CHALLENGES OF REGULATORY REQUIREMENTS ON MEDICINES REGISTRATION IN ZAMBIA- PERCEPTIONS OF LOCALLY BASED PHARMACEUTICAL COMPANIES.

By

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DECLARATION

I Sakeni Hadebe hereby declare that this dissertation entitled challenges of regulatory requirements on medicines registration in zambia- perceptions of locally based pharmaceutical companies represents my own work and has not been presented either wholly or in part for a degree at the University of Zambia or at any other University and it is not being submitted concurrently for any other degree

Signature ……..Date……..

APPROVAL

This dissertation of Sakeni Hadebe has been approved as fulfilling the requirements for the award of Master of Public Health by the University of Zambia

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ABSTRACT

Introduction

The Zambia Medicines Regulatory Authority (ZAMRA) has been mandated by the by the Medicines and Allied Act of the laws of Zambia to ensure quality, safety and efficacy of medicines. Since about 90% of medicines are imported from abroad, registration process contribute to the availability of quality, safe and efficacious medicinal products in the country. In this regard the registration process needs to be effective and should avoid unnecessary delays in order to increase the classes of medicines registered in the country.

Study objective

The aim of this study was to identify challenges of medicines registration requirements as perceived by locally based pharmaceutical companies

Methodology

A descriptive cross sectional study design was used to survey the regulatory local technical representative for foreign based applicants . Forty-Seven local technical representative was involved in the study. A designed medicines status form was used to assess dossier applications received in the past two years; 2018 and 2019. A total of 940 dossiers of applications submitted at ZAMRA during this period were assessed.

Results

Among 47 Local technical representative, more than half (74.46%) had low knowledge on medicines registration process with a significant association between training and knowledge of medicines evaluation.

Medicines registration process in Zambia is faced with challenges mainly from Local technical representative to quality of dossiers submitted for registration representatives due to limited knowledge on medicines registration concept.

DEDICATION

This work is dedicated to my wife Miriam Ngulube Hadebe, my daughters Grace, Mildred and son Joshua Sabelo Hadebe for having being there for me all the way and for them to work hard and depend on GOD alone as the only sustainer.

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First and uppermost, I would like to acknowledge the presence of Almighty GOD, the who gave me strength, encouragement and word of wisdom during my course and thesis write-up.

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Finally, to my loving wife Mirriam Ngulube, and our children, thanks you so much for all your supports and encouragements.

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LIST OF ABBREVIATIONS AND ACRONYM

API	Active Pharmaceutical Ingredient
CI	Confidence Interval
CTD	Common Technical Document
DMC	Director of Medicines and Control
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
WHO	World Health Organization
ZAMRA	Zambia Medicines Regulatory Authority

CHAPTER ONE

INTRODUCTION

1.0 Introduction

The purpose of this study was to determine challenges faced by locally based pharmaceutical companies during medicine registration process. The main objective of evaluation is to ensure that before a medicine is placed on the Zambian market, there is enough evidence that it has been properly formulated, manufactured and adequately tested and meets the criteria of safety, efficacy and quality established by Zambia Medicines Regulatory Authority. The outcome of the drug registration process is either the issuance or the denial of a pharmaceutical product marketing authorization or licence. The process may be tedious leading to some application being queried or rejected depending on the deficiencies noted in the application documents.

1.1 Background to the study

In the last two decades, medicines regulation had become more organised at international and regional level for instance International Council on Harmonisation (ICH) and European Medicines Agency (EMA) respectively. Since 1989, over forty guidelines have been harmonised in the European Union, Japan and USA through the ICH and in July 2003 a Common Technical Document (CTD) that assists in medicine application among the three regions was finally implemented (Willemen, 2011; Kidd, 1996). Nowadays, many African medicines regulatory authorities (MRAs) structure their dossier requirements along with WHO and global CTD format in respect to their national settings as part of the African harmonisation initiative (Moran et al. 2010). The same format was adopted by Zambia Medicines Regulatory Authority (ZAMRA) in 2015 and implemented in 2016 (DMC-2016 guidelines).

