REVIEW OF THE EFFECTIVENESS OF THE MEDICINES REGULATORY SYSTEMS IN ZAMBIA OVER THE PERIOD 1995 TO 2015

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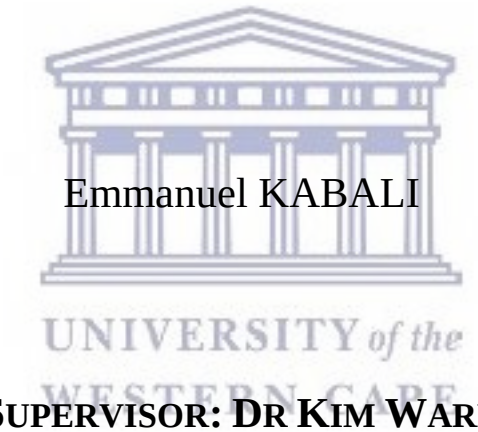

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RESEARCH PROJECT SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF
M.SC. IN PHARMACY ADMINISTRATION AND POLICY REGULATION

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ABSTRACT

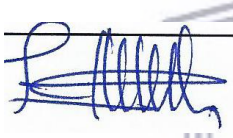
Due to inadequacy of data on the effectiveness of medicines regulatory systems in Zambia, this study was framed. The aim was to evaluate legislative provisions for medicines regulation under three legal-regulatory-frameworks in place over the period from 1995 to 2015. The study was structured in two distinct phases: the first involved document review of available legislation and secondary data relevant to the subject matter, covering the study period; the second involved a questionnaire survey for health practitioners to gather opinions on the effectiveness of the medicines regulatory systems in Zambia. Assessment of secondary data reported by Ministry of Health, and World Health Organisation on treatment outcomes and medicines regulation was conducted. Reviewed data showed relative reduction in incidence of some selected diseases of national importance. It was also evident that the regulatory systems had improved considerably over the study period. Responses from Health Practitioners and other players in the health and pharmaceutical sectors indicated that they were aware of medicines regulatory requirements, supported the need for medicines regulation, and indicated the need for regional collaboration and increased public awareness raising as means for improving current medicines regulatory systems. It was recommended that more comprehensive studies be undertaken to establish causal relationships between medicines regulatory systems, and disease outcomes. A further recommendation was made to implement more integrated information management systems in the Ministry of Health, and the Zambia Medicines Regulatory Authority.

KEYWORDS

Medicines Regulatory Systems, Effectiveness, Disease Outcomes, Review, Zambia.

DECLARATION

I declare that this thesis that I now submit for assessment on the programme of study leading to the degree Master of Science in Pharmacy Administration and Policy Regulation has not been submitted for the purpose of a degree at this or any other higher education institution. It is entirely my own work and has not been taken from the work of others, save the extent that such work has been cited and acknowledged within the text of my work. I agree to deposit this thesis in Hibernia College's institutional repository and the University of Western Cape's library or allow the library to do so on my behalf, subject to Irish and South African Copyright Legislation and Hibernia College Libraries and the University of Western Cape's conditions of use and acknowledgement.

Signed:  Dated: 13th March, 2018

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LIST OF ABBREVIATIONS

ADB	African Development Bank
ADRs	Adverse Drug Reactions
AMRH	African Medicines Regulatory Harmonisation Initiative
ART	Antiretroviral Therapy
CAP	Chapter (Capitulus)
CDH	Cancer Diseases Hospital, Lusaka ZAMBIA
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CI	Confidence Interval
CPGs	Compliance Policy Guides
CSD	Committee on Safety of Drugs
CTD	Common Technical Document
Cum.	Cumulative
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EEC	European Economic Community
EFTA	European Free Trade Association
EMA	European Medicines Agency
EU	European Union
EUC	European Union Commission
EUDRALEX	European Drug Regulatory Legislation
FDA	Food and Drugs Agency
FDAMA	Food and Drug Administration Modernization Act
GNC	General Nursing Council of Zambia
HIV/AIDS	Human Immuno-deficiency Virus/ Acquired Immune Deficiency Syndrome

HPCZ	Health Professions Council of Zambia
IND	Investigational New Drug
IRB	Institutional Review Board
MA	Marketing Authorisation
NEPAD	the New Partnership for Africa's Development
NMRA	National Medicines Regulatory Authority
No.	Number
OECD	Organization for Economic Cooperation and Development
PDUFA	the Prescription Drug User Fee Act
PQP	Pre-Qualification Program
PRA	Pharmaceutical Regulatory Authority
RIA	Regulatory Impact Assessment
SADC	Southern African Development Community
SRAs	Stringent Regulatory Authorities
StdDev	Standard Deviation
TM	Trademark
UK	United Kingdom
US	United States
USA	United States of America
WHO	World Health Organisation
ZAMRA	Zambia Medicines Regulatory Authority
Zazibona	A SADC Collaborative Medicines Registration Initiative, originated as a collaborative initiative amongst NMRAs from Zambia, Zimbabwe, Botswana, and Namibia

LIST OF KEY WORDS

The words included here, unless otherwise specified, carry the meaning here assigned:

Disease Outcome means observable disease patterns at Macro level (such as number of cases in a population per annum).

Effectiveness means ability to attain the set goals.

Medicines Regulation means activities under a legal and regulatory framework or system to ensure or assure that the medicines being made available for use meet the requirements in terms of quality, safety, and efficacy.

Regulatory Authority means a government institution given a mandate by law to undertake regulatory function on behalf of its government (example, the Zambia Medicines Regulatory Authority).

Review means to look critically over information for the purpose of elucidating specific evidence to fulfil a set objective.

Treatment outcome means results or consequences of the use of medicine(s) in combating disease

CHAPTER 1: INTRODUCTION

1.1. Background

This study attempted to evaluate the evolution of medicines regulatory systems in Zambia, focussing on the 20-year period from 1995 to 2015. Over this period, the principle laws providing a legal basis for medicines regulation was changed twice. The first change was initiated by recommendations made through the National Drug Policy published in 1999, which highlighted the need to put in place a better framework for regulation of medicines in Zambia. At that time, the law in force was the Pharmacy and Poisons Act CAP 299 of the Laws of Zambia (Government of Zambia, 1994). A process of reviewing this law resulted in the enactment of the Pharmaceutical Act, 2004 (Act No. 14 of 2004) of the Laws of Zambia (Government of Zambia, 2004). The new law provided a legal framework that was focused more on medicines, and excluded poisons that did not have medicinal application. The Pharmaceutical Act, 2004 was sooner reviewed as it was identified to be extensively bureaucratic, and a hindrance to investment in the sector. In 2013, after extensive consultation, the Pharmaceutical Act was repealed and replaced by the Medicines and Allied Substances Act, 2013 (Act No. 3 of 2013) of the laws of Zambia (Government of Zambia, 2013). The new law was acclaimed to have addressed most of the concerns raised by various stakeholders, and was being applied in the regulation of medicines and related health products at the time this study was conducted.

From an international perspective, medicines regulation developed mainly in response to major safety events involving medicines. This was illustrated in well documented literature, especially published in Europe and America (Carpenter, 2010; Williams, 2009; Rägo and Santoso, 2008; Ratanawijitrasin, 2002; Lipsky and Sharp, 2001; Abraham, 1997; Mortimer, 1995; Penn, 1979; Strathy *et al*., 1920). Most regulatory interventions were initiated through enactment of legislation and development of guidelines or standards. Over the years, there had been three types of regulatory systems implemented

in various regions of the world; Self-Regulation, National/Federal Regulatory Authorities, and Regional Regulation. Some functions undertaken by the World Health Organisation (WHO) may be construed as functions of a global regulatory system for medicines.

In the African Region, efforts over the preceding half century had included attempts to harmonise medicines regulatory systems across the continent through various regional initiatives. Sub-regional efforts had also been made, with some successes recorded. Some of the regional and sub-regional initiatives had varied impact on the implementation of medicines regulatory systems in Zambia. In order to evaluate the effectiveness of these medicines regulatory systems, various methodologies were employed, borrowing concepts from the WHO, and the Organization for Economic Cooperation and Development (OECD), who had conducted various assessments using tools and methodologies developed over many years. Factors considered in conducting assessment of effectiveness included the *"need for"*, *"make-up of"*, and *"impact of"* effective medicines regulatory systems (Rägo *et al.*, 2014; Lumpkin, 2012; Ratanawijitrasin, 2002).

1.2. Rationale

This study was intended to provide insight into regulatory systems for medicines in Zambia and their relationship with medical treatment outcomes. It was also intended to provide an overview of the evolution of the medicine regulatory systems over the period from 1995 to 2015. This study was necessitated by the scanty information available on this subject matter at the time.

1.3. Significance of Study

The study was exploratory, as very few studies had been undertaken in Zambia on this subject matter. In most documentation reviewed, there was little evidence showing comprehensive evaluation of the contribution of medicines regulatory systems to treatment outcomes.

1.4. Main Objective

The aim of this study was to review the effectiveness of the medicines regulatory systems in relation to disease treatment outcomes at the national level, over the period from 1995 to 2015.

1.5. Specific Objectives

The specific objectives were to:

1. Highlight the changes in the legal provisions for medicines regulation over the period from 1995 to 2015 in Zambia;
2. Evaluate how the changes to the laws impacted the regulatory framework; and
3. Investigate the relationship between changes in annual registration of medicines (as a proxy for changes in medicines regulatory frameworks), and changes in disease prevalence and treatment outcomes at the national level.

CHAPTER 2: LITERATURE REVIEW

2.1. Medicines Regulation

2.1.1. An International Historical Perspective

Medicines are products believed to be as old as mankind (Rägo and Santoso, 2008). Medicines regulation developed or evolved independently, mainly in response to safety incidences involving pharmaceutical products (Ratanawijitrasin, 2002). Major historical safety incidences associated with the development of medicines regulation included tragedies like the Sulphanilamide tragedy of 1937 – in which a formulation of an elixir was made in diethylene glycol without testing the mixture's toxicity, leading to 107 deaths out of 353 patients who ingested the Elixir (Lumpkin *et al.*, 2012; Rägo and Santoso, 2008); and the Thalidomide tragedy recognised in 1961 – in which the sedative drug first synthesized in 1953 was used to treat morning sickness in pregnancy in Europe (11 countries), Africa (7 countries), Asia (17 countries), and America (11 countries) between the period from 1956 to 1961, resulting in child birth defects observed in children born from the treated women (Kim and Scialli, 2011; Annas and Elias, 1999; Penn, 1979).

The point above was reinforced upon looking in detail at development of regulatory systems in key markets and regions in the world. In the United States of America (USA), for instance, major events led to responses towards development and escalation of pharmaceutical regulations. Some examples include the 1941 amendment to the Federal Food, Drugs and Cosmetics Act which required the US Food and Drugs Agency (FDA) to certify Insulin potency – a step on the road to demonstration of efficacy; and the empowering of the FDA to establish standards for product labelling in 1943, a mandatory requirement only found in the USA (Carpenter, 2010). These events resulted in 2 of the "four legs" of Drug Approval, the four being *Efficacy, Safety, Purity and Labelling* (Rägo and Santoso, 2008; Lipsky and Sharp, 2001).

Other events included the Thalidomide incidence in 1961 which led to the 1962 Kefauver-Harris amendments which contained requirements for "*the IND (Investigational New Drug) process"*, made adverse events reporting mandatory, clarified labelling and advertising requirement, and made requirements for inspection of manufacturing sites (Rägo and Santoso, 2008; Abraham, 1997; Penn, 1979). These were coupled with concurrent events such as the development of the United States Pharmacopoeia (USP), the Durham-Humphry Amendment of 1951, the Orphan Drug Act of 1983, the Waxman-Hatch Amendment of 1992, the *PDUFA* and the *FDAMA* (Thaul, 2007; Lipsky and Sharp, 2001).

In the United Kingdom (UK), major events which led to responses towards pharmaceutical regulations included the Drug and Stuffs Act (1540) issued under the Apothecary Wares, requiring that the manufacture of compounded preparations be made subject to supervision (Rägo and Santoso, 2008); the London Pharmacopoeia (1518) which laid down the standards for manufacture of pharmaceutical products (Rägo and Santoso, 2008; Penn, 1979); between 1864 and 1877, the Royal College of Physicians setup various medical enquiries into the safety of Chloroform in anaesthesia (109 fatalities), resulting in establishment of critical relationship between dose and effect (Penn, 1979); the batch-released requirement by the Medical Research Council on Salvarsan (Arsphenamine) imported from Germany to the UK in 1907, with encouragement for reports on incidences of jaundice and hepatic necrosis, possibly the first adverse drug reaction reports (ADRs) (Williams, 2009; Mortimer, 1995; Penn, 1979; Strathy *et al.*, 1920); and, the enactment of the Therapeutic Substances Act (1925) which provided for the regulation of the manufacturing of biological products, set standards for quality, labelling, manufacturing, factory inspections, and in-process controls (Penn, 1979).

European regional regulation also had some milestone events that were significant to the development of medicines regulatory systems. Besides the events highlighted above, some key early events included the development of the Florence Pharmacopoeia in 1498; the Dublin Pharmacopoeia in 1807; and the British Pharmacopoeia in 1864 (Penn, 1979; Urdang, 1951). However, up until the 1950s, there was no major concern in Europe with the way medicines were manufactured, placed on the market and controlled (Abraham and Lewis, 2000; Penn, 1979).

In 1957, 109 people died in France and 100 more suffered paraplegia as a result of Stalinon used for boil treatment. These adverse drug events were due to formulation error, where marketed batches contained five (5) times more of one of the active ingredients than the amount used in clinical trials. As a result, France introduced in 1959 more stringent expert committee review requirements. These additional controls may have accounted for why Thalidomide was never marketed in France (Abraham and Lewis, 2000). After the Thalidomide tragedy, the WHO recommended the monitoring of drug safety at a national level.

In 1963, the Committee on Safety of Drugs (CSD) in the UK was setup. The CSD had no legal powers as it operated in voluntary cooperation with industry. The expertise for a central authority was assembled, which included the WHO, USA, and Canada. The CSD continued in existence until the Medicines Act of 1968 was enacted (Penn, 1979). After setup of the CSD, the yellow card scheme, a spontaneous reporting of ADRs, was introduced in 1964 (Santosh and Tragulpiankit, 2011). In 1965, the first EEC Directive to Control Medicines – Directive 65/65/EEC – was introduced. In 1971, following a pilot project, the International Drug Monitoring Programme was initiated, and, following an agreement signed between WHO and the government of Sweden in 1978, the WHO Drug Monitoring Centre based in Uppsala, Sweden was established as an International System for monitoring adverse reactions (Olsson, 1998).

2.1.2. A Perspective on Types of Regulatory Systems

To have a good perspective on types of regulatory systems, a brief review was done looking at the types of systems employed by countries or regions considered to have stringent regulatory authorities (SRAs). Three types of regulatory systems – Self-Regulation, National/Federal Regulatory System, and Regional Regulatory System – are discussed hereafter.

2.1.2.1. Self-Regulation

Self-regulation referred to a system where the regulated entities were allowed to manage a system of regulation amongst them. In the case of the pharmaceutical industry, players may develop a self-regulation system in which members of the group targeted for regulation organize some means of mutual control among themselves (Abbott, 2009; Ratanawijitrasin, 2002). From an international perspective, national regulatory systems may be considered as a form of self-regulation (Abbott, 2009).

2.1.2.2. National/Federal Regulatory Authorities

National/federal regulation is a system employed at national level to provide regulatory oversight for medicines. There were various models of national regulatory systems, amongst them:

- Single national regulatory Authority,
- Decentralized semi-autonomous (provincial/state/county) regulatory authorities with a National (Central) Regulatory Authority providing oversight.

The FDA in the United States of America (USA), a good example of a national/federal regulatory system, was responsible for regulation of foods and drugs. Its role was summarised in its mission which outlined the role of "*Protecting the public health by assuring that foods are safe, wholesome, sanitary and properly labelled. Human and veterinary drugs, and vaccines and other biological products, and medical devices intended for human use are safe and effective; Assuring cosmetics and*

dietary supplements are safe and properly labelled; Protecting the public from electronic product radiation; Regulating tobacco products; Advancing the public health by helping to speed product innovations; and, Help the public get the accurate science-based information they need to use medicines, devices and foods to improve their health" (US Food and Drugs Administration, 2017a; Maisel, 2008, pg. 987).

The scope of products regulated by the FDA included animal and veterinary products, dietary supplements, drugs, and foods. Others were medical devices, radiation-emitting products, tobacco products, vaccines, blood, and biologicals.

The FDA was established in 1906 with the passage of the 1906 Pure Food and Drugs Act, and it is the oldest drug regulatory authority in the world (US Food and Drugs Administration, 2017b). It progressed from the enforcement arm of the US Department of Agriculture to the scientific, technical, administrative and bureaucratic agency (US Food and Drugs Administration, 2017b). It enforced laws enacted by the US Congress and regulations established by the agency to protect consumers' health, safety, and pockets. The Federal Food, Drug and Cosmetics Act, with numerous amendments, was arguably the most extensive law of its kind in the world (Noah, 2008). Labelling was the "Fourth Arm" of drug approval, and much of the power of the FDA was exercised by its control of what a label said, based on a principle common in US commerce (Rägo and Santoso, 2008; Lipsky and Sharp, 2001). Although the FDA had been an effective regulator, the fall-out from the Cox-2 Inhibitor withdrawals by Merck in 2005 was arguably the most tumultuous event at the FDA in its recent history (Topol, 2004).

The hierarchy of FDA authority (legal framework) included: (1) Laws enacted by US Congress, frequently as amendments to the Federal Food, Drug and Cosmetic Act; (2) Regulations implemented laws, such as CFR Title 21; (3) Guidances were "informal" documents to clarify regulations, and were not binding of Sponsors or the FDA; (4) Compliance Policy Guides (CPGs) were an organised

repository for statements of FDA compliance policy; (5) Advisory Opinions came from interactions such as end-of-phase II meetings, and pre-IND meetings (in relation to clinical trials during drug development process); and (6) Informal Advice involved ad-hoc communications during drug development between FDA and Sponsor.

The FDA was part of the Department of Health and Human Services, headed by a Commissioner who was a political appointment with deputy heads for each of the centres or offices. The FDA had nine (9) divisions and it was a federal agency covering all the United States of America (US Food and Drugs Administration, 2017b).

2.1.2.3. Regional Regulation

Regional regulation was a system employed at regional or sub-region level to provide regulatory oversight for medicines. Although regional regulatory systems covered several countries, two types could be differentiated, being Regional if it had continental coverage or Sub-regional if it covered countries of a specific sub-continent (Abbott, 2009). The European Medicines Agency (EMA) and the European Directorate for the Quality of Medicines (EDQM) under the European Union Commission (EUC) were a good example of a regional regulatory system.

The European Economic Community established the European Economic Area (EEA) in 1957, which united the 27 EU member states, and Iceland, Liechtenstein and Norway (Dinan, 2005; Baldoni, 2003). In 1994, the EEA agreement allowed the member countries access to the single EU market under the same rules that apply to full EU members, but they had to adopt all EU single market legislation, except those that related to agriculture and fisheries; and make a financial contribution (Baldoni, 2003). Iceland, Liechtenstein and Norway were also members of the European Free Trade Association (EFTA), along with Switzerland (Ito and Krueger, 1997).

The EU pharmaceutical law was in "the Rules Governing Medicinal Products in the European Union", edited by EUDRALEX (Lorenz, 2008). These Rules were contained in the Legislative texts (Regulations and Directives) contained in Volume 1, and in the Supportive guidelines (Human and veterinary medicines) contained in Volumes 2 to 10 (European commission, 2017a). The hierarchy of EU legislation (legal framework) included Primary Law (Treaties) ratified by National Parliaments, and Secondary Law - *Regulations* (Council or Commission regulations) which were binding in all member states and superseded all other legislation in the specific regulatory area at national and EU level; *Directives* which bound member states, companies, and individuals; *Decisions* which were binding in all aspects for those addressed (member states, companies, and/or individuals); and *Soft Laws* which were not legally enforceable (recommendations, opinions, communications, and guidelines) (European commission, 2017b).

