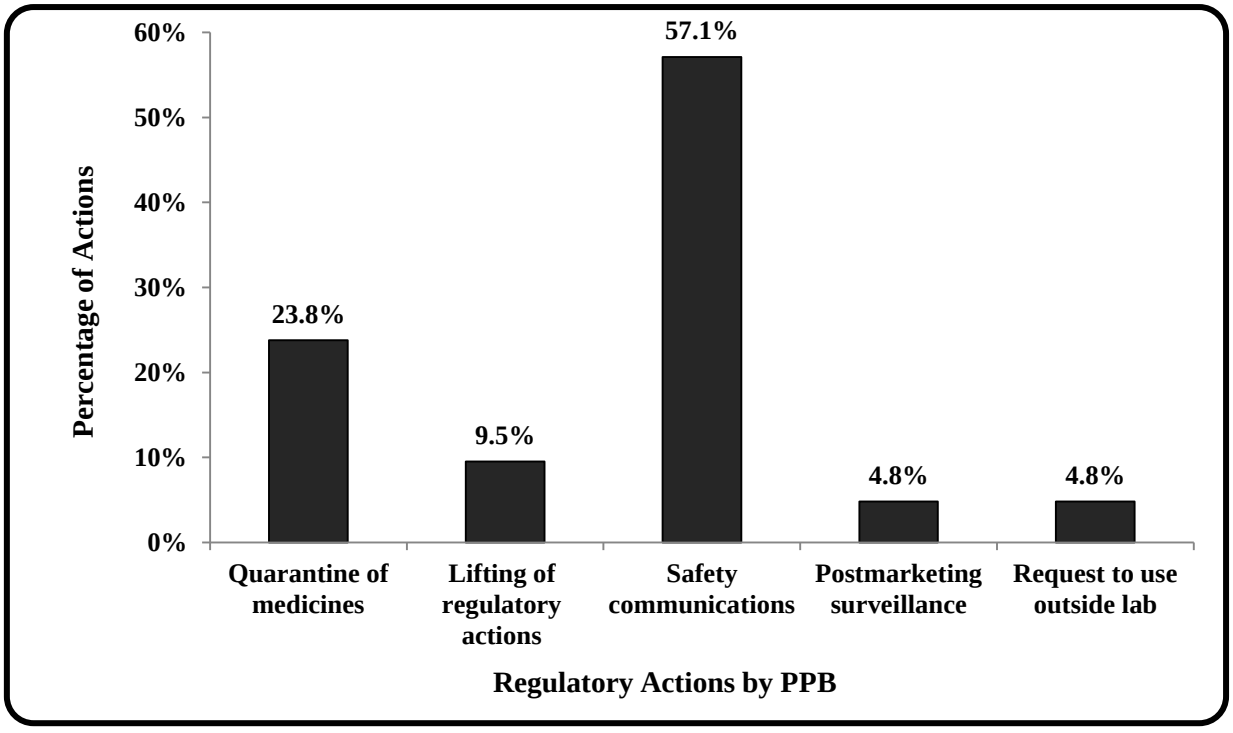


Figure 7: Regulatory actions taken by the Pharmacy and Poisons Board in 2015

The eight (8) regulatory actions that were taken by MAHs were either initiated by the company itself or were as a result of PPB imposing regulatory actions on them. The highest proportion of these actions included voluntary quarantine of 3 drug batches after they failed some tests. This

accounted for 37.5% of all the actions taken by the MAHs. The other actions accounted for 12.5% each and included: 1 voluntary recall, 1 voluntary withdrawal, 1 appeal of a recall imposed by PPB, 1 request by an MAH to use a quarantined raw material and 1 response by an MAH to PPB on actions they had taken after they voluntarily recalled a medicinal product.

The quarantined medicines were those that did not meet the United States Pharmacopoeia (USP) specifications. For 1 product previously recalled and another quarantined, these actions were lifted after investigations carried out showed that the products complied with the USP specifications and were thus considered safe for human use.

Drug safety communications were targeted at the public, MAHs, healthcare professionals, within PPB itself and to the directorate of criminal investigations. Those directed to the MAHs included: a request to pull down an advert that was considered misleading, a notification that a previously imposed recall was to remain effective till further investigations were conducted, a request for a report on voluntary recall initiated by a MAH, a rejection of rebranding proposed by an MAH as it was thought it would cause medication errors and a notification sent to an MAH on reported poor product quality asking the MAH what actions they had taken.

Safety communications to other stakeholders included: a safety alert on a suspected substandard drug targeted to the public, a recommendation to healthcare workers on storage conditions for oxytocin, an internal communication to regional heads on an unregistered poor quality product detected through post-marketing surveillance, as well as a communication to the directorate of criminal investigations, informing them of the detected unregistered medicine.

PPB conducted a joint post-marketing surveillance to investigate presence of unregistered products in the Kenyan market for selected antibiotics, antiretrovirals and anti-tuberculosis medications. This was a joint effort of the PPB, National AIDS and STIs Control Programme (NASCOP) and Division of Leprosy, Tuberculosis and Lung Disease (DLTLD).There was also a request to carry out further tests in South Africa on batches of the tetanus toxoid vaccine that were suspected to contain the Human Chorionic Gonadotropin (β-HCG) hormone.

4.4.RISK MANAGEMENT PRACTICES AS CARRIED OUT BY PPB AND MULTINATIONAL PHARMACEUTICAL COMPANIES

For this study, key informants included regulatory affairs specialists and/or pharmacovigilance specialists from selected multinational innovator pharmaceutical companies as well as personnel working in the pharmacovigilance department in PPB.

A list of multinational innovator pharmaceutical companies that submitted risk management documents such as RMPs and PSURs was drafted. Their physical addresses were obtained and their regulatory affairs specialists and/or pharmacovigilance specialists were contacted and asked if they would be willing to take part in an interview.

A total of seven key informants were approached from the multinational innovator pharmaceutical companies. Four of them gave consent and were interviewed. Five key informants were approached from PPB and they all consented and were interviewed. Thus a total of nine key informants were recruited and interviewed as shown in **figure 8**.

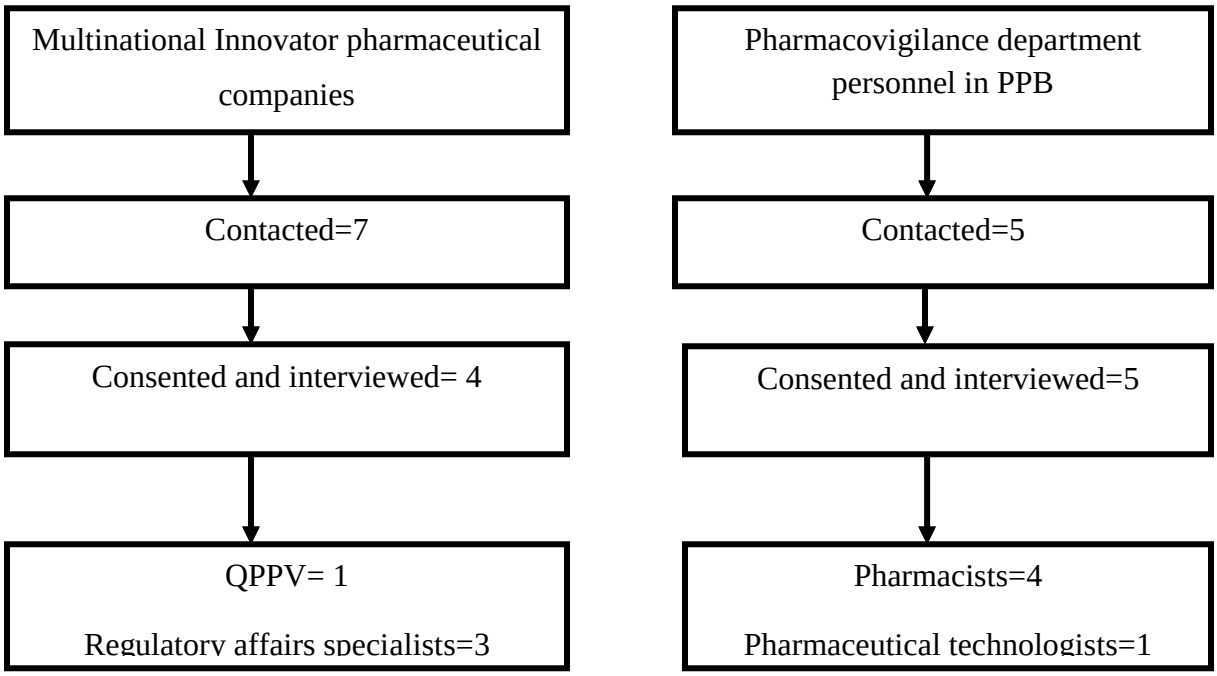


Figure 8: Flow chart of key informants' selection for the in-depth interview

Ten thematic codes were used to explore the role of PPB and the multinational innovator pharmaceutical companies in managing risks for medicinal products in Kenya.

These included:

Perception of policy framework for pharmacovigilance

Sources of information on drug safety

Pharmacovigilance reporting system

Communication of medicine-related safety concerns

In-house pharmacovigilance activities of local companies

Risk management strategies

Formal pharmacovigilance studies

Addressing potential for medication errors

Strengthening safety monitoring

Challenges faced.

Theme 1: Perception of policy framework for pharmacovigilance

All 5 interviewees from PPB reported that there was currently no policy or guidance document that required MAHs to submit RMPs in Kenya.