In Zambia, initially medicines registration also known as marketing authorization or product registration was gradually introduced by the pharmacy and poisons board under Ministry of Health through smooth transition taken as a notification from 1941 (Pharmacy and poisons Act, 1941). During that time several applications were received, and products were easily available on the

market. The Pharmacy and poisons Act, 1941 was repealed and replaced by the Pharmaceutical Act, 2004 which established the Pharmaceutical Regulatory Authority (PRA) as an autonomous board responsible for regulation of medicines. The act provided conditions under which a medicinal product may be registered in Zambia that included ensuring that all medicines available in the country, whether of domestic or foreign origin conform to the required standards of safety, quality and efficacy throughout their chain of distribution/supply, manufacturing, promotion, sale and use. There was a transition period purposely to give ample time for the Authority to prepare guidelines to assist applicants and evaluators to respectively submit and evaluate correctly the required information. Following the preparation of the CTD guidelines, the applications were received and implementation of the guidelines gradually commenced.

The pharmaceutical act, 2004 was repealed and replaced by the medicines and allied substances Act, 2013 that renamed PRA to ZAMRA with a wider scope of regulations including provision of the repealed Pharmaceutical Act, 2004.After establishment of ZAMRA in 2013, the registration of medicines was made under Section V of the MASA, 2013. Currently, ZAMRA has gained expertise and knowledge of medicine evaluation. This knowledge and expertise has led to changes in medicines registration requirements which has resulted in most of dossiers submitted ending up in non-conformance, rejection or queried hence prolonged registration time. Subsequently, this have resulted in unavailability of medicines within the medicines supply chain (National Health Policy/Drug Policy [2012] p, 39).Studies conducted (WHO 2006; Molzon J.A 2010; New partnership for Africa's development [NEPAD] 2010 and Handoo 2012;) concluded that, although there is a continuous process of harmonization taking place all around the world, still we see a huge challenge, which is yet to be overcome by the Pharmaceutical industry in case of country specific registration requirements. This is due to the heterogeneity in the regulatory landscape of the various countries.

A study conducted by Kaplan and Laing (2003) in 34 developing countries reported that fees charged by drug regulatory authority (DRA) may be used as a policy instrument to speed up regulatory approval, to encourage retention of quality staff and to stimulate introduction of generics versus new chemical entities. However, the study revealed that there is little relationship between National Regulatory Authority registration fees and drug approval time in developing countries.Despite various studies that have been done on challenges experienced by the

pharmaceutical companies in medicines registration process in many parts of the world including Africa to which Zambia is unexceptional, there is still a gap in the literature specifically here in Zambia about challenges experienced by pharmaceutical companies in medicines registration process hence the need to conduct research and avail evidence based information about the various challenges being experienced in Zambia.

1.2 Statement of the problem

The constant availability of affordable medicines of assured quality, safety and efficacy is an important aspect of any national health care system. According to Medicines and Allied Substances Act [2013], The Republic of Zambia through the Zambia Medicines Regulatory Authority [ZAMRA] is committed to ensuring that all medicines available in the country, whether of domestic or foreign origin conform to the required standards of safety, quality and efficacy throughout their chain of distribution/supply, manufacturing, promotion, sale and use. Registration of medicines is one way to ensure the quality, safety and efficacy of medicines provided to the population. However, the registration of medicines may be cumbersome, requiring considerable regulatory compliance from applicants. Despite existence of drug legislation, regulation, registration procedure and guidelines that support medicines registration in Zambia, applicants are still facing a number of challenges that prevent smooth medicines registration process. Thus, this study seeks to ascertain those challenges perceived by applicants as well as the authority that hinder smooth registration process in Zambia and consequently availability of quality medicines at primary healthcare level.

1.3 purpose of the study

Registration of medicines in Zambia began in 1940 under pharmacy and poisons board which was established by the pharmacy and poisons Act No. 38 of 1940. The process passed through a transition period that began with abridged applications until registrations guidelines where finalised. The registration process of medicines continued under the same guidelines until 2004 when the Pharmacy and Poisons Act was repealed and replaced by the Pharmaceutical Act of 2004. The Pharmaceutical Regulatory Authority (PRA) established under the Pharmaceutical Act modified the guidelines to assist the applicants and the assessors to respectively submit and assess correctly the required information with regards to quality, safety and efficacy. The guidelines were being aligned to global requirements to ensure that only safe, quality and efficacious medicines

are registered in Zambia. The Pharmaceutical Act was repealed and replaced by the Medicines and allied substances Act of 2013 which introduced a new format of product application known as Common Technical Document format (CTD). The format entails that all applications are submitted in five modular form and the same information (modules) is applicable globally.

