# STRUCTURE AND PROCESS OF PERIODIC SAFETY UPDATE REPORTING SYSTEM OF MEDICINES IN KENYA

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**November, 2014**

**DECLARATION**

I, GATIMBU KIOGORA MWITI declare that the work contained herein is my original work and has not been presented at any other university.

Signature……. Date……..

**Approval by supervisors**

This thesis has been submitted with approval of university supervisors.

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I fondly dedicate this work to my loving parents and siblings.

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## LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| ADR | Adverse drug reaction |
| CCSI | Company core safety information |
| CCDS | Company core data sheet |
| CHMP | Committee for Medicinal Product for Human Use |
| CIOMS | Council for International Organizations of Medical Sciences |
| CPS | Cognitive Pharmaceutical Services |
| EC | European Commission |
| EMEA | European Medicines Agency |
| EU | European Union |
| FDA | Food and Drug Administration |
| ICH | International conference on harmonization |
| IBD | International birth date |
| KNH | Kenyatta National Hospital |
| MAH | Market authorisation holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PSUR | Periodic safety updates reports |
| WHO | World Health Organization |

## DEFINITION OF TERMS

**Company Core Data Sheet (CCDS)**: A document prepared by the Marketing Authorization Holder containing, in addition to safety information, material relating to indications, dosing, pharmacology, and other information concerning the product.

**Company Core Safety Information (CCSI)**: All relevant safety information contained in the CCDS prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.

**Data Lock Point (Data Cut-off Date)**: The date designated as the cut-off date for data to be included in a PSUR. It is based on the international birth date (IBD) and should usually be in 6-month increments.

**International Birth Date (IBD)**: The date of the first marketing authorization for a new medicinal product granted to any company in any country in the world.

**Listed adverse drug Reaction (ADR)**: An ADR whose nature, severity, specificity, and outcome are consistent with the information in the CCSI.

**Spontaneous Report or Spontaneous Notification**: An unsolicited communication to a company, regulatory authority, or other organization that describes an adverse reaction in a patient given one or more medicinal products and which does not derive from a study or any organized data collection scheme.

**Unlisted Adverse Drug Reaction**: An ADR whose nature, severity, specificity, or outcome is not consistent with the information included in the CCSI.

**Medication error**: Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer. They are the most common single preventable cause of adverse events in medication practice.

**Off label use**: Use of pharmaceutical drug for unapproved indication or in an unapproved age group, unapproved dosage or unapproved form of administration.

**Drug Abuse/misuse**: Refers to the persistence or sporadic, intentional, excessive use of medicinal products which is accompanied by harmful physiological or physical effects.

**Over dosage**: The term drug overdose (or simply overdose or OD) describes the ingestion or application of a drug or other substance in quantities greater than are recommended or generally practiced. An overdose may result in a toxic state or death.

**Signal**: Reported information on possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.

## ABSTRACT

### Introduction

A Periodic Safety Update Report (PSUR) is a mechanism by which a company may summarise and evaluate medicinal products safety data for a particular interval time in a standardised manner for submission to medicines regulatory authorities**.** During medicine development, only a limited number of patients are included in the clinical trials. However, once the product is submitted for market approval, its efficacy and evaluation for safety is based on thousands of patients. Therefore, detection of rare adverse reactions is difficult and hence need for Periodic Safety Update reporting

**Objective:** To assess the structure, content and process of Periodic Safety Update reporting of medicines in Kenya.

**Methodology:** A cross-sectional study of documentary materials and structured key informants interviews at the Pharmacy and Poisons Board (PPB), Kenya.

**Results:** Most (68.8%) of the PSURs did not include a cover letter which is an essential component of PSUR. For most of the reviewed PSURs, the medicinal products (93.8%) had not experienced any change to the marketing authorization status, and none had any actions taken for any safety reasons. Nearly all the PSURs (96.9%) had used Company Core Data Sheet( CCDS ) as the reference document and most of them between 56.3 to 96.9%, did not have any sections of the reference safety document changed. Of all PSURs submitted, 50% used defined daily doses as a methodology for exposure number calculations. Only 21.8% of the PSURs had targeted new studies and 71.9% had published studies. Majority of the PSURs (87.5%) did not have a risk management plan neither did 71.9% have risk benefit analysis report.

PSURs considerably differed in presentation of overall safety evaluation. At least, 65.6% reported medication error, 62.5% reported abuse or misuse, 59.4% reported drug interactions, and 56.3% reported off-label use. At least, 50% of the PSURs had potential safety concerns.

With regard to the organizational structure of reporting system, the Pharmacy and Poisons Board (PPB) PSUR review committee, was composed of four pharmacists, two pharmaceutical technologists and two clerical staff. The Department is fully computerized with reliable internet connection. Critical information by any submitting Marketing Authorization Holder (MAH) is sent within 48hours.

In regard to process, the MAH submits two hard copies of the PSURs alongside a softy copy, a cover letter is signed and one is retained at the department while the other goes back to the MAH. This is coded and entered into an excel sheet awaiting review. However, there are no scheduled dates for review

**Conclusion**

The Pharmacy and Poisons Board had a well laid down structure for Periodic Safety Update reporting, however there was need for a harmonized format for capturing information and a mandatory requirement for MAHs to timely submit the PSURs. In addition, a policy to be put in place with additional staff and government to allocate funds to facilitate regular reviews.

# CHAPTER ONE

## 1.0 INTRODUCTION

### 1.1 Background

A Periodic Safety Update Report (PSUR) is a mechanism by which a company may summarise and evaluate safety data for a particular interval in time in a standardised manner for submission to regulatory authorities (1). Among the data that is summarised and evaluated are reports of adverse events that are communicated spontaneously by a variety of sources.

The events may be reported by patients, family members, health care professionals, and others. The events may be due to a variety of factors, including the underlying disease for which the medication has been prescribed or another health condition. Other sources may include medications or substances a patient is taking, environmental factors, events or exposures that are unknown or undisclosed, or the drug itself. Frequently, the available information pertaining to such factors is incomplete.

A PSUR provides a listing of all adverse events, regardless of the cause of the event. The listing of or discussion of any adverse event in a PSUR, including any statement of relatedness of the event to the use of a drug, is not intended to suggest, imply or admit that a causal relationship exists between the adverse event and the use of the drug (1)
PSURs owe its origin to the Council for International Organizations of Medical Sciences (CIOMS) II Guideline of 1992; this guideline became widely accepted in all the International Conference on Harmonization (ICH) regions.

ICH is a project that brings together the regulatory authorities of Europe, Japan and USA and experts from the Pharmaceutical industry in the three regions to discuss scientific and technical aspects of Pharmaceutical product registration (2).

PSURs aim is to provide an update of worldwide safety experience with a specific medicinal product. It includes data from spontaneous reports, safety data from interventional and/or observational studies, as well as other relevant safety information (3). PSURs are intended to proactively present, analyse, and evaluate new or changing safety data from any source evaluated in relation to estimates of exposure to the product, although total coverage of data sources may have limitations in practice (4).

PSURs are compiled by Marketing Authorization Holders (MAHs) and submitted to regulatory authorities for assessment at predetermined time points. In the European Union (EU), PSURs also need to be submitted alongside applications to renew the initial marketing authorization, which is valid for a period of 5 years. Both regulatory authorities and MAHs spend significant resources on the creation and assessment of PSURs (5). However, the outcomes of these efforts have not been well described.

The concept of PSUR reporting in its current form stems from 1992 (6). It has been noted at several platforms, including the International Conference of Harmonization (ICH) and the EU that PSUR reporting has not kept pace with developments in pharmacovigilance, such as electronic adverse event reporting and risk management planning (7). In 2010, this awareness resulted in changes in European legislation laying down the requirements for PSUR reporting (8).

In an earlier study on the determinants of safety-related regulatory actions for biopharmaceuticals, it was found that PSUR evaluations contributed to 38 % of post authorization regulatory actions in a sample of biopharmaceuticals (9). In addition, in 2010, Alvarez et al. found that 64 % of a selection of adverse drug reactions (ADRs) originated from PSURs (10). Both these studies examined the contribution of PSURs to identified safety signals, which does not provide insights as to how PSURs contribute to monitoring safety, or which fraction of PSURs leads to regulatory action. Multiple factors, including product

characteristics, regulatory approval status and timing of approval could potentially affect the outcome of PSUR evaluations.

Several recent studies have reported on the specifics of pharmacovigilance for biopharmaceuticals. The nature of reported adverse events for biopharmaceuticals seems to differ from those for small molecules, which may lead to different safety-related regulatory actions and could necessitate a distinctive pharmacovigilance approach (11).

### 1.2 Problem statement

Adverse Drug Reactions (ADRs) are an important public health issue that threatens the safety of drug therapy and results in significant economic burden to the healthcare system. ADRs can worsen a patient's medical problems, place patients in life-threatening situations and extend patients' length of stay in hospital thus leading to increased healthcare costs. A landmark study by Lazarou et al found ADRs to be among the top six leading causes of death in the USA, with serious ADRs accounting for 6.7% of hospitalized admissions (12).

In Kenya, a weak referral system and poor case detection of ADRs is a major health issue. Weak regulatory system for prompt action in case of need is also a major concern. Lack of guidelines on reporting of various commodities on their general safety after marketing and lack of reporting by MAHs and the non-mandatory requirement by the Kenyan government on submission of PSURs.

### 1.3 Study justification

The main objective of a PSUR is to present a comprehensive, concise and critical analysis of the risk- benefit balance of the medicinal product taking into account new or emerging information in the context of cumulative information on risks and benefits. ADRs are an important public health issue that threatens the safety of drug therapy and results in significant economic burden to the healthcare system (12).