The scope of products regulated included Medicinal Products for human and veterinary use intended to be placed on the market and prepared by an industrial process (included homeopathies, herbals, gene and cell therapy, and radiopharmaceuticals). However, it excluded medical devices, whole blood, food supplements, and cosmetics which were covered in separate EU legislation. In case of borderline products, the provision in legislation for medicinal products prevailed.

The EU regulatory system is composed of a regional regulatory body (bodies) and individual national regulatory agencies (Lorenz, 2008).

2.1.2.4. Global Regulation

Although the WHO was not a regulatory agency, it had a global mandate which was pertinent to medicines regulation in member states. The WHO had a fourfold role in medicine regulation (Rägo and Santoso, 2008), which was: "*Issuing necessary norms and standards through its Expert committees and Expert committee-like bodies; Supporting regulatory capacity building leading to*

implementation of medicines regulation at national level, and its harmonisation on regional and global level; Ensuring the quality, safety and efficacy of limited high public health value essential medicines and vaccines through "Prequalification" – a regulatory activity mimicking medicines regulation; and, Plays a very important role for exchange of regulatory information amongst medicines regulators" (Rägo and Santoso, 2008, pg. 74).

The WHO provided model regulations and guidelines for use in developing and implementing medicines regulatory systems. Although these regulations and guidelines were available to all WHO member states, adoption and implementation of these at national and regional level was voluntary, and dependent on consensus (Ratanawijitrasin, 2002). The WHO published an International Pharmacopoeia, a collection of quality specifications for pharmaceutical substances for reference by any WHO member state. It focused on substances included in the WHO Model List of Essential Medicine (World Health Organisation, 2015).

2.1.3. A Perspective on the African Regional Regulatory Systems

Africa had had a regional political governing body, the African Union (previously the Organisation of African unity) since 1963 (SAHO, 2016). This body spearheaded the harmonisation of medicines regulatory systems through initiatives like the African Medicines Regulatory Harmonization (AMRH) Initiative launched in 2009 (Ball et al, 2016) and the New Partnership for African Development (NEPAD) (AMRH Consortium, 2010). However, it was difficult to say that there was a regional medicines regulatory system in place in Africa. Developments, such as the approval of the model medicines regulation law in 2015 were good signs of things to come (AMRH Consortium, 2010). However, the impact and success of the model law were yet to be seen.

Sub-regional initiatives for medicines regulation were also in place, with varied success scored at the time. In East Africa, the Common Technical Document (CTD) format for submission of medicine

information for purposes of regulatory review prior to issuance of marketing authorisation (MA) was adopted around 2013. A total of six countries, namely Tanzania, Kenya, Uganda, Zanzibar, Burundi and Rwanda, were party to the initiative. This offered opportunity for capacity building and work sharing.

In the Southern Africa Development Community (SADC), similar initiatives had been undertaken for more than ten years at the time, with limited successes scored. The most recent development was the Zazibona initiative for regulatory work sharing, which appeared to gain momentum as an initiative open to all SADC member states. The scope of the collaborative initiative involved work sharing of evaluation dossiers in CTD format, conducting of joint inspections of medicines manufacturing facilities to evaluate compliance to current good manufacturing practices (cGMP), and capacity building. The initiative offered hope of good success, and received overwhelming support from the WHO, through the PQP and capacity development programs (Masekela, 2016).

2.1.4. A Perspective on the Zambian Regulatory Systems

The Zambia Medicines Regulatory Authority (ZAMRA) was responsible for medicines regulation in Zambia. Its role was summarised in the mission statement: *"Mission is to effectively regulate and control medicines and allied substances being made available to the Zambian population to ensure conformity to set standards thereby safeguarding public health"* (Zambia Medicines Regulatory Authority, 2015b, pg. ix). The scope of products regulated by ZAMRA included medicines for human and veterinary use; medical devices including in-vitro diagnostic; vaccines and biologicals; and medical supplies (referred to as allied substances).

Although the legislation that brought ZAMRA into existence was enacted in 2013, the Regulatory Authority had been in existence long before. Under the Pharmacy and Poisons Act CAP 299 of the laws of Zambia, there was a provision for the Pharmacy and Poisons Board, which was an advisory

body to the Minister of Health on medicines regulatory issues. This was the case until the Pharmacy and Poisons Act was repealed in 2004, replacing it with the Pharmaceutical Act, 2004 of the laws of Zambia. The Pharmaceutical Act brought into existence an autonomous National Medicines Regulatory Authority (NMRA), with a mandate to regulate the products as outlined above.

The hierarchy of the legal framework included Acts enacted by the Parliament of Zambia to provide legal mandate, Regulations issued by the Minister of Health to provide further clarity to the principal law, and Guidelines issued by the Authority to provide more detail and clarity to the provisions of the Acts and Regulations.

ZAMRA, as a Statutory Board, was under the Ministry of Health. The Minister of Health delegated the regulatory functions to the Authority through an Act of Parliament. The Minister was responsible for appointing the Board of the Authority, which was given the mandate to appoint the Director General and such other staff as it deemed necessary for the carrying out of the Authority's mandate. ZAMRA's mandate covered the whole country, and it was the only competent authority responsible for medicines regulation in Zambia.

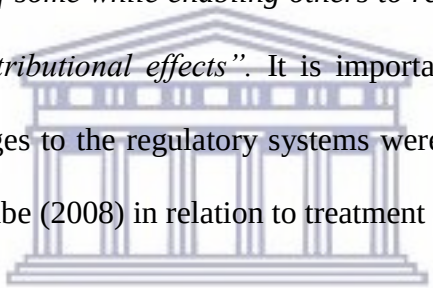
2.2. Evaluation of Regulatory Systems

2.2.1. Effectiveness of Regulatory System

2.2.1.1. Effective Medicines Regulatory System

A regulatory system is necessary to safeguard the aspirations of an individual, a group of people or institutions that have a common goal, but not necessarily the same ideologies. Cafaggi and Pistor (2013, pg. 2) indicated that *"The purpose of public regulation is to create common rules that govern a specific issue or domain … and command compliance without express consent by those operating in the relevant domain".* This simple purpose statement portends the major components required in

a regulatory system for it to be effective. To command the necessary compliance in any domain, a system must have specific activities of players in a domain which it is attempting to address. An effective medicines regulatory system must, therefore, have a scope specific to applicable areas of medicines, and should outline its reach and limits. It should also make provisions to ensure capacity to enforce its provisions and also elicit the necessary compliances by all players and stakeholders. Cafaggi and Pistor (2013, pg. 2) further provided more insight on the requirements stating that *"establishing a regulatory regime entails defining the issues and actors that shall be regulated, the means and ends of regulation, access to rule making or amendment processes and sanctions for non-compliance. Every regulatory regime exerts differential effects on regulators, the direct targets of regulation (the regulated), its beneficiaries, as well as others who are indirectly affected by it. Regulation restricts the choices of some while enabling others to realize their preferences. As such, every regulatory regime has distributional effects".* It is important to attempt retrospectively to establish the purposes why changes to the regulatory systems were made in Zambia and a case in point is as outlined by Sipilanyambe (2008) in relation to treatment regimens for Malaria.



2.2.1.2. Need for Effective Medicines Regulatory System

On this subject matter, it could be said that "if you cannot afford any form of regulatory system as a nation, afford a system for medicines regulation". It can also be said that "medicines security and safety is a key player in assuring national security, productivity, longevity and development". The views expressed above are reinforced by Rägo *et al* (2014, pg. 69) who stated that *"Drugs are not ordinary consumer products as they directly affect the lives of people who take them…complex products…their quality cannot be seen by looking at them. They can restore…health, but all medicines can have adverse effects"*. It is the protection of the patient from the potential adversities that may arise from the use of medicines that makes effective medicines regulation an important component of governance, both at national and international levels. Although governments are responsible for the protection of the people that fall within their jurisdictions, it is an acceptable norm

in this modern era that the function of protecting patients from harm caused by medicines is the direct (albeit delegated) responsibility of national medicines regulatory authorities (Rägo *et al.*, 2014).

2.2.1.3. Make-up of Effective Medicines Regulatory System

Although it is the responsibility of the national medicines regulatory authorities to protect public health from harms of medicines, effective regulation requires full participation of various stakeholders. Key players as outlined by Rägo *et al.* (2014) include manufacturers, importers, exporters, consumers, health-care professionals, researchers, and other government institutions (besides NMRA). When regulators are left to act in isolation, the regulatory systems cannot be effective, as the regulator has limitations in the reach of their decisions and scope of enforcement. The outcome of such regulatory environments is most often the blaming of the regulators of having failed the public by either allowing medicines whose benefits do not outweigh the risks paused on users; or, preventing medicines with clear benefits to patients, especially where alternative treatments are lacking, from being placed on the market (Lumpkin, 2012). A list of parameters, that should be inherent in all the stakeholders involved in the medicines' development and supply chain, must be met in order for a medicines regulatory system to function effectively (Rägo *et al.*, 2014; Ratanawijitrasin, 2002).

2.2.2. Impact of Effective Medicines Regulatory Systems

The impact of major focus for effective medicines regulation is public health protection. However, more effective medicines regulatory systems aim at being both protector and promotor of public health (Lumpkin, 2012). Specifically, an effective medicines regulatory system should have adequate capacity to undertake rigorous scientific assessment of medicines and assure the public that they are accessing safe, effective medicines of good quality and meeting current international regulatory standards (Rägo *et al.*, 2014).

2.2.3. Methods of Evaluating Effectiveness of Medicines Regulatory Systems

Apart from WHO audit reports and EU assessment reports, no published evidence could be found to show that such a study had been undertaken before, hence necessitating this study, albeit an exploratory one. However, ideas were borrowed from the WHO, which had developed guidelines for assessing national medicines regulatory systems (World Health Organisation, no date). Although the WHO carried out assessment of regulatory systems in various countries, the scope of their assessments did not adequately capture views and opinions of all stakeholders as outlined above, mainly due to resource and time limitations, and lack of willingness of some to participate, since such assessments were conducted based on voluntary request of countries and stakeholders. Therefore, it was prudent to utilize such WHO initiatives and tools as a basis for conducting further assessments and studies that can be more detailed, focused and tailored towards the local set-up and specific needs.

2.2.4. Model Evaluation Tools

2.2.4.1. WHO Evaluation Tool

The WHO assessments were tailored to focus on specific areas outlined in their data collection tools and applicable guidelines (World Health Organisation, 2007). In addition, the assessments made reference to previous assessments conducted in a given country, but rarely delved into detailed comparative analysis of deficiencies found and trends seen in series of assessments. It was therefore a good basis for conducting a review of effectiveness of regulatory systems over a period of time, as was proposed in this study, to utilize several WHO country assessment reports covering the period under review. For Zambia, WHO had conducted several assessments of the regulatory systems, and generally found that there were some improvements in the regulatory systems in the country (Handema *et al.*, 2012; World Health Organisation, 2012). However, the current systems had various limitations and deficiencies. It was the intention of this study to utilize the results from these assessments to provide a consolidated review of the medicines regulatory framework in Zambia.

2.2.4.2. OECD Evaluation Tool

The OECD had developed tools for evaluation of regulatory systems. These tools were not specific to any particular area of regulation, but covered the general components of regulatory systems. The OECD had conducted regulatory assessments in OECD member countries using its tools such as the assessments conducted in 1995, 2005 and 2008 (OECD, 2009). The OECD assessment tools also prescribed parameters for conducting regulatory impact analysis (RIA), and were useful in developing country-specific tools for use in assessment of regulatory systems.

2.2.4.3. Regulatory Impact Assessment Tools

Regulatory Impact Assessment (RIA) is a system of assessing risks against the benefits in order to make informed decisions on whether to implement new regulatory interventions or retain old ones. The government of the republic of Zambia had recently adopted the use of RIA in attempts to promote development and implementation of smart regulatory policies and systems. Although RIA was currently being used to a limited extent in Zambian policy development, the legal framework as provided by the Business Regulatory Act, 2014 (Act No. 3 of 2014) of the laws of Zambia was still being operationalised. The Southern African Development Community (SADC), through the SADC Technical Regulation Liaison Committee (SADCTRLC), promulgated Regulatory, and Risk and Impact Assessment (RIA) Guidelines (Khumalo, 2015), which were later published in 2015. RIA tools were useful in assessing regulatory systems, providing guidance on key questions.

Although the WHO had conducted some evaluations of national regulatory systems in Zambia, it was felt that there was need for further review and assessment of the regulatory systems in Zambia using studies such as this one, to also capture opinions of various stakeholders and players in the medicines supply chain. This would provide opportunities for openness, awareness, consultation and continuous improvement of the existing medicines regulatory systems.

CHAPTER 3: METHODOLOGY

3.1. Study Design

A retrospective cross-sectional mixed study design was used, because the specific objectives of the study could not be realized by utilising quantitative or qualitative data only (Ells, 2011). Therefore, the study employed both quantitative and qualitative survey data collection techniques to enable the complete and synergistic utilization of data (Wisdom and Creswell, 2013; O'Cathain *et al.*, 2007). Specifically, the study involved the following two distinct data collection phases:

1. Document review of legislation for medicines regulation, related policy documents, strategic plans, annual reports for Ministry of Health and assessment reports for national medicines regulatory systems covering the study period; and
2. Questionnaire survey involving health care professionals and medicines supply chain players.

All data collection in the two phases was carried out by the same person, thereby removing the element of variations in application of the methods employed. The methods applied were selected particularly because they were cost-effective, and they did not require large numbers of human resource (could be implemented by one person).

3.1.1. Document Review

This first phase of detailed document review of available literature was used to assess the legislative provisions contained in the three aforementioned pieces of legislation using an adapted evaluation template. The review was intended to determine the appropriateness of these laws for medicines regulation, in comparison with the recommended model law for medicines regulation at national level. The data extraction tool used (see Appendix 1) was customised from the WHO assessment tool and the OECD tool for regulatory impact assessment (OECD, 2008; World Health Organisation,

2007). The tool was populated with scores based on the presence of provisions in the specific legislation, coupled with the level of implementation of specific regulatory interventions.

For the detailed data extraction tool, six levels of score categories were used (see *"Key"* in Appendix 1). Provisions of the three pieces of legislation were collated and summarised in a matrix showing the seven minimum functions of a national medicines regulatory authority, as recommended by the WHO (Ratanawijitrasin, 2002). The level of implementation was categorised into six different categories based on the level of implementation of each specific function. The six categories were: 1. Function not implemented, 2. Function minimally implemented, 3. Function implemented by a dedicated individual member of staff, 4. Function implemented by a limited staff complement in a designated unit, 5. Function implemented by a limited staff complement although a full departmental structure is well outlined but not filled, and, 6. Function implemented by a full staff complement in a well outlined departmental structure.

The data extraction tool was designed to be used by a person with a basic qualification in medicine, and required minimal appreciation of the regulatory requirements for medicines, and an understanding of the structure of the legislative system in Zambia. The researcher met both requirements, and was able to utilise the tools to collect data to the extent possible in the given timeframe.

Other available literature was reviewed during this phase, in order to establish patterns in the regulatory systems for medicines; prevalence of diseases such as HIV/AIDS, Malaria and Tuberculosis in Zambia; and changes in the treatment outcomes for selected diseases over the period under study. National disease prevalence data for HIV/AIDS, malaria, tuberculosis, hypertension, and cancer was extracted from the Ministry of Health (MoH) Health Management Information System (HMIS) by senior M&E officers. Data extraction was based on list of parameters, mainly the

disease incidence, morbidity, and mortality rates. Data on national drug supply, and vaccination levels were collected for the years within the period under review. The findings from this phase were used to compare the changes in the laws against the changes in health outcomes.

3.1.2. Questionnaire Survey

The second phase involved administration of a questionnaire survey to various categorises of healthcare professionals and medicines supply chain players in Zambia. The survey was aimed at capturing opinions of these groups of people about the appropriateness of the medicines regulatory systems in Zambia, how the regulatory framework had evolved over the period under review, and whether the changes in the regulatory systems had impacted (positively or negatively) the treatment outcomes for selected diseases. In addition, their opinions on the best mode of medicines regulation were captured. The survey was conducted by delivering electronic copies of the questionnaire to respondents within Zambia through e-mails generated via Survey Monkey™. The questionnaire (see Appendix 4) was developed by the researcher, and it composed of both open-ended and closed-ended questions to capture respondents' opinions. It was pretested on ten individuals, and the responses were used to develop the data entry tool, used to process the responses prior to statistical analysis. The questionnaire was also reviewed by the ethics review committee, assuring suitability for use.

3.1.2.1. Sampling

The target study population was healthcare professionals registered with the Health Professions Council of Zambia (HPCZ) and the General Nursing Council of Zambia (GNC).

3.1.2.1.1. Sample Size Determination and Selection

The total number of health practitioners and para-medicals registered with the HPCZ was about 13,000 (HPCZ, 2014). The total number of nursing professionals registered with the GNC at the time of the study was about 25,000.

For purpose of sample size determination, the desired confidence level was 95%, while the margin of error was 5%. Using the formulae for sample size for a finite study population – *Sample Size = (Z-score)² * StdDev*(1-StdDev) / (margin of error)²* (Smith, 2015) – the minimum required samples from the two registers were 370 from HPCZ registered practitioners, and 373 from the GNC registered nursing professionals.

Two levels of sampling were done from the information provided by the professional regulators. The first step was to purposively select registered professionals who had an e-mail address included in the registered. The second step was to randomly select professionals using a random number sampling tool available at https://www.randomizer.org/, to draw the required sample size from each register.

3.1.2.2. Questionnaire Survey process

Selected respondents were contacted by e-mail and provided with copies of the Respondent's Information Leaflet, consent form, and the questionnaire. An initial sample of 783 was picked, composed of 383 health professionals (from HPCZ register) and 400 nursing professionals (from GNC register). An additional sample of 264 composed of health professionals was made, since a total of 331 e-mails initially sent were not delivered. The total number of questionnaires sent was 1,047, of which 716 were successfully delivered.

3.1.1. Data analysis

Disease outcome continuous data were collated and processed to generate graphical illustrations of disease patterns over the period under review. Incomplete datasets were excluded in the analysis. Continuous data on medicines registration by ZAMRA were collated and graphically illustrated. Correlation of continuous data on national disease outcomes and medicines registration was assessed using the Pearson's test. Qualitative data from the review of legislation and assessment reports were analysed by using scores to determine the level of compliance of the medicines regulatory systems in Zambia to the recommended components of effective medicines regulatory systems. The analysis of

findings was done in an attempt to demonstrate whether there was a relationship between changes in regulatory systems and changes in disease outcomes at national level.

Data from the questionnaire survey was automatically collated by the online statistical package (Survey Monkey™) and individual survey records were generated and entered in Epi Info™. Results from the survey were analysed using frequencies for categorical and ordinal data to generate descriptive statistics. All analysis results were included in the results and discussion sections. The student conducted all the components of this research, in consultation with the assigned supervisors.

The flow diagram below (Figure 1) summarizes the methodology.