Despite existence of medicines legislation, regulations and guidelines that support the registration process, applicants are still facing several challenges that prevent smooth registration process. Based on the recent ZAMRA (Department of Medicines Control [DMC] 2018) annual report, Three Hundred and eighty (380) applications where evaluated and only Fifty-One (51) complied and were approved leaving the rest of the applications either provisional approved or deferred depending on the level of discrepancy with the guidelines. As a result, much needed medicines may lack availability in both public and private sector.

The purpose of this study was to ascertain those challenges perceived by applicants as well as the authority that hinder smooth registration process in Zambia.

1.4 Study Objectives

1.4.1 General Objective

The general objective of the study was to assess the challenges experienced by locally based pharmaceutical companies when applying for medicines registration in Zambia.

1.4.2 Specific Objectives

1. To assess the level of knowledge of personnel involved in dossier submission
2. To assess quality of dossiers submitted for evaluation with respect to the registration guidelines
3. To determine factors hindering applicants in the process of medicines registration in Zambia.

1.5 Research Question

1. What is the level of knowledge of personnel involved in dossier submission?
2. What is the level of compliance of dossiers submitted for evaluation to ZAMRA with respect to the registration guidelines?
3. What are the factors hindering applicants in the process of medicines registration in Zambia?

1.6 Research hypothesis

The study was exploratory in nature meant to understand the challenges experienced by locally based pharmaceutical companies when applying for medicines registration in Zambia.

1.7 Significance of the study

The constant availability of affordable medicines of assured quality, safety and efficacy is an important aspect of any national health system.

Results from this study may help in the formulation of strategies within ZAMRA to meet its registration timelines. Smooth and timely registration could increase the number and quality of registered medicines and therefore increase competition among registered medicines. This could eventually lower prices, increase availability and affordability of essential medicines in the country.

1.8 Scope of the study

The study focused only on challenges from applicants and evaluators perspective with regards to compliance with technical requirements. The financial implications of the registration process are outside the scope of this study.

1.9.0 Conceptual framework

The figure below on the conceptual framework brings into view the key factors of the registration process of medicines. The researchers constructed framework was based on the literature review and depict the possible hindrance to smooth registration process of medicines.

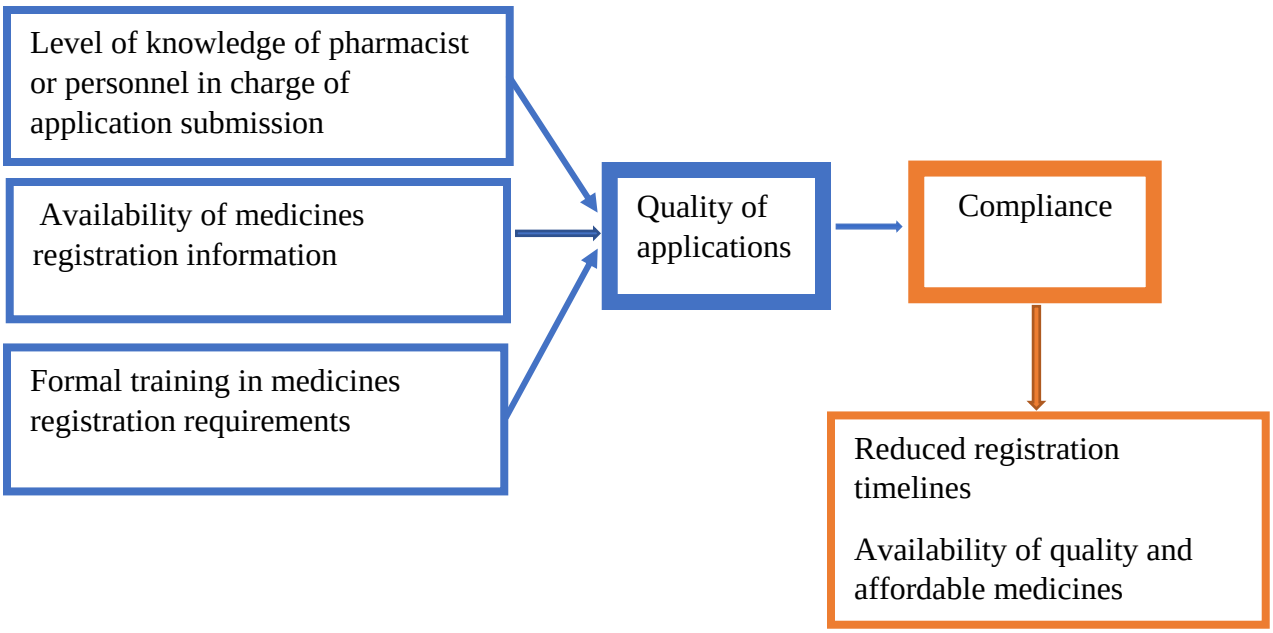

Figure 1.0 conceptual framework of the medicine registrations process.