ADRs can worsen a patient's medical problems, place patients in life-threatening situations and extend patients' length of stay in hospital thus leading to increased healthcare costs. There is also a weak referral system in case of suspicion of an ADR and a weak regulatory system for prompt action in case of need and hence need for a clear framework and policy on PSURs. It should be made mandatory for all MAHs within Kenya to submit PSURs for the safety of general public and hence risk minimization.

## 1.4 Research question

1. What are the content, organizational structure as well as handling process involved in the PSUR system in Kenya?

## 1.5 Objective

### 1.5.1 Broad objective

To assess the structure, content and processes of Periodic Safety Update Reports in Kenya.

### 1.5.2 Specific objectives

1. To examine content of Periodic Safety Update Reports in Kenya.
2. To explore the organizational structure of Periodic Safety Update Reports in Kenya.
3. To examine the process of periodic safety update reporting in Kenya

# CHAPTER TWO

## 2.0 LITERATURE REVIEW

### 2.1 Introduction

Whenever a new medicinal product is submitted for marketing approval, except in special situations, the demonstration of its efficacy and the evaluation of its safety are based at most on several thousand patients (13). The limited number of patients included in clinical trials, the exclusion at least initially of certain patients at-risk, the lack of significant long-term treatment experience, and the limitation of concomitant therapies do not allow a thorough evaluation of the safety profile. Under such circumstances, the detection or confirmation of rare adverse reactions is particularly difficult, if not impossible (14).

In order to develop a comprehensive picture of clinical safety, medicinal products should be closely monitored, especially during the first years of commercialization (13). Surveillance of marketed drugs is a shared responsibility between regulatory authorities and Marketing Authorization Holders (MAHs). They often record information on drug safety from different sources based on procedures that have been developed to ensure timely detection and mutual exchange of safety data (15).

Because all information cannot be evaluated with the same degree of priority, regulatory authorities have defined the information to be submitted on an expedited basis. In most countries this rapid transmission is usually focused on the expedited reporting of adverse drug reactions (ADRs) that are both serious and unexpected (16). A reevaluation of the benefit/risk ratio of a drug is usually not possible for each individual ADR case, even if serious. Therefore, periodic safety update reports (PSURs) present the worldwide safety experience of a medicinal product at defined times post authorization. PSURs are essential for reporting all the relevant new information from appropriate sources

Relating these data to patient exposure, summarizing the market authorization status in different countries and any significant variations related to safety.

PSURs are also necessary to create an opportunity for periodic safety reevaluation and indicate whether changes should be made to product information in order to optimize the use of the product

The concept of PSUR evolved from the Council for International Organizations of Medical Sciences (CIOMS) Working Group II report (6). The process that culminated in the publication of that report was initiated in 1989, at a time when several countries had requirements for periodic safety updates. Individual local regulatory authorities were requesting that both foreign and domestic data be presented according to different inclusion criteria, formats and time intervals, and the number of reports that had to be produced was placing a high administrative burden on manufacturers.

The purpose of CIOMS II was to explore the possibility of developing a harmonized approach to preparing PSURs that would meet most existing needs and forestall any diversity in future requirements. CIOMS II formed the basis for the International Conference on Harmonization E2C Guidance for Industry (13,16), which defined the format and content for PSURs and introduced the concept of an international birth date (IBD), the date of first approval in the world. ICH E2C set the period for review of interval (rather than cumulative) safety data as 6 months. After it was adopted, practical considerations regarding the content and preparation of the report were addressed in the CIOMS Working Group V report (17). Many of the recommendations in that report formed the basis of an addendum to ICH E2C (18).

The addendum introduced to the PSUR, new concepts that were not in E2C but that reflect current Pharmacovigilance practices. These include confidentiality of proprietary information, risk management programmes and benefit–risk analyses. The PSUR has now been adopted in

many European countries, Japan and the United States. It is emerging as a gold standard of safety evaluation for marketed drugs and an important Pharmacovigilance tool.

However, if PSURs required in the different countries where the product is on the market require a different format, content, period covered, and filing date, MAHs would need to prepare on an excessively frequent basis different reports for the same product. In addition, under such conditions, different regulators could receive different kinds and amounts of information at different times. Thus, efforts are needed to harmonize the requirements for PSURs, which will also improve the efficiency with which they are produced (7). The current situation for periodic safety update reports on marketed drugs is different among the three ICH regions.

## 2.2 Overview of PSUR System

### 2.2.1 Purpose of the PSUR

The PSUR creates the opportunity for a periodic overall safety evaluation to show whether a product's safety profile has remained the same or has undergone change since it was authorized and to indicate whether changes should be made to product information to optimize the use of a product. The main reason for review is because clinical trials tend to be of short duration and include a limited number of patients. After a product is launched, it may be used by patients not studied in clinical trials, for example children, the elderly, pregnant or breastfeeding women or patients with co-morbidities such as hepatic or renal disease. After approval, a drug becomes readily available for immediate use in large populations, so rare adverse drug reactions (ADRs) can be more easily identified. The drugs also become available for indefinite use and delayed onset ADRs become easier to identify.

### 2.2.2 General principles of PSUR

All dosage forms and formulations as well as indications for a given pharmacologically active substance should be covered in one PSUR. Within the single PSUR, separate presentations of data for different dosage forms, indications, or populations (e.g., children versus adults) may be appropriate.

For products authorized to more than one Market Authorization holder (MAH), each MAH is responsible for submitting PSURs even if different companies market the same product in the same country. In case companies get involved in contractual relationships, arrangement for sharing safety information should be clearly set out.

2For combinations of substances also marketed individually, safety information for the fixed combination may be reported either in a separate PSUR or included as separate presentations in the report for one of the separate components, depending on the circumstances. Cross referencing all relevant PSURs is considered important (19).

### 2.2.3 Scope of information

All relevant clinical and nonclinical safety data should cover only the period of the report (interval data) with the exception of regulatory status information on authorization applications and renewals. The main focus of the report should be ADRs. A listed ADR is one whose nature, severity, specificity and outcome are consistent with the company core safety information (CCSI) (20). A serious ADR is defined as any untoward medical occurrence that at any dose results in death, is life threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or in a congenital abnormality/birth defect (21).

For spontaneous reports, unless indicated otherwise by the reporting health-care professional, all adverse experiences should be assumed to be ADRs. For clinical study and literature cases, only those ADRs judged not related to the drug by both the reporter and the manufacturer/sponsor should be excluded. Reports of lack of efficacy specifically for drugs

used in the treatment of life threatening conditions may represent a significant hazard and, in that sense, be a safety issue.

Although these types of cases should not be included with the usual ADR presentations, (line listings and summary tabulations), such findings should be discussed within the PSUR if deemed medically relevant. Increase in the frequency of reports for known ADRs have traditionally been considered as relevant new information. Although attention should be given in the PSUR to such increased reporting, no specific quantitative criteria or other rules are recommended. Judgment should be used in such situations to determine whether the data reflect a meaningful change in ADR occurrence or safety profile and whether an explanation can be proposed for such a change for example, population exposed and duration of exposure) (19).

### 2.2.4 International birth date (IBD) and frequency of reporting

Each medicinal product should have as an international birth date (IBD) the date of the first marketing authorization for the product granted to any company in any country in the world. For administrative convenience, if desired by the MAH, the IBD can be designated as the last day of the same month.

When a report contains information on different dosage forms, formulations, or uses (indications, routes, and populations), the date of the first marketing authorization for any of the various authorizations should be regarded as the IBD and, therefore, determines the data lock point for purposes of the unified PSUR. The data lock point is the date designated as the cutoff for data to be included in a PSUR. The need for a report and the frequency of report submission to regulatory authorities are subject to local regulatory requirements. The age of a drug on the market may influence this process. In addition, during the initial years of marketing, a drug will ordinarily receive authorizations at different times in different countries; it is during this early period that harmonization of reporting is particularly important.

However, independent of the required reporting frequency, regulatory authorities should accept PSURs prepared at 6-month intervals or PSURs based on multiples of 6 months. Therefore, it is recommended that the preparation of PSURs for all regulatory authorities should be based on data sets of 6 months or multiples thereof. Once a drug has been marketed for several years, the need for a comprehensive PSUR and the frequency of reporting may be reviewed, depending on local regulations or requests, while maintaining one IBD for all regulatory authorities.

In addition, approvals beyond the initial one for the active substance may be granted for new indications, dosage forms, populations, or prescription status for example, children versus adults, prescription to nonprescription status. The potential consequences on the safety profile raised by such new types and extent of population exposures should be discussed between regulatory authorities and MAHs since they may influence the requirements for periodic reporting. The MAH should submit a PSUR within 60 days of the data lock point (19).

### 2.2.5 Reference safety information

The objective of a PSUR is to establish whether information recorded during the reporting period is in accord with previous knowledge on the drug's safety, and to indicate whether changes should be made to product information. Reference information is needed to perform this comparison. Having one reference source of information in common for the three ICH regions would facilitate a practical, efficient, and consistent approach to the safety evaluation and make the PSUR a unique report accepted in all areas (17).

It is a common practice for MAHs to prepare their own Company Core Data Sheet (CCDS) which covers material relating to safety, indications, dosing, pharmacology, and other information concerning the product. The practical option for the purpose of periodic reporting is for each MAH to use, as a reference, the safety information contained within its central document (CCDS), which would be referred to as Company Core Safety Information (CCSI). For purposes of periodic safety reporting, CCSI forms the basis for determining whether an ADR is already listed or is still unlisted. This is terms introduced to distinguish them from

the usual terminology of expectedness or labeledness that is used in association with official labeling. Thus, the local approved product information continues to be the reference document upon which labeledness/expectedness is based for the purpose of local expedited post marketing safety reporting (19).