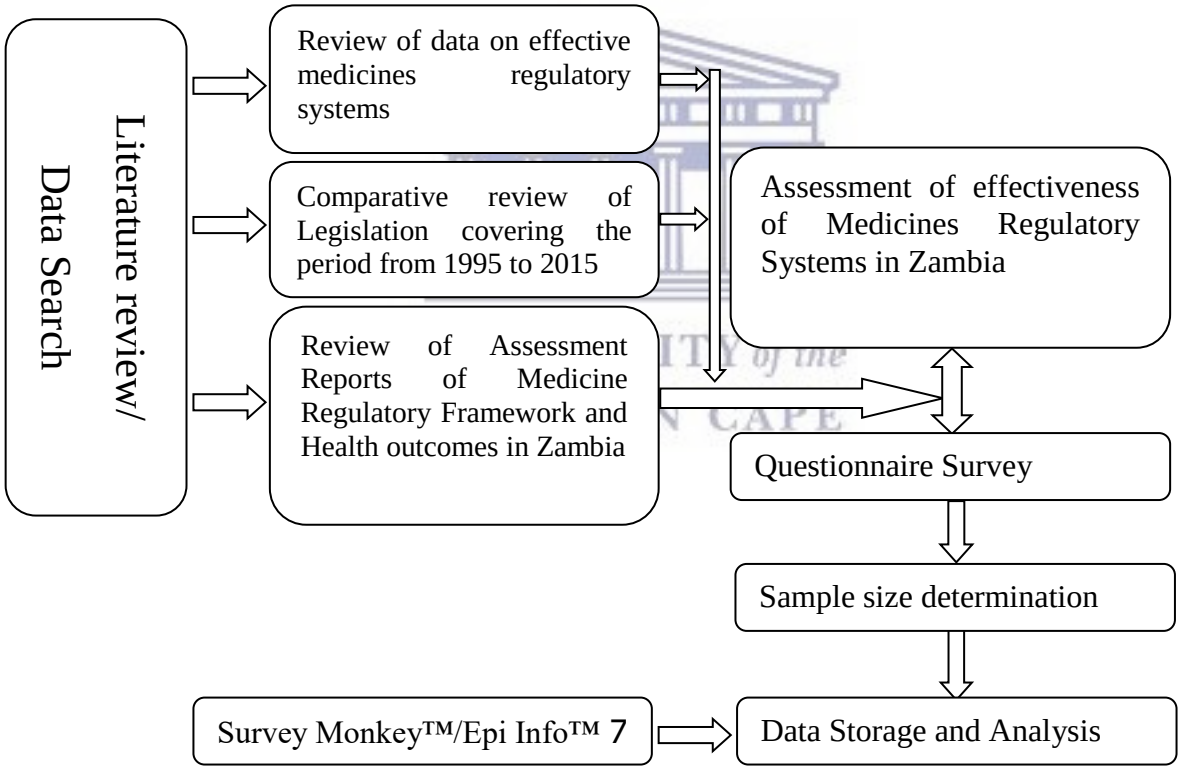


Figure 1: Flow diagram summarizing the methodology

3.2. Ethical Considerations

The study involved health service providers, and did not employ any interventions such as use of medicinal products or collection of biological samples. It was considered that there were no major

Research Participants' Welfare issues to be addressed. In the sample selection procedure, the researcher accessed information of health professionals and medicines supply chain personnel through the Professional Regulatory Agencies. Accessing this information raised a potential ethical issue, as the researcher accessed, processed and analysed the data about participants and from their responses to the questionnaire survey. Data collected was only handled by the researcher and for this study's purposes only. Personal information collected in the course of the research was treated with high level of confidentiality, and was protected at all times. None of this information was shared with any person. Participants were assured that their participation in the survey would have no impact on their relationship with ZAMRA or the MoH. No conflict of interest was foreseen as the study was wholly funded by the student. The student had to overcome the challenge of making opinions on the activities concerning his place of work. Ethical Clearance was sought from, and granted by the University of the Western Cape Senate Research Committee, and ERES Converge IRB of Lusaka, Zambia.

CHAPTER 4: FINDINGS, ANALYSIS AND DISCUSSION

4.1. Results and Analysis

4.1.1. Results from Desk Review of Legislation

Appendix 1 shows the comparison of key legal provisions for medicines regulation as contained in the Pharmacy and Poisons Act CAP 299, the Pharmaceutical Act, 2004, and the Medicines and Allied Substances Act, 2013 of the laws of Zambia. Table 1 shows the level of implementation of the *"seven minimum functions of a national medicines regulatory authority"* under the three pieces of legislation over the period under review.

Table 1: Matrix showing comparison of the level of implementation of the seven minimum functions of a national medicines regulatory authority under the 3 pieces of legislation

S/N	Description of minimum National Medicines Regulatory Authority functions	Pharmacy and Poisons Act CAP 299	Pharmaceutical Act, 2004	Medicine and Allied Substances Act, 2013
1.	Ensuring that all medicines manufacturing, importation, exportation, wholesale and distribution establishments are licensed. Activities and premises must comply with Good Manufacturing Practices and Good Distribution Practice requirements.	+++	++++	++++
2.	Before medicines are marketed, assess their safety, efficacy and quality	+	++++	++++
3.	Monitoring the quality and safety of medicines on the market to prevent harmful, substandard and counterfeit medicines from reaching the public.	+	+	++++
4.	Regularly inspect and control the informal market, including e-commerce, to prevent illegal trade of medicines	+++	+++	+++
5.	Monitor advertising and promotion of medicines, and provide independent information on their rational use to the public and professionals	-	++	+++
6.	Participate in sub-regional and regional regulatory networks and international meetings of drug regulatory authorities to discuss issues of mutual interest and concern, facilitate timely exchange of information and promote collaboration	-	+++++	+++++
7.	Monitor and evaluate performance to assess if perceived regulatory objectives have been met, to identify weaknesses and take corrective action	-	+	+

Key:

- \- Not Implemented
+ - Minimally Implemented
++ - Implemented by an individual member of staff
+++ - Implemented by a limited staff complement in a designated Unit
++++ - Implemented by a limited staff complement although a full Departmental Structure is well outlined but not filled
+++++ - Implemented by a full staff complement in a well outlined Departmental Structure

A trend of improvement in regulatory systems in Zambia was observed with each subsequent change in legislation. The most significant improvements were seen following the enactment of the Pharmaceutical Act, 2004 (Government of Zambia, 2004), with the NMRA participating in most collaborative initiatives at Sub-regional, Regional and Global level. The leading role played by

ZAMRA and her counterpart NMRAs in spearheading the Zazibona collaborative initiative attests to this. Monitoring of quality and safety of medicines on the market improved significantly after enactment of the Medicines and Allied Substances Act, 2013 of the laws of Zambia (Government of Zambia, 2013), as a new organisational structure was put in place, which provided for a designated unit responsible for post-marketing surveillance (PMS) activities. However, the structure was not fully implemented at the time of the study. Implementation of a system for monitoring advertising and promotion of medicines, and inspection and control of informal market, e-commerce and illegal trade in medicines was implemented to a limited extent. Monitoring and evaluation activities to assess performance and level of attainment of institutional goals were minimally implemented.

4.1.2. Review of Literature on Health Outcomes and Peer Assessment of Medicines Regulatory Functions

4.1.2.1. Changes in Prevalence of HIV, TB and Malaria over the period 2005 to 2015

Figure 2 shows the number of individuals that were tested for HIV in each year, and the number of HIV patients that were taking ART medication in each year.

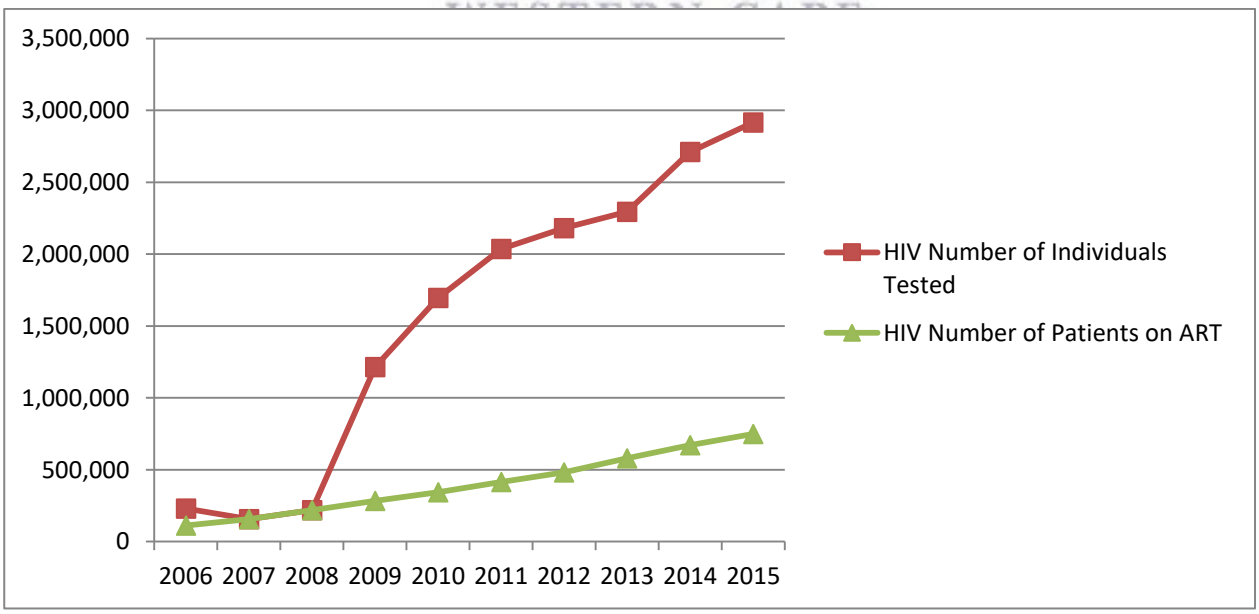


Figure 2: National figures for HIV tests and enrolment onto the ART program ***(Source: M&E Section, Directorate of Policy and Planning, Ministry of Health, Zambia)***

There was a sharp upward increase in numbers of individuals tested for HIV from 2008, and a steady and consistent increase in the number of patients on ART annually. Considering that any person can be infected with HIV, it was expected that the upward trend in the number of individuals tested could continue in subsequent years with the possibility of universal coverage, since the population of Zambia at the time of the study was estimated at slightly over 15Million. The upward trend in number of patients enrolled on ART was seen to have limiting factors such as the number of individuals found to be reactive to the HIV test, and the cost of medication, among others.

Figure 3 below shows the incidence of TB notification, the incidence of malaria, and malaria-related case fatality in each year. There was a notable downward trend in the incidence of TB notifications and a reduction in numbers of TB cases over the reported period (also see applicable table in Appendix 2).

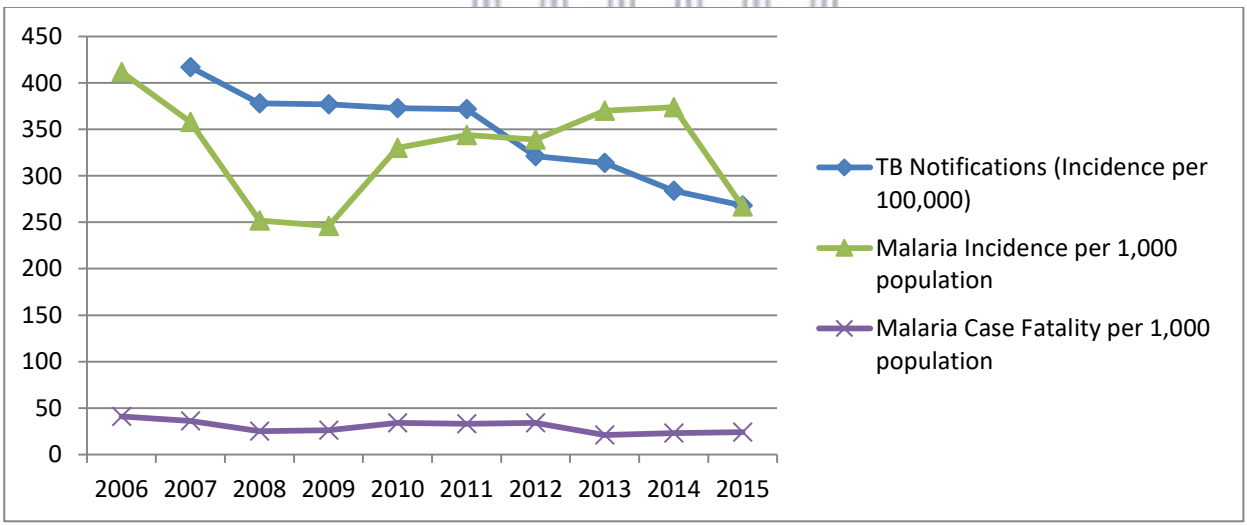
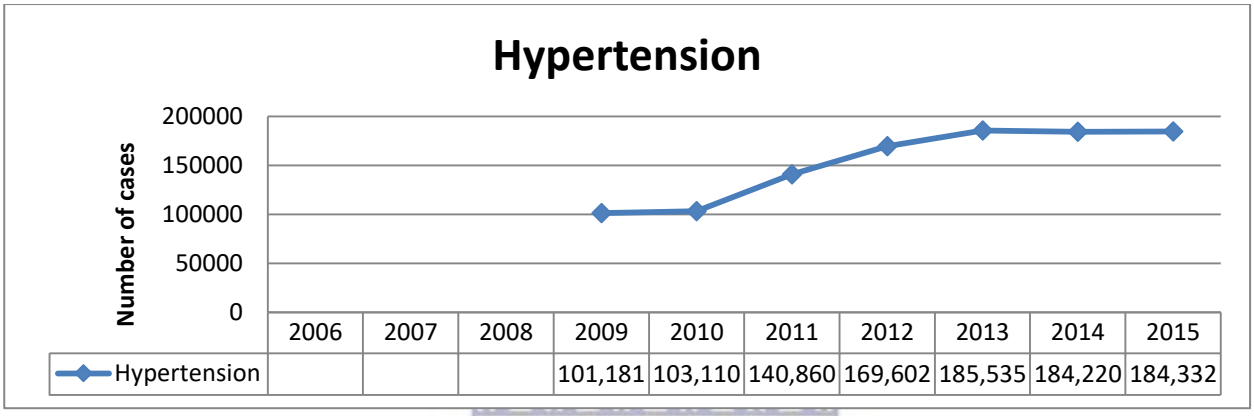


Figure 3: National TB incidence, and Malaria incidence and case fatality ***(Source: M&E Section, Directorate of Policy and Planning, Ministry of Health, Zambia)***

Although the trend in the annual incidence of malaria was erratic, it showed a net reduction over the reported period. However, there was a clear and steady reduction in the malaria-related annual case fatality over the same period.

4.1.2.2. Changes in Prevalence of selected non-communicable diseases over the period 2006 to 2015

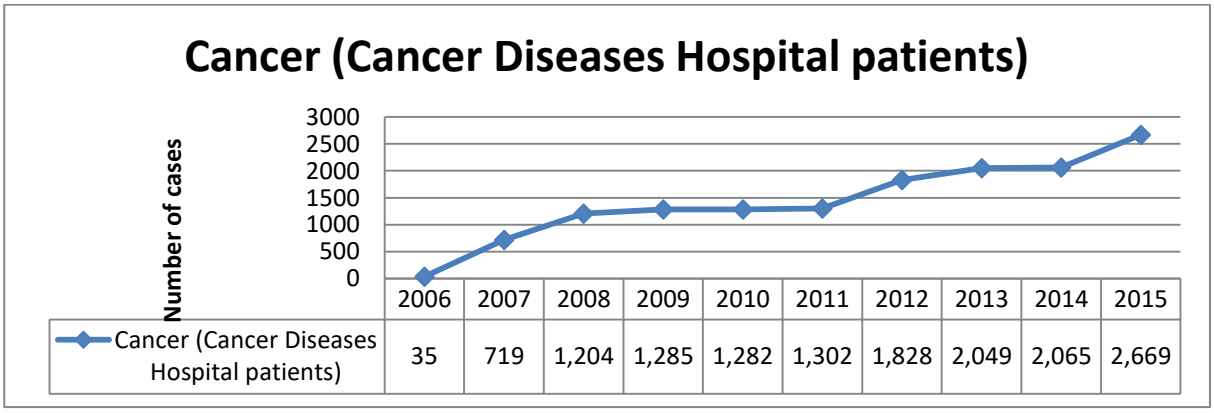
Figure 4 shows the number of cases of hypertension attended to during each year from 2009 to 2015 as figures for the years prior to 2009 were not available. The trend over this period showed an increase in cases of hypertension, which appeared to peak and stabilised from 2013 onwards.



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Hypertension				101,181	103,110	140,860	169,602	185,535	184,220	184,332

Figure 4: National cases of Hypertension ***(Source: M&E Section, Directorate of Policy and Planning, Ministry of Health, Zambia)***

Figure 5 shows the number of cancer cases reported at the Cancer Diseases Hospital, located within the University Teaching Hospital (UTH) grounds, in Lusaka.



	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Cancer (Cancer Diseases Hospital patients)	35	719	1,204	1,285	1,282	1,302	1,828	2,049	2,065	2,669

Figure 5: Cancer cases recorded by the Cancer Diseases Hospital, Lusaka ***(Source: M&E Section, Directorate of Policy and Planning, Ministry of Health, Zambia)***

A trend of exponential increase in reported cancer cases was demonstrated, with a dramatic increase in cases from 35 in 2006 to 2,669 in 2015.

4.1.2.3. Changes in Availability of Drugs in Selected Health Facilities over the period 1995 to 2015

See Appendix 2 for some available data, which was incomplete at the time of reporting.

4.1.2.4. Trends in Medicines Registration

Figure 6 shows the number of medicinal products for human use registered with ZAMRA each year over the period from 2004 to 2015. It also indicates the cumulative totals of registered products over the same period.

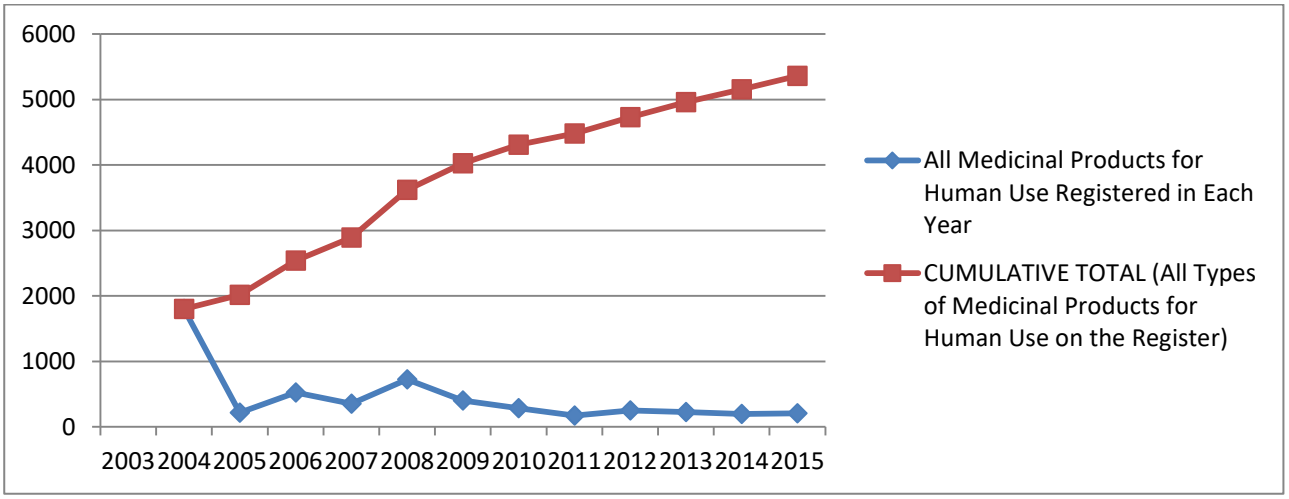


Figure 6: Cumulative totals of medicinal products for human use registered by ZAMRA, and figures of medicinal products for human use registered annually *(Source: SIAMED Database, Marketing Authorisation Section, Directorate of Medicines Control, Zambia Medicines Regulatory Authority)*

The trend seen for annual registration of medicinal products indicates that number of products registered annually dropped significantly in 2005, showed an upward trend between 2005 to 2008, before dropping again between 2008 and 2010, and stabilising to between 173 to 249 products annually thereafter.

4.1.2.5. Correlation Analysis between Trends in Medicine Registration and Selected Disease Patterns

Table 2 shows results of the analysis of correlation between selected disease trends and the trends in registration of medicines for human use. The results illustrated strong positive correlation between total drugs registered with number of HIV patients on ART (0.9531), hypertension national cases (0.9314), and cancer cases reported at the CDH (0.9543). A strong negative correlation was illustrated between total drugs registered and TB notifications. A weak negative correlation was seen between total drugs registered and national malaria incidence.

Table 2: Matrix showing correlation between trends in total medicines registered annually with annual incidence rates for HIV, TB, Malaria, Hypertension and Cancer. Pearson's correlation was used and the r-statistic is reported, with 95% statistical significance. The period covered is from 2004 to 2015.