"*There is no policy or guidance requiring them to submit RMPs, but there is a draft QPPV guideline.*" [Interviewee 1, PPB]

"*There is no policy so we rely on the WHO recommendations*." [Interviewee 3, PPB]

Four of the interviewees from PPB reported that there was no regulation or guideline requiring MAHs to submit PSURs.

"*They are not required to do so, but there is a draft QPPV guideline that addresses that*". [Interviewee 1, PPB]

"*There is no regulation, but this is under review in the revised guideline*". [Interviewee 2, PPB]

All 5interviewees from PPB reported that there were no set timelines for submission, review and providing feedback to MAHs on the PSURs they submitted. However two interviewees reported that this had been addressed in the draft QPPV guideline.

"*The timelines for submission is as per the WHO guidelines*". [Interviewee No.3, PPB]

One interviewee from the pharmaceutical industry stated that: *"There is no regulation that enforces submission of PSURs and RMPs. Though we submit them, we do not get feedback from PPB*". [Interviewee No. 2, pharmaceutical industry]

As to whether MAHs were required to conduct postmarketing studies, 4 out of the 5 interviewees from PPB stated that there was no policy or regulation that gave PPB the authority to require MAHs to conduct such studies.

"*It's a mutual agreement. The PV guideline states that they should share information from such studies*". [Interviewee No.1, PPB]

"*PPB takes it upon itself to conduct some of these studies*". [Interviewee No.3, PPB]

"*Submission of PSURs and information collected from postmarketing surveillance is stated under pharmaceutical industry in the pharmacovigilance guideline. Thus, PPB has such authority as stated under the pharmacovigilance guidelines*". [Interviewee No.4, PPB]

"*It is not specified. However, PPB has the mandate to ensure overall safety and quality. It is difficult to ask MAHs to conduct studies since it is not specified in law*". [Interviewee No.5, PPB]

Theme 2: Sources of information on drug safety

Two of the interviewees from the pharmaceutical industry reported that they gathered information on risks associated with their products from market surveillance, ICSRs and journal reviews.

"*The data is compiled from our mother company and the information submitted to PPB. This is because pharmacovigilance has not been taken up well in sub-Saharan Africa*" [Interviewee 1, pharmaceutical industry]

"Mostly it is through ICSRs if there is anything information has been reported. We deal with a global database. In fact, reporting in Kenya has been a bit difficult. We are still trying to get people to report, because people are not reporting."[Interviewee no. 4, pharmaceutical industry]

Three of the key informants from PPB reported that there was a system of monitoring new safety reports from outside sources. Two of them reported getting information on new signals from the WHO-Uppsala Monitoring Centre (UMC).

"*We get information on signals from WHO-UMC via Vigibase. MAHs also send us reports when there are new signals*." [Interviewee No.1, PPB]

"*SOPs are being developed on monitoring safety reports. We get alerts from the WHO-UMC".* [Interviewee No.2, PPB]

"*We have an EAC platform where communication on safety signals is shared amongst the regional countries*". [Interviewee No.4, PPB]

"*We have access to websites. There is a body of regulators, the National Medicines Authorities, where information is shared" We also have a PV reporting system where we get information on ADRs and poor quality drugs*" [Interviewee No.5, PPB]

Theme 3: Pharmacovigilance reporting system

Three of the key informants from the pharmaceutical industry reported that they received information on emerging safety concerns from healthcare professionals directly as well as from their company sales reps who directly engaged with physicians and other healthcare professionals.

"*We have a generic mailbox for reporting safety issues related to our products as well as to make enquiries on safety issues as these present another avenue for reporting*".[Interviewee No.1, pharmaceutical industry]

Four of the interviewees from PPB stated that the pharmaceutical industry was mandated to submit reports on manufacturing and/or product defects to PPB. This was through submission of distribution lists of quantities supplied and if the product was withdrawn, quantities withdrawn.

"*Manufacturing and/or product defects are mainly noted from post marketing studies conducted by the pharmaceutical companies and alerts are then sent to PPB's good manufacturing practices department."*[Interviewee no.5, PPB]

Majority of the interviewees from PPB stated that there was no database for products requiring additional monitoring and no measures were undertaken with regards to these medicines. However, one interviewee stated, "*We monitor high risk medicines and narcotics by collaborating with the National Authority for the Campaign against Alcohol and Drug Abuse (NACADA) and Kenya Medical practitioners and Dentists union (KMDU) in ensuring there was controlled access of narcotics.*"[Interviewee No.5, PPB]

Theme 4: Communication of medicine-related safety concerns

Majority of the key informants from the pharmaceutical industry reported that they communicated the benefit risk profile of their products to PPB mainly through submission of PSURs.

"Other than educational materials, we use promotional materials, medically approved videos shared in roundtable meetings, company websites, DHCPs, detailers". [Interviewee No.1, pharmaceutical industry]

"*We do it via the patient information leaflet and safety updates*". [Interviewee No. 2, pharmaceutical company]

"*This is done through annual submission of PBRERs per product. We gather information from market surveillance, compile the information and submit it*. "*Other than PBRERs, we also submit risk management plans to PPB*" [Interviewee No. 3, pharmaceutical industry]

"*We have patient information leaflets that give information to patients on how to use the devices, and other information such as where to inject, reactions that may occur*." [Interviewee No.4, pharmaceutical industry]

As to whether the effectiveness of these tools was measured, majority of the interviewees from the pharmaceutical industry state they were not. However, on interviewee stated, *"We measure their effectiveness by the number of reports received by the patient safety department*." [Interviewee No. 3, pharmaceutical industry]

Majority of the interviewees from the PPB stated that there were guidelines on how MAHs present SPCs during registration of medicinal products in Kenya. Two interviewees stated that PPB had the authority to require labelling documents from MAHs. However there was no timeframe for the submission of and review of updates to these labelling documents.

All the interviewees from the pharmaceutical industry stated that safety communication was mainly targeted to healthcare professionals, and the regulator, PPB. The communication to PPB was via reports compiled and sent to them in both electronic and manual form. Communication to healthcare professionals was through DHCPs and trainings.

All the interviewees from the pharmaceutical industry stated that none of the safety communications were directed to the public, since this responsibility was taken up by PPB. However, two interviewees stated there had been instances when a customer had called the company to enquire on safety related issues with the company's products.

"We rarely get any information on our products from the public directly, but rather any information from the public is gotten from the healthcare professionals who then talk to our

medical representatives and the information reaches our company". [Interviewee No. 3, pharmaceutical industry]

All interviewees from the pharmaceutical industry stated that the goal of the safety communication was to keep the target audience updated on new safety updates as well as patient safety and that the effectiveness of these communications was not evaluated locally. However, one interviewee stated, *"Any implemented activity is audited. Any education and program undertaken is audited internally."* [Interviewee No. 4, pharmaceutical industry]

Majority of the interviewees from PPB stated that safety related issues were communicated through the E-shot system and newsletters and that there was no definite schedule. However, the frequency of these communications depended on the number of cases/alerts and their severity. Three of the interviewees stated that newsletters were published yearly, while one interviewee stated that 2pagers were communicated quarterly.

"We use our inspectorates to provide information to the areas that they are overseeing."[Interviewee no.2, PPB]

"*We use press conferences, social media through our Facebook page, newsletters, E-shots and 2 pagers*."[Interviewee no. 4, PPB]

"*We communicate through newsletters, trainings, media articles and adverts, road shows, print media, emails directed to healthcare professionals and social media through our Facebook and twitter pages*."[Interviewee no.5, PPB]

Four of the interviewees stated that PPB had undertaken public and/or community education activities relating to medicines safety in 2015. They included: a PPB stand at various Agricultural Society of Kenya (ASK) events, road talk shows to different counties and a television morning show.

As to whether the effectiveness of these communications was evaluated, four of the interviewees from PPB stated it was not. However, one interviewee stated *"Evaluation is done once a year through customer satisfaction interviews."*[Interviewee No.4, PPB]

Theme 5: In-house management of emerging safety concerns

All key informants from the pharmaceutical industry stated that when emerging safety concerns arose, they first dealt with them in-house before being reported to PPB and that majority of the pharmacovigilance plans addressed the safety concerns.

"*We evaluate the type of risk, its severity and the populations affected. Once these are mapped out, we come up with different action plans and inform PPB.*"[Interviewee 1, pharmaceutical industry]

"*We discuss the risks internally with our bosses, then alert PPB about the risk and determine the way forward*."[Interviewee no.2, pharmaceutical industry]

"*We collect safety information and contact the healthcare professionals for further information. We assess the risk and check whether the risk has been captured before in our company database system. We assess the severity of the risks, whether mild, severe or moderate and on the basis of severity, we formulate action plans, such as withdrawal, recalls. However, we have not encountered any severe safety issues so far."* [Interviewee No.3, pharmaceutical industry]

All key informants stated that they submitted new safety concerns as variations to PPB. "*Approval is sought from PPB before making the necessary changes. Once the approval is granted, safety updates are provided and changes communicated to healthcare professionals, in the form of DHCPs*." [Interviewee no.4, pharmaceutical industry]

Majority of the key informants from the pharmaceutical industry stated that there had been no safety issues that they had to deal with locally.

"*In case of such an issue, we would need to come up with corrective action plans (CAPA) such as changes in safety labels, carrying out educational symposiums, and training various cadres of health professionals*".[Interviewee No. 1, pharmaceutical industry]

"*We once had a user issue but we had our company representatives flown from abroad to train healthcare professionals*" [Interviewee No.3, pharmaceutical industry]

Theme 6: Risk management strategies

In terms of risk management strategies implemented by the pharmaceutical industry to minimize risks, all the interviewees from the pharmaceutical industry stated that they conducted healthcare provider-based training as well as provided educational programs and materials. Only one

interviewee stated that they implemented restrictions on distribution and dispensing of medicines to minimize risks.