### 2.2.6 Description of the reaction

Until an internationally agreed coding terminology becomes available and its use broadly implemented, the event terms used in the PSUR will generally be derived from whatever standard terminology ("controlled vocabulary" or "coding dictionary") is used by the reporting company. Whenever possible, the notifying reporter's event terms should be used to describe the ADR. However, when the notifying reporter's terms are not medically appropriate or meaningful, MAHs should use the best alternative compatible event terms from their ADR dictionaries to ensure the most accurate representation possible of the original terms.

In many cases, this will be the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA was developed in the early 1990s under the auspices of the ICH and is an important step towards the standardization of terminology regarding the registering, documenting and safety monitoring of medical products. Its use in spontaneous reporting systems is now a regulatory requirement in some countries and it is widely used in the preparation of PSURs. MedDRA is also a key part of the electronic database systems used by European and Japanese authorities (13)

### 2.2.7 Role of organizational theory in understanding safety reporting systems

PSURs are submitted to regulatory authority organization which consists of a group of individuals working towards specific goals, whose behavior is modified by rules and structure. This is a simple and well-accepted definition of an organization that is useful for introducing organizational theory to pharmacy practice research. The components of an organization can be described as participants, social structure, goals, technology and environment (22).As shown in figure 1 below.

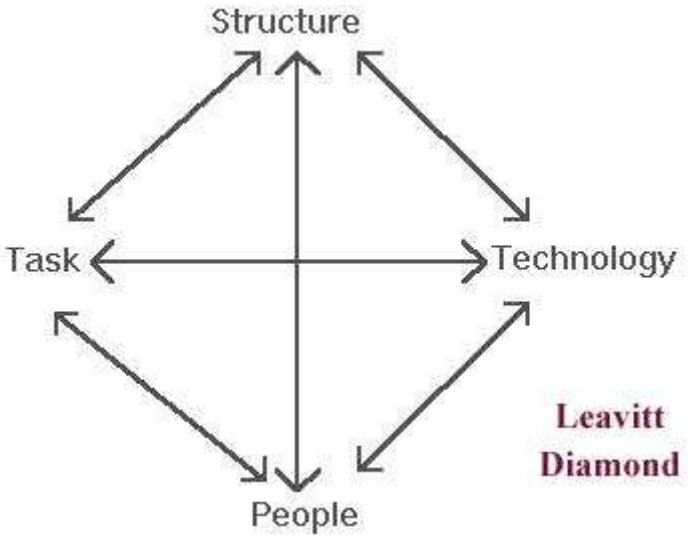


Figure 1**: Scott's adapted version of Leavitt's Diamond Model**

Participants are the people in the organization such as pharmacists, their culture, and their roles. The knowledge and skills of participants is particularly important and has been raised on many occasions as a key factor in the success or failure of interventions in community pharmacy (23).

Goals are the outcomes that the participants or actors are attempting to achieve, such as improving patient health outcomes or increasing customer satisfaction.

They are especially important in the understanding of organizations. If the goals of the different participants are not in some way aligned with each other, success may be compromised (24). In Leavitt's original diamond, this component was known as 'tasks', and therefore Cognitive Pharmaceutical Services(CPS) could also be incorporated here (25).

Social structure refers to the relationships existing between participants in an organization, particularly those that involve regular or consistent interaction. In a community pharmacy, this could encompass interactions between pharmacists and other pharmacy staff, and the way

they organize themselves in the pharmacy. If this definition is expanded, structure could describe not only the human interactions, but also the influence of external factors such as financial resources, and physical structures such as the pharmacy layout (25).

Technology is used in all organizations. It refers not only to machines or computers, but also the procedures in the organization, such as protocols or guidelines for quality control (26). The environment in which an organization exists is important as it affects the types of relationships the organization will need to establish in order to survive such as community pharmacists' working relationships. Conversely, the organization can affect its environment. One notable example of this in pharmacy is the deregulation of pharmaceuticals (27). Organizational theory provides a useful perspective for recognizing and describing the important components of an organization, and how they may affect each other and the whole organization.

# CHAPTER THREE

## 3.0 METHODOLOGY

### 3.1 Study design

The study methodology employed was qualitative cross-sectional analysis of documentary materials. A comparison of International Conference on Harmonization (ICH) guidelines and Kenya's reporting requirements was done. To identify similarities and differences across the standards and regulation, the text of each document was examined line by line. After aligning the relevant terms and text in each document, their requirements were compared.

### 3.2 Study site

The study site was the Pharmacy and Poisons Board (PPB) Kenya. This is the drug regulatory authority established under the Pharmacy and Poisons act, chapter 244 of laws of Kenya. The board regulates the practice of pharmacy and the manufacture and trade in drugs and poisons. The board aims to implement appropriate regulatory measures to achieve the highest standard of safety, efficacy and quality for all drugs.

### 3.3 Study subjects

PSURSs submitted by Marketing Authorization Holders to PPB and the Key informants at PPB.

### 3.4 Sample size

All PSURs submitted for the period between January, 2013 and January 2014.

### 3.5 Inclusion Criteria and Exclusion Criteria

All PSURs submitted to Pharmacy and poisons Board between January, 2013 and January, 2014 were included. Incomplete, physically damaged or otherwise illegible Periodic Safety Update Reports s were excluded

.

### 3.6 Sampling Method

All documents labeled as PSURs dated between January, 2013 to January, 2014 were eligible for inclusion in the study. A total 120 documents were identified for review. However, 31 documents were excluded because of being in such in a poor physical condition; it was not possible to analyze them. A further 57 documents were excluded because, though they had been filed as PSURs, they did meet the minimum criteria for PSURs but were other documents as listed in table 1 below.

**Table 1: Submitted documents marked as PSURs**

| Type of document submitted | Total |
|---|---|
| **Periodic safety update reports(PSURs)** | **32** |
| Safety update | 2 |
| Global data sheet | 2 |
| Amendment package insert update | 2 |
| Package insert update | 8 |
| Prescribing information update | 23 |
| Amendment for prescribing information | 9 |
| Core safety risk management plan | 2 |
| Worldwide pharmaceutical operation | 1 |
| Periodic benefit risk evaluation | 1 |
| Application to spc | 1 |
| Package leaflet | 3 |
| Summary bridging report | 1 |
| Core data sheet | 1 |
| PSUR assessment | 1 |

A sampling frame for all submitted PSURs for the period January, 2013 to January, 2014 was done and the eligible PSURs were isolated for review.

### 3.8 Data Collection

The data collection tool was designed, piloted and validated. The tool was used to abstract data on overall safety studies; update of regulatory authority, marketing authorization holders .Key informant interviews were carried out and abstracted information on the organizational structure at the PPB and the processes involved in submission of PSURs.

### 3.9 Data Management

Confidentiality was maintained by not recording PSUR number in the data collections forms. All the raw data collected was and kept under lock and key by the researcher. The data identifying each PSUR by name was kept confidential and was only be accessible to the principal investigator.

All data generated was directly entered in the raw data recording forms (Appendix IV). All the data were examined for inconsistencies and any errors were duly corrected. The PSURs submitted were revisited for verification of any missing information. The data was entered in an excel spreadsheet and later copied to stata 10.0 databases. The data was cleaned and any changes made to the original were recorded. Accuracy of the data entry was checked randomly by sampling at least 16 submitted PSURs and comparing with the hard copies and the data entered into the spread sheet.

All the data and documents were backed up at the end of each day in a CD (Compact disc) and flash disk, a second copy was stored by the principal supervisor under lock and key in his office. This was done regularly to avoid loss or tampering. All data were password protected.

#### 3.9.0 Data analysis

Data that was collected was coded and entered in a pre-formed Microsoft excel data sheet. It was then exported to stata version 10.0 which had a range and consistency checks embedded in the software for analysis.

Descriptive data was analysed quantitatively using descriptive statistics and presented in form of proportions, percentages pie charts and tables as appropriate.

#### 3.9.1 Key informant selection

Key informants were identified and a list of potential key informants was made to gather information from the target population. The list was reviewed and two persons were identified and provided the needed information.

A face to face interview was scheduled and it provided a free exchange of ideas. A convenient place and time was scheduled for the interview.

### 3.9.2 Key informant tool

An interview tool to guide the discussion was developed. It contained an outlined script and a list of open ended questions. It began with most factual and easy to answer questions and then followed by those questions that asked informants opinion. Probing questions were asked as it helped get detailed information. Note taking was used to record the interview responses.

### 3.9.3 Ethical Considerations

Ethical approval for this study was sought from KNH-UON ethics and Research Committee, Ref No. KNH-ERC/A/280. Written informed consent was obtained from Pharmacy and Poisons and Board and (Appendix II). Information was abstracted from the PSURs and did not involve direct contact.

Pharmacy and Poisons Board was informed about the study through oral presentation regarding the purpose and procedures to be carried out.

There were no direct benefits to the Pharmaceutical companies submitting the PSURs neither were there any risks involved. However, the findings were communicated to PPB Pharmacovigilance department to contribute to improving the quality of services offered there.

Confidentiality of PSURs was assured by reviewing the submitted PSURs at the Department of Pharmacovigilance. PSURs numbers were not included in data collected instead a unique identification number was assigned. The extracted data were stored securely.

# CHAPTER FOUR

## 4.0: RESULTS

### 4.1 Periodic Safety Update Report Content.

**Cover letter**

Out of the 32 PSURs submitted (n), 31.3% had the cover letter included and 68.8% did not include the cover letter. The cover letter contained all information as per the guidelines in only 21.9% of the reviewed PSURs and 78.1% did not contain all the information as per ICH guidelines. At least 68.8% of the reviewed PSURs had their cover letter signed by the MAH while 31.3% did not. Summary of the findings is as shown in Table 2 below.