Source: researcher's Construction, 2023.

1.9.1 Dependent Variable

Compliance -this is the state of being in accordance with established guidelines. The level of compliance will be assessed using the medicines applications status form and structured questionnaire.

1.9.2 Independent Variables

Independent predictors include level of knowledge of pharmacist or personnel in-charge of dossier submission, availability of information on registration requirements and formal training in

medicines registrations procedures. In both, evaluators and pharmacist in-charge for each question a zero (0) point will be awarded for an incorrect answer and one (1) point for the correct answer. Therefore, the knowledge scale will be graded as low (0-2), medium (3-5) and high (6-8).

1.10 Operational definition

The following definitions apply to product registration status

- **Approved:** the product is granted marketing Authorisation by the committee after satisfying all the registration requirements set out by the regulatory Authority.
- **Provisional approval:** The product is granted conditional approval pending minor deficiency noted by the expert and advisory committee.
- **Deferred application:** These are application whose registration is postponed pending major deficiency as noted by the expert and advisory committee.
- **Rejected applications:** these are deferred applications that do not meet the registration requirements even after addressing initial deficiencies.

1.11 Ethical Considerations

Ethical clearance to carry out the research was obtained through The University of Zambia Biomedical research ethics Committee (UNZABREC) with REF. 3617-2023 and National Health Research Authority Ref No: NHRA00001/21/03/2023. Permission to conduct the study in the selected sites was granted by pharmaceutical company's owners and ZAMRA. According to Declaration of Helsinki, principles related to conducting researches on human subjects were followed to ensure that ethical standards that promote respect for all human subjects and protect their life, health, dignity, integrity, right to self-determination, privacy, and confidentiality were adhered to. Names of participants or any information leading to direct identification of individuals will not be used and thus, privacy and confidentiality of personal information will be upheld through applying a coding ID system that will not include the participant's name or personal data. Consent was also obtained from individual(s) or respective respondents (including signing a consent form as an assurance of confidentiality) and the nature and purpose of the study was made clear to them. The respondents were assured that the information obtained from them will be used for the purpose of study only and that feedback will be provided to them where appropriate.

CHAPTER TWO

2.0 REVIEW OF RELATED LITERATURE

2.1 Historical Overview

Regulation of medicines is a process encompassing various activities aimed at ensuring the safety, efficacy and quality of drugs as well as appropriateness and accuracy of product information (WHO, 1999). The regulation started 50 years back in which regulatory standards were set primarily to ensure the quality of medicinal products (Hill and Johnson, 2004). Eventually, in the early 1960s drug regulation led to the development of standards for testing efficacy and safety of new medicines (Willemen, 2011). Despite the existence of standards for drug regulation for at least 50 years, there are still many problems with the safety and quality of medicines in many countries (Hill and Johnson, 2004).

Recent studies conducted (WHO 2006; Molzon J.A 2010; New partnership for Africa's development [NEPAD] 2010 and Handoo 2012;) concluded that, although there is a continuous process of harmonization taking place all around the world, still we see a huge challenge, which is yet to be overcome by the Pharmaceutical industry in case of country specific registration requirements. This is due to the heterogeneity in the regulatory landscape of the various countries. Kirti Narsai in his recent article [2012] stipulates that, "Pharmaceutical companies operating in Africa are experiencing difficulties in complying with the technical requirements of medicines registration for individual African markets". Zambia is among the African countries where similar challenges are experienced.

A study conducted by Ratanawijitrasin and Wondemagegnehu (2002) reported that the time taken to assess and register a product should be long enough to ensure medicines are effectively assessed

for safety, efficacy and quality, however should not lead to loss of lives, disincentive to research and development. Moreover, registration time should not be compromised to endangering the health of patients and the public. A study conducted by Kaplan and Laing (2003) in 34 developing countries reported that fees charged by drug regulatory authority (DRA) may be used as a policy instrument to speed up regulatory approval, to encourage retention of quality staff and to stimulate introduction of generics versus new chemical entities. However, the study revealed that there is little relationship between DRA registration fees and drug approval time in developing countries.