	Total Drugs Registered	HIV number of patients on ART	TB notifications (incidence per 100,000 population)	Malaria incidence per 1,000 population	Hypertension national cases	Cancer cases reported at the CDH
Total Drugs Registered	1.0000	0.9531	-0.9281	-0.2188	0.9314	0.9543

4.1.3. Questionnaire Survey Results

4.1.3.1. Respondents' Social and Demographic Characteristics

Table 3 reports some social and demographic characteristics of respondents to the survey. A total of 57 respondents submitted complete questionnaires that were included in the data analysis. The majority of respondents were in the age ranges of 22 to 35 and 36 to 50 (93.0%). No respondents were aged below 22 years. The gender of respondents was skewed towards the males, with only 39.3% respondents being female. Medical doctors, nurses, clinical officers and pharmacists provided the most responses, accounting for a combined 68.3% of the respondents. Medical practitioners and dispensers accounted for 80.7% of the respondents, while respondents in public and civil service accounted for 69.6%.

Table 3: Respondents social, demographic and professional characteristics (N=57)

Parameter	Categories	Number of respondents (n)	Percentage (%)
Age Range (in years)	18-21	0	0
	22-35	34	59.7
	36-50	19	33.3
	Above 50	4	7.0
Gender	Female	22	39.3
	Male	34	60.7
Profession	Medical Doctor	12	21.0
	Veterinary Surgeon	1	1.8
	Pharmacist	8	14.0
	Physiotherapist	4	7.0
	Environmental Technologist	4	7.0
	Clinical Officer	9	15.8
	Nurse	10	17.5
	Laboratory technologist	1	1.8
	Specialist	3	5.3
	Biomedical Scientist	5	8.8
Type of Employer	Public Service	15	26.8
	Civil Service	24	42.8
	Private Sector	16	28.6
	Cooperating Partner	1	1.8
Role in Medicines Supply Chain	Regulator	3	5.3
	Distributor	2	3.5
	Retailer	3	5.3
	Dispenser	11	19.3
	Medical Practitioner	35	61.4
	Others (Accountant, Procurement Specialist)	3	5.3

4.1.3.2. Respondents' Perceived Knowledge of Medicines Regulatory Systems and Requirements

Table 4 reports the opinions of respondents on their length of service and awareness of medicines regulatory requirements.

Table 4: Respondents' perceived knowledge of medicines regulatory systems and requirements (N=56)

Description	Responses	Frequency (n)	Percent (%)	Cum. Percent (%)	95% CI Lower (%)	95% CI Upper (%)
How long have you worked for in this Sector	<1 year	11	19.64	19.64	10.23	32.43
	1-5years	20	35.71	55.36	23.36	49.64
	5-10years	10	17.86	73.21	8.91	30.40
	10-20years	11	19.64	92.86	10.23	32.43
	>20years	4	7.14	100.00	1.98	17.29
	TOTAL	**56**	**100.00**	**100.00**		
Are you aware of the medicines regulatory requirements in force in Zambia	Yes	36	65.45	65.45	51.42	77.76
	No	19	34.55	100.00	22.24	48.58
	TOTAL	**55**	**100.00**	**100.00**		
Over the Time you have worked in this sector, how would you say the medicines regulatory systems have been improved	Significantly Improved	14	25.00	25.00	14.39	38.37
	Slightly Improved	26	46.43	71.43	32.99	60.26
	No Change	14	25.00	96.43	14.39	38.37
	Slightly Worsened	1	1.79	98.21	0.05	9.55
	Significantly Worsened	1	1.79	100.00	0.05	9.55
	TOTAL	**56**	**100.00**	**100.00**		

The respondents were left-skewed in terms of length of time they had worked in the sector, with majority having worked for less than 10 years. Two-thirds of the respondents indicated that they were aware of medicines regulatory requirements in force in Zambia, while the majority (71.43%) indicated that the medicines regulatory systems had improved over the period they had been in the sector.

4.1.3.3. Respondents' Opinions on Impact of Medicines Regulation on Treatment Outcomes

Table 5 contains the opinions of respondents regarding the relationship and impact of medicines regulation on health/treatment outcomes.

Table 5: Respondents' opinions on impact of medicines regulation on treatment outcomes (N =55)

Description	Responses	Frequency	Percent (%)	Cum. Percent (%)	95% CI Lower (%)	95% CI Upper (%)
Do you agree that medicines regulation is necessary to assure product quality, safety and efficacy	Strongly Agree	47	85.45	85.45	73.34	93.50
	Agree	5	9.09	94.55	3.02	19.95
	Not Sure	3	5.45	100.00	1.14	15.12
	Disagree	-	-	-	-	-
	Strongly Disagree	-	-	-	-	-
	Total	**55**	**100.00**	**100.00**		
In your opinion, do you think there is a relationship between medicines regulation and quality of health care	Yes	51	92.73	92.73	82.41	97.98
	No	2	3.64	96.36	0.44	12.53
	Not Sure	2	3.64	100.00	0.44	12.53
	Total	**55**	**100.00**	**100.00**		
In your opinion, how has the current regulatory system impacted on the quality of health care and treatment outcomes	Improved treatment outcomes	38	69.09	69.09	55.19	80.86
	Worsened treatment outcomes	5	9.09	78.18	3.02	19.95
	No Impact on treatment outcomes	12	21.82	100.00	11.81	35.01
	Total	**55**	**100.00**	**100.00**		
In your opinion, whose responsibility is it to regulate medicines	Government	7	12.96	12.96	5.37	24.90
	The Regulatory Authority	15	27.78	40.74	16.46	41.64
	The Local Authority	1	1.85	42.59	0.05	9.89
	Medical Practitioners	4	7.41	50.00	2.06	17.89
	Business Houses	-	-	-	-	-
	Every Player in the Supply Chain including General Public	26	48.15	98.15	34.34	62.16
	I do not Know	1	1.85	100.00	0.05	9.89
	Total	**54**	**100.00**	**100.00**		

The results showed that 94.55% of respondents were of the opinion that medicines regulation was necessary to assure quality, safety and efficacy of medicines. 92.73% indicated that there was a relationship between medicines regulation and the quality of health care received. About two-thirds (69.09%) of the respondents were of the view that the current medicines regulatory systems had

impacted positively on the quality of health care and improved treatment outcomes. About half (48.15%) of the respondents indicated that it was the responsibility of all players in the medicines supply chain, including the general public, to regulate medicines.

4.1.3.4. Respondents' Opinions on Improvement of Medicines Regulatory Systems

Table 6 indicates the opinions of respondents with regards to improvement of regulatory systems and their opinions on regional harmonisation as a method of improving regulatory systems. The results showed that 66.2% of the respondents recommended increased public awareness campaigns as a way to improve current regulatory systems, while employing more staff under the regulatory authority was least recommended by only 30.99% of the respondents.

Table 6: Respondents' opinions on ways of improving current regulatory system and regional collaboration

Description	Responses	Frequency (n)	Percent (%)	95% CI Lower	95% CI Upper
How Do you think the current medicines regulatory systems could be improved	Decentralization	32	45.07	33.23	57.34
	Strengthen Legal Provisions	28	39.44	28.03	51.75
	Increase funding to the regulatory authority	31	43.66	31.91	55.95
	Employ more staff under the regulatory authority	22	30.99	20.54	43.08
	Increase public awareness campaigns on regulation of medicines	47	66.20	53.99	77.00
	TOTAL (N)	**71**	**100.00**		
Do you think Regional Regulation and Collaboration could improve the medicines regulation in Zambia	Strongly Agree	22	40.00	27.02	54.09
	Agree	27	49.09	35.35	62.93
	Not Sure	4	7.27	2.02	17.59
	Disagree	2	3.64	0.44	12.53
	Strongly Disagree	0	0	0	0
	TOTAL (N)	**55**	**100.00**		

4.2. Discussion

4.2.1. Desk Review of Medicines Regulation in Zambia

4.2.1.1. Development of Medicines Regulatory Systems in Zambia

The results of the review of the change and implementation of legislation for medicines regulation, and their impact, showed a trend of improvement in regulatory systems. Whereas the governance model during the era of the Pharmacy and Poisons Act (Government of Zambia, 1994) was focused on a centralized and fully government-controlled regulatory system, the enactment of the

Pharmaceutical Act, 2004 of the laws of Zambia (Government of Zambia, 2004) brought into existence an autonomous regulatory agency, with a clear mandate to regulate all medicines. This in itself was a significant improvement, since medicines regulation is carried out more effectively when the government establishes an autonomous regulatory agency, as opposed to regulatory functions integrated in the mainstream government structure (Rägo, 2008). This may be due to the wide range of high priority functions, in the case of the integrated governance structures (large Ministries or Departments), which results in some regulatory functions being given a priority lower than is necessary, especially under circumstances compounded by factors such as inadequate time, human, financial and material resources.

Delegating regulatory functions to an autonomous body, therefore, allows for better focus on core functions and also unlocks resources which would have otherwise been unavailable. It also affords the authorities (such as the Minister of Health and Cabinet) better control over critical high-level policy matters, based on streamlined information received through mandatory periodic operational reports useful as basis for decision making. In addition, autonomous regulatory functions also ensure that other mainstream government functions, either within the line ministry (in this case the Ministry of Health) or in other related ministries (such as Agriculture, Livestock, Veterinary Services, etc.) are brought under better and less biased regulatory check through the application of the same rules and standards as are enforced on private-sector businesses and other non-governmental sector players; and by highly competent and specialized personnel (Rägo, 2008). This study, however, did not measure the extent to which such benefits have been attained following the creation of the autonomous NMRA in Zambia.

The legislation of the NMRA in Zambia indicated that a centralised regulatory system was still being employed, bringing all functions related to regulation of medicines (for human and animal use) under a single national competent authority. It must be noted here however, that the definition of a medicine

under both the Pharmaceutical Act, 2004 (Government of Zambia, 2004) and the Medicines and Allied Substances Act, 2013 of the laws of Zambia (Government of Zambia, 2013) excluded medicines used in plants, by categorically defining Medicine as *"…human medicine, veterinary medicine,….or any substance or mixture of substances for human or veterinary use ….or the symptoms of disease in a person or animal"*. This narrowed definition may prove critical, especially under the current trends of the "One Health" approach, which includes regulation, and control of medicinal substances used in plants as a critical component of promoting and protecting public health. However, there was no evidence at the time to demonstrate any concerns or upward trend in the use of medicinal substances for plants in Zambia that would pose an immediate challenge.

One particularly significant improvement seen following the enactment of the Pharmaceutical Act, 2004 (Government of Zambia, 2004) was the increased participation by the NMRA in most collaborative initiatives at Sub-regional, Regional and Global level. A key partner that appeared to have played a pivotal role in this was the WHO, through support programs such as the Prequalification Program (PQP) for essential medicines. The participation in the WHO initiatives may have been responsible for the adoption and development of data management systems which made it possible to improve regulatory information management. This was also seen in the availability of data on medicinal products with Marketing Authorisation which could only be traced back to 2004, around the time when the Pharmaceutical Act, 2004 was enacted. A significant outcome from participation in collaborative activities was the Zazibona Collaborative Initiative, a SADC initiative spearheaded by ZAMRA and counterpart NMRAs for Zimbabwe, Botswana and Namibia. The Zazibona collaborative initiative was recognised as a technical working group (TWG) under the SADC Medicines Regulator's Forum and endorsed in January 2015, and the Terms of Reference approved on 12th November 2015, by the SADC Ministers of Health (Masekela, 2016).

Another notable achievement from both the creation of an autonomous NMRA and its participation in collaborative initiatives was the increased stringency in the assessment of safety, efficacy and quality of medicines before they are authorised to be marketed. This was evidenced by the findings of the desk review, which showed increased staffing and assigning specific roles and responsibilities, coupled with trainings provided mainly through collaborative initiatives. The drop seen in the number of medicines issued with marketing authorisation annually over the period from 2008 to 2011 (see Figure 6 above) may have been a result of this increase in competence and capacity, with a net increase in stringency.

However, it is also important to note that there are some regulatory areas that have not shown much improvement following the enactment of the later pieces of legislation. The area that seemingly has seen the least improvement is the monitoring and evaluation of institutional performance. This function is critical in the attainment of institutional goals, in providing useful evidence to higher authorities, and for resource mobilisation and capacity building. Although the legislation provided for these functions, and evidence was provided demonstrating intent to create functional quality management systems (QMS), and monitoring and evaluation (M&E) systems, implementation was still in its early stages (ZAMRA, 2015b).

In the area of inspections and control of informal markets, it was evident from periodic reports that, there were challenges especially with respect to the aspect of prevention of illegal trade in medicines. The vastness of the country, which is landlocked (or land-linked), surrounded by eight neighbouring countries with porous borders compounded the situation. The inadequacy of staff to enforce and conduct regular inspections was highlighted as the major factor in the challenges being faced in the implementation of these functions (ZAMRA, 2015a). In addition, the financial circumstances of the institution at the time could not allow the engagement of additional staff, although a revised

organisational structure had been approved, providing for more staff in all functional areas including inspectorate (ZAMRA, 2015a).

In the area of monitoring advertising and promotion of medicines, progressive improvement was observed as subsequent legislation was passed. Although the status of enforcement of the provision of the act through inspectorate activities was similar to the control of illegal trade in medicines, some improvement in term of review and authorisation of advertisements and promotional materials prior to use had been seen. The major challenge highlighted was the lack of sufficient human resource designated to implement this key regulatory area (ZAMRA, 2015a).

In addition, evidence was provided showing that there were efforts being made to promulgate regulations to detail and operationalise most regulatory functional areas. The process employed, although not clearly documented, seemed to involve most stakeholders and interested parties, with the leadership being provided by senior staff from the Ministry of Health (ZAMRA, 2015a). However, the process of development of regulations was complicated and highly dependent on other government departments. This meant that there were no clear timelines attached to these processes and therefore it was not possible to predict timeframes for implementation of key provisions of the principle Law.

4.2.1.2. Trends in Prevalence of Selected Diseases in Zambia

HIV has been an important disease globally since the mid-1980s, and in Zambia, its occurrence caused numerous losses to individuals, families and the nation at large. The data collected showed that over the period from 2006 to 2015, testing for HIV had exponentially increased by over 1000%. Concurrently, enrolments onto the ART treatment for individuals with HIV increased by about 700% over the same period (see Figure 2 above). Various factors may be attributed for this increase, which can be viewed as positive from a public health and humanitarian point of view. In Zambia, concerted

efforts by the Government, the Health Sector, NGOs and Cooperating Partners played a huge role in ensuring that interventions to diagnose and contain HIV/AIDS were scaled up. Although prevalence of HIV among adults had only reduced by minimal margins, from 15.6% in 2001 to 13.3% in 2014 (Ministry of Health, 2015), other health and social benefits were more significant. This was reinforced by improvements such as the increased life expectancy at birth for Zambia from 46.9 years in 1990 to 51.3 years in 2010 (Ministry of Health, 2015; African Development Bank, 2006). An additional benefit was the development of the National Drug Policy in 1998 and the subsequent enactment of the Pharmaceutical Act, 2004 of the laws of Zambia, which was justified in part by the need for better regulatory systems to be put in place in order to mitigate disease burdens, and associated socio-economic challenges.

Trends in annual incidence of Malaria were rather erratic, substantially dropping over the period from 2006 to 2008, but surging back up from 2009 to 2013, before posting another drastic drop between 2014 and 2015. These changes may be attributed to the short-term impact characteristic of project-mode interventions mainly provided with support from Cooperating Partners, in which case positive developments scored may be rapidly lost when the support is withdrawn. Other factors that could be attributed to these include behavioural changes by communities, such as reduced adherence to preventive measures like use of insecticide-impregnated mosquito nets (especially when successes are recorded) and development of drug resistance. It is important to note that although a gradual and persistent reduction in malaria case fatalities was recorded over the period under review, it was not significant when viewed as a proportion of the Malaria Incidence.

Interesting trends were recorded in selected non-communicable diseases (Hypertension and Cancers). Although there was no information available on hypertension prior to 2009, the gathered data indicated a steady increase in cases by about 80% over a 3-year period from 2010 to 2013. However, the hypertension cases appeared to have peaked since 2013, but largely remained unchanged

thereafter (Ministry of Health, 2013). The upward trend could be attributed to changes in life style, including increased reporting and check-ups, while the stable peak could be a result of availability of affordable medications or limited healthcare service providers.

The cases of cancer reported at the Cancer Diseases Hospital (CDH) increased significantly between 2006 and 2015 from only 35 to 2,669 cases. This could be attributed mainly to the introduction of facilities at this new hospital, and the availability of more treatment methods. There are reports, from various parts of the world, indicating that increased use of some medicinal products, such as chemical contraceptives in women, may have also contributed to the upward increase (Gadducci *et al.*, 2011; Modan *et al*., 2001; Celentano *et al.*, 1987). Occurrences of diseases such as HIV/AIDS have also been implicated in the increased incidences of certain cancers (Silverberg *et al.*, 2012; Gadducci *et al.*, 2011; Engels *et al.*, 2006).

4.2.2. Correlation Analysis between Trends in Medicine Registration and Selected Disease Patterns

The reported results showed that for HIV, Hypertension, and Cancer, higher values of medicines registered by ZAMRA were associated with higher values of annual disease incidence, hence illustrating a positive correlation; while for TB, and Malaria, higher values of medicines registered by ZAMRA were associated with lower values of annual disease incidence, hence illustrating a negative correlation (Laerd Statistics, No date). In this case, a negative correlation may be viewed as a good outcome, since the main objective for medicines regulation is the reduction of disease incidence.

However, although analysis results showed strong relationships between medicines registration, and incidences in diseases as mentioned above, the results could not be viewed as a true reflection. This was because there was no information available to provide evidence showing that specific medicines

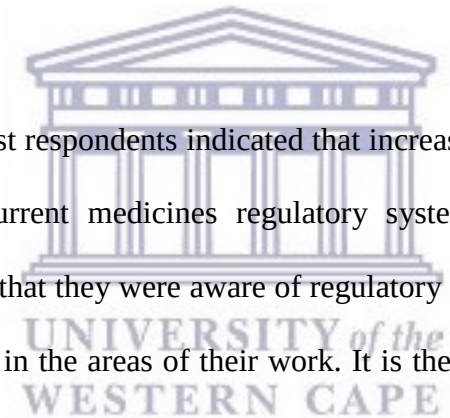
indicated for any of these diseases were registered in any of the given years, and therefore it would be erroneous to attribute the depicted relationships to any interventions. Furthermore, there is possibility that there were other factors that may have influenced the changes in incidences of diseases.

4.2.3. Opinions and Perceptions of Medical and Nursing Practitioners on Medicines Regulatory Systems in Zambia

The responses given showed that the majority of respondents were aware of the need for medicine regulation, and they were in support of this important function. The majority were of the view that the medicines regulatory systems had improved over the course of their work, which ranged from 1 to 20 years for most of them. Most of the respondents indicated that medicines regulation was necessary to assure product quality, safety and efficacy, with only 5.45% stating that they were not sure, while none said it was not necessary. This support for the regulatory functions by the majority could be interpreted as indication of high expectation of the medicines regulatory authorities and government to deliver. Such support may be positive, as it would provide justification for government to increase investment into the regulatory systems. However, the high support may also have negative impact if the regulators and government are seen not to be doing enough to deliver on their mandate. This may result in resentment, distrust and lack of support overtime.

Furthermore, most respondents were of the opinion that there was a relationship between medicines regulation and quality of health care. Over two-thirds of the respondents indicated that current medicines regulatory systems had improved the quality of healthcare and treatment outcomes. These opinions reinforce the high support for the regulatory system and signals opportunities for improvement by utilising this good will to improve the regulatory systems, especially in those functions which are not performing well.

The opinion by almost half of respondents that medicines regulation was the role of all players in the medicines supply chain is the strongest indication of support for the regulatory authority. This support is important for successful implementation of the regulatory systems through a more decentralised approach. Implementing more self-regulatory policies especially for lower risk processes could build on this support and result in improved quality of medicines being made available to the general public (Abraham, 1997). For instance, the overwhelming support from these players could be utilised in the fight against illegal trade in medicines, and in sensitizing the general public on the need to only access medicines through authorized channels of distribution and supply. The responses of the other respondents also provide vital information to the NMRA and government, to plan more communication activities to educate stakeholders on the role that every player has in medicines regulation.