Table 2**: Components of the cover letter**

| Component | Yes; n (%) | No; n (%) | Total |
|---|---|---|---|
| Cover letter included | 10 (31.3) | 22 (68.8) | 32 |
| Cover letter contains require information | 7 (21.9) | 25 (78.1) | 32 |
| Cover letter signed by MAH | 22 (68.8) | 10 (31.3) | 32 |

**Executive summary**

The executive summary contains worldwide marketing authorization status in all the 32 reviewed PSURs (100%), while 90.6% had regulatory information included during the PSUR period and only 9.4% lacked the regulatory information during the period. Patient exposure was reported in 96.9% of the reviewed PSURs reporting patient exposure. The numbers of new case reports received during the period covered by the PSUR were 21.9%. Safety concerns investigated were recorded in 81.3% of the PSURs reviewed. Overall finding and companies' conclusion were all contained in executive summaries of all PSURs submitted for that period. Summary of the findings are as shown in table 3 below.

**Table 3: Executive summary of PSURs**

| Component | Yes; n (%) | No; n (%) |
|---|---|---|
| Worldwide marketing authorization status | 32 (100) | 0 (0) |
| Regulatory action taken | 29 (90.6) | 3 (9.4) |
| Patient exposure | 31 (96.9) | 1 (3.1) |
| Number of new case reports received during the period | 7 (21.9) | 25 (78.1) |
| Safety concerns investigated | 26 (81.3) | 6 (18.8) |
| Overall findings of the PSUR | 32 (100) | 0 (0) |
| The Company's conclusion | 32 (100) | 0 (0) |

**Introduction and Worldwide Market Authorization Status**

All 32 reviewed PSURs had authorized indication for their products. In the component of worldwide marketing authorization status for the PSUR period, all the products had worldwide market approval and none of the MAHs for the period had withdrawn application for the authorization. A large percentage 93.8% of the reviewed PSURs had not experienced any change to the marketing authorization status as shown in table 4 below.

Table 4: **Introduction and Worldwide Market Authorization Status**

| Component | Yes; n (%)) | No; n (%) |
|---|---|---|
| Authorized indication | 32 (100) | 0 (0) |
| Authorized but not marketed | 2 (6.3) | 30 (93.8) |
| Products approval | 0 (0) | 32 (100) |
| Withdrawal of application for authorization | 0 (0) | 32 (100) |
| Change to the marketing authorization status | 2 (6.3) | 30 (93.8) |

**Updates –Regulatory actions on Market Authorization**

Out of 32 PSURs sampled, none had any actions taken on them for any safety reasons and a very small percentage of between 3.1- 6.3 percent had missing data as shown in table 5 below.

**Table 5: Updates –Regulatory actions on Market Authorization**

| Component | Yes, n (%) | No; n (%) | Missing, n (%) |
|---|---|---|---|
| Marketing authorization withdrawal, revocation or suspension | 0 (0) | 31 (96.9) | 1(3.1) |
| Renewal of Market Authorization | 0 (0) | 31 (96.9) | 1 (3.1) |
| Restrictions on distribution | 0 (0) | 31 (96.9) | 1 (3.1) |
| Clinical trial suspension | 0 (0) | 31 (96.9) | 1 (3.1) |
| Dosage modification | 0 (0) | 30 (93.6) | 2 (6.3) |
| Changes in target population or indications | 0 (0) | 30 (93.6) | 2 (6.3) |
| Formulation changes | 0 (0) | 30 (93.8) | 2 (6.3) |
| Urgent safety restrictions | 0 (0) | 30 (93.6) | 2 (6.3) |

**Changes to Reference Safety Information**

All the reviewed PSURs used CCDS a there reference document. There were changes to reference safety information in Posology and method of administration to about 6.3 percent and high percentage of 43.8 and 37.5 was observed on changes to reference safety information on special warnings and interaction with other medicinal products. Other parameters ranged from 3.1% to 21.9% with sections of the reference safety having been changed during the period covered by the PSUR as shown in table 6 below.

**Table 6: Changes to Reference Safety Information**

| Component | Yes; n (%) | No; n (%) | Total |
|---|---|---|---|
| Is the CCDS the reference document | 31 (96.9) | 1 (3.1) | 32 |
| Changes on document covered by PSUR | | | |
| Posology and method of administration | 2 (6.3) | 30 (93.8) | 32 |
| Contraindications | 1 (3.1) | 31 (96.9) | 32 |
| Special warnings and precautions for use | 14 (43.8) | 18 (56.3) | 32 |
| Drug Interaction | 12 (37.5) | 20 (62.5) | 32 |
| Pregnancy and lactation | 7 (21.9) | 25 (78.1) | 32 |
| Effects on ability to drive and use machines | 2 (6.3) | 30 (93.8) | 32 |
| Undesirable effects | 8 (25) | 24 (75) | 32 |
| Overdose | 5 (15.6) | 27 (84.4) | 32 |

**Patient Exposure**

Out of the 32 PSURs reviewed, 90.6% PSURs had patient exposure in clinical trials and a similar percentage of products had market experience. There was neither change in methodology used for calculation or patient exposure as illustrated in the table 7 below.

**Table 7: Patient Exposure and post marketing experience**

| Component | Yes; n (%) | No; n (%) | Total |
|---|---|---|---|
| Exposure in clinical trials | 29 (90.6) | 3 (9.4) | 32 |
| Market experience | 29 (90.6) | 3 (9.4) | 32 |
| Change in methodology used for calculation | 0 (0) | 32 (100) | 32 |
| Overall change in patient exposure | 0 (0) | 32 (100) | 32 |

**Methodology for exposure number calculations**

Defined Daily Doses was the most commonly used methodology for patient exposure calculations standing at 50%. Patients per day had the lowest methodology for exposure at 3.1%. Number of doses stood at 21.9% and others which had a total percent of 25 had units, bottles as their methodology for exposure, as shown in Table 8 and Figure 3 respectively.

Table 8**: Methodology for exposure number calculations**

| Parameter | Frequency n=32 | % |
|---|---|---|
| Defined Daily Dose | 16 | 50.0 |
| Patients/day | 1 | 3.1 |
| Number of doses | 7 | 21.9 |
| Units/bottles | 8 | 25.0 |

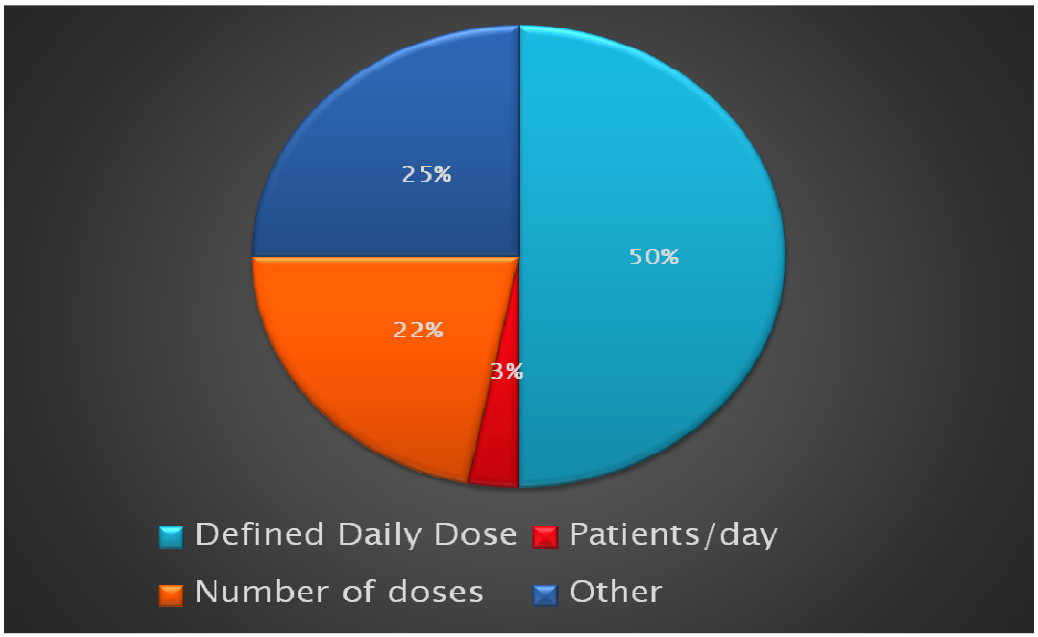


**Figure 2: Methodology for exposure number calculations**

**Studies and other information**

Among the sampled PSURs, 21.8% had targeted new studies with a large number having no study during the PSUR period. At least 71.9% of the reviewed PSURs had published studies and a big percentage about 87.5 did not have any newly analyzed company sponsored studies, only a few of the reviewed PSURs concentrated on other studies standing at 25%.

In "other information", most of the reviewed PSURs, accounting to 87.5% did not have risk Management plan neither did 71.9% have risk benefit analysis report. About 12.5% of reviewed PSURs had late breaking news, as shown in the Table 9 and Figure 3 below respectively.