Regarding risk management strategies employed by PPB, all of the key informants from PPB stated DHCPs were used as additional risk minimization measures, while educational materials such as patient alert cards, job aids to public facilities and faith based organizations and trainings were implemented. They also stated that pregnancy prevention programs were not implemented in Kenya, though one interviewee stated *"It is done by Population Services Kenya and then approved by PPB*". [Interviewee No. 4, PPB]

In terms of whose responsibility it was to implement the above measures, all five interviewees stated that the MAHs initiated the DHCP communications, though the letters had to be verified by PPB before distribution. Four of the interviewees from PPB stated that controlled access programs were implemented in Kenya with one of the interviewees adding that "*they are implemented by the Ministry of Health (MOH) by use of the old schedule though reviewing of the scheduling is being done*". [Interviewee No. 1, PPB]. Educational materials were initiated by both the PPB and MAH.

As to whether the effectiveness of these risk management strategies was evaluated, three of the interviewees stated it was not was not evaluated, although one interviewee indicated that it this was done through surveillance by the inspectorate department.

Theme 7: Local formal studies

Four of the interviewees from the pharmaceutical industry reported that they had not conducted medication error surveys, ineffectiveness of product surveys and utilization review studies in the last 5 years for their products. Two interviewees stated that their companies had conducted prospective registry studies, while only one interviewee stating that they had conducted an epidemiological study

Two interviewees stated that their Quality Assurance (QA) department was responsible for looking into any quality issues that might occur with their products.

All five respondents from PPB reported that PPB had initiated postmarketing active surveillance in the last five years. These included two (2) cohort event monitoring (CEM) studies involving antimalarials and antiretrovirals in 12 sentinel sites: 5 sites for antimalarials and 7 sites for

antiretrovirals. The antimalarials study had been completed while the antiretroviral one was still on-going.

There were also product quality surveys that were conducted to assess the quality of various medicinal products. These included: joint post-marketing studies between PPB, NASCOP and the DLTLD to investigate quality of selected antibiotics, antimalarials and antituberculosis medication in the Kenyan market, as well as product quality studies of various antihypertensive medicines and medicines used in reproductive health.

"*There's a product quality survey of antihypertensive medication that was initiated in 2014 and is done twice a year. We have not initiated any registry as PPB but there were some registries initiated by KEMRI and one in Webuye"* [Interviewee No. 4, PPB]

"*We conducted one causality assessment study for ADRs in 2015.*"[Interviewee No.5, PPB]

All the five interviewees from PPB stated that there was no register/document in place that provided information on the status of post authorization safety studies conducted by MAHs and for which annual reports had been submitted though one interviewee stated there were protocols in place for the above studies. There was also no annual publication of reports for studies conducted by PPB, but one interviewee stated that

"*We are working on a publication for the antimalarial study that was completed.*"[Interviewee No.5, PPB]

Theme 8: Addressing potential for medication errors

Two of the interviewees stated that their companies used colour coding for products that were likely to be confused by Healthcare professionals. Two other interviewees stated that this was addressed via information given to Healthcare professionals through labelling such as SPCs and patient leaflets, training of bigger healthcare professionals groups, as well as one on one provider training.

"*Our company conducts extensive research and development for our products to minimize the possibility of medication errors. We consider the naming of their products in the final packaging to avoid confusion. We also use standardized fonts in the primary and secondary packages*". [Interviewee no.2, pharmaceutical industry]

Theme 9: Presence of a committee to strengthen safety monitoring in Kenya

All of the key informants from PPB stated that there was currently no committee mandated to strengthen safety monitoring in Kenya. Two of the interviewees stated that there was an expert safety review panel for reviewing ADRs, while one specified that there is an expert committee on clinical trials.

"*It is carried out by the department of post-marketing surveillance quarterly*." [Interviewee no.3, PPB]

Theme 10: Challenges faced by the pharmaceutical industry

All key informants stated that their main challenge was lack of feedback after submitting reports to PPB. They rarely received feedback on any PPB review of the reports submitted.

"Since RMP submission is not a requirement, it presents a gap in the local assessment of the risk benefit profile of medicinal products. Is there even a concern for not having RMP submission a requirement? Also, Lack of awareness of PV among some healthcare professionals and the general public makes it difficult for the pharma industry to have adequate local data that could be incorporated in the reports and thus, much of the information on the reports is from outside sources."[Interviewee no.1, pharmaceutical industry]

"Off-label use of medicinal products in Kenya has not been addressed leaving a lot of loopholes for such use." [Interviewee No .3, pharmaceutical industry]

4.5.APPRAISAL OF PHARMACOVIGILANCE ACTIVITIES USING THE INDICATOR PHARMACOVIGILANCE ASSESSMENT TOOL

The Indicator Pharmacovigilance Assessment Tool (IPAT) was used in assessing the pharmacovigilance and medicines safety systems at PPB. However, since this study was not assessing the pharmacovigilance system as a whole, only indicators that pertained to risk management were used in this assessment. Thus, only indicators 1.4, 2.10, 4.1, 4.2, 4.3, 4.5, 5.1, 5.3, 5.5, 5.6, 5.7 and 5.9 were assessed.

A score of 2 was given for a core indicator fulfilled, 1 for a supplementary indicator fulfilled and 0 if neither the core nor supplementary indicators were fulfilled **(table 14).**The assessment included use of structured interviews and documentary evidence.

4.5.1 Policy, Law and regulation

The assessment on policy, law and regulation was done using only one indicator: indicator 1.4. The Pharmacy and Poisons (registration of drugs) Rules; rule (9) sub-rule (2) gives a provision for conditional registration of a drug. It states that PPB can register a product and require MAHs to conduct clinical trials as well as provide details on other investigations required after a product was registered (112). The "Guidelines for the National Pharmacovigilance System in Kenya" also requires MAHs to furnish PPB with post-marketing surveillance data (26). However, there is no specific legislation that gives PPB the authority to mandate MAHs to conduct post-marketing studies for medicinal products for which stringent MRAs such as US-FDA and EU-EMA have stipulated should be done.

4.5.2 Systems, structures and stakeholder coordination

An assessment of the systems, structures and stakeholder coordination was also done using only one indicator: indicator 2.10. PPB has an established PV newsletter that addresses various pharmacovigilance issues and is available on the PPB website. However, the bulletin is not published every 6 months.

Table 14: Assessment of pharmacovigilance activities using the indicator-based pharmacovigilance assessment tool

	Indicator	Indicator type	Score
Policy, Law, Regulation			
1.4	Legal provisions require that MAHs conduct the same or similar post-marketing surveillance activities for products as required by stringent MRAs	SS	0
Systems, Structures and Stakeholder Coordination			
2.10	Existence of an ADR or medicines safety bulletin or any other health related newsletter that routinely features ADR or medicines safety issues published in the last six months	CS	0
Risk assessment and evaluation			
4.1	Number of medicine utilization reviews carried out in the last year	SP	0
4.2	Pharmaceutical product quality survey conducted within the last five years	SP	1
4.3	Incidence of medication errors quantified in the last year	SP	0
4.5	Number of active surveillance activities currently ongoing or carried out in the last five years	CP	2
Risk management and communication			
5.1	Risk mitigation plans currently in place that are targeted at high-risk medicines	SO	0
5.3	Number of medicine safety information requests received and addressed in the last year	SO	0
5.5	Number of medicine safety issues of local relevance identified from outside sources (e.g., from another country, or from regional or international sources) and acted on locally in the last five years.	SO	0
5.6	Number of "Dear health care professional" letters or other safety alerts developed and distributed in 2015	SO	1
5.7	Average time lag between identification of safety signal of a serious ADR or significant medicine safety issue and communication to health care workers and the public	CO	0
5.9	Public or community education activities relating to medicine safety carried out in 2015	SO	2

Key: CO refers to Core outcome, SO refers to Supplementary Outcome, CS refers to Core Structural, SS refers to Supplementary Structural, CP refers to Core Process, SP refers to Supplementary Process, and ADR refers to Adverse Drug Reactions

4.5.3 Risk assessment and evaluation

Analysis of risk assessment and evaluation was done using four indicators, 4.1, 4.2, 4.3 and 4.5, with 2out of the 4 indicators being achieved **(table 14).** There were significant deficiencies in this evaluation withal the interviewees from the pharmaceutical industry stating that they had not conducted medication errors surveys, quality and ineffectiveness of product surveys and drug utilization reviews in the last 5 years.

This could be attributed to lack of laws and regulations to mandate the pharmaceutical industry to conduct active surveillance. The national pharmacovigilance guideline states that among the roles and responsibilities of the pharmaceutical industry is to furnish PPB with ADR reports and share postmarketing surveillance data(26). However, there is no specific legislation enforcing the conduct of these studies. This is unlike in the EU and the US, where the new EU pharmacovigilance legislation and the FDAAA require MAHs to conduct such studies (65,113).

The interviews however revealed that a joint product quality survey had been carried out between PPB, NASCOP and the DLTLD **(table 14).** This was done to find out if there were any unregistered medicinal products in the market and was targeted for selected antibiotics, antimalarials and antituberculosis medication. This information was confirmed from a file on regulatory actions taken in 2015 and communications were sent internally and externally, concerning unregistered drugs that were found in circulation and led to recall of poor quality medicines that were circulating in the market.