It was important to note that most respondents indicated that increased public awareness campaigns would help to improve the current medicines regulatory systems. Although the majority of respondents indicated earlier on that they were aware of regulatory requirements, this response may be telling of the actual situation in the areas of their work. It is therefore important for the NMRA and government to direct more efforts towards increasing public awareness. It was also interesting to note that the least recommended interventions for improvement of regulatory systems was employment of more staff and strengthening of legal provisions. These responses may also be important in informing the NMRA and government of the feeling of the professionals with regard to the level of stringency prescribed in the legislation. It may also be informing the regulatory authority that the feeling amongst these important stakeholders is that regulatory staff may not be delivering up to expectation, are not visible, or are being underutilised.

The general opinion in support of regional integration may be construed as a result of the level of awareness of the current international trends of regional and international collaboration. Adoption of

international best practices arguably provides a fast-track route to attainment of institutional objectives, thereby increasing the efficiency of an organisation. As this was also found to be one of the areas where the NMRA had posted the most improvement over the years, the responses would be useful in reinforcing the need to sustain participation in collaborative initiatives.

4.2.4. Study Limitations

The failure to mobilise sufficient respondents for the questionnaire survey implied that the findings could not be generalised to the study population, which was the medical practitioners and other players in the pharmaceutical industry. Although literature indicated that response rates to online surveys were low, around 40% (FluidSurvey Team, 2014; Nulty, 2008), the response rate was much lower in this study (at 13.1%).

The format of the survey instrument (Questionnaire) with some questions providing data that was difficult to analyse, may have limited the usefulness of such data. For instance the use of Likert Scales for age rather than continuous variables limited the usability of the data collected as most parametric tests could not be used. As a result, an attempt to use cross-tabulation and Chi-square test did not yield valid test results. The use of recommended tests for the ordinal data was also a challenge due to limited experience in the use of statistical software, and comparison of results from desk review to establish correlation and/or causality was difficult.

The reliance on one researcher may have limited this study as there was limited proof of concept and verification of results by a second researcher. However, this being an academic study with limited resources, the supervisors provided advice and guidance to the extent required for ensuring that the final outcome met acceptable standards for research.

Changes in institutional processes which were outside the control of the researcher made it difficult to obtain ethical approval as initially planned. The Institutional data management systems were not user friendly and this resulted in failure to retrieve certain desired information within the targeted study period. Data format and information type was not robust enough for analysis, limiting the usefulness of some data collected.

Time allocated to the study was limited since the sources of the relevant information were out of the control of the researcher. This resulted in delayed completion of the study. In addition, financial challenges resulted in delayed applications (for ethical approval to a private IRB) and payments of subscriptions (Survey Monkey™) resulting in further delays to start data collection.

CHAPTER 5: CONCLUSIONS AND RECOMMENDATIONS

5.1. Conclusions

Overall the trends seen reflect a net improvement in disease outcomes over the period under review. The evidence gathered also demonstrated that there was significant improvement in the medicines regulatory systems over the period under study. Weaknesses in the current regulatory systems were highlighted, and identified as possible areas of focus in order to stimulate further improvements in these systems. There was also strong evidence indicating that the Health Practitioners and other players in the health and pharmaceutical sectors were aware of the medicines regulatory requirements (in general terms), and were largely in support of the need for medicines regulation. However, the study did not provide sufficient evidence to demonstrate association, correlation or causality between improvement of medicines regulatory systems and changes in quality of medical treatment and disease outcomes.

5.2. Recommendations

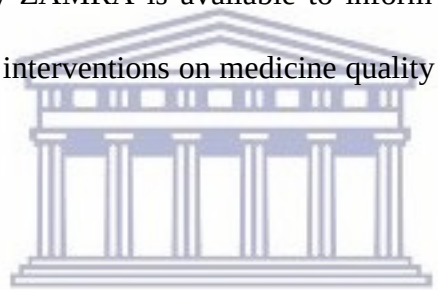
It was recommended that ZAMRA, as NMRA for Zambia, should consider conducting a more comprehensive review of the effectiveness of current regulatory interventions by collecting feedback from sufficient representatives of all sectors and players in the industry. This would provide more statistically significant information which could act as basis for informing policy change and also mobilising resources for better implementation of its mandate.

It was also recommended that ZAMRA should consider developing/revising its public awareness strategy in order to improve information dissemination and public sensitisation of its mandate, roles, functions and benefits to the general public. This would build a better image of the Authority by the general public, with potential to mobilise much needed public support. Increased public awareness

also offers opportunities to increase compliance and improve achievement of regulatory objectives, which ultimately results in better protection and promotion of public health.

It is further recommended that ZAMRA should, working with the Ministry of Health, expedite the promulgation of regulations that would facilitate implementation of regulatory functions that were still not fully implemented at the time of the study.

It is recommended that the Ministry of Health and ZAMRA should consider implementing integrated information management systems in order to ensure that institutional information is captured, maintained and managed better, so that it can be easily retrievable and useable. This would ensure that all information processed by ZAMRA is available to inform policy and can also be used to evaluate the impact of regulatory interventions on medicine quality and safety, and their impacts on health outcomes.



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APPENDICES

APPENDIX 1: MATRIX COMPARING PROVISIONS OF THE THREE PIECES OF LEGISLATION AND IMPLEMENTATION OF LEGAL PROVISIONS

S/N	*DESCRIPTION*	*Pharmacy and Poisons Act CAP 299*	*Pharmaceutical Act No. 12 of 2004*	*Medicine and Allied Substances Act No. 3 of 2013*
1.	Registration and Regulation of Pharmacy Professionals	√√	-	-
2.	Give the National Medicines Regulatory Authority Autonomy	-	√√√	√√√
3.	Licensing of Manufacturers and Manufacturing facilities	√√	√√√	√√√
4.	Licensing Importers and Exporters	√√	√√√	√√√
5.	Licensing of Distribution facilities (Wholesales)	√√	√√√	√√√
6.	Licensing Retailing and Dispensing facilities	√√	√√√	√√√
7.	Regulation of Promotion and Advertising of Medicines	√√	√√√	√√√
8.	Assessing the Safety, Efficacy and Quality of Medicines	√	√√√	√√√
9.	Issuing Marketing Authorisation (Product Registration) for individual Products	√	√√√	√√√
10.	Inspecting and Surveillance of Manufacturers	√	√√√	√√√
11.	Inspection and surveillance of Importers and Ports of Entry	√	√√√	√√√
12.	Inspection and Surveillance of Wholesalers	√√√	√√√	√√√
13.	Inspection and Surveillance of Dispensers	√	√√√	√√√
14.	Controlling and Monitoring the quality of Medicines on the market	√	√√√	√√√
15.	Controlling and Monitoring the Promotion and Advertising of Medicines	√√	√√√	√√√
16.	Monitoring Safety of marketed Medicines including collecting and analysing adverse reaction reports	-	√√√	√√√
17.	Providing independent information on medicines to professionals and the public	-	√	√
18.	Providing for the establishment of a Medicines Quality Control Laboratory	-	√√√	√√√
19.	Providing for the promotion of effective cooperation between the National Medicines Regulatory Authority and other law enforcement agencies (such as Customs, Police and Local authorities)	√√	√	√√√
20.	Providing for Market control	√	√	√
21.	Providing for regulation of Controlled substances	√√	√	√√√
22.	Providing for Accountability and transparency of the National Medicines Regulatory Authority	√	√√√	√√√
23.	Providing for National Medicines Regulatory Authority to collect fees from regulatory services provided and retain them for use in carrying out regulatory functions	√	√√√	√√√
24.	Providing for National Medicines Regulatory Authority to gets funds from regular budget of government	√√√	√√√	√√√
25.	Providing for National Medicines Regulatory Authority to receives funds from other sources	-	√√√	√√√
	MA RELATED PROVISIONS			
26.	Existence of legal provisions requiring marketing authorization of all pharmaceutical products	-	√√√	√√√
27.	Publicly available criteria for assessing applications for marketing authorization of pharmaceuticals	-	√	√√√

S/N	DESCRIPTION	Pharmacy and Poisons Act CAP 299	Pharmaceutical Act No. 12 of 2004	Medicine and Allied Substances Act No. 3 of 2013
28.	Existence of legal provision requiring National Medicines Regulatory Authority to make available a list of registered pharmaceuticals with defined periodicity	-	√√√	√√√
29.	Registration of medicines by their INN name or Brand name + INN	-	-	-
30.	Legal provisions requiring paying a fee for medicine registration	-	√√√	√√√
31.	Legal provision requiring the provision of information about variations in existing market authorization	-	√√√	√√√
32.	Legal provisions requiring the publication of Summary Product Characteristics of registered medicines	-	-	-
33.	Legal provisions requiring expert committee involvement in MA application process	-	-	√√√
34.	Certificate of Pharmaceutical products in accordance with WHO certification scheme required as part of the MA application	-	-	-
35.	Legal provision requiring the declaration of potential conflict of interests for experts involved in assessment and decision making for registration	-	-	√√√
36.	Legal provisions allow applicants to appeal against National Medicines Regulatory Authority decisions	-	√√√	√√√
37.	Legal provision stating timeline for review of application Marketing Authorisation	-	-	-
	INSPECTORATE RELATED PROVISIONS			
38.	Legal provisions for the appointment of government pharmaceutical inspectors	√√√	√√√	√√√
39.	Legal provisions permitting inspectors to inspect premises	√√	√√√	√√√
40.	Legal provision requiring inspection to be performed	√√√	√√√	√√√
41.	Inspection is a pre-requisite for licensing facilities	-	-	√
42.	Inspection requirements same for both public and private facilities	-	√√√	√√√
	IMPORT CONTROL RELATED PROVISIONS			
43.	Legal provisions requiring importers to be licensed	-	√√√	√√√
44.	Legal provisions requiring authorization to import medicines	√√√	√√√	√√√
45.	Legal provisions allowing sampling of imported products for testing	-	√	√
46.	Legal provisions requiring importation of medicines through authorized ports of entry	-	-	√√√
47.	Legal provisions allowing inspection of imported products at the authorized port of entry	-	-	-
	GMP RELATED PROVISIONS			
48.	Legal provisions requiring manufacturers to be licensed	-	√√√	√√√
49.	Legal provisions requiring compliance with GMP	-	√	-
50.	The National Medicines Regulatory Authority publishes GMP requirements	-	-	√
	GDP RELATED PROVISIONS			
51.	Legal provisions requiring wholesalers and distributors to be licensed	√	√√√	√√√
52.	Legal provisions requiring compliance with GDP	-	-	-
53.	Government publishes GDP requirements	-	√	√
54.	Legal provisions requiring private pharmacies to be licensed	√√√	√√√	√√√
55.	Legal provisions requiring public pharmacies to be licensed	-	√√√	√√√
56.	National Good Pharmacy Practice Guidelines are published	-	√√√	√√√
57.	Legal provisions requiring the publication of a list of different categories of pharmaceutical facilities	√	√√√	√√√
	MARKET CONTROL AND QUALITY CONTROL RELATED PROVISIONS			

S/N	DESCRIPTION	Pharmacy and Poisons Act CAP 299	Pharmaceutical Act No. 12 of 2004	Medicine and Allied Substances Act No. 3 of 2013
58.	Legal provisions for controlling the pharmaceutical market	-	√	√√√
59.	Laboratory exist in the country for Quality Control	-	√	√
60.	Samples are collected by inspectors for post marketing surveillance testing	√	√	√
61.	Results of quality testing in the past two years publicly available	-	-	-
	PROVISIONS RELATED TO ADVERTISING AND PROMOTION OF MEDICINES			
62.	Legal provisions to control the promotion and/advertising of prescription medicines	√	√	√√√
63.	Legal provisions to prohibit direct advertising of prescription medicines to the public	√	√	√√√
64.	Legal provisions require pre-approval for medicines advertisements and promotional materials	√	√	√√√
65.	Guidelines/regulations for advertising and promotion of non-prescription medicines	-	-	-
	CLINICAL TRIAL RELATED PROVISIONS			
66.	Legal provisions requiring authorization for conducting Clinical Trials by the National Medicines Regulatory Authority	-	√√√	√√√
67.	Legal provisions requiring authorization by an ethics committee or institutional review board of the clinical trials to be performed	-	-	-
68.	Legal provisions requiring registration of the clinical trials into international/national/regional registry	-	-	-
69.	Legal provisions for GMP compliance of investigational products	-	-	-
70.	Legal provisions require sponsor, investigator to comply with good clinical practice (GCP)	-	-	-
71.	National GCP regulations are published	-	-	-
72.	Legal provisions permitting the inspection of facilities where clinical trials are performed	-	√	√√√
	PROVISIONS RELATED TO CONTROLLED SUBSTANCES			
73.	Signatory to the single convention on Narcotic Drugs 1961	√	√	√
74.	Signatory to the 1972 Protocol amending the Single Convention on Narcotic Drugs 1961	√	√	√
75.	Signatory to the convention on Psychotropic substances 1971	√	√	√
76.	Signatory to the United Nations Convention against the illicit Traffic in Narcotic Drugs and Psychotropic Substances 1988	√	√	√
77.	Existence of national laws and regulations for the control of narcotic and psychotropic substances and precursors	√	√	√
78.	The laws and regulations for the control of narcotic and psychotropic substances and precursors has been reviewed by a WHO International Expert or Partner Organization to assess the balance between the prevention of abuse and access for medical need	-	-	-
	PHARMACOVIGILANCE RELATED PROVISIONS			
79.	Legal provisions in the medicines act provides for pharmacovigilance activities	-	-	√
80.	Legal provisions requiring MA holder to continuously monitor safety of the products and report to the National Medicines Regulatory Authority	-	-	-
81.	Legal provisions about monitoring ADR	-	-	√
82.	National pharmacovigilance centre linked to National Medicines Regulatory Authority	-	√	√√√
83.	An analysis report by the pharmacovigilance centre has been published	-	√	√
84.	Pharmacovigilance centre publishes an ADR Bulletin	-	-	√
85.	Existence of an official standard form for reporting ADRs	-	√	√√√
86.	Existence of a national ADR data base	-	√	√√√

S/N	*DESCRIPTION*	*Pharmacy and Poisons Act CAP 299*	*Pharmaceutical Act No. 12 of 2004*	*Medicine and Allied Substances Act No. 3 of 2013*
87.	ADR reports are sent to WHO database in Uppsala	-	√	√√√
88.	ADRs monitored in at least one public health program	-	√	√√√
89.	Feedback is provided to ADR reporters	-	√	√
90.	ADR database is computerized	-	√	√
91.	Medication errors are reported	-	√	√
92.	Risk management plan is presented as part of product dossier submitted for MA	-	-	√
93.	Regulatory decision based local Pharmacovigilance data	-	-	√
94.	Institution of training courses in pharmacovigilance	-	-	√

Key:

- - No provision made in the Act
√ - General Provision made in the Act
√√ - General provision made in the Act supported by provisions in a specific Regulation
√√√ - Extensive provision made in the Act
√√√√ - Extensive provision made in the Act supported by provisions in a specific Regulation
√√√√√ - Extensive provision made in the Act supported by provisions in more than one (1) specific Regulation

APPENDIX 2: TABULATIONS OF DATA FROM ZAMRA AND MINISTRY OF HEALTH

		PREVALENCE OF THE SPECIFIC DISEASE IN EACH YEAR									
DESCRIPTION		**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
HIV	Number Tested	229,321	156,299	219,576	1,215,737	1,696,123	2,036,898	2,180,048	2,294,123	2,712,237	2,915,664
	On ART	112,091	156,299	219,576	283,863	344,407	415,685	480,925	580,118	671,066	750,000
TB	TB Notifications (Incidence per 100,000)	-	417	378	377	373	372	321	314	284	268
	TB Notifications (Number)	51,179	50,415	47,333	48,591	48,616	48,594	45,269	45,793	42,716	41,588
Malaria	Incidence per 1,000 population	412	358	252	246	330	344	339	370	374	267
	Case Fatality per 1,000 population	41	36	25	26	34	33	34	21	23	24

(Source: M&E Section, Directorate of Policy and Planning, Ministry of Health, Zambia)

	PREVALENCE OF SELECTED NON-COMMUNICABLE DISEASES IN EACH YEAR									
DESCRIPTION	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Hypertension	-	-	-	101,181	103,110	140,860	169,602	185,535	184,220	184,332
Cancer (Cancer Diseases Hospital patients)	35	719	1,204	1,285	1,282	1,302	1,828	2,049	2,065	2,669

(Source: M&E Section, Directorate of Policy and Planning, Ministry of Health, Zambia)

	LEVEL OF DRUG AVAILABILITY IN EACH YEAR									
DESCRIPTION	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Health Centre	74%	70%	69%							
Hospitals	86%	84%	77%							
ARVs						85%	100%	100%		
Immunization coverage	87%	85%	90%	94%	94%	93%	99%	85%	81%	90%

(Source: M&E Section, Directorate of Policy and Planning, Ministry of Health, Zambia)

	NUMBER OF MEDICINAL PRODUCTS WITH MARKETING AUTHORISATION												
DESCRIPTION	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
ART Medicines													
Anti-TB Medicines													
Anti-Malarial Medicines													
Anti-Hypertension Medicines													
Anti-Cancer Medicines													
Vaccines													
All Products Registered in the Year	-	1799	219	523	352	726	405	284	173	249	229	197	207
TOTAL (All Types of Medicines)	**-**	**1799**	**2018**	**2541**	**2893**	**3619**	**4024**	**4308**	**4481**	**4730**	**4959**	**5156**	**5363**

(Source: SIAMED Database, Marketing Authorisation Section, Directorate of Medicines Control, Zambia Medicines Regulatory Authority)

APPENDIX 3: RESEARCH PROPOSAL

University of the Western Cape
in partnership with
Hibernia College, Ireland

MASTER OF SCIENCE IN PHARMACY ADMINISTRATION AND POLICY REGULATION

CONTINUOUS ASSESSMENT COVER PAGE

Name:	Emmanuel Kabali
Student Number:	3480023 (University of the Western Cape) MRS101309 (Hibernia College, Ireland)
Student Cohort:	October, 2013
Assessment Title:	Applied Research Project module: Research Proposal
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Submission Date:	N/A

I agree that I have researched and written the work submitted in this assessment, and that the work submitted is my own. Any information and opinions drawn from other sources are attributed by means of a reference to that source.

√

TITLE: REVIEW OF THE EFFECTIVENESS OF THE MEDICINES REGULATORY SYSTEMS IN ZAMBIA OVER THE PERIOD 1995 TO 2015

5.3. Background and Introduction

5.3.1. Background

This study is an attempt to evaluate the evolution of medicines regulatory systems in Zambia. The study will focus on the 20 year period from 1995 to 2015. Over this study period, the principle laws providing a legal basis for medicines regulation has under gone amendments twice. The initial amendment was initiated by recommendations made through the National Drug Policy published in 1999, which recommended the need to put in place a better framework for regulation of medicines being made available to the Zambian public. At that time, the law that was in force was the Pharmacy and Poisons Act CAP 299 of the Laws of Zambia. A process of reviewing this law was initiated and this resulted in the enactment of the Pharmaceutical Act No. 14 of 2004 of the Laws of Zambia. The new Law repealed the old, and it provided a legal framework that was focused more on medicines, and excluded chemicals or poisons that did not have medicinal application. The pharmaceutical Act was sooner reviewed and various clauses were highlighted as necessitating or providing sufficient justification to have the Act repealed, rather than amended. In 2013, following a lengthy consultative review process, the Pharmaceutical Act was repealed and replaced by the Medicines and Allied Substances Act No. 3 of 2013. The new Law was acclaimed to have addressed most of the concerns raised by various stakeholders, and it is currently being applied in the regulation of medicines and related health products.

5.3.2. Rationale for Study

This study is intended to provide insight into the current regulatory systems for medicines in Zambia and the relationship of the regulatory systems with medical treatment outcomes. It is also intended to provide an overview of the evolution of the medicine regulatory systems over the twenty-year period from 1995 to 2015. This study has been necessitated by the scanty information available on this subject matter.

5.3.3. Significance of Study

This study is more exploratory, as there are very few studies that have been undertaken in Zambia to specifically evaluate the performance of the regulatory systems in relation to treatment outcomes. In all the documentation reviewed so far, there was little evidence to show that the contribution of the medicines regulatory systems in Zambia to treatment outcomes was adequately assessed or evaluated.