Table 9**: Studies and other information**

| **Component** | **Yes; n= (%)** | **No; n (%)** | **Missing; n (%)** |
|---|---|---|---|
| Newly-Analyzed company sponsored Studies | 3 (9.4) | 28 (87.5) | 1(3.1) |
| Targeted New Safety Studies | 7 (21.8) | 25 (78.1) | 0 (0) |
| Published Studies | 23 (71.9) | 8 (25) | 1 (3.1) |
| Other studies | 8 (25) | 22 (68.8) | 2 (6.3) |
| Efficacy-related Information | 8 (25) | 23 (71.8) | 1 (3.1) |
| Late Breaking Information | 4 (12.5) | 26 (81.3) | 2 (6.3) |
| Risk Management Plan | 2 (6.3) | 28 (87.5) | 2 (6.3) |
| Risk-Benefit Analysis Report | 6 (18.8) | 23 (71.9) | 3 (9.4) |

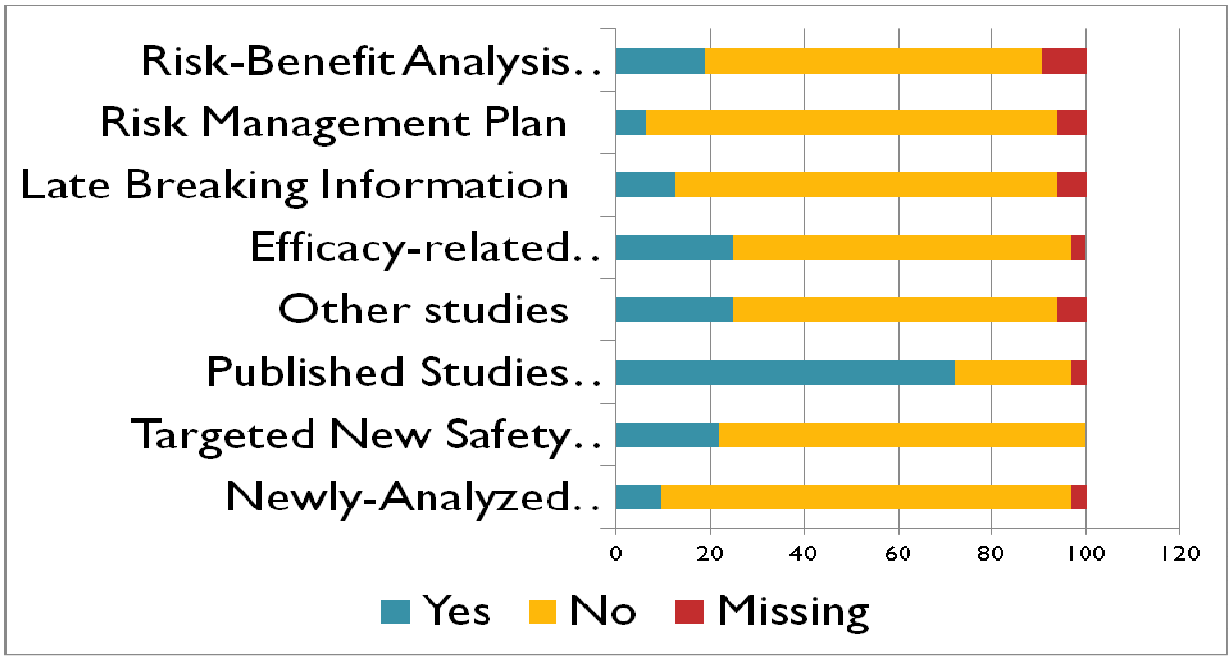


**Figure 3: Studies and other information**

**Drug interactions**

Of the 32 PSURs reviewed 59.4% reported drug interactions while 15.3% reported no cases of drug interaction and 25% did not report whether or not drug interaction took place.

**Pregnancy and lactation**

Out of 32 PSUR reviewed, 37.5 % reported cases of drug use in pregnancy and lactation and a similar percentage reported no cases of pregnancy and lactation. In addition, 25 % did not mention cases of pregnancy and lactation. A cumulative reporting rate of 75% was achieved. This is an area we expected a very high reporting rate because of the risks associated with medicine use in pregnancy.

**Overdosage**

Overdosage was reported in 53.1% of the submitted PSURs and 25% did not report cases of overdosage. In addition, 21.9% did not report whether or not overdosage took place. Reporting rate for this parameter stood at 78.1%.which is slightly above the set threshold for good reporting.

**Drug abuse or misuse**

Of the 32 PSURs reviewed, 62.5%% reported drug misuse or abuse, where as 21.9%% reported no misuse or abuse. However 15.6% failed to report whether or not drug misuse or abuse took place. The reporting rate for this parameter stood at 83.4% which was above the set threshold for good reporting.

**Special population**

Cumulative reporting rate of the special population was 75% which just met the set criteria. Of the 32 PSURs sampled, 53.1% reported drug use in special population while21.9% reported no cases in special population. In addition, 25% did not mention whether or not cases in special populations were reported.

**Long term treatment**

The reporting rate for this parameter stood at 71.9% .Of the 32 PSURs sampled, 34.4% reported long term treatment, where 37.5% reported no cases of long term treatment. However, 28.1% did not mention whether or not there were cases on long term treatment. This fell below the threshold for reporting.

**Medication errors**

Of the 32 PSURs sampled, 65.6%% reported medication errors, where 18.8% reported no cases of medication error, in addition, 15.6% did not mention cases of medication errors. A cumulative reporting rate of 84.4% was achieved. This was above the set criteria for good reporting.

**Off label use**

Of the 32 PSURs sampled, 56.3% reported cases of off label use whereas 18.8% reported no off label use. Overall reporting rate for this indicator was 75.1%. Therefore from this study, the prevalence of off-label use was 56.3%.

Table 10**: Overall safety Evaluation**

| Component | Yes; n (%) | No; n (%) | Missing; n (%) |
|---|---|---|---|
| Drug interaction | 19(59.4) | 5(15.3) | 8(25.0) |
| Overdose | 17(53.1) | 8(25.0) | 7(21.9) |
| Abuse or misuse | 20(62.5) | 7(21.9) | 5(15.6) |
| Pregnancy/ lactation | 12(37.5) | 12(37.5) | 8(25.0) |
| Special populations | 17(53.1) | 7(21.9) | 8(25.0) |
| Long-term treatment | 11(34.4) | 12(37.5) | 9(28.1) |
| Medication errors | 21(65.6) | 6(18.8) | 5(15.6) |
| Off label use | 18(56.3) | 6(18.8) | 8(25.0) |

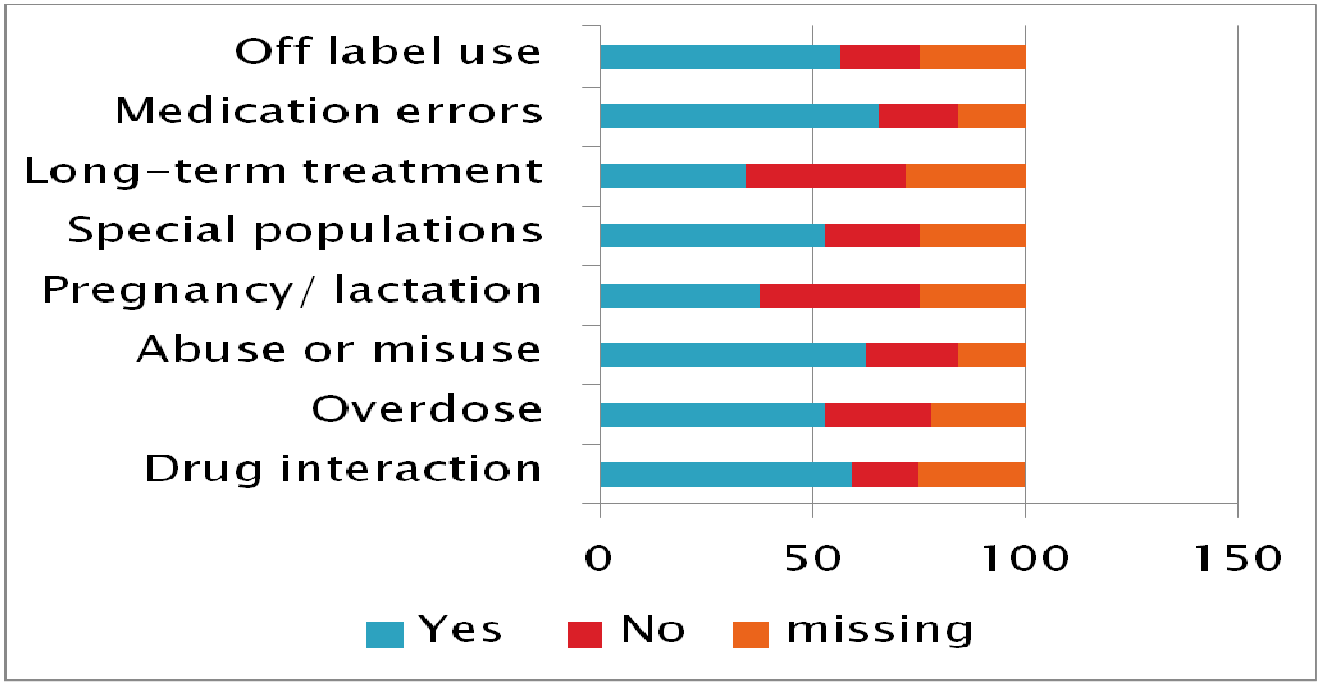


**Figure 4: Overall safety information**

**Conclusion and appendices**

All the reviewed PSURs had MAH conclusions. The appendices were attached to 68.8% of the reviewed PSURs. See table 11 below.

Table 11**: Conclusion and appendices**

| Component | Yes; n (%) | No; n (%) |
|---|---|---|
| MAH conclusion | 32(100) | 0 |
| Appendices attached | 22(68.8) | 10(31.3) |

**PSURs pages**

The characteristics of PSURs varied considerably for the different products. The median length of the PSURs was 154.5(range 73-226.5) pages with the least number of pages being 6 and the largest 412.

**4.2 Organization of the reporting systems: Kenya**

**Participants:** The PSUR committee was formed to help in evaluation of potential signals, evaluate change in products and make recommendation and purpose solution regarding better reporting and submission of PSUR. The PSUR review committee is composed of 4 pharmacists, 2 pharmaceutical technologist and 2 clerical staff. Handling of PSURs is purely by personnel in the Medicine information and Pharmacovigilance department who have already been trained.

**Goals and Tasks:** The Medicines Information and Pharmacovigilance department receives PSURs and professional staff reviews them when need arises, there is no definite set date. The committee reviews the PSURs and other reports involving serious reactions or recently marketed medicines. Drug safety monitoring of medicines include assessment of ADR reports and Periodic safety Update Reports for the MAHs. In Kenyan system, there are no budgeted resources for evaluation of PSURs but the interview revealed that plans are underway for allocation of funds to support the review activity for financial year 2014-2015.