A study conducted by Bate et al. (2010) reported that there were significant differences in the length of time taken by various drug authorities to evaluate registration applications. The average period was three to six months for developing countries while emerging countries (middle income countries like Russia, Brazil, China, India and Thailand) took 12-18 months. Different renewal policies exist between countries. In Tanzania registration certificates are valid for a period of five years (TFDA Customer Service Charter, 2012) while other country such as India, renewal is after every three years. In other countries such as Russia once re-registration is granted then an open-ended certificate is granted (Bate et al. 2010). Therefore, Zambia should rely on its own registration procedure in order to maintain its mission of safeguarding her public health.

Based on the recent ZAMRA (Department of Medicines Control [DMC] 2015) annual report, 380 applications where evaluated and only 51 complied and were approved leaving the rest of the applications either provisional approved or deferred depending on the level of discrepancy with the requirements and criteria. As a result, much needed medicines may lack availability in both public and private sector.The inconsistent supply of essential pharmaceuticals and medical supplies has remained a major problem in Zambia (National Health Policy/Drug Policy [2012] p, 39). This has been attributed to a combination of factors including weak regulatory framework and management systems.

The Ministry's Strategic Plan (2006-2010) is also categorical in specifying that the ministry would encourage the establishment of a strong local pharmaceutical industry to lower the costs of drugs (National Health Sector Strategic Plan, 2006:33). Section 5 of the NDP, has a provision that discriminatory tariffs promoting imported finished pharmaceuticals was to be abolished. Furthermore, the policy mentions that MoH shall use Government drug funds to procure locally manufactured pharmaceuticals (National Drug Policy, 1999:10). The Pharmaceutical Act No. 14

of 2004 is also in place that helps with registration and regulation of the pharmaceutical business. An assessment of local production of medicines conducted by a WHO team of experts in some African countries indicated that out of forty six (46) countries, thirty four (34) have secondary level production and nine (9) countries have no production capacity. Mhamba and Mbirigenda (2010) revealed that the pharmaceutical manufacturing companies lacked advanced equipment or machinery, and skilled trained personnel. In the UNIDO report (2010), it is indicated that better machinery and equipment will increase production capacity for pharmaceutical companies. Zambian Pharmaceutical companies lack the advanced technology in modern day manufacturing thereby affecting productivity (MeTA, 2010). Pharmaceutical production is capital, technology and knowledge intensive, which means that the appropriate technical expertise is absolutely critical, both in terms of sufficient numbers and appropriate skills, (Seita, 2005)

World Health Organization, 2001 began drug prequalification program as a "surrogate" regulatory approval mechanism on which international procurement groups such as the Global Fund to Fight AIDS, Tuberculosis and Malaria could rely on while developing country capacity for drug regulation was being strengthened (WHO report, 2012; Moran et al 2007). Under this program medicine evaluations are conducted by mixed teams of developed and developing country experts, with around one-third of reviewers from Africa (Moran et al. 2010).A study conducted by Kaplan and Laing (2003) in 34 developing countries reported that fees charged by drug regulatory authority (DRA) may be used as a policy instrument to speed up regulatory approval, to encourage retention of quality staff and to stimulate introduction of generics versus new chemical entities. However, the study revealed that there is little relationship between DRA registration fees and drug approval time in developing countries. Different renewal policies exist between countries. In Tanzania registration certificates are valid for a period of five years (TFDA Customer Service Charter, 2012) while other country such as India, renewal is after every three years. In other countries such as Russia once re-registration is granted then an open-ended certificate is granted (Bate et al. 2010). Therefore, Zambia should rely on its own registration procedure in order to maintain its mission of safeguarding her public health.

CHAPTER THREE

3.0 METHODOLOGY

According to Burns & Grove 1998:745, Methodology and research design direct the researcher in planning and implementing the study in a way that is most likely to achieve the intended goal while Mouton (1996:35) describes methodology as the means or methods of doing something. This chapter covered the research design that was used for the study. This includes target population, sample size and sampling procedure. It also covered the type of instruments to be used in data collection procedures that was used in data collection and how data was analyzed The methodologies used to achieve the research objectives is presented below.