The research questions which this study attempts to answer are:

1. How have the medicines regulation legal provisions in the Laws of Zambia changed over the 20-year period from 1995 to 2015?
2. Have the changes to the medicines regulation laws improved the regulatory framework in place?
3. How have the prevalence of human diseases of national importance and their treatment outcomes evolved over the last 20 years?
4. Is there a relationship between the changes in medicines regulatory frameworks and the changes in disease prevalence and treatment outcomes?

5.3.4. Aim/Main Objective

The main aim of this study is to review the effectiveness of the medicines regulatory systems under the three different pieces of legislation (namely, The Pharmacy and Poisons Act CAP 299, The Pharmaceutical Act No.14 of 2004, and The Medicines and Allied Substances Act No.3 of 2013) over the period from 1995 to 2015, in relation to disease treatment outcomes.

5.3.5. Specific Objectives

The following are the specific objectives:

4. To highlight the changes in the legal provisions for medicines regulation in the Laws of Zambia over the 20-year period from 1995 to 2015;
5. To evaluate how the changes to the laws for regulation of medicines has impacted the regulatory framework in place in Zambia;
6. To highlight how the prevalence of human diseases of national importance and their treatment outcomes has evolved over the same 20-year period; and

7. To investigate the relationship between the changes in medicines regulatory frameworks and the changes in disease prevalence and treatment outcomes.

5.3.6. Hypothesis

The hypothesis to be tested is as follows:

5.3.6.1. Null Hypothesis

As the medicines regulatory systems in Zambia were improved, the treatment outcomes from the use of the medicines were becoming better.

5.3.6.2. Alternative Hypothesis

As the regulatory systems for regulation of medicines in Zambia were improved, the treatment outcomes did not improve as the regulation of medicines is not a major factor.

5.4. Ethical Considerations

Since the study will generally involve health service providers, and will not employ any interventions, use of medicinal product, administration or collection of biological samples; it is the researchers' considered view that there will be no major Research Participants' Welfare issues to be address.

In the proposed sample selection procedure, the researcher will access information of registered health personnel and players in the medicines supply chain in Zambia. Although this information is publicly available in data bases that can be accessed at a prescribed fee, it poses a potential ethical challenge, as the researcher will have access to the participants' information, and will also process and analyse the data that will be collected through participants' responses to the questionnaire survey. Data collected in this research will be handled only by the researcher (Principal Investogator), and will be used solely for academic purposes. Any personal information that will be collected in the course of this research will be treated with the highest level of confidentiality, and will be protected at all times. No information will be shared with any person that is not relevant to the successful completion of this study.

Another ethical issue may arise from the fact that some respondents, especially those that are part of the medicines supply chain are regulated by the Zambia Medicines Regulatory Authority (ZAMRA), were the researcher is an employee. As a result of this relationship, some respondents may have some reservations to provide honest responses, especially negative opinions on the current regulatory frameworks for medicines regulation; as they may feel that this could affect their relationship with the regulatory Authority. However, it will be incumbent upon the researcher to provide sufficient information to the participants (in the Respondents' Information Leaflet and through any additional information) to assure them that their responses will be confidential, and will not affect them or their relationship with ZAMRA in anyway. This assurance will be important in ensuring that the responses provided are a true reflection of the respondents' honest opinions that are not unduly influenced.

Based on the proposed study plan, it is the researchers' considered view that there will be minimal risks, if any, paused to the participants in this study. This is because there will be no intervention being made during the study, and the information that will be collected in the survey will be opinions that do not include confidential personal information. However, any potential risk that may arise for the respondents will be addressed by the researcher and brought to the attention of the respondents as soon as is practicable.

Since all the costs associated with this study will be borne by the researcher, no conflicts of interest will arise in relation to a sponsor. Although the subject of medicines regulation is part of the researchers' occupation, there are no conflicts of interest that will arise, as the study will be conducted in a professional manner. However, there will be need for caution to prevent any potential biases, especially when analysing data, to ensure that all the findings will be reported correctly without exclusions or omissions.

Finally, all respondents' personal information and opinions will be treated with the utmost confidentiality, and will only be used for the purposes of this research work. Informed consent will be sought prior to administration of each questionnaire; and the consent will be written, were practicable. All information will be handled by the researcher only, and hard copy data will be stored securely. Electronic data will be stored on the researchers' personal computer, backed-up on an external hard disc drive, and will be password

protected. All hard copy data will be destroyed by shredding/tearing and burning; while all electronic data will be disposed of by safe permanent deletion, upon completion of the research module of the degree program being pursued.

5.5. Literature Review

5.5.1. Medicines Regulation

5.5.1.1. An International Historical Perspective

Medicines are a product which some believe is as old as mankind (Rägo, No date). Medicines regulation was mainly developed or evolved independently in response to safety incidences involving pharmaceutical products (Ratanawijitrasin, 2002). Major historical safety incidences associated to the development of medicines regulation includes the Sulfanilamide tragedy and the Thalidomide tragedy.

In the Sufanilamide tragedy of 1937, a formulation of an elixir was made in diethylene glycol. The mixture's toxicity was not tested, leading to 107 deaths out of 353 patients who ingested the Elixir (Lumpkin *et al*, 2012; Rägo, No date). The Thalidomide tragedy was recognised in 1961 in which the sedative drug first synthesized in 1953 was used to treat morning sickness in pregnancy. The drug was used in Europe (11 countries), Africa (7 countries), Asia (17 countries), and America (11 countries) between the period from 1956 to 1961. Child birth defects were observed in the children born from the women that had used the drug (Hibernia, 2015).

In the United States of America (USA), major events led to responses towards pharmaceutical regulations. In 1941, the amendment to the Federal Food, Drugs and Cosmetics Act required the United States Food and Drugs Agency (FDA) to certify Insulin potency – a step on the road to demonstrate Efficacy, which is the "third leg" of drug approval (Hibernia, 2015). In 1943, the FDA was empowered to establish Standards for product labelling, which is the "fourth leg" of drug approval (Hibernia, 2015). It is important to note that this requirement to have a product labelled as meeting the standard is only found in USA (Hibernia, 2015). The "four legs" of Drug Approval, widely accepted internationally, are Efficacy, Safety, Purity and Labelling (Hibernia, 2015).

In 1962, the Thalidomide incidence in 1961 (Rägo, No date) led to the 1962 Kefauver-Harris amendments which contained requirements that: drugs should be demonstrated to be effective prior to first approval (called the *IND process*) (Abraham, 1997); made adverse events reporting mandatory; clarified labelling and advertising requirements; and inspection of manufacturing sites should be undertaken (Hibernia, 2015).

Concurrent to the above historical events, was the development of the United States Pharmacopoeia (USP). The following hallmark historical activities were also important in the development of medicines regulation in the USA: the Durham-Humphry Amendment of 1951; the Orphan Drug Act of 1983; the Waxman-Hatch Amendment of 1992; the PDUFA; and the FDAMA (Hibernia, 2015).

In the United Kingdom (UK), similar major events led to responses towards pharmaceutical regulations. In 1540, under the Apothecary Wares, the Drug and Stuffs Act (1940), manufacture of compounded preparations was made subject to supervision (Rägo, No date). In 1518, the London Pharmacopoeia (1518) laid down the standards for manufacture of pharmaceutical products (Rägo, No date). Between 1864 and 1877, the Royal College of Physicians setup various medical enquiries into the safety of Chloroform in anaesthesia (109 fatalities), critical relationship was established between dose and effect (Hibernia, 2015).

In 1907, Salvarsan (Arsphenamine) was imported from Germany to UK; each batch had to be released by the Medical Research Council, who also encouraged reports on incidences of Jaundice and Hepatic Necrosis following its use – these were possibly the first adverse drug reaction reports (ADRs) (Hibernia, 2015). The Therapeutic Substances Act (1925) was enacted in 1925, and it provided for the regulating of the manufacturing of biological products, set standards for quality, labelling, manufacturing, factory inspections, and in-process controls (Hibernia, 2015).

In the case of Europe regional regulation also has some milestone events that were key to development of medicines regulatory system. Some key early events include the development of the Florence Pharmacopoeia in 1498, the Dublin Pharmacopoeia in 1807, and the British Pharmacopoeia in 1864 (Hibernia, 2015). However, up until the 1950s, there

was no major concern in Europe with the way medicines were manufactured, placed on the market and controlled (Hibernia, 2015).

In 1957, 109 people died in France and 100 more suffered paraplegia as a result of Stalinon used for boil treatment. These adverse drug events were due to formulation error, where marketed batches contained five (5) times more of one of the active ingredients than used in clinical trials. In 1959, France introduced more stringent expert committee review requirements. These additional controls may have accounted for why Thalidomide was never marketed in France (Hibernia, 2015). After the Thalidomide tragedy, the World Health Organisation (WHO) recommended the monitoring of drug safety at a national level.

In 1971, the WHO Drug Monitoring Center based in Uppsala, Sweden was established following a pilot project as an International System for monitoring adverse reactions, which gave birth to the International Drug Monitoring Programme (WHO, 2006). In 1963, the Committee on Safety of Drugs (CSD) in the UK was setup. The CSD had no legal powers as it operated in voluntary cooperation with industry. The expertise for a central authority was assembled, which included the WHO, USA, and Canada. The CSD continued in existence until the Medicines Act of 1968 was enacted (Hibernia, 2015). Thereafter, the yellow card scheme, a spontaneous reporting of ADRs, was introduced (Hibernia, 2015). In 1965, the first EEC Directive to Control Medicines – Directive 65/65/EEC – was introduced (Hibernia, 2015).

5.5.1.2. A Perspective on Types of Regulatory Systems

To have a good perspective on types of regulatory systems, a brief review was done looking at the types of systems employed by countries or regions considered to have stringent regulatory authorities (SRAs). The three types of regulatory systems are discussed hereafter.

5.5.1.2.1. Self-Regulation

Self-regulation refers to a system where the regulated entities are allowed to manage a system of regulation amongst them. In the case of the pharmaceutical industry, players may develop a self-regulation system in which members of the group targeted for regulation

organize some means of mutual control among themselves (Abbott, 2009; Ratanawijitrasin, 2002). From an international perspective, national regulatory systems may be considered as a form of self-regulation (Abbott, 2009).

5.5.1.2.2. National/Federal Regulatory Authorities

A national/federal regulatory system is a system employed at national level to provide regulatory oversight for medicines. There are various models of national regulatory systems, amongst them are the following:

- Single national regulatory Authority
- Decentralized semi-autonomous (provincial/state/county) regulatory authorities with a National (central) regulatory Authority providing oversight.

5.5.1.2.2.1. <u>The United States Food and Drugs Administration (FDA)</u>

The FDA is responsible for regulation of foods and drugs in the USA. Its role is summarised in its mission in where the following statements are made:

- Protecting the public health by assuring that foods are safe, wholesome, sanitary and properly labelled. Human and veterinary drugs, and vaccines and other biological products and medical devices intended for human use are safe and effective
- Assuring cosmetics and dietary supplements are safe and properly labelled
- Protecting the public from electronic product radiation
- Regulating tobacco products
- Advancing the public health by helping to speed product innovations
- Help the public get the accurate science-based information they need to use medicines, devices and foods to improve their health (Hibernia, 2015).

The scope of products regulated by the FDA includes:

1. Animal and veterinary;
2. Dietary supplements;
3. Drugs;
4. Foods;
5. Medical devices;
6. Radiation-emitting products;
7. Tobacco products; and

8. Vaccines, blood and biologicals.

The FDA was established in 1906. It is the oldest drug regulatory authority in the world (Hibernia, 2015). It progressed from the enforcement arm of the US Department of Agriculture to the current scientific, technical, administrative and bureaucratic agency (Hibernia, 2015). It enforces laws enacted by the US Congress and regulations established by the agency to protect consumers' health, safety, and pockets (Hibernia, 2015). The Federal Food, Drug and Cosmetics Act, with numerous amendments, is the most extensive law of its kind in the world (Hibernia, 2015). Labelling is the "Fourth Arm" of drug approval, and much of the power of the FDA is exercised by its control of what a label says, based on a principle common in US commerce (Hibernia, 2015). Although the FDA has been an effective regulator, the fall-out from the Cox-2 Inhibitor withdrawals by Merck in 2005 was arguably the most tumultuous event at the FDA in its recent history (Hibernia, 2015).

The hierarchy of FDA authority (legal framework) includes:

- Laws enacted by US Congress, frequently as amendments to the Federal Food, Drug and Cosmetic Act
- Regulations implement laws, such as CFR Title 21
- Guidances are "informal" documents to clarify regulations, and these are not biding of Sponsors or the FDA
- Compliance Policy Guides (CPGs) are an organised repository for statements of FDA compliance policy
- Advisory Opinions come from interactions such as end-of-phase II meetings, and pre-IND (Investigational New Drug) meetings (in relation to clinical trials during drug development process)
- Informal Advice involves ad-hoc communications during (drug) development between FDA and Sponsor.

The FDA is part of the Department of Health and Human Services, headed by a Commissioner who is a political appointment with deputy heads for each of the centers or offices (Hibernia, 2015). The FDA has nine (9) divisions as follows:

1. Office of the Commissioner;

2. Center for Drug Evaluation and Research;
3. Center for Biological Evaluation and Research;
4. Center for Food Safety and Applied Nutrition;
5. Center for Devices and Radiological Health;
6. Center for Veterinary Medicine;
7. National Center for Toxicological Research;
8. Office of Regulatory Affairs; and
9. Center for Tobacco Products.

The FDA is a federal agency covering all the United States of America (Hibernia, 2015); and as such it is a good example of a National/Federal regulatory system.

5.5.1.2.3. Regional Regulation

A regional regulatory system is a system employed at regional or sub-region level to provide regulatory oversight for medicines. Although regional regulatory systems cover several countries, two types can be differentiated, being Regional if it has continental coverage or Sub-regional if it covers countries of a specific sub-continent (Abbott, 2009).

5.5.1.2.3.1. The European Union Commission (EUC), the European Medicines Agency (EMA), and the European Directorate for the Quality of Medicines (EDQM)

The European Economic Community established the European Economic Area (EEA) in 1957, which unites the 27 EU member states, and Iceland, Liechtenstein and Norway (Hibernia, 2015). In 1994, the EEA agreement allowed the member countries access to the single EU markets under the same rules that apply to full EU members, but they have to adopt all EU single market legislation, except those that relate to agriculture and fisheries, and make a financial contribution (Hibernia, 2015). Iceland, Liechtenstein and Norway are also members of the European Free Trade Association (EFTA), along with Switzerland (Hibernia, 2015).

The EU pharmaceutical law is in "the Rules Governing Medicinal Products in the European Union", edited by EUDRALEX (Hibernia, 2015). These Rules Governing Medicinal Products in the European Union are contained in the following:

- The Legislative texts (Regulations, and Directives)
    - Volume 1

- Supportive guidelines (Human medicines)
    - Volume 2 – notice to applicants and procedural guidelines
    - Volume 3 – human medicine guidelines
    - Volume 4 – good manufacturing practices (GMP)
    - Volume 9 – pharmacovigilance
    - Volume 10 – clinical trials (Hibernia, 2015).

The hierarchy of EU legislation (legal framework) includes:

- Primary Law
    - Treaties (ratified by National Parliaments)
- Secondary Law
    - Regulations (Council or Commission regulations): which are binding in all member states and supersedes all other legislation in the specific regulatory area at national and EU level
    - Directives: which bind member states, companies, and individuals
    - Decisions: which are binding in all aspects for those addressed (member states, companies, and/or individuals)
    - Soft Laws: which are not legally enforceable (recommendations, opinions, communications, and guidelines) (Hibernia, 2015).

The scope of products regulated includes:

1. Medicinal Products for human and veterinary use intended to be placed on the market and prepared by an industrial process. These include:

    a. Homeopathies
    b. Herbals
    c. Gene and cell therapy, and
    d. Radiopharmaceuticals.

    However, it excludes:

    a. Medical devices
    b. Whole blood

c. Food supplements, and
d. Cosmetics (covered in separate EU legislation);

2. In case of borderline products, the provision in legislation for medicinal products prevails.

The EU regulatory system is composed of a regional regulatory body (bodies) and individual national regulatory agencies (Hibernia, 2015); and as such it is a good example of a Regional regulatory system.

5.5.1.2.4. Global Regulation

The WHO tends to take up the role of a global medicines regulator; however, it is not. WHO has a fourfold role in medicine regulation (Rägo, No date), which is:

1. Issuing necessary norms and standards through its Expert committees and Expert committee-like bodies;
2. Supporting regulatory capacity building leading to implementation of medicines regulation at national level, and its harmonisation on regional and global level;
3. Ensuring the quality, safety and efficacy of limited high public health value essential medicines and vaccines through "Prequalification" – a regulatory activity mimicking medicines regulation; and
4. Plays a very important role for exchange of regulatory information amongs medicines regulators (Rägo, No date).

The WHO provides model regulations and guidelines for use in developing and implementing medicines regulatory systems. Although these regulations and guidelines are available to all WHO member states, adoption and implementation of these at national and regional level is voluntary, and dependent on consensus (Ratanawijitrasin, 2002).

The WHO publishes an International Pharmacopoeia, a collection of quality specifications for pharmaceutical substances for reference by any WHO member state. It focuses on substances included in the WHO Model List of Essential Medicine (WHO, 2015).

5.5.1.3. A Perspective on the African Regional Regulatory Systems

African has had a regional political governing body, the African Union (previously the Organisation of African unity) since 1963 (SAHO, 2016). This body has spearhead the harmonisation of medicines regulatory systems through initiatives such as the New Partnership for African Development (NEPAD) (AMRH Consortium, 2010). However, it is difficult to say that there is a regional medicines regulatory system in place in Africa. Current developments, such as the development and approval of the model medicines regulation law in 2015 (AMRH Consortium, 2010) are good signs of things to come. However, the impact and success of the model law remains to be seen in the near future.

Sub-regional initiatives for medicines regulation are also in place, with varied success scored so far. For instance in East Africa, the Common Technical Document (CTD) format for submission of medicine information for purposes of regulatory review prior to issuance of marketing authorisation was adopted around 2013. A total of six countries, namely Tanzania, Kenya, Uganda, Zanzibar, Burundi and Rwanda, have party to the initiative. This offers opportunity for capacity building and work sharing.

In the Southern Africa Development Community (SADC), similar initiatives have been undertaken for more than ten years now, with limited successes scored so far. The most recent development is the ZaZiBoNa initiative for regulatory work sharing, which appears to be gaining momentum as an initiative open to all SADC member states. The scope of the collaborative initiative involves work sharing of evaluation dossiers in CTD format, conducting of joint inspections of medicines manufacturing facilities to evaluate compliance to current good manufacturing practices (cGMP), and capacity building. The initiative offers hope of good success, and has received overwhelming support from the WHO, through the PQP and capacity development programs.

5.5.1.4. A Perspective on the Zambian Regulatory Systems

The Zambia Medicines Regulatory Authority (ZAMRA) is responsible for Medicines regulation in Zambia. Its role is summarised in the mission statement which says that *"Mission is to effectively regulate and control medicines and allied substances being made available to the*

Zambian population to ensure conformity to set standards thereby safeguarding public health".

The scope of products regulated by ZAMRA includes:

1. Medicines for Human and Veterinary use;
2. Medical devices including in-vitro diagnostic;
3. Vaccines and biologicals;
4. Medical supplies (refered to as allied substances).

Although the current legislation that brought the ZAMRA into existence was enacted in 2013, the Authority has been in existence long before then. Under the Pharmacy and Poisons Act, there was a provision for the Pharmacy and Poisons Board, which was an advisory body to the Minister of Health on medicines regulatory issues. This was the case until the repeal of the Pharmacy and Poisons Act in 2004, when it was replaced by the Pharmaceutical Act No. 14 of 2004.

The Pharmaceutical Act brought into existence an autonomous national regulatory authority, with a mandate to regulate the products as outlined above. The hierarchy of the legal frame is as follows:

- Laws enacted by the Parliament of Zambia provide legal mandate
- Regulations issued by the Minister of Health provide further clarity to the principal law
- Guidelines issued by the Authority provide further detail and clarity to the provisions enshrined in the principal law and its regulations.