**Social structure:** Entering the submitted PSURs into excel sheet is done by trained clerical personnel. The whole directorates of Medicine Information and Pharmacovigilance in collaboration with other directorates are involved in assessment and review of PSURs.

Discussion between the pharmacovigilance team about the PSURs takes place though it is irregular. Signal detection and new indications are discussed and communicated to the relevant MAHs. The Pharmacists, Pharmaceutical Technologists and clerical staff are placed in an open plan office or a boardroom where they collaboratively do reviews.

**Technology:** The whole unit of Medicine information and Pharmacovigilance is fully computerized and adequately connected to the internet. Critical information by any submitting MAH is sent within 48hours to PPB. An e-mail is sent in advance awaiting the hardcopies. PSURs are coded and keyed into the excel sheet awaiting review.

In Kenya, the pharmacovigilance team does not usually exchange data electronically with the MAHs and other EU companies..

**Environment:** The Kenya system is a standalone and all PSURs are reviewed by the Pharmacovigilance team.

### 4.3 Process of periodic safety updates reporting system

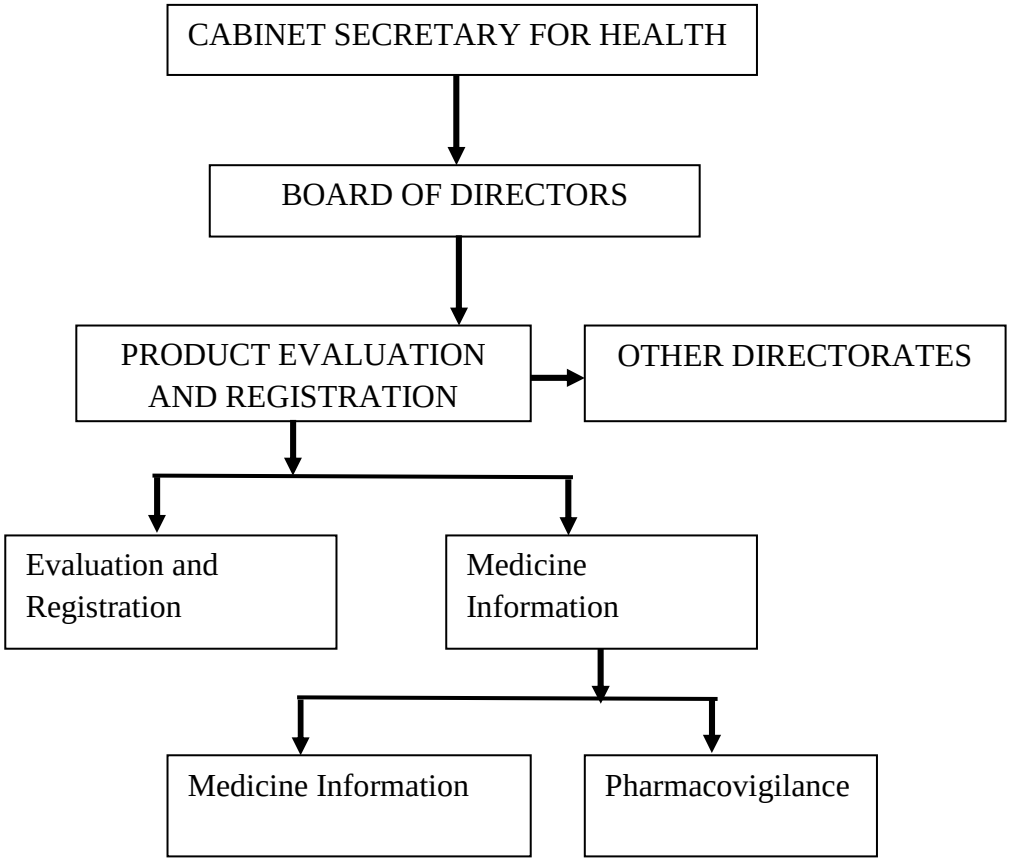


**Figure 5: Pharmacy and Poisons Board organizational structure**

Marketing authorization holders (MAHs), submit 2 hard copies alongside soft copy

A cover letter is signed and a copy is retained at the Pharmacovigilance department.

They are coded and entered in an excel sheet awaiting assessment and review

# CHAPTER FIVE

## 5.0 DISCUSSION

In this study we sought to assess the structure, content and processes of periodic safety update reporting in Kenya.

The study's findings demonstrate that 68.8% of PSURs submitted lacked cover letter. PSURs are written by MAH and submitted to regulatory authorities for assessment at predetermined time (30). However, this study revealed submission of PSURs is not mandatory and review and assessment are not done at a predetermined time points.

The concept for PSUR reporting stems from 1992 (17). It had been noted, including ICH and EU, that PSUR reporting had not kept pace with developments in Pharmacovigilance such as electronic adverse event reporting and risk management planning (31). However in Kenya this study revealed there is continued effort by the Pharmacovigilance department to train and promote electronic reporting from various facilities and MAHs. In this study, 87.5% of submitted PSURs did not have any form of risk management plan. About 71.9% of the reviewed PSURs, the MAHs did not incorporate Risk Benefit Management Plan.

This reveals most MAHs do not have adequate risk management plans just in case a product causes harm in the market. In a related study on determinants of safety related regulatory action for biopharmaceuticals, it was found out that PSURs evaluation contributed to 38% of post authorization regulatory actions in a sample of biopharmaceuticals (9).

In addition, Al varez et al found that 64% of selection of adverse drug reactions originated from PSURS (10).Both the studies examined the contribution of PSURs in identification of safety signal. This study revealed considerably high medication error reported by the MAHs which stood at 65.6%.Drug abuse and misuse at 62.5%, drug interaction occurring in 59.4% of submitted PSURs. There was a high prevalence of drug overdose and off label use. Related studies have reported a prevalence of between 21 and 79% (29). A study by shah *et al* found that 78.9% of children discharged from pediatric hospitals were taking at least one off-label

medication. Therefore, there should be emphasis by regulatory authority to make it mandatory to timely submit the PSURs by the concerned MAHs and regular reviews by the regulatory authority to timely identify any kind of signals warranting regulatory actions.

The study revealed, however much there are standard ICH guidelines, PSURs considerably differ in structure, content and presentation of safety data which may complicate assessment procedure. These differences may originate from the fact that different MAHs have different working methods. Therefore, there should be deliberate effort to have a harmonized format for easy review and assessment.

PSURs are intended to be summaries to facilitate Periodic Safety evaluation. Many PSURs are long and complicated documents. A more concise document that includes a discussion of both benefits and risks with emphasis on identifying changes in overall benefit-risk balance may be considered. Similar proposal has been released for consultation by ICH (32).

Potential safety concerns were present in 16 (50%) of the PSURs. In one case, 2 PSURs required risk management update and another 2 required update and change in the CCDS. One was added in the reference safety information. This study also revealed there were no submission time lines required by the regulatory authority on MAHs and no local MAHs were submitting PSURs.

The Multinational MAHs submit them as an obligation from their parent countries' regulations. Submission process is in conformity with international standards. Review of submitted PSURS to generate safety signals is inadequate. The reporting rates for overall safety evaluation data items were low.

Though Pharmacy and Poisons Board uses the ICH guidelines to inform the procedure for submission of the PSURs, there lacks a checklist and/or standard operating procedures. The clerical personnel that receive these documents therefore have no way of enforcing that a proper cover letter be submitted. A cover letter is necessary to authenticate the PSURs as having been submitted by a specified MAH. When a cover letter is not submitted, the PSUR submitted may not be considered authentic.

As to organizational structure of PSURs, it is well established and organized, with a staff of 8, 4 pharmacists, 2 pharmaceutical technologists and 2 clerical officers and has a PSUR committee in place. In Australia, the ADR advisory committee which is an equivalent of PSUR committee in Kenya, is composed of independent medical officer with expertise in areas of importance to evaluation of medicine safety comprising of 13 staff, 4 senior medical officer, 1pharmacist and 6 clerical officers (33).

The government of Kenya needs to allocate budget resources for the evaluation of PSURs so as to support the initiative. There is good collaboration in the pharmacovigilance team, however, main problem is that reviews are not done regularly, this may affect when the signals are picked and others may be noticed late. One of the setbacks in the department is that they have no set dates when to review the medicines information .They need to have set dates either monthly or biannually and also to meet as and when need arises. A strong point is that the whole unit is fully computerized and Critical information by any submitting MAH is sent within 48hours.An e-mail is sent in advance awaiting the hardcopies. In Australia, the pharmaceutical industry must report within 72hours any new serious safety problem including what measures have been taken (27). All the PSURs are well coded and keyed.

With regard to process, the Pharmacy and Poisons Board consists of five directorates which include Business Support Services, Inspection and Surveillance, Product Evaluation and Registration, Quality control Laboratory and Pharmacy Practice and Regulation of Training. The department of Medicine Information and pharmacovigilance falls under the directorate of Product Evaluation and Registration. The cabinet secretary appoints the Board of directors and the Board is headed by the Chief Pharmacist who automatically becomes the Registrar.

Under the department of Medicine information and Pharmacovigilance, there exist three divisions; medicines information, which deals with advertisement of medicines and provision of medicine information to the public. The division of Pharmacovigilance which deals with trainings and management of reports and regulatory actions and finally division of clinical trials, which receives clinical trials applications and their approval. PSURs are submitted to department of Medicines and Pharmacovigilance in line with ICH recommendations. When

received, they are coded and entered into an excel sheet awaiting reviews and recommendations. However, there are no scheduled dates for review.