3.1 Research Design

A descriptive cross-sectional study design utilising quantitative research methods to analyse data was used. This approach emphasizes the collection and analysis of numerical data or statistical data and descriptive statistics was used to report open-ended questions. Structured questionnaires, medicines status form were used for data collection from local technical representative are attached as appendix.

3.2 Study Site

The study was conducted specifically in Lusaka. Lusaka is conveniently chosen because all pharmaceutical companies dealing with medicines registration and ZAMRA head office, a regulatory body mandated to perform all activities regarding medicines registration in Zambia is located within Lusaka.

3.3 Study Population

The study population was composing of representatives of manufacturer and pharmacists‟ in-charge as obtained from ZAMRA database. Study participants were being interviewed through questionnaires in order to get the information required to achieve study objectives.

3.4 Study Sample size

A convenient sampling technique was used to get the sample size due to the small number of pharmaceutical companies involved in medicines registration in the country. Based on ZAMRA Register 2020, there are fifty-six active registered representatives and 47 (83.93%) participants who were willing and available during the survey at the study were included. Retrospective data of all applications received in the past two years was collected (2018 and 2019). The rationale for selecting the period of 2018-2019 was based on the fact that the current Act was enacted in 2013 and dossiers are subjected to new guidelines. Factors that hinder smooth registration process was evaluated based on the number of applications registered, queried or rejected within the specified period.

3.5 Sampling Technique

Purposive and simple random sampling technique was used in the study. Purposive sampling is a non-probability sampling method and it occurs when elements selected for the sample are chosen by the judgment of the researcher (Payne and Payne, 2004).

3.6 Data Collection instruments

3.6.1 Assessment of Knowledge among pharmacist's in-charge

Structured questionnaire comprised of technical questions apart from demographic questions targeted to pharmacist's in-charge to assess their knowledge with regards to medicines registration procedures and requirements. The questions are based on importance of medicines evaluation and information required to be included in the applications and for each question a zero (0) point was awarded for an incorrect answer and one (1) point for the correct answer. Therefore, the knowledge scale was graded as low (0-4) and high (5-8).

3.6.2 Medicines applications status form

A reflective record review form was used to capture data for the past Two years on the application submitted to assess the status of applications received. The record review focused on the collection of the information on the outcome of application with the intention of determining the number of applications received, evaluated, rejected and queried. The assessment provided information on

the quality of the applications submitted hence determine the challenges faced from the ZAMRA perspective during medicines registration. The period was purposely considered in order to reduce confounding factors among different years.

3.7 Data collection procedure

The researcher got permission from the Director General at ZAMRA in Lusaka were the research was conducted before starting the process. Thereafter the researcher got the informed consent from the participants and then the research was carried out by administering the questionnaire.

3.8 Data Analysis

The data collected from the study was cleaned and counter-checked for their clarity and validity. The data was later coded and analyzed using STATA version 16. Measure of the central tendency and dispersion was analyzed by using descriptive statistics. The frequency distribution was used to show distribution of both the outcome and explanatory variables. Regression analysis will be used to determine the relationships between variables. Fischer exact test was used to test for associations between the outcome variables (knowledge) and the explanatory variables including gender, professional status, work experience and in- service training and A P-value of less than 0.05 was considered as statistically significant, at 95% confidence interval.

3.9 Summary

This chapter had discussed the research design used which is the descriptive phenomenology. It has also looked at the study population, sample size and the sampling procedure. The instruments for data collection which are the in-depth structured and interview guide have also been discussed. Lastly the data collection procedure and how data has been analysed has also been discussed.

CHAPTER FOUR

4.0 PRESENTATION OF FINDINGS

4.1 Socio-demographic information of participants

Out of the 47 applicants 32/47(68.09%) were pharmacists, 8/47(17.02%) were regulatory affairs, 4/47(8.51%) were scientists and only 3/47(6.38%) were pharmacy technologists. Out of the 16 females, 5/16(31.25%) were pharmacists, 3/16(18.75%) were pharmacy technologists, 8/16(50.00%) were regulatory affairs and none of the females was a scientist. Out of the 31 males, 27/31(87.10%) were pharmacists and 4/31(12.90%) were scientists while none of the males were pharmacy technologists or regulatory affairs. Figure 4.1 below shows the proportions of applicants by profession.