ZAMRA, as a Statutory Board, is under the Ministry of Health. The Health Minister delegates the regulatory functions to the Authority through the Principal Law, which an Act enacted by parliament. The Minister appoints the Board of the Authority, which appoints the Director General and such other staff as it determines to be necessary for the carrying out the mandate of the Authority. ZAMRA's mandate covers the whole country, and it is the only competent authority responsible for medicnes regulation.

5.5.2. Evaluation of Regulatory Systems

5.5.2.1. Effectiveness of Regulatory System

5.5.2.1.1. Effective Medicines Regulatory System

As a starting point in the review of the effectiveness of a medicines regulatory system, the question that requires to be answered is "what is an effective medicines regulatory system?" To answer this question, one has to wonder what the purpose for having a medicines regulatory system in place is. A regulatory system is necessary to safeguard the aspirations of an individual, a group of people or institutions that have a common goal, but not necessarily the same ideologies. Cafaggi and Pistor (2013) indicates that "*The purpose of public regulation is to create common rules that govern a specific issue or domain (food safety, finance, fair trade, etc.) and command compliance without express consent by those operating in the relevant domain"*. Although this purpose statement seems simple, it portends the major components required in a regulatory system for it to be effective. If a system has no specific issues it is attempting to address, it cannot command the necessary compliance in any domain. An effective medicines regulatory system must, therefore, have a scope specific to applicable areas of medicines, and should outline its reach and limits. It should also make provisions to ensure capacity to enforce its provisions and also elicit the necessary compliances by all players and stakeholders. Cafaggi and Pistor (2013) further provided some insight on the requirements for establishing a regulatory system, saying *"Establishing a regulatory regime entails defining the issues and actors that shall be regulated, the means and ends of regulation, access to rule making or amendment processes and sanctions for non-compliance. Every regulatory regime exerts differential effects on regulators, the direct targets of regulation (i.e. the regulated), its beneficiaries, as well as others who are indirectly affected by it. Regulation restricts the choices of some while enabling others to realize their preferences. As such, every regulatory regime has distributional effects".* It is important to attempt retrospectively to establish the purposes why changes to the regulatory systems were made in Zambia and a case in point is as outlined by Sipilanyambe (2008), in relation to treatment regimens for Malaria.

5.5.2.1.2. Need for Effective Medicines Regulatory System

The next question that requires to be answered is "Why do we need an effective medicine regulatory system?" On this subject matter, it can be said that "if you cannot afford any form of regulatory system as a nation, afford a system for medicines regulation". It can also be said that "medicines security and safety is a key player in assuring national security, productive, longevity and development". The views expressed here are reinforced by the statement of Rägo *et al* (2014) who stated that *"Drugs are not ordinary consumer products as they directly affect the lives of people who take them…complex products…their quality cannot be seen by looking at them. They can restore…health, but all medicines can have adverse effects"*. It is the protection of the patient from the adversities that arise from the use of medicines that makes effective medicines regulation an important component of governance, both at national and international levels. Although governments are responsible for the protection of the people that fall within their jurisdictions, it is an acceptable norm in this modern era that the function of protecting patients from harm caused by medicines is the direct (albeit delegated) responsibility of national medicines regulatory authorities (Rägo *et al,* 2014).

5.5.2.1.3. Make-up of Effective Medicines Regulatory System

It is also important to answer another question of "what makes a medicines regulatory system effective?" The answer to this question is central to the purpose of this study, as adequately answering it, provides a basis for reviewing and assessing any given medicines regulatory system for effectiveness. It is important in answering this question to realize that, although it is the responsibility of the national medicines regulatory authorities to protect public health from harms of medicines, effective regulation take full participation of various stakeholders. Key players as outlined by Rägo *et al* (2014) include manufacturers, importers, exporters, consumers, health-care professionals, researchers and other government institutions (besides medicines regulator authority). When regulators are left to act in isolation, the regulatory systems cannot be seen to be effective, as the regulator has limitations in the reach of their decisions and scope of enforcement. The result of such regulatory environments is the blaming of the regulators of having failed the patients by either allowing medicines whose benefits do not outweigh the risks paused on users; or the vice versa, preventing medicines with clear benefits to patients, especially where alternative treatments are lacking, from being placed on the market (Lumpkin, 2012). A list of

parameters that should be inherent in all the stakeholders involved in the medicines' development and supply chain must be met in order for a medicines regulatory system to be function effectively (Rägo *et al,* 2014; Ratanawijitrasin and Wondemagegnehu, 2002).

5.5.2.2. Impact of Effective Medicines Regulatory Systems

The ultimate impact of effective medicines regulation is public health protections. However, the more effective medicines regulatory system should aim at being both protector and promotor of public health (Lumpkin, 2012). More specifically, an effective medicines regulatory system should have adequate capacity to undertake rigorous scientific assessment of medicines and assure the public that they are accessing safe, effective medicines of good quality meeting current international regulatory standards (Rägo *et al,* 2014).

5.5.2.3. Methods of Evaluating Effectiveness of Medicines Regulatory Systems

The final question that needs to be answered is "how is review and/or assessment of the effectiveness of a regulatory system done?" Of the questions paused in this literature review, this one stands out as the toughest. In Zambia, no published evidence could be found to show that such a study has been undertaken before, hence necessitating this study, albeit an exploratory one. However, ideas can be borrowed from the World Health Organisation (WHO) which has developed guidelines for assessing national medicines regulatory systems (World Health Organisation, no date). Although the WHO carries out assessment of regulatory systems in various countries, the scope of their assessments are limited, as they do not adequately capture views and opinions of all stakeholders as outlined above, mainly due to resource limitations, time limitations, and lack of willingness of some to participate (such assessments are conducted based on voluntary request of countries and stakeholders to participate). Therefore, it is prudent to utilize such WHO initiatives and tools as basis for conducting further assessments and studies that can be more detailed, focused and tailored towards the local set-up for specific national environments.

5.5.2.4. Model Evaluation Tools

5.5.2.4.1. WHO Evaluation Tool

The WHO assessments are also tailored to focus on specific focus areas outlined in their data collection tools and applicable guidelines (World Health Organisation, 2007). In additions, the assessments make reference to previous assessment conducted in a given country, but rarely delve into detailed comparative analysis of deficiencies found and trend seen in series of assessments. It is therefore a good basis for conducting a review of effectiveness of regulatory systems over a period of time, as proposed in this study, to utilize several WHO country assessment reports covering the period under review. For Zambia, WHO has conducted several assessments of the regulatory systems, and generally found that there were some improvements in the regulatory systems in the country. However, the current systems had various limitations and deficiencies, mainly related to the overall governance system, inadequate human resource capacity, lack of financial resources to implement key regulatory functions, among others. It is intended to utilize the results from these assessments to provide a consolidated review of the medicines regulatory framework in Zambia.

5.5.2.4.2. OECD Evaluation Tool

The OECD has developed tools for evaluations of regulatory systems. These tools are not specific to any particular area of regulation, covers the general tenents of a regulatory systems. The OECD has conducted regulatory assessments using its tools such as the assessments conducted in 1995, 2005 and 2008. The OECD assessment tools also prescribe parameters for conducting regulatory impact analysis (RIA). The OECD assessment tools are useful in developing tools for use in assessment of regulatory systems, as in the case of this study.

5.5.2.4.3. Regulatory Impact Assessment Tools

Regulatory Impact Assessment (RIA) is a system of assessing risks against the benefits in order to make informed decisions when deciding on whether to implement new regulatory interventions or retain old ones. The government of the republic of Zambia recently adopted the use of RIA in an attempt to promote development and implementation of smart regulatory policy and systems. Although RIA is currently being used to a limited extent in Zambian policy development, the legal framework as provided by the Business Regulatory

Act No. 3 of 2014 is still being operationalised. RIA tools are useful in assessing regulatory systems, as it provides guidance on key questions to be asked.

Based on the review conducted, it can be stated that there is need for more review and assessment of the regulatory systems in Zambia. Although the WHO has conducted some evaluations of national regulatory systems, these studies are not adequate to foster growth and improvement of the current regulatory frameworks, to ensure a more efficient and effective regulation of medicines in Zambia. Studies such as this one, with the intention of capturing opinions of the various stakeholders and players in the medicines development and supply chain will provide more opportunities for openness, awareness, consultation and continuous improvement of the currently existing regulatory systems.

5.6. Methodology

5.6.1. Study Design

A retrospective cross-sectional mixed (both qualitative and quantitative) study design will be used. The study will employ both quantitative and qualitative survey data collection techniques. The study will involve the following two distinct data collection phases:

3. Desk review of legislation for medicines regulation, and
4. Questionnaire survey involving health care providers and players in the medicines supply chain.

5.6.1.1. Desk Review of Legislation

The first phase will involve a detailed literature search/desk review of available literature. This phase will be used to assess the legislative provisions made in the three aforementioned laws, and determine the appropriateness of these laws for medicines regulation. A data extraction tool, derived from the WHO assessment tool and the OECD tool for regulatory impact assessment will be used to collate and compare the provisions of the three pieces of legislation. This phase will also review other available literature in order to establish patterns in the regulatory systems for medicines; prevalence of diseases such as HIV/AIDS, Malaria and Tuberculosis in Zambia; and changes in the treatment outcomes for major diseases using medicines. The finding from this phase will be used to compare the changes in the

laws against the changes in health outcome. Analysis of the findings will be done to demonstrate whether there is a relationship between changes in regulatory systems and changes in disease outcomes.

5.6.1.2. Questionnaire Survey

The second phase will involve administration of a questionnaire survey to various categorises of health care providers and players in the medicines supply chain in Zambia. The survey will be aimed at capturing opinions of these groups of health personnel and business people on the appropriateness of the medicines regulatory systems in place in Zambia, how the regulatory framework has evolved over the period under review and whether the changes in the regulatory systems have impact positively (or negatively) the treatment outcomes for major diseases in Zambia. In addition, their opinions on the best mode of medicines regulation will be captured through the questionnaire. The survey will be conducted by delivering hard copy questionnaires to respondents within Lusaka regional and by e-mailing the questionnaires to respondents outside Lusaka.

5.6.1.2.1. Sampling

The target study population is registered healthcare professionals registered with both the Health Professions Council of Zambia (HPCZ) and the General Nursing Council of Zambia (GNC).

5.6.1.2.1.1. Sample Size Determination

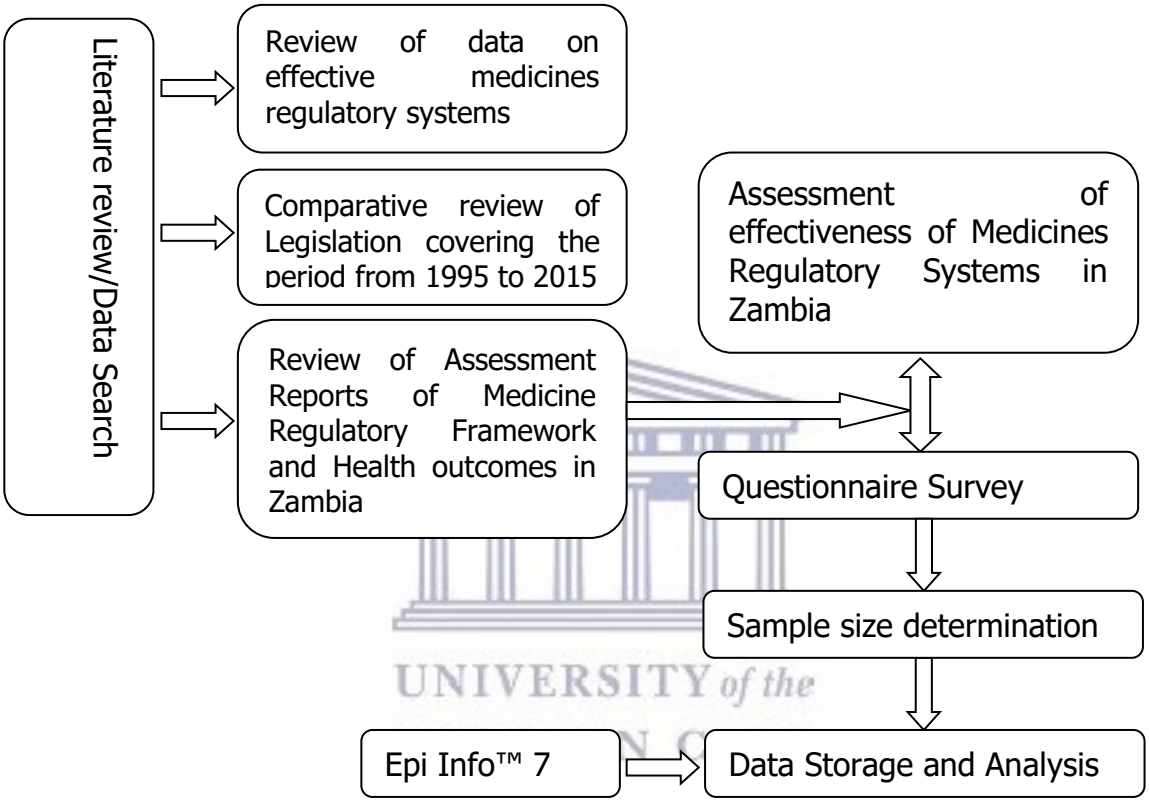
The total number of health practitioners and para-medicals registered with the HPCZ is about 13,000 (HPCZ, 2014). The total number of nursing professionals registered with the GNC is about 10,000 (Craig, no date; Chipili, 2006).

For purpose of sample size determination, the desired confidence level is 95%, while the margin of error is 5%. Using the formulae for sample size for a finite study population – $Sample\ Size = (Z\text{-}score)^2 * StdDev*(1\text{-}StdDev) / (margin\ of\ error)^2$ (Smith, 2015) – the minimum required samples from the two registers are 373 from HPCZ registered practitioners, and 370 from the GNC registered nursing professionals.

5.6.1.2.1.2. Conduct of Questionnaire Survey

Selection of respondents from the HPCZ and GNC databases will be done using random number tables. Selected respondents will be contacted by e-mail and provided with copies of Respondent's Information Leaflet for them to receive information about the research and to give informed consent to participate in the survey, before a questionnaire is given to them.

The flow diagram below summarizes the methodology.



Data from the questionnaire survey will be automatically collated by the online statistical package (Survey Monkey) and will be analysed to generate statistics that will be discussed in the final report. The principal investigator/student will conduct all the components of this research, in consultation with the supervisors, and were need arises, in consultation with a statistician.

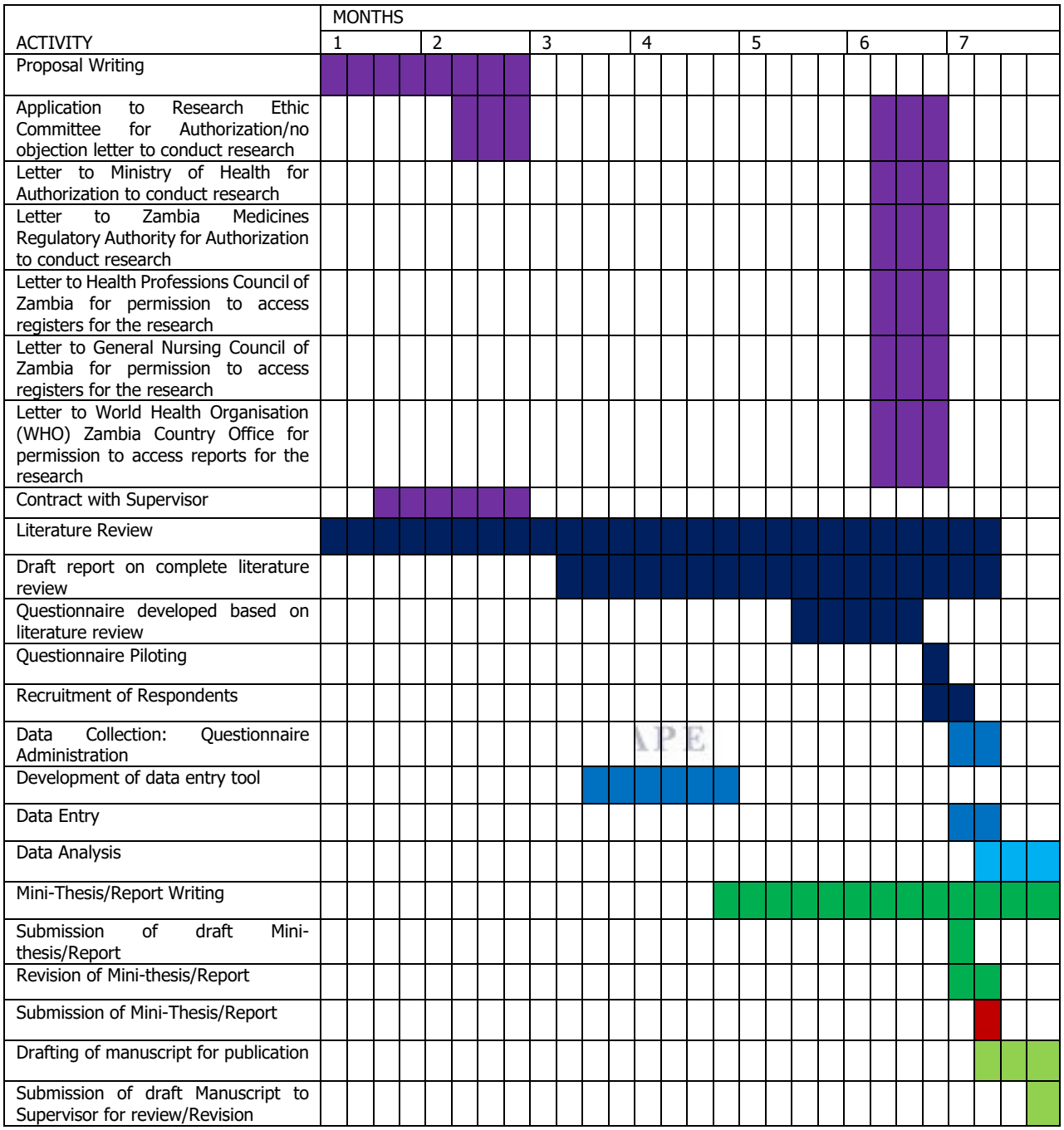
5.7. Budget

The table below outlines the costs anticipated in order to successfully undertake this study. The outlined costs will be borne by the principle investigator, and there is no sponsorship from any institution or persons.

BUDGET SUMMARY			
DESCRIPTION	**QTY**	**UNIT PRICE (ZMK)**	**AMOUNT (ZMK)**
DATA COLLECTION			
Data Collection (electronically) inclusive of internet costs, statutory fees for data retrieval for questionnaire survey sampling			22,000.00
Questionnaire Pre-testing			500.00
Results Dissemination			2,000.00
Survey Monkey Subscriptions	1	2,000.00	2,000.00
SUBTOTAL			**26,500.00**
STATIONARY			
Reams Paper	10	45	450.00
Laptop Computer	1	6,000.00	6,000.00
Printer	1	950.00	950.00
Cartridge	2	1,150.00	2,300.00
Pencils/Pens			50.00
Writing pads	3	15.00	45.00
Clipboards	3	10.00	30.00
SUBTOTAL			**9,820.00**
TRAVEL EXPENSES			
Fuel and vehicle consumables for Principal Investigator (X 21 Days)	21	300.00	6,300.00
SUBTOTAL			**6,300.00**
TOTAL			**42,620.00**

5.8. Time Frame

The chart below indicates the estimated time and projected period for conducting specific segments of this research.



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APPENDIX 4: QUESTIONNAIRE

QUESTIONNAIRE

Enumerator Initials……	Questionnaire no……	Interview Date……..

Instructions: *Tick [√] or cross [X] in the appropriate square brackets to select a response*

SECTION 1: PERSONAL INFORMATION

1. Name of Respondent *(optional)*: .....

2. Age range *(in years)*:

[ ] 18-21 [ ] 22-35 [ ] 36-50 [ ] above 50

3. Gender:

[ ] Male [ ] Female

4. Profession *(Select Applicable)*:

[ ] Specialist [ ] Medical Practitioner [ ] Veterinary Surgeon [ ] Pharmacist

[ ] Dental Surgeon [ ] Biomedical Scientific Officer [ ] Physiotherapist

[ ] Clinical Officer [ ] Nurse [ ] Environmental Health Officer

[ ] Pharmacy Technologist [ ] Environmental Health Technologist

[ ] Medical Laboratory Technologist [ ] Radiographer

[ ] Other, Specify .....