A panel from different directorates is usually set when a time for review comes and usually gives recommendations. In case of any signal detection, appropriate and immediate regulatory actions are taken.

In Kenya, the MAH submits two hard copies of the PSURs alongside a softy copy, a cover letter is signed and one is retained at the department while the other goes back to the MAH. Most countries in the European Union require soft copy of the PSUR either by email or on CD-ROM with a PDF and Word versions and a cover letter. All sampled PSURs had their MAH as multi nationals and no local MAH had submitted their PSUR during the time of study. It was also noted that there was no law that compels the MAHs to submit the PSURs.

In Europe, the EMA requires PSURs every 6 months for 2 years, annually for the 3 following years, and then every 5 years (at the time of renewal of registration). In Japan, the authorities require a survey on a cohort of a few thousand patients established by a certain number of identified institutions during the 6 years following approval, with systematic information reported annually on this cohort. Regarding other post-approval experience, adverse reactions that are non-serious, but both mild in severity and unlisted, must be reported every 6 months for 3 years and annually thereafter (19)

# CHAPTER SIX

## 6.0 CONCLUSION AND RECOMMENDATIONS

### Conclusion

The Pharmacy and Poisons Board had a well laid structure for Periodic Safety Update reporting, however there was need for a harmonized format for capturing information and a mandatory requirement for MAHs to timely submit the PSURs. PSURs submitted to the PPB considerably in presentation of overall safety evaluation with nearly two thirds reporting medication errors and abuse/misuse. Nearly half of the reported PSURs reported drug interactions, off-label use and 50% of the PSURs had potential safety concern. In addition, a policy to be put in place with additional staff and government to allocate funds to facilitate regular reviews

### Recommendation

There is an urgent need for the regulatory authority to have policies in place for the regulation processes of PSURs in the country for this will streamline the reporting process. The board to employ adequate staff to run the pharmacovigilance department and this will facilitate regular PSURs reviews and hence timely detection of any signal and hence facilitate timely regulatory actions.

The pharmacovigilance team should develop and implement a structured PSUR review tool as this will enhance uniformity and hence better and timely picking up of signals. The board to develop comprehensive guidelines and standard operating procedures regarding content ,structure ,frequency of reporting, regulatory actions and processes of submitting PSURs to the regulatory authority in Kenya. The Board to adapt a more concise document that includes discussion of both benefits and risks with emphasis on identifying change in the overall benefit -risk balance.

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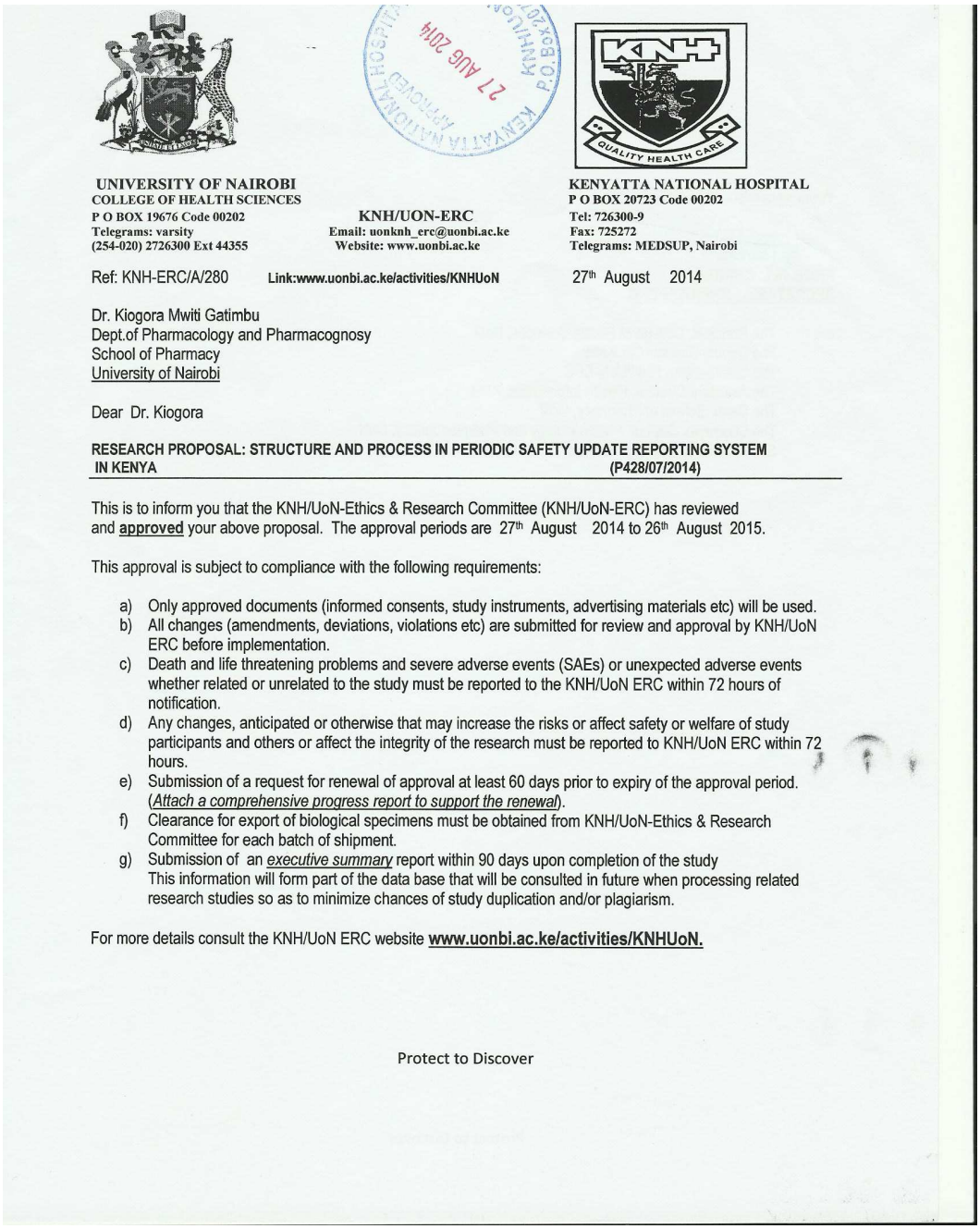
# APPENDICES

## Appendix I: Ethics and Research Committee Approval




UNIVERSITY OF NAIROBI
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Telegrams: varsity
(254-020) 2726300 Ext 44355

KNH/UON-ERC
Email: uonknh_erc@uonbi.ac.ke
Website: www.uonbi.ac.ke

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


Ref: KNH-ERC/A/280 Link:www.uonbi.ac.ke/activities/KNHUoN 27th August 2014

Dr. Kiogora Mwiti Gatimbu
Dept.of Pharmacology and Pharmacognosy
School of Pharmacy
University of Nairobi

Dear Dr. Kiogora

**RESEARCH PROPOSAL: STRUCTURE AND PROCESS IN PERIODIC SAFETY UPDATE REPORTING SYSTEM IN KENYA (P428/07/2014)**

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 27th August 2014 to 26th August 2015.

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 severe 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-Ethics & Research Committee 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 **www.uonbi.ac.ke/activities/KNHUoN.**

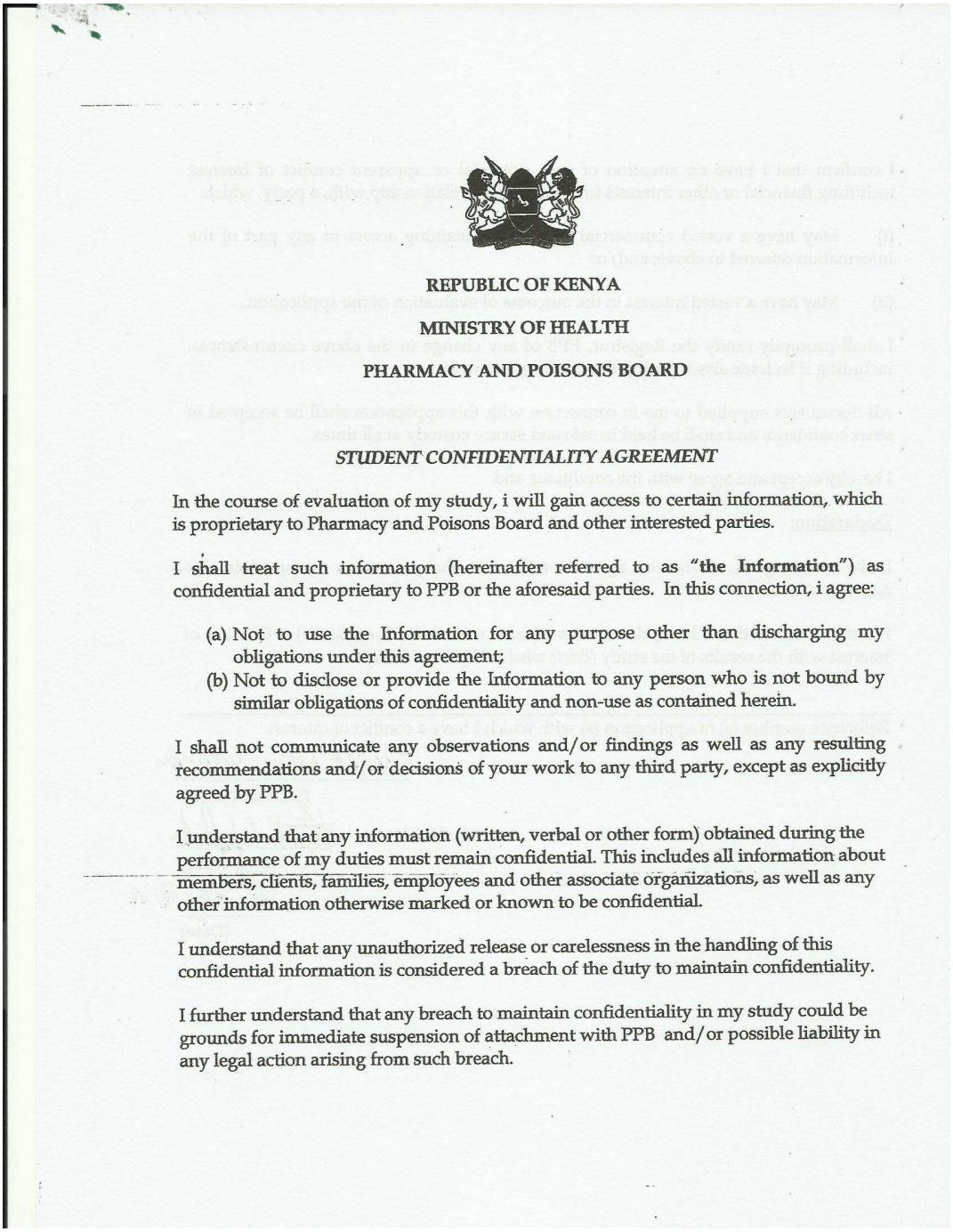
Protect to Discover

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 Chairperson, KNH/UoN-ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chairman, Dept.of Pharmacology and Pharmacognosy, UoN
Supervisors: Dr. George Osanjo, Dr. James Riungu, Dr. Wesley Rono