PPB also initiated postmarketing active surveillance studies in 2010. These included supporting two (2) CEM studies involving antimalarials and antiretrovirals in 12 study sites. The antiretroviral study was still ongoing while the antimalarials study had been completed, though there were no final study reports for the finalized study. Registries had also been initiated by MAHs and other stakeholders in various areas such as Webuye, with some were being overseen by KEMRI.

4.5.4 Risk management and communication

The assessment of risk management and communication was carried out using six indicators with only two out of the six indicators being fulfilled. The main reason for this was lack of documentation. For instance, for indicators 5.2 and 5.5, there was no documentation of receipt of the medicine safety information requests and medicine safety issues of local relevance that were

identified and there was no documentation stating if any actions had been taken in response to the requests and the identified safety issues.

The average time lag between identification of safety signals and communication to healthcare workers and the public could not be determined since there was no documentation. There is no legislation enforcing submission of RMPs for high risk medicines, thus most pharmaceutical companies don't submit these documents.

PPB had however, issued safety alerts on drugs. These included caution on effects of a flood in Narok on the safety of medicines and an alert on substandard drugs. Community and public education activities were conducted through road shows in various counties educating the public on medicine safety issues. PPB also had a stand at the various ASK events where they also educated the public.

4.6.COMPARISON OF THE RISK MANAGEMENT SYSTEM OF MEDICINAL PRODUCTS IN THE EUROPEAN UNION, UNITED STATES OF AMERICA AND KENYA

Unlike in the EU and USA, Kenya currently does not have an Act of Parliament that spells out the statutory requirements for risk management of medicinal products. Kenya borrows from the ICH guidelines for the submission of RMPs and PSURs. A comparison of the risk management systems of Kenya, US and EU is shown in **table15.**

Similarities exist between the various risk management components. Kenya, just like the EU, uses PILs and patient alert cards in providing information about drugs to patients, as well as various sections in the SPC to communicate important information to the prescribers. Just like the US, Kenya relies on provider-based training to keep the healthcare professionals abreast with new or updated information on medicines.

Kenya has an inadequate risk management framework. This is largely due to lack of appropriate policy and legislation that enforces submission of RMPs and PSURs. There is currently no committee similar to the EU-Pharmacovigilance Risk Assessment Committee and the US- Drug safety and risk management advisory committee, which is tasked with the sole responsibility of evaluating risk management reports and providing recommendations on pharmacovigilance matters. However, there is an expert safety review panel in place that provides technical expertise in matters related to pharmacovigilance.

Table 15: Comparison of the risk management system of medicinal products in USA, EU and Kenya

Country	USA	EU	Kenya
Risk management system	REMS	RMP	None
Legislation enforcing risk management system	FDAAA of 2007	Amendment to directive 2001/83/EC by directive 2004/27/EC	None
Committee that reviews risk management system documents	Drug safety and risk management advisory committee	Pharmacovigilance Risk Assessment Committee (PRAC)	None
Risk management components			
Provision of patient information	Medication guide, patient information sheet	Patient information leaflet, patient alert cards	Patient information leaflet, patient alert cards
Provision of provider information	Highlighted information for prescribers	Through the Summary of Product Characteristics	Through the Summary of Product Characteristics
Provider-based training	Training of healthcare professionals	Educational program	Training of healthcare professionals
Patient monitoring	Submission of documentation of monitoring of patients receiving medication	Prospective registry and epidemiological studies. Specific AEs and PSUR requirements	None

Key: FDAAA -Food and Drugs Administration Amendment Act, EC refers to European Community, REMS-Risk Evaluation and Mitigation Strategies, RMP-Risk Management Plans, PSUR refers to Periodic Safety Update Report, USA refers to United States of America, and EU refers to European Union

Kenya also lacks an appropriate patient monitoring system, due to lack of appropriate policy **(table 15)**. Legislation mandates MAHs to conduct postmarketing studies in the EU as agreed upon prior or after marketing authorization has been granted when a safety concern arises. In the US, there are prescription drug monitoring programs in the various states to collect prescription data on controlled medicines and this minimizes 'doctor shopping' (114). These reports are available to healthcare practitioners, regulatory boards, pharmacists and law enforcement agencies to identify inappropriate and misuse of controlled substances.

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1.Discussion

5.1.1.Adequacy of a risk management system, policy, law and regulation

This study showed that the risk management system for medicinal products in Kenya is inadequate due to an inadequate regulatory framework since there is no Act of Parliament that requires Marketing Authorization Holders (MAHs) to submit Risk Management Plans (RMPs).This was evident from the fact that only 10 RMPs were submitted in 2015 in comparison to 248 PSURs. This was attributed to the fact that PPB does not have the authority to require MAHs to submit RMPs though through the national pharmacovigilance and clinical trial guidelines, Periodic Safety Update Reports (PSURs) are submitted.

PPB requires MAHs to submit the safety profile of medicinal products when seeking for marketing authorization to enable it to adequately evaluate the benefit-risk profile of a medicinal product. This safety profile is presented in pharmacovigilance documents such as PSURs, RMPs as well as in Individual Case Safety Reports (ICSRs). From an evaluation of these documents, PPB decides whether the benefit-risk profile is favourable or whether additional activities are needed to address any safety concerns that are present. When these documents are not submitted, a regulatory authority lacks crucial knowledge to make effective decisions.

This study also revealed lack of cohesion in the submission of both RMPs and PSURs. This was because out of the 16 MAHs that submitted PSURs, only one 1 of them had submitted RMPs, yet out of the 248 PSURs submitted, 47.3% of them had an active RMP, REMS or both in place. Of the 10 RMPs submitted, only 1 of them had a corresponding PSUR, yet the PSUR is linked to the RMP as an RMP explains how the risks identified in the PSUR will be managed (76).

In the US, the FDAAA of 2007 gave FDA the authority to require MAHs to develop and comply with Risk Evaluation and Mitigation Strategies (REMS) (54).This was as a result of intensified scrutiny caused by withdrawal of several medicines due to safety concerns. In the EU, the legal context for RMP submission is found in Directive 2001/83/EC and Regulation (EC) No 726/2004 (60).A new pharmacovigilance legislation came into effect in 2012 after it was discovered that 197,000 deaths per year in the EU were as a result of ADRs , leading to societal costs of 79 billion Euros per year (63,115).

In the US and EU, REMS and RMP submission is mandatory for some products; at the time of seeking marketing authorization, at the behest of the regulator, or when a safety concern arises that may affect the benefit-risk profile. However, in Kenya, the same products may receive marketing authorization without a system in place that explains how the risks associated with the product will be minimized. For instance, in the EU and USA, there is an RMP and REMS respectively in place for Isotretinoin and thalidomide yet in 2015 there were no RMPs submitted in Kenya for the same, yet the products received marketing authorization. This means that measures taken to prevent fetal exposure, such as having certified prescribers prescribing it, certified pharmacies dispensing it and having a pregnancy registry are not implemented here in Kenya (116).

RMPs can be seen as a tool for improving pharmacovigilance as some contain proposed additional pharmacovigilance activities that offer more timely evidence on drug safety as opposed to passive surveillance. Proposed additional risk minimization measures such as educational brochures for prescribers and patients indicated in RMPs serve as a risk communication tool as compared to the traditional SPC tool. Mandating MAHs to conduct postmarketing studies and ensuring that these studies are adequate for identified risks, potential risks and missing information would add value to a country’s pharmacovigilance system (45).

5.1.2.Risk assessment and evaluation

This study revealed that there was no drug utilization reviews conducted in 2015 by PPB and the pharmaceutical industry. This study also showed that neither PPB nor the interviewed pharmaceutical companies had conducted any medication errors surveys in 2015. The current reporting system, which addresses product quality (through a pink reporting form), doesn’t address mediation error reporting (25).

Some countries have in place DUR studies to detect and quantify drug use problems. For instance, the Medicaid DUR program in the US monitors prescription drug claims for potential medication errors such as therapeutic duplication, as well as to identify fraudulent claims and unnecessary medical care in each of the US states (117). The states submit an annual report of their prescribing habits, cost savings from the program and any innovative practices that they have come up with (117).

In the US, preventable medication errors cause about 7,000 deaths, and the cost of the errors is about $16.4 billion annually and $4.2 billion annually for inpatient and outpatient settings (11,118). Through the Division of Medication Error Prevention and Analysis (DMEPA) of the FDA medication errors sent to the MedWatch program are evaluated, causality assessed, and solutions to curb the errors are developed. The FDA and EMA have published guidance documents for industry to minimize errors and provide guidance in matters relating to the reporting, evaluation and prevention of medication errors (119,120).

This study revealed that PPB had conducted product quality surveys for selected antibiotics, antimalarials and antituberculosis medications with some public health programs, though the results were not published. However, communication was sent to the department of crime and investigations on the presence of a substandard product identified from this survey. The published reports of these activities would go a long way in showing what work PPB is doing and in fast-tracking some of the legislations that are much needed.

A study by Bate *et al*, in 2012 revealed that 7% of medicines manufactured in Kenya failed basic ingredient quality tests, while 13% failed spectrophotometry tests (121). The issue with high rate of substandard medicines is due to lack of comprehensive pharmaceutical policy as well as a disjointed health ministry (122). Some countries have initiated programs to combat this issue. In the USA, FDA has established the Drug Quality Sampling and Testing (DQST) compliance program in an effort to protect the public from non-compliant and poor quality drugs (123). This is achieved by sampling finished products, excipients, Active Pharmaceutical Ingredients (API), compounded drugs from wholesalers, distributors and retail pharmacies and then conducting product quality tests.