5. Type of Employer *(Select only one)*:

[ ] Public Service [ ] Civil Service [ ] Private Sector

[ ] Cooperating Partner [ ] Other, Specify .....

6. Role in Medicines Supply Chain *(Select only one)*:

[ ] Regulator [ ] Manufacturer [ ] Distributor

[ ] Retailer [ ] Dispenser [ ] Medical Practitioner/End User

[ ] Other, Specify .....

7. District: .....

8. Province: .....

SECTION 2: AWARENESS OF MEDICINES REGULATORY SYSTEMS

1. How long have you worked for in this Sector?

[ ] Less than 1 year [ ] 1-5 years [ ] 5-10 years

[ ] 10-20 years [ ] More than 20 years

2. Are you aware of the medicines regulatory requirements in force in Zambia?

[ ] Yes

[ ] No *(skip to Section 3, question 1)*

3. Over the Time you have worked in this sector, how would you say the medicines regulatory systems have been improved?

[ ] Significantly Improved

[ ] Slightly Improved

[ ] Not Changed

[ ] Slightly Worsened

[ ] Significantly Worsened

SECTION 3: IMPACT OF MEDICINES REGULATION

1. Do you agree that medicines regulation is necessary to assure product quality, safety and efficacy?

[ ] Strongly Agree

[ ] Agree

[ ] Not Sure

[ ] Disagree

[ ] Strongly Disagree

2. In your opinion, do you think there is a relationship between medicines regulation and quality of health care?

[ ] Yes

[ ] No

[ ] Not Sure

3. In your opinion, how has the current regulatory system impacted on the quality of health care and treatment outcomes?

[ ] Improved treatment outcomes

[ ] Worsened treatment outcomes

[ ] No impact on treatment outcomes

4. **In your opinion, whose responsibility is it to regulate medicines?** *(select only one option)*

[ ] Government

[ ] The Regulatory Authority

[ ] The Local Authority

[ ] Medical Practitioners

[ ] Business Houses

[ ] Every player in the supply chain including the general public

[ ] I do not know

SECTION 4: IMPROVEMENT OF REGULATORY SYSTEMS FOR MEDICINES

1. **How do you think the current medicines regulatory systems could be improved?** *(Select all applicable options)*

[ ] Decentralization

[ ] Strengthen Legal Provisions

[ ] Increase funding to the regulatory authority

[ ] Employ more staff under the regulatory authority

[ ] Increase public awareness campaigns on regulation of medicines

[ ] Others. Specify

a) .....

b) .....

c) .....

d) .....

2. **Do you think Regional Regulation and Collaboration could improve the medicines regulation in Zambia?**

[ ] Strongly Agree

[ ] Agree

[ ] Not Sure

[ ] Disagree

[ ] Strongly Disagree

End of questionnaire. Thank you for your time and Candide responses. Please return the questionnaire to the enumerator.

APPENDIX 5: CONSENT FORM

University of the Western Cape
in partnership with
Hibernia College, Ireland

CONSENT FORM

CONSENT FORM

Protocol Title:

REVIEW OF THE EFFECTIVENESS OF THE MEDICINES REGULATORY SYSTEMS IN ZAMBIA OVER THE PERIOD 1995 TO 2015

Please tick the appropriate answer.

I confirm that I have read and understood the Respondents' Information Leaflet dated _____ attached, and that I have had ample opportunity to ask questions all of which have been satisfactorily answered. ☐**Yes** ☐**No**

I understand that my participation in this study is entirely **voluntary** and that I may withdraw at any time, without giving reason. ☐**Yes** ☐**No**

I understand that my identity will remain confidential at all times. ☐**Yes** ☐**No**

I have been given a copy of the Respondents' Information Leaflet and this Consent form for my records. ☐**Yes** ☐**No**

FUTURE USE OF ANONYMOUS DATA:
I agree that I will not restrict the use to which the results of this study may be put. I give my approval that collated unidentifiable data from my responses may be stored or electronically processed for the purpose of scientific research, but may not be used for any other purpose other than what has been indicated in the Respondents' Information leaflet

☐**Yes** ☐**No**

Respondent _____ _____
Signature and dated Name in block capitals

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06 JUN 2016
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P/BAG 125, LUSAKA.

To be completed by the Investigator or his nominee.

I the undersigned have taken the time to fully explain to the above respondent the nature and purpose of this study in a manner that he/she could understand. I have explained the risks involved the experimental nature of the treatment, as well as the possible benefits and have invited him/her to ask questions on any aspect of the study that concerned them.

Signature:	**Name in Block Capitals:**	**Qualification:**	**Date:**

3 copies to be made: 1 for respondent, 1 for PI and 1 for the respondents' institution records.

Version 3.0 30/12/2015

APPENDIX 6: RESPONDENTS' INFORMATION LEAFLET

University of the Western Cape
in partnership with
Hibernia College, Ireland

RESPONDENTS' INFORMATION LEAFLET

Respondents' Information Leaflet

Protocol Title:

REVIEW OF THE EFFECTIVENESS OF THE MEDICINES REGULATORY SYSTEMS IN ZAMBIA OVER THE PERIOD 1995 TO 2015

Principal Investigator's Name: **Emmanuel Kabali**

Principal Investigator's Title: **Dr.**

Telephone No. of Principal Investigator: **+260 977 723137**

You are being invited to take part in a questionnaire survey. You have been randomly chosen from amongst all registered health/nursing care and pharmaceutical supply chain professionals, to participate in this study. You have been selected because your opinions are important in this study.

Before you decide whether or not you wish to take part, you should read the information provided below carefully. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the benefits of participating in this study so that you can make a decision that is right for you – this process is known as Informed Consent.

You are not obliged to take part in this study and failure to participate will have no effect in any way on your future endeavors. You may change your mind at any time (before the start of the study or even after you have commenced participating in the study) for whatever reason without having to justify your decision and without any negative impact on you.

WHY IS THIS STUDY BEING DONE?

The main aim of this study is to review the effectiveness of the medicines regulatory systems under the three different pieces of legislation, in relation to disease treatment outcomes. Specifically, the study aim to:

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1. To highlight the changes in the legal provisions for medicines regulations in the Laws of Zambia over the last 20- years period from 1995 to 2015;
2. To evaluate how the changes to the law for regulation of medicines has improved the regulatory framework in place in Zambia;
3. To highlight how the prevalence of human diseases of national importance and their treatment outcomes has evolved over the last 20 years; and
4. To investigate the relationship between the changes in regulatory frameworks for medicines regulation and the changes in disease prevalence and treatment outcomes.

WHO IS ORGANISING AND FUNDING THIS STUDY?

The study is being conducted as a partial fulfilment of academic requirements for the Master of Science in Pharmacy Administration and Policy Regulation. The study is funded by the Principal Investigator, and no funds are being received from any Institution or organization for any part of this study.

HOW WILL IT BE CARRIED OUT?

Your selection as a participant on this survey was carried out using stratified random sampling. Selection was done from the official register maintained by your Professional Council. Only information relevant to the sampling process and contacts for purposes of administering this questionnaire to you was accessed. The questionnaire is located at the link provided in the email sent to you. You are only required to provide responses to the questionnaire following the provided information. It will take you approximately 20 minutes to complete the questionnaire. Once you reach the end of the questionnaire, kindly submit it back to the provider as instructed.

WHAT WILL HAPPEN TO ME IF I AGREE TO TAKE PART?

Other than providing required responses to the questionnaire, there will be nothing more that will be done to you. NO PAYMENT WILL BE PROVIDED TO RESPONDENTS.

BENEFITS:

No direct benefit will come to any of the respondents. However, the findings will be useful in improving the regulatory systems for medicines in Zambia.

RISKS:

There are very minimal risks associated with this study, in form of stress and loss of time taken to answer the questionnaire.

CONFIDENTIALITY ISSUES

All the information about you obtained from your professional council, and obtained from your responses will be strictly confidential and will only be used for the purposes of this study. After completion of the study, all identifiable information will be permanently destroyed, and will not be retained. However, collated unidentifiable data from your responses may be stored or electronically processed for the purpose of scientific research, but may not be used for any other purpose.

IF YOU REQUIRE FURTHER INFORMATION

If you have any further questions about the study or if you wish to withdraw from the study, you may do so without justifying your decision.

For additional information now or any future time please contact:

Dr. Emmanuel Kabali *(Principal Investigator)*
C/O Zambia Medicines Regulatory Authority
Plot 6903 Tuleteka Road, Off Makishi Road
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APPENDIX 7: APPROVAL LETTERS

ETHICS APPROVAL

ERES CONVERGE

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Email: eresconverge@yahoo.co.uk

I.R.B. No. 00005948
F.W.A. No. 00011697

6th June, 2016

Ref. No. 2015-Oct-003

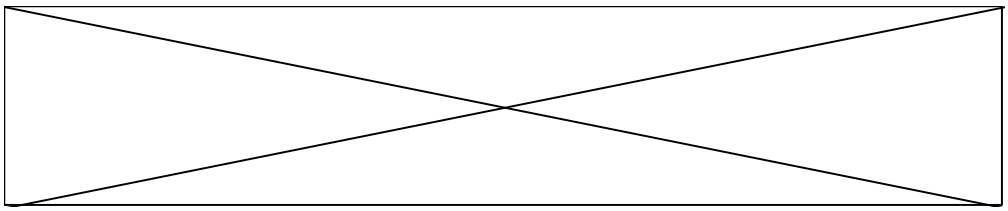
The Principal Investigator
Dr. Emmanuel Kabali
C/o Zambia Medicines Regulatory Authority
Plot No. 6903, Tuleteka Road, Off Makishi Road,
P.O. Box 31890,
LUSAKA.

Dear Dr. Kabali,

RE: REVIEW OF THE EFFECTIVENESS OF THE MEDICINES REGULATORY SYSTEMS IN ZAMBIA OVER THE PERIOD 1995 TO 2015.

Reference is made to your corrections dated 25th May, 2016. The IRB resolved to approve this study and your participation as Principal Investigator for a period of one year.

Review Type	**Ordinary**	Approval No. **2015-Oct-003**
Approval and Expiry Date	Approval Date: 6th June, 2016	Expiry Date: 5th June, 2017
Protocol Version and Date	Version-Nil	5th June, 2017
Information Sheet, Consent Forms and Dates	• English.	5th June, 2017
Consent form ID and Date	Version-Nil	5th June, 2017
Recruitment Materials	Nil	5th June, 2017
Other Study Documents	Questionnaire.	5th June, 2017
Number of participants approved for study	743	5th June, 2017



Print - Close Window - Click More at the bottom of the email to print a single message

Subject:Fw: Thesis Title Registration
From: emmanuel kabali (cutrite50@yahoo.co.uk)
To: Rafik Bapoo rbapoo@uwc.ac.za; ekabali@zamra.co.zm;
Date: Wednesday, 22 July 2015, 18:26

FYA

On Wednesday, 22 July 2015, 17:26, emmanuel kabali <cutrite50@yahoo.co.uk> wrote:

Dear Rafik

Thank you every much for the confirmation.

I will proceed to carry out the rest of the research and prepare the thesis accordingly, with the able support of my supervisor and the co-supervisor.

Best regards
Emmanuel

On Wednesday, 22 July 2015, 16:03, Rafik Bapoo <rbapoo@uwc.ac.za> wrote:

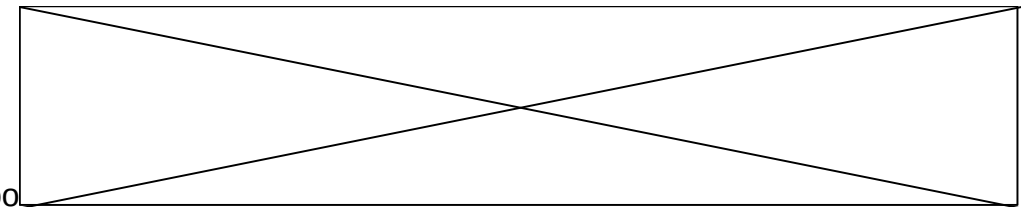
Dear Emmanuel
The thesis title of your research project has been approved by the relevant Senate committee.

Review of the effectiveness of medicines regulatory systems in Zambia over the period 1995 to 2015

Please keep in contact with your supervisor to complete the work necessary and submit

timeously.

Regards

Rafik A Bapoo 

MINISTRY OF HEALTH AUTHORIZATION

All Correspondence should be addressed to the
Permanent Secretary
Telephone: +260 211 253040/5
Fax: +260 211 253344

REPUBLIC OF ZAMBIA
MINISTRY OF HEALTH

In reply please quote:
MH /71/3/8
No.....

NDEKE HOUSE
P. O. BOX 30205
LUSAKA

6th May 2016

Emmanuel Kabali (Dr.),
University of the Western Cape,
South Africa.

RE: REQUEST FOR AUTHORISATION TO ACCESS HEALTH POLICY DOCUMENTS AND NATIONAL DISEASE OUTCOME REPORTS FOR THE PERIOD FROM 1995 – 2015: SUBMISSION OF ADDITIONAL INFORMATION

Reference is made to your letter dated 25st April 2016, requesting for authority to access the above mentioned documents.

You are kindly advised to contact the Policy and Monitoring and Evaluation Units to access the said documentations. You are also advised to use the required documentation strictly for academic purposes.

Wishing you all the success in your study.

Dr. Peter Mwaba,
Permanent Secretary
MINISTRY OF HEALTH

ZAMBIA MEDICINES REGULATORY AUTHORITY AUTHORIZATION

All correspondence should be addressed to the Director General

In reply, please quote .....

ZAMBIA MEDICINES REGULATORY AUTHORITY

19th April 2016.

Dr E. Kabali
C/O Zambia Medicines Regulatory Authority
Plot No. 6903 Tuleteka Road, Off Makishi Road
P.O Box 31890
Lusaka.

Dear Sir

RE: REQUEST FOR ATHORISATION TO ACCESS MEDICINES/HEALTH POLICY DOCUMENTS FOR THE PERIOD FROM 1995-2015 FOR RESEARCH PURPOSES.

Reference is made to your letter dated 29th March 2016 on the above subject matter.

We have no objection to your request to access the relevant documents and reports needed for you to successfully undertake your study.

Furthermore, we will be happy to receive a copy of your final report and wish you all the best in your studies.

Yours Faithfully,
For/**Zambia Medicines Regulatory Authority**

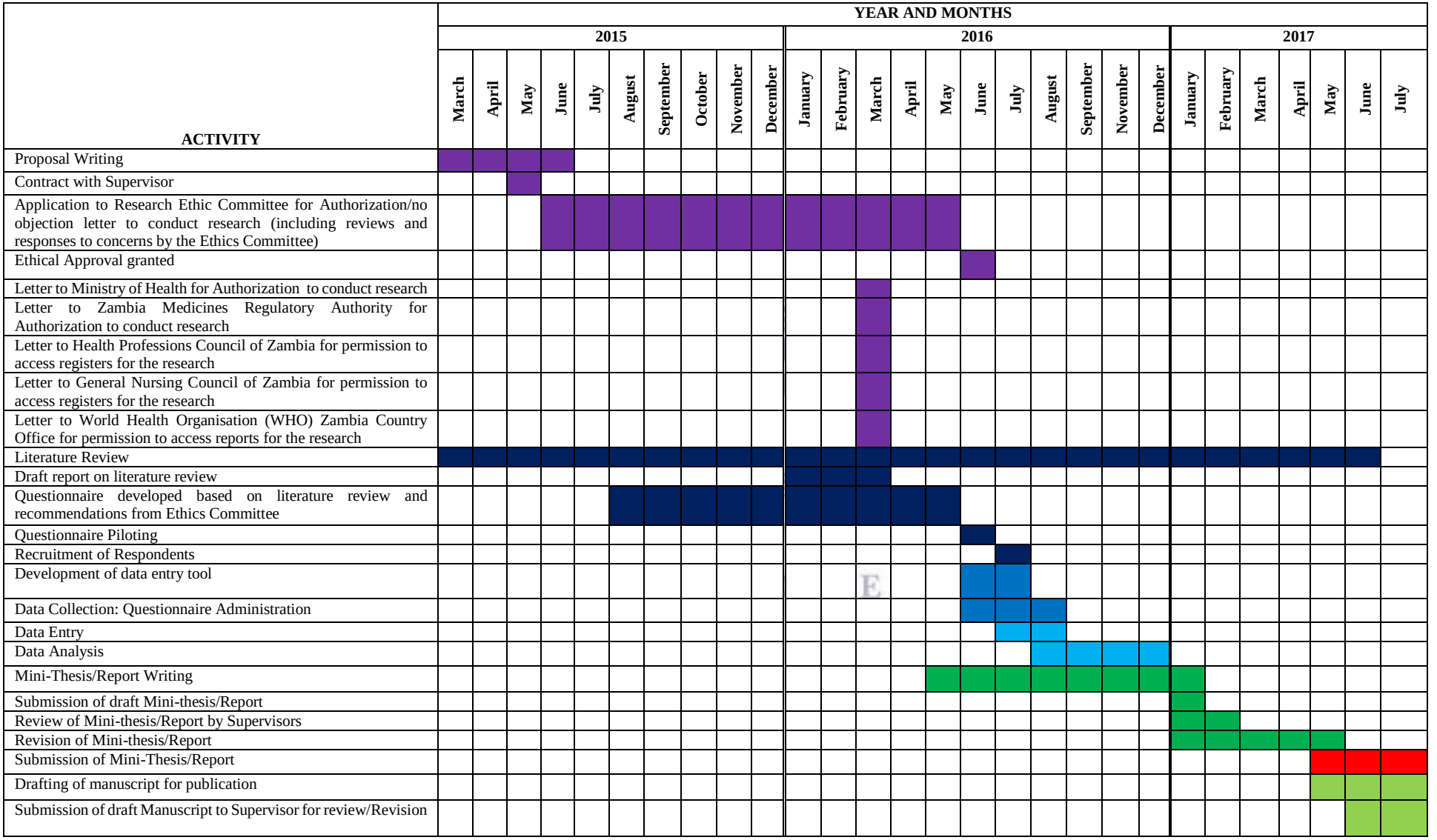
Z.Munkombwe (Dr)
Director Medicines Control
FOR/DIRECTOR GENERAL

Head Office
Plot No: 6903, TuletekaRoad/ Off Makishi Road
P.O. Box 31890 Lusaka, ZAMBIA
Tel: +260 211 220429, Telefax: +260 211 238458
E-mail: pharmacy@zamra.co.zm

Ndola Office
No: 41 Kafironda Drive, Itawa
P.O. Box 70876
Telefax: +260 212 610522
Website: www.zamra.co.zm

Report Adverse Reactions to:
Pharmacovigilance Unit, Lusaka
Tel: +260 211 220088 / 220098 / 220109
E-mail:pharmacy@zamra.co.zm

APPENDIX 6: CHART OF WORK/ACTIVITY FLOW



APPENDIX 7: RESEARCH ASSOCIATED COSTS (EXCLUDES TUITION AND OTHER FEES)

COST SUMMARY			
DESCRIPTION	**QTY**	**UNIT PRICE (ZMK)**	**AMOUNT (ZMK)**
DATA COLLECTION			
Ethical Clearance Costs	1	1,200.00	1,200.00
Data Collection (electronically) inclusive of internet costs	9	500.00	4,500.00
Questionnaire Pre-testing	1	400.00	400.00
Results Dissemination	6	200.00	1,200.00
Survey Monkey Subscriptions (Monthly)	11	286.00	3,146.00
SUBTOTAL			**10,446.00**
STATIONARY			
Reams Paper	4	45.00	180.00
Laptop Computer	1	6,000.00	6,000.00
Printer	1	950.00	950.00
Printer Ink Cartridge	2	1,150.00	2,300.00
Pens	5	10.00	50.00
Writing pads	3	15.00	45.00
Clipboards	1	10.00	10.00
SUBTOTAL			**9,535.00**
TRAVEL EXPENSES			
Fuel and vehicle consumables for Principal Investigator (20 days)	20	300.00	6,000.00
SUBTOTAL			**6,000.00**
TOTAL			**24,781.00**