## Appendix II: Declaration of confidentiality form



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 your 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 results of the study (*delete what is NOT applicable*)

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

KIOGORA MWITI CATHBERT

(Student Name)

(Signature)

22nd Aug 2014

(Date)

**Appendix III: Assurance on confidentiality**

All information obtained from your records and interviews conducted will be kept confidential and used for the purpose of this study only. Your records will be kept under lock and key and information will be accessible to authorized persons only.

**Contacts**

For any further information about this study you may contact me, my academic department or the Kenyatta National Hospital/University of Nairobi Ethics and research Committee using the contacts provided below:

Kiogora Mwiti Gatimbu,
Department of pharmacology and pharmacognosy
School of Pharmacy,
University of Nairobi
P.O Box 157-00202 KNH. Tel: 0720-790-655

Dr. George Osanjo,
Department of Pharmacology and Pharmacognosy
School of Pharmacy, University of Nairobi

P.O Box 19676- Nairobi. Tel: 0737-434204

The chairperson,
The Kenyatta National Hospital/University of Nairobi Research and Ethics Committee,
P.O Box 19676- Nairobi. Tel: 020-2726300 Ext 44102

## Appendix IV: PSURs Review Tool.

**Cover letter**

| PSURs components | Findings | Comments |
|---|---|---|
| Included | [ ] yes [ ] No | |
| Contain all information as the guidelines | [ ] Yes [ ] No | |
| Signed by the MAH | [ ] Yes [ ] No | |

1. **Executive summary**

| PSURs components | Findings | Comments |
|---|---|---|
| Worldwide Marketing authorization status | | |
| Regulatory info. During the PSUR period | | |
| Patient exposure | | |
| Number of new case reports received during the period covered by the PSUR and the cumulative numbers | | |
| Safety concerns investigated | | |
| Overall findings of the PSUR | | |
| The Company's conclusion | | |

**2. Introduction**

| PSURs components | Findings | Comments |
|---|---|---|
| Authorized Indication | | |

3. **Worldwide Market Authorization Status**

| PSURs components | Findings | Comments |
|---|---|---|
| Cumulative information | | |
| Number of Authorization countries | | |
| Authorized but not marketed | [ ] Yes [ ] No | |
| Lack of approval | [ ] Yes [ ] No<br>If yes MAH explanation | |
| Company withdraw the **application** for authorization | [ ] Yes [ ] No<br>If yes MAH explanation | |
| Has there been a change to the marketing authorization status | [ ] Yes [ ] No<br>If yes specify | |

4. **Update of Regulatory Authority or Marketing Authorization Holder Actions taken for Safety Reasons**

| PSURs components | Findings | Comments |
|---|---|---|
| Marketing authorization withdrawal, revocation or suspension | [ ] Yes [ ] No<br>[ ] Not mentioned<br>If yes MAH explanation | |
| Failure to obtain a marketing authorization renewal | [ ] Yes [ ] No<br>[ ] Not mentioned<br>If yes MAH explanation | |
| Restrictions on distribution | [ ] Yes [ ] No<br>[ ] Not mentioned<br>If yes MAH explanation | |
| Clinical trial suspension | [ ] Yes [ ] No<br>[ ] Not mentioned<br>If yes MAH explanation | |
| Dosage modification | [ ] Yes [ ] No<br>[ ] Not mentioned<br>If yes MAH explanation | |
| Changes in target population or indications | [ ] Yes [ ] No<br>[ ] Not mentioned<br>If yes MAH explanation | |
| Formulation changes | [ ] Yes [ ] No<br>[ ] Not mentioned<br>If yes MAH explanation | |

| | | |
|---|---|---|
| Urgent safety restrictions | [ ] Yes [ ] No<br>[ ] Not mentioned<br>If yes MAH explanation | |

5. **Changes to Reference Safety Information**

| **PSURs component** | **Findings** | **Comments** |
|---|---|---|
| Is the CCDS the reference document? | | |
| Date of the last reference document | | |
| Which sections of the reference safety document have been changed during the period covered by the PSUR?<br>1. Posology and method of administration<br>2.contraindications<br>1. special warnings and precautions for use<br>2. interaction with other medicinal products and other forms of interaction<br>3. pregnancy and lactation<br>4. effects on ability to drive and use machines<br>5. undesirable effects<br>6. Overdose<br><br>Please specify the safety | | |

| | | |
|---|---|---|
| relevant changes | | |
| | | |

6. **Patient Exposure**

| **PSURs component** | **Findings** | **Comments** |
|---|---|---|
| Exposure in clinical trials | | |
| Market Experience | | |
| Methodology used for the exposure number calculation: | [ ] Defined Daily Dose<br>[ ] Patients/day<br>[ ] Number of prescriptions<br>[ ] Number of doses<br>Other (please specify) | |
| Comparison with previous PSUR, if information is available: | Change in methodology used for calculation:<br>[ ] Yes [ ] No<br>MAH justification: | |
| | Overall change in patient exposure:<br>[ ] Yes [ ] No<br>If yes, [ ] Increase [ ] Decrease<br>MAH comment: | |
| | | |
| | | |

7. **Presentation of Individual Case Histories**

| **PSURs component** | **Findings** | **Comments** |
|---|---|---|
| Serious cases including fatalities | Serious unlisted=<br>Serious Listed= | |
| Number of fatal cases | | |
| Non-serious | Serious unlisted=<br>Serious Listed= | |
| This PSUR with ≠ cumulative | describe any change in incidence of ADR taking into consideration patient exposure><br><br>In PSUR period:<br>Number of cases/ Patient exposure=<br><br>Cumulative:<br>Number of cases/ Patient exposure= | |
| | | |

**8. Studies**

| **PSURs component** | **Findings** | **Comments** |
|---|---|---|
| Newly-Analyzed company sponsored Studies | [ ] Yes [ ] No<br>[ ] Not mentioned | |
| Targeted New Safety Studies | [ ] Yes [ ] No<br>[ ] Not mentioned | |
| Published Studies (literature) | [ ] Yes [ ] No<br>[ ] Not mentioned | |

| | | |
|---|---|---|
| Other studies | [ ] Yes [ ] No<br>[ ] Not mentioned | |

## 9. Other Information

| **PSURs component** | **Findings** | **Comments** |
|---|---|---|
| Efficacy-related Information | [ ] Yes [ ] No<br>[ ] Not mentioned | |
| Late Breaking Information | [ ] Yes [ ] No<br>[ ] Not mentioned | |
| Risk Management Plan | Is there a RMP [ ] Yes [ ] No<br>[ ] Not mentioned<br><br>Is this RMP submitted previously or attached with the PSUR [ ] Yes<br>[ ] No | |
| Risk-Benefit Analysis Report | [ ] Yes [ ] No<br>[ ] Not mentioned | |

**10. Overall Safety Evaluation**

| PSURs component | Findings | Comments |
|---|---|---|
| Drug interaction | [ ] Yes [ ] No<br>[ ] Not mentioned | |
| Overdose | [ ] Yes [ ] No<br>[ ] Not mentioned | |
| Abuse or misuse | [ ] Yes [ ] No<br>[ ] Not mentioned | |
| Pregnancy/ lactation | [ ] Yes [ ] No<br>[ ] Not mentioned | |
| Special populations | [ ] Yes [ ] No<br>[ ] Not mentioned | |
| Long-term treatment | [ ] Yes [ ] No<br>[ ] Not mentioned | |
| Medication errors | [ ] Yes [ ] No<br>[ ] Not mentioned | |
| Off label use | [ ] Yes [ ] No<br>[ ] Not mentioned | |

## 11. Conclusion

| PSURs component | Findings | Comments |
|---|---|---|
| MAH conclusion | | |

## Appendices

| PSURs component | Findings | Comments |
|---|---|---|
| Attached as specified by the guidelines | [ ] Yes [ ] No | |

**Appendix V: Key informant interview**

1. How many people work in your department……

2. What are their responsibilities?

   I. ……..
   II. ……..
   III. ……..
   IV. …….
   V. ……

3. What is their educational background?

……

……..

……

……

……

4. When are PSURs submitted?

……

……

5. Where are they submitted first and who receives them?

……

……

……

6. Who handles them first?

……
……

7. What do you do with them?

……

……

……

……

8. Do local MAH submit PSURs (infusion
Medicare)…….

10. Are there budgeted resources for PSUR review…….

11. Do you have any standard operating procedure or checklist to guide during PSUR review?
.....