Key informants stated that PPB had initiated active surveillance. This was through Cohort Event Monitoring (CEM) for antimalarial and antiretroviral products in 2014.As per the interviewees;

the antiretroviral study was ongoing, while the antimalarials study had been completed though the report had not been published.

The deficiencies of the spontaneous ADEs reporting systems have necessitated the development of active surveillance by both MRAs and the pharmaceutical industry. A study by *Yu-Ling Huang et al* identified 9 active surveillance systems worldwide that collect ADE reports from existing databases (124). These active surveillance programs are in the US, EU, UK, Canada and Asia for both drugs and vaccines. The most notable ones include: The FDA Sentinel Initiative, the Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge (EU-ADR) Alliance in the EU and in Asia, there is the Asian Pharmacoepidemiology Network (AsPEN) and the Shanghai Drug Monitoring and Evaluative System (SDMES) (124).

The UK uses data from dispensed prescriptions available in the National Health Services (NHS) database to identify patients on new medication therapies or those on existing treatments but for new indications to be included in its Prescription Event Monitoring (PEM) studies (125). The Drug Safety Research Unit (DSUR) has obtained clinical data of over 700,000 patients from 65 PEM studies and this has enabled it to collect outcome data on populations that are usually left out in clinical trials such as pregnant women, children and the elderly (126).

CEM studies have been initiated to monitor the safety of antimalarials, antiretroviral and antituberculosis medicines by national pharmacovigilance centres in other sub-Saharan African countries such as Ghana, Nigeria, Tanzania and Zimbabwe (127). Through these studies, pharmacovigilance capacity has been enhanced. For instance, CEM for antimalarials in Kenya led to a new treatment policy being implemented that made it mandatory to test for malaria before antimalarial drugs could be initiated (127).

These active surveillance systems have played a supportive role to spontaneous ADEs reporting systems in refining signals for chemical entities and signal detection for vaccines .For instance, the Canadian Network for Observational Drug Effect Studies (CNODES) in Canada evaluated the association between use of high-potency statins and acute kidney injury at Health Canada's request (124). These active surveillance initiatives have been used in revision of labels as well as in maintaining marketing authorization for some of the medicines once a strong association between a drug/vaccine and an ADE could not be proved (128,129).

From the key informant interviews, it was established that PPB did not have the authority to enforce postmarketing authorization safety studies (PASS) for high risk medicines, for which the same was required by stringent MRAs such as FDA and EU. Although there is a record of all ongoing and completed clinical trials studies in the PPB website for the public and healthcare professionals to view, there is no register of PASS studies initiated by MAHs, and neither is there an annual published report of these studies.

While the national pharmacovigilance guideline states that the pharmaceutical industry has the responsibility of sharing data obtained from postmarketing surveillance with the PPB, there is no specific legislation giving PPB the power to enforce these studies. Unlike Kenya, the EU and US have specific legislation mandating MAHs to conduct these studies, either at the time of seeking marketing authorization or after marketing authorization has been granted (64,97,130) .

However there remain some gaps. It is necessary to have a legislation that does give PPB powers to enforce postmarketing studies, so that there is data available that is relevant to the local population and so that when there are safety concerns that are of local relevance, it is easier for PPB to impose these studies. PPB also needs proper structures and systems to evaluate these studies, i.e. a register for these studies, a committee to evaluate the studies, the timelines for submission of protocols and study reports, the timelines for review and feedback of these study reports as well as publishing the status of these studies on the website.

5.1.3.Risk management

This study revealed that only 10 risk mitigation plans were submitted by only 2 MAHs in 2015, yet 47.3% of the PSURs submitted had an active RMP, REMS or both. Two out of the four respondents from the pharmaceutical industry admitted to not submitting RMPs to PPB since it was not a requirement to do so. This study found out that there were no set timelines for evaluation and providing feedback with regards to PSURs and RMPs submission.

The low number of RMPs received by PPB could be due to the fact that Kenya has not enforced submission of these plans. The EU pharmacovigilance legislation requires that MAHs submit RMPs when applying for marketing authorization or when there is a significant change to the marketing authorization for products not requiring an RMP (60). An updated or modified RMP is submitted together with a PSUR if the changes are as a result of the PSUR (60).

The importance of timely review of PSURs and RMPs cannot be overemphasized, as PSURs serve as communication tool between MAHs and MRAs. 37% of assessed PSURs for biopharmaceuticals led to labelling changes, while 9% led to a regulatory action in the subsequent PSUR. 64% of safety signals have been identified from PSUR assessment, while 40% of type II variations were as a result of PSUR assessment (131,132).

PPB should consider single assessment of related PSURs just like in the EU. This entails assessing PSURs of medicines having the same active substance or same combination of active substances and simplifies the evaluations. The outcome of these assessments and recommendations are made available to the public.

The study also found that there is lack of documentation on number of medicines safety information requests received and addressed as well as number of medicine safety issues of local relevance that were identified from outside sources. Lack of documentation undermines the effectiveness of the risk management framework. Standard operating procedures are thus necessary in ensuring that this information is readily available and feedback is given so as to boost confidence in the risk management framework.

5.1.4.Risk communication

Kenya relies heavily on communicating risks through the SPC and PIL just like the EU. An SPC and PIL are necessary during the registration process and are updated as new information comes along. PPB published a guideline for submission to applications for registration of medicinal products in 2010 that set out the format and presentation of the SPC and PIL, "Registration of drugs-Guideline to submission of applications" (133). However, there has not been any update to this guideline as yet although there were plans to update it.

A study done by Raynor *et al* in 2013 regarding the Mefloquine (Lariam®) and Mycophenolate (Cellcept®) SPCs showed that navigation of the SPCs was difficult and the information not well understood, hence necessitating revision of the SPC wording as well as implementation of user testing (134). A study by Arguello *et al* in 2015 assessing information on pregnancy and lactation in EU SPCs showed that this information was missing and that the quality of information over time did not increase once marketing authorization had been granted (86). For Kenya to rely heavily on SPCs and PILs, it must ensure that the information is adequate, regularly updated and possibly, easily accessible via the PPB website. PPB should regularly post when an SPC has been updated, as this information is vital.

DHCP communication is another avenue used in communicating risks in Kenya. This study showed that PPB does not ask MAHs to distribute DHCP letters; rather it is the MAHs that use this channel when they need to communicate any safety related information on a product. There is also no guidance on the content and format of the DHCP letter. However, MAHs are required to seek approval before they distribute the DHCP letters to healthcare professionals.

In a study evaluating effectiveness of dear healthcare professional letters in Ghana, 89.7% of healthcare professionals state that they were effective (135).This was attributed to the content and format of the letters, which was concurrent with findings from a study conducted by Mazor *et al* that showed that if the format and content of the DHCP letter is regulated, it leads to more effective communication (88). The Food and Drugs Authority of Ghana distributed majority of these DHCP communications and remained the main source of safety communications (135). *Piening et al* study found that a half and a third of all DHCPs issued in the Netherlands between 2000 and 2008 resulted in substantial reduction in short and long-term drug use respectively (136).

PPB was able to carry out a variety of medicines safety communication activities. This included 12 safety communications to MAHs, the public, healthcare professionals, internal communications and communications to other stakeholders. PPB publishes pharmacovigilance newsletter, safety alerts and press releases on its website to communicate on new safety information as well as warn the public on any poor or substandard products that are on the market. A survey carried out on FDA alerts showed that the potential signals report boosted consumers' confidence in the FDA and in the system though it needed to be written more clearly as it was too technical (81). The PPB website recently received uplift and it will be interesting to see what is new with the website.

5.2.Conclusions

This study showed that Kenya has an inadequate risk management system for medicinal products. The PPB has made great strides in pharmacovigilance, including conducting active surveillance, product quality surveys and communicating safety concerns but due to an inadequate regulatory framework mandated by regulations and legislations, it becomes difficult for PPB to ensure that the pharmaceutical industry complies with safety monitoring**.** However, there is a draft qualified person of pharmacovigilance guideline, that if enforced would see more pharmaceutical companies submitting drug safety reports.

5.3.Recommendations

5.3.1.Policy changes

Relevant policy and legislative reforms to address safety monitoring of medicines in Kenya

The Pharmacy and Poisons Act, CAP 244, lacks provisions to adequately enforce risk management and there is no other law to enforce the same, hence hampering efforts of safety monitoring of medicines. This means there is limited ability to what PPB can require the pharmaceutical industry to do in terms of pharmacovigilance activities.

Kenya needs a pharmacovigilance legislation that would put into force a risk management approach possibly based on the EU model. This would give PPB the power to enforce mandatory submission of RMPs for high risk medicines when seeking marketing authorization as part of the product dossier, or as a standalone document or when safety concerns arise that may distort the benefit-risk balance of a drug. The legislation would also give PPB the authority to require the pharmaceutical industry to conduct PASS and also implement the proposed risk minimization measures in the RMPs, thus ensuring additional safety for patients.

The draft QPPV guideline should be implemented as it addresses issues such as timelines on submission of PSURs, RMPs, protocols for postmarketing surveillance studies, timelines of data review from these reports, provision of feedback to the pharmaceutical industry and also institutes the position of a QPPV in the pharmaceutical industry. The QPPV is vital as he/she would be responsible for pharmacovigilance of marketed products in a pharmaceutical company and would be the person contacted by PPB in case any safety concerns arose with a medicinal product.

Set up a committee that responsible for assessing and monitoring safety monitoring

This committee which would be established by relevant legislation would assess matters of risk management of medicines such as carrying out pharmacovigilance audits, providing recommendations on pharmacovigilance, evaluation of risk management reports such as RMPs and PSURs and giving advice on risk communication. This would ease the burden currently put on the expert safety review panel.

Develop a database for drugs requiring additional monitoring

There is need to have a database for medicines that require additional monitoring and controlled medicines in specific schedules whose dispensing should be monitored closely.

Improve drug safety communication

Efforts should be made to avail updates on labelling information such as SPCs, PILs, on the PPB website as they occur. A guideline on drug safety communication should be developed or adopted from other countries, which should describe the various communication channels to use and the timeliness of such communication. For instance, there should be a guideline on the format, content and timeline of submission of DHCPs.

Reports from postmarketing surveillance, product quality surveys as well as emerging drug safety information from local and outside sources should be published promptly in the PPB website for transparency and distributed electronically to boost public confidence in the Kenyan pharmacovigilance system.

Formal local postmarketing studies

PPB and the pharmaceutical industry should collaborate in developing protocols for postmarketing studies especially for high risk medicines for which the same is required by strict medicines regulatory authorities, in order to have local data. There should be a register for these studies to ensure transparency and encourage exchange of data, as occurs with clinical trials. This would be boosted by pharmacovigilance legislation, which would give PPB the authority to require MAHs to conduct such studies.

Revision of current guidelines on labelling

SPCs are still the main avenue for pharmaceutical risk communication for healthcare workers and form the basis for the development of the PILs for patients in Kenya. As it stands, the format and content of the SPCs and PILs is contained in the guideline to submission for applicants, which was published in 2010. A separate guideline for SPCs and PIL should be published or a revision of the 2010 guideline done to improve on the content, comprehension and readability. Effectiveness of the SPCs and PILs in communicating risks should be audited by using user acceptability testing so as to form the basis for revision of the guidelines.

Improve staffing and funding for Pharmacovigilance activities

The department of pharmacovigilance is relatively short staffed with only 4 staffs, as well as having limited funds allocated in the budget to conduct pharmacovigilance activities. More staff should be added and more funding provided to improve on this.

5.3.2. Future research

Based on this study's findings, a study on the effectiveness of the SPCs and PILs communications may help in the revision of the current guidelines. It may also be of interest to research on the effectiveness of educational materials for practitioners, patient alert cards, DHCPs, and safety alerts/notices on the overall communication of drug risks.

5.4.Study limitations

The anticipated number of interviewees from the pharmaceutical industry, and more so pharmacovigilance experts was not achieved due to non-response and lack of time. There was also lack of documentation on pharmacovigilance activities conducted by PPB, thus clarification on some aspects was not done.

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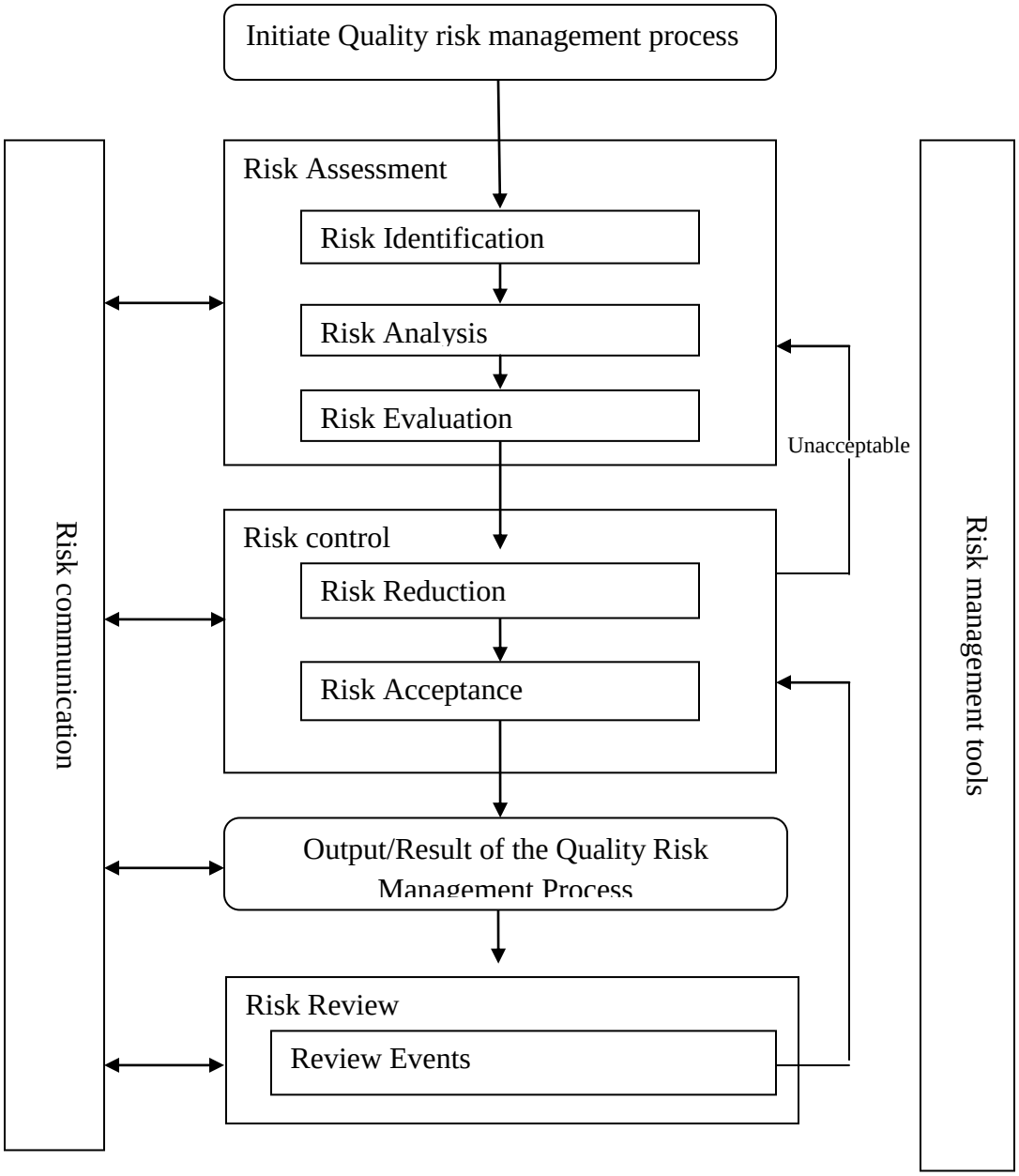
APPENDICES

APPENDIX 1: INTERNARTIONAL CONFERENCE ON HARMONIZATION HARMONIZED TRIPARTITE GUIDELINE ON QUALITY RISK MANAGEMENT (Q9)



APPENDIX 2: RISK EVALUATION AND MITIGATION STRATEGIES OUTLINE

I. PROPOSED REMS

a. Goals

The goals and objectives of the REMS.

b. REMS elements

i. Medication guide- To be dispensed with every prescription

ii. Communication plan

iii. Elements To Assure Safe Use (ETASU)- for mitigate the risks, the labelling may state:

- Prescribers of a particular drug should be specially certified, or should have special training.
- Hospitals, prescribers, pharmacies that dispense a particular drug should be specially certified

iv. Implementation system- A system describing how the implementation of the above elements will be monitored and evaluated

v. Timetable for submission of assessments- A schedule of how the MAH will submit the assessed REMS. Proposed timelines are 18months, 3years and 7 years.

I. REMS supporting documents

a. Background

b. Goals

c. Supporting information on proposed REMS Elements

i. Medication guide

ii. Communication plan

iii. Elements To Assure Safe Use (ETASU)

iv. Implementation system

v. Timetable for assessments of the REMS

vi. Information needed for assessment

II. Other relevant information

APPENDIX 3: RISK MANAGEMENT PLAN OUTLINE

Part I: Product(s)overview

Part II: Safety Specification

Module SI-Epidemiology of the indication(s) and target population(s)

Module SII-Non-clinical part of the safety specification

Module SIII-Clinical trial exposure

Module SIV-Populations not studied in clinical trials

Module SV-Post-authorization experience

Module SVI-Additional EU requirements for the safety specification

Module SVII-Identified and potential risks

Module SVIII-Summary of the safety concerns

Part III: Pharmacovigilance Plan

iii.1 Routine pharmacovigilance activities

iii.2 Additional pharmacovigilance activities

iii.3 Summary table of additional pharmacovigilance activities

Part IV: Plans for post-authorization efficacy studies

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

v.1 Routine risk minimization measures

v.2 Additional risk minimization measures

v.3 Summary table of pharmacovigilance and risk minimization activities by safety concern

Part VI: Summary of the risk management plan

II.A List of important risks and missing information

II.B Summary of important risks

II C.1 Post-authorization development plan

II. C.2 Studies which are conditions of the marketing authorization

Other studies in post-authorization development plan

Part VII: Annexes

APPENDIX 4: INFORMED CONSENT FORM

UNIVERSITY OF NAIROBI

COLLEGE OF HEALTH SCIENCES

SCHOOL OF PHARMACY

DEPARTMENT OF PHARMACOLOGY AND PHARMACOGNOSY

P. O. Box 19676, NAIROBI, 00202 TEL. 0202 725099

This informed consent form (**Appendix 4**) is for participants taking part in the interview- 'Evaluation of risk management system for medicinal products in Kenya.'

Principal Investigator:

Wanjiru Wangari Wambu.

P.O.BOX 38-00600, NGARA. Tel: 0725-730-090.

Supervisors:

Prof. G.O. Osanjo, PhD School of Pharmacy, University of Nairobi

Dr. S.N. Ndwigah, PhD School of Pharmacy, University of Nairobi

Dr. A.K. Sinei, PhD School of Pharmacy, University of Nairobi

Part I: Information Sheet

Introduction

You are invited to take part in a research study conducted by Wanjiru Wangari Wambu, a student at the University of Nairobi. The above study is in a partial fulfilment of the master's degree in pharmacovigilance and pharmacoepidemiology.

Purpose of the research

Risk management systems for a medicinal product are crucial in ensuring that the overall benefits of a medicinal product outweigh the risks and thus a medicines regulatory authority

should ensure that one is available for specific drugs before marketing authorization can be given. This research is trying to get an understanding of the risk management system for medicinal products in Kenya and activities that have been carried out as part of the risk management approach.

Study procedure

You are invited to take part in this research due to your knowledge and expertise in risk management system for medicinal products. The interview will take approximately one hour at a time and venue of your convenience, should you accept to take part in the study. Face to face interviews will be conducted using pre-selected questions adapted from the Indicator based Pharmacovigilance Assessment Tool (IPAT) which is designed and validated by MSH and SPS program and assesses PV systems in developing countries.

Should you wish not to answer any questions asked, you may state so and the interviewer will move to the next question. The information you provide will be strictly confidential, and no one else apart from Wanjiru Wangari will have this information obtained during the interview. Should you agree, the interview will be recorded but no-one will be identified by name. The recording will be kept in a password protected computer and the information recorded is confidential. The recording will be destroyed after completion of the study.

Voluntary Participation

Your participation is voluntary in this research and you may choose whether or not to participate. If you agree to take part in this research, you may withdraw at any time if you so wish. You may decline to answer any question and still remain in this study.

Ethical approval

Ethical approval will be sought from the Kenyatta National Hospital-University of Nairobi Ethical Research Committee, P.O.BOX 20723-00100, Nairobi. Tel 2726300/2716450 Ext 44102.

Benefits and risks

There are no anticipated direct benefits and risks to you from your participation in this study. The overall goal is to evaluate the risk management system for medicinal products in Kenya and the findings may provide a better understanding in this area.

Reimbursements

You will not be provided with any incentives to take part in the study.

Confidentiality

Any information obtained in this study will remain confidential. The information collected about you will be coded as initials or numbers and will be stored separately from the rest of the data, in a password protected computer. The interview will be tape-recorded, if you approve. Voice masking will be carried out as a precautionary measure to safeguard your identity. No information on your identity will be mentioned during publishing of the results of the research.

Right to refuse or withdraw

You may refuse or withdraw from participating in this study at any time that you so wish. At the end of the interview, you may review your remarks and modify them accordingly.

Who to contact

Any questions or concerns may be directed to the following:

- The lead investigator Wanjiru Wangari on 0725730090 or w_wambu@yahoo.com
- The supervisor Prof. George Osanjo on 0721 794 666 or gosanjo@yahoo.com
- KNH/UoN Ethics Committee on 2726300, Ext 44102 or erc@uonbi.ac.ke

Part II: Certificate of consent

I……, having read and understood the information pertaining to this study, willingly give my consent to participate in this study.

NAME OF PARTICIPANT:

SIGNATURE:

DATE:

Statement by researcher:

I have read out the information pertaining to this study accurately to the participant and answered all questions correctly to the best of my ability.

NAME OF RESEARCHER …….

SIGNATURE……

DATE……..

APPENDIX 5: WORLD HEALTH ORGANIZATION'S PHARMACOVIGILANCE TOOL USED IN ASSESSING RISK MANAGEMENT PRACTICES FOR MEDICINAL PRODUCTS IN KENYA AND FORMULATING QUESTIONS FOR PHARMACY AND POISONS BOARD.

Indicator	**Assessment questions**	**Data sources used**
C02	How many regulatory actions were taken in the preceding year consequent on national pharmacovigilance activities? a) How many product label changes (variation)? b) How many safety warnings on medicines to: i, health professionals ii, the general public? c) how many withdrawals of medicines?	File on regulatory actions taken
P10	How many registered products had a pharmacovigilance plan and/or a risk management strategy from market authorization holders exist in 2015?	RMPs
P11	What is the percentage of market authorization holders submitting periodic safety update reports (PSURs) to the regulatory authority as stipulated in the country?	PSURs
P12	How many products were voluntarily withdrawn by market authorization holders because of safety concerns in 2015?	Regulatory actions file
P12a	How many summaries of product characteristics (SPCs) were updated by market authorization holders because of safety concerns in 2015?	Variations minutes

APPENDIX 6: INDICATOR-BASED PHARMACOVIGILANCE ASSESSMENT TOOL USED IN FORMULATING QUESTIONS FOR THE PHARMACY AND POISONS BOARD AND ASSESSING RISK MANAGEMENT PRACTICES FOR MEDICINAL PRODUCTS IN KENYA.

	Indicator	**Assessment questions**	**Answer to indicator**	**Comments and Reference source**
	Component 1: Policy, Law, Regulation **Core indicators**			
1.5	Legal provisions that require that the MAH to conduct the same or similar post-marketing surveillance activities for products as required by PPB	1. Are there laws or regulations requiring the MAH to conduct post-marketing safety activities? 2. What is the specific act or section of the legislation or regulation that address mandatory Post-marketing safety activities for the MAH?	Supplementary structural	
	Component 2. Systems, Structures and Stakeholder Coordination			
2.10	Existence of an ADR or medicines safety bulletin or any other health related newsletter that routinely features ADR or medicines safety issues published in the last six	1. 1. Does an ADR bulletin or a medicine information bulletin that regularly features pharmacovigilance topics exist? 2. Has the bulletin been published within the last six months?	Core structural	

	months			
	Component 4. Risk Assessment and Evaluation			
4.1	Number of medicine utilization reviews carried out in the last year	1. Has a medicine utilization review study and/or a drug use survey been carried out in the last year? 2. Was a report of the medicine utilization review study circulated or published?	Supplementary process	
4.2	Pharmaceutical product quality survey conducted within the last five years	1. Has a Pharmaceutical product quality survey been carried out in the last five years? 2. Was a report of the survey circulated or e4published?	Supplementary process	
4.3	Incidence of Medication errors quantified in the last year	1. What was the number of medication errors reported in the last year?	Supplementary process	
4.5	Number of active surveillance activities currently ongoing or carried out in the last five years	1. Has any active surveillance study been initiated or carried out in the last five years? 2. Number of active surveillance activities currently ongoing or carried out in the last five years	Core process	
	Component 5. Risk Management and Communication			
5.1	Risk mitigation plans currently in place that are targeted at high-risk medicines	1. Is there any form of effort to control the use of high-risk medicines because of concerns about their safety when used incorrectly? 2. What are the existing and proposed activities to mitigate risk of such high-risk medicines?	Supplementary outcome	

5.3	Number of medicine safety information requests received and addressed in the last year	1. What is the number of pharmacovigilance-related information requests received in the last year? 2. How many of these requests were addressed?	Supplementary outcome	
5.5	Number of medicine safety issues of local relevance identified from outside sources (e.g., from another country, or from regional or international sources) and acted on locally in the five years.	1. Is there a system for monitoring for new safety reports from outside sources? 2. How many medicine safety issues of local relevance identified from outside sources were acted on locally in the last year?	Supplementary outcome	
5.6	Number of "Dear health care professional" letters or other safety alerts developed and distributed in the last year	1. How many "Dear health care professional" letters or any other type of regulatory safety alert letters were developed and distributed in the last year? 2. Is the inventory of the regulatory alert letters and the distribution list available for review?	Supplementary outcome	
5.7	Average time lag between identification of safety signal of a serious ADR or	Are safety signals and significant safety issues promptly communicated to health workers and the public?	Core outcome	

	significant medicine safety issue and communication to health care workers and the public			
5.9	Presence of public or community education activities relating to medicine safety carried out in 2015	1. How many public and educational activities relating to medicines safety were carried out in 2015	Supplementary outcome	

APPENDIX 7: INTERVIEW PROTOCOL FORM (MULTINATIONAL INNOVATOR PHARMACEUTICAL INDUSTRY)

Project: Evaluation of the risk management system of medicinal products in Kenya

Date:

Organization:

Department:

Interviewer:

Interviewee:

Notes to interviewee

The goal for this research is to evaluate the existing risk management system for medicinal products and evaluate if it is in accordance with the ICH guidelines. This interview protocol will aim to get a more in-depth understanding of this system.

1. How is the assessment and presentation of a medicinal product's risk- benefit profile carried after marketing authorization has been granted?
2. How are significant changes in established products (e.g., new dosage form, new route of administration, or new manufacturing process for a biotechnologically-derived product) addressed?
3. a) When safety concerns (risks) have been identified with a medicinal product, what are the various action plans (pharmacovigilance plans) that are undertaken to address the safety concerns

   b) What forms the basis of these action plans?
4. a) How do you get information on major emerging safety concerns with regards to established and new medicinal products?

   b) How do you address these major emerging safety concerns locally and how does it defer with how it is addressed internationally?
5. Are all the safety concerns identified adequately addressed by the pharmacovigilance plans or is risk minimization necessary for some safety concerns?
6. What are some of the routine risk minimization activities and tools that you implement to address the major safety concerns after obtaining marketing authorization?
7. How is the assessment of the effectiveness of the risk minimization activities as a measure to reduce risks carried out and how often is this done?

8. When routine/current risk minimization activities are deemed insufficient, what measures do you propose to minimize the safety concerns?
9. a) Are additional educational materials (other than patient leaflets/ package leaflet, SPC, medication guides) provided for medicinal products and what do they address?

   b) What are some of these materials?

   c) How do you evaluate the effectiveness of these materials?
10. a) Have you been able to implement the following for any of your medicinal products that have received marketing authorization locally?

    i. Educational programs and materials

    ii. Restrictions on distribution and dispensing

    iii. Healthcare provider based training

    iv. Prospective registry studies

    v. Prospective epidemiology studies e.g. Cohort event monitoring

    b) If yes, do you assess the effectiveness of the above and how often?
11. a) How are safety concerns communicated to healthcare stakeholders?

    b) Who is the target audience and is the communication to all stakeholders the same?

    c) What is the objective and goal of the communication?

    d) Is an assessment done to evaluate the effectiveness of the communication?
12. How is the potential for medication errors addressed and reduced in the final design of the medicinal product, product information and packaging?
13. a) Have any of the following surveys been carried out on your approved medicinal products, locally in the last 5 years?

    i. Medication errors

    ii. Utilization review studies?

    iii. Quality of products?

    iv. Ineffectiveness of product?

    b) How have you addressed the safety concerns as well as any positive data that was collected?
14. Do you receive any communication about your medicinal product (safety concerns or benefits) directly from the public and how do you address the concerns raised?
15. What are some of the challenges that you face while managing risks for medicinal products locally and what recommendations would you provide to improve the risk management process?

APPENDIX 8: INTERVIEW PROTOCOL FOR THE PHARMACY AND POISONS BOARD

1. Is there a policy, regulation, guidance requiring MAHs to submit risk management plans (RMPs) for products with an active RMP/ REMS?
2. a) Is there a regulation/ guideline requiring MAHs to submit PSURs?
   b) What are the set timelines for submissions of PSURs?
   c) After submission of PSURs, what is the timeline for review of PSURs and giving feedback to the MAHs?
3. a) Does PPB enforce postmarketing studies commitments to MAHs (either imposed as a condition of marketing authorization or as a specific obligation of marketing authorization?
   b) Is there a regulation that gives PPB the powers/ authority to require MAHs to carry out the above studies in Kenya?
4. a)How many PASS have been ongoing or completed in Kenya in the last 5 years?(e.g. DUS, observational studies, registry studies, Surveillance studies)
   b) Is there a document/register that provides information on the status of any PASS that MAHs have agreed to conduct and for which annual reports have been submitted?
   c) Is there any annual publication of reports of such studies?
5. Are there a set of guidelines for how MAHs present the prescribing information, patient information leaflet, SPC?
6. a) Are there policies that give powers to the PPB to require or ask for labelling changes/updates to labelling documents?
   b) What are the timeframes for the submission of and review of updates to labelling documents?
7. a) Is there a system for monitoring new safety reports from outside sources?
   c) How many medicine safety issues of local relevance identified from outside sources were acted on locally in 2015?
8. a) How are safety-related regulatory actions and safety alerts communicated to the public, HCPs, consumer organizations, healthcare professional associations?
   b) How often is this done?
   c) How is the effectiveness of this communication evaluated and how often is this done?

9. a) Are any of the following proposed additional risk minimization activities implemented in Kenya?
    i. Controlled access programmes- specialist prescribers, dispensers, patient registries
    ii. Educational tools provision
    iii. Pregnancy Prevention Programmes
    iv. DHPCs
    b) Are the above proposed by PPB or initiated by MAHs themselves?
    c) If yes, how is the effectiveness of such activities carried out?
10. What was the number of medicine safety information requests received and addressed in 2015?
11. a) Are there any public or community education activities relating to medicine safety that were carried out in 2015?
    b) If yes, how many were they?
12. a) Is there a PPB database of products that require additional monitoring?
    b) What measures does PPB take with regards to such products?
13. Is there a committee constituted to strengthen safety monitoring in Kenya by assessing different aspects of risk management relating to medicinal products?
14. Where there are manufacturing and / or product defects affecting a medicinal product, are MAHs mandated to submit any reports to PPB such as filed alert reports?

APPENDIX 9: DATA ANAYLYSIS DUMMY TABLES

Dummy table 1: Summary of documents surveyed

Variable	**N %**
Study site	
PPB	
Pharmaceutical industry	
Types of documents surveyed	
PSURs	
RMPs	
Notifications	
Regulatory actions file	
When submitted	
2015	
Classes of drugs for which risk management was submitted	
New chemical entities	
Biologics	

Dummy table 2: Summary of the risk management components

Component	**N%**
EU RMPs	
Routine risk minimization activities	
SPC special warnings and precautions for use	
SPC contraindications	
SPC undesirable effects	
Additional risk minimization measures	
Educational programs	
Patient alert cards	
Additional pharmacovigilance	
Specific AE and PSUR reporting requirements	
Prospective registry studies	

Prospective epidemiology studies	
Additional data analysis	
Prescription surveys	
Non-interventional studies to capture off-label use	
FDA REMS	
REMS components	
Patient medication guide	
Provider communication plan	
Elements to assure safe use	
Implementation system	
Additional REMS attributes	
Routine monitoring of risk mitigation plan	
Patient survey	
Registry	
Monitoring of patients receiving medication	

Dummy table 3: Extent of compliance to EU and FDA requirement

Variable	**N%**
Compliance with risk management components	
Active surveillance	
Pharmacoepidemiological studies	
Registries	
Medicines utilization reviews	
Medicines safety issues acted upon	
Safety communication to Healthcare workers	
Dear professional letters	
Communication safety to public	
Product quality tests	

APPENDIX 10: ETHICAL REVIEW COMMITTEE APPROVAL

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/31

30th January 2017

Wambu Wanjiru Wangari
Reg. No.U51/81403/2015
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Wambu

REVISED RESEARCH PROPOSAL: "EVALUATION OF THE RISK MANAGEMENT SYSTEM FOR MEDICINAL PRODUCTS IN KENYA (P596/08/ 2016)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above revised proposal. The approval period is from 30th January 2017 – 29th January 2018.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Protect to discover

Yours sincerely,

PROF M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Assistant Director, Health Information, KNH
The Chair, KNH- UoN ERC
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmacology and Pharmacognosy, UON
Supervisors: Dr. George Osanjo, Dr. Stanley Ndwigah, Dr. K.A. Sinei

APPENDIX 11: PHARMACY AND POISONS BOARD STUDY APPROVAL AND STUDENT CONFIDENTIALITY AGREEMENT

REPUBLIC OF KENYA
MINISTRY OF HEALTH
PHARMACY AND POISONS BOARD

Telegram: "MINHEALTH" Nairobi
Telephone: 020-2716905/6, 020-3562107
Cellphone: 0733-884411/0720 608811
Fax: 2713409
E-mail: info@pharmacyboardkenya.org
Website: www.pharmacyboardkenya.org

LENANA ROAD
P.O. BOX 27663-00506
NAIROBI

When replying please quote

PPB/MIP/PMS/LET/183/16

28th November, 2016

Wanjiru Wangari Wambu
P.O. Box 38-00600
Ngara,
Nairobi

Dear Madam,

RE: Research project M Pharm (Pharmacoepidemiology and Pharmacovigilance):

Reference is made to your letter received at PPB on 31st Mar2016, requesting for data collection on evaluation of risk management systems of medicinal products in Kenya.

The Board allows you to go on with the study on conditions of the stipulated student confidentiality agreement enclosed herein.

Be informed that Pharmacy & Poisons Board shall terminate your data collection activity should any of the stated conditions be violated. You are further to provide a copy of your final thesis work for information and future reference to the Medicines Information and Pharmacovigilance Directorate.

Yours faithfully,

Dr. Kipkerich C. Koskei
Registrar
CK/ma

REPUBLIC OF KENYA

MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

STUDENT CONFIDENTIALITY AGREEMENT

In the course of evaluation of my study, I will gain access to certain information, which is proprietary to Pharmacy and Poisons Board and other interested parties.

I shall treat such information (hereinafter referred to as "**the Information**") as confidential and proprietary to PPB or the aforesaid parties. In this connection, I agree:

(a) Not to use the Information for any purpose other than discharging my obligations under this agreement;
(b) Not to disclose or provide the Information to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

I shall not communicate any observations and/or findings as well as any resulting recommendations and/or decisions of my work to any third party, **except as explicitly** agreed by PPB.

I understand that any information (written, verbal or other form) obtained during the performance of my duties must remain confidential. This includes all information about members, clients, families, employees and other associate organizations, as well as any other information otherwise marked or known to be confidential.

I understand that any unauthorized release or carelessness in the handling of this confidential information is considered a breach of the duty to maintain confidentiality.

I further understand that any breach to maintain confidentiality in my study could be grounds for immediate suspension of attachment with PPB and/or possible liability in any legal action arising from such breach.

I confirm that I have no situation of real, potential or apparent conflict of interest including financial or other interests in, and/or other relationship with, a party, which:

(i) May have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or

(ii) May have a vested interest in the outcome of evaluation of the application.

I shall promptly notify the Registrar, PPB of any change in the above circumstances, including if an issue arises during the course of my work.

All documents supplied to me in connection with this application shall be accepted in strict confidence and shall be held in safe and secure custody at all times.

I hereby accept and agree with the conditions and

Declaration:

I, the undersigned, do hereby agree to adhere to the provisions contained in this agreement.

I hereby declare that I have/do not have (*delete what is NOT applicable*) a Conflict of Interest with the following application(s)/any of the applications that I have been requested to review (*delete what is NOT applicable*)

_____

Reference number (s) of application (s) with which I have a conflict of interest

Nanjira Wangeci Wambi
(Student Name)

(Signature)

6/12/2016
(Date)