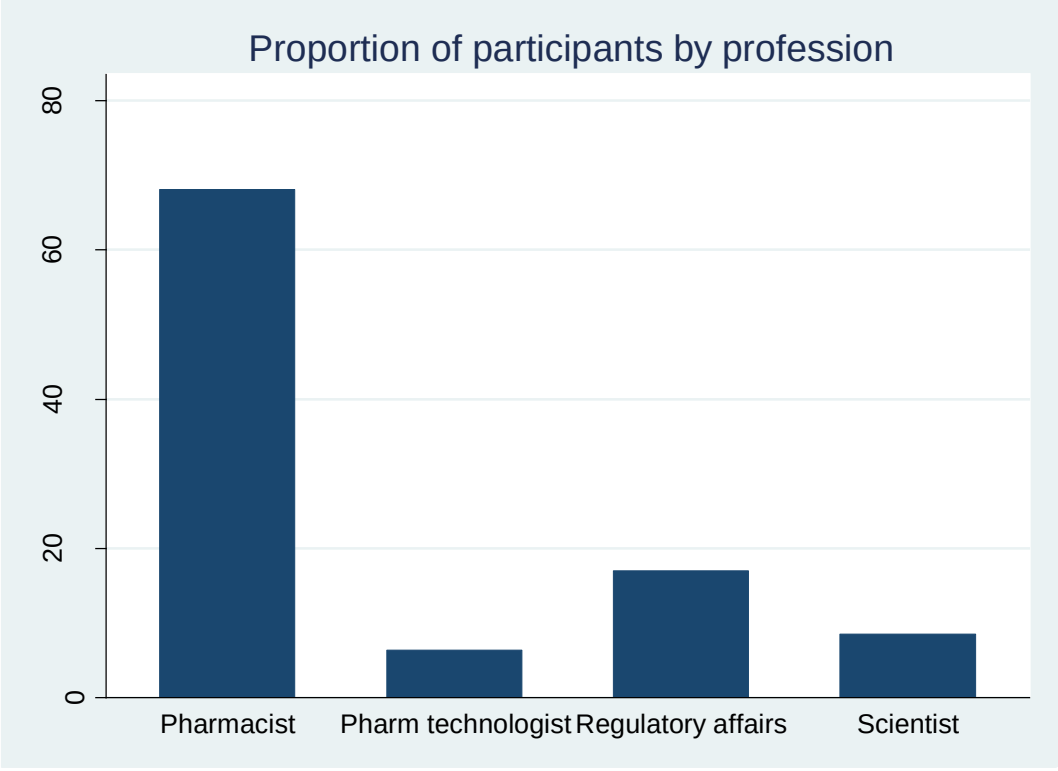

Figure 4.1 bar graph showing the professions of participants

In the study, there was a total of 47 applicants out of which 12 (25.53%) had good compliance while 35/47(74.46%) had poor compliance to medicine registration. Of the 47 applicants, 16/47(34.04%) were females and 31/47 (65.96%) were males.100%(16/16) of the females had poor compliance to medicine registration, while 23/31(74.19%) of the males had poor compliance. There was no statistical difference in the compliance levels of males and females (p – value=0.088). Table 4.1 Baseline characteristics stratified by compliance levels.

Table 4.1 Baseline characteristics stratified by compliance levels.

Variable	***High compliance (N=12)***	***Low compliance (N=35)***
Sex of applicant		
Female	5(18.70%)	14(81.25%)
Male	7(21.74%)	21(78.26%)
Profession of applicant		
Pharmacist	7(15.63%)	26(84.38%)
Pharmacy technologist	0(0.00%)	2(100.00%)
Regulatory affaire	0(0.00%)	8(100.00%)
Scientist	5(75.00%)	1(25.00%)
Number of years working in the same position		
0 to 1 year	0(0.00%)	4(100.00%)
2 to 5 years	4(21.05%)	15(78.95%)
6 to 10 years	0(0.00%)	4(100.00%)

Above 10 years	4(20.00%)	16(80.00%)
Convenient time allocated for medicine registration		
Strongly disagree	5(20.83%)	19(79.17%)
Disagree	3(15.79%)	16(84.21%)
Agree	0(0.00%)	4(100.00%)
Professional training adequate for dossier review		
Yes	6(18.18%)	27(81.82%)
No	2(14.29%)	12(85.71%)
Received in-house training for dossier preparation		
Yes	5(17.24%)	24(84.76%)
No	3(16.67%)	15(83.33%)
Knowledge levels		
High	5 (21.74%)	18(78.26%)
Low	3(16.67%)	15(83.33%)

4.2 Knowledge levels of local technical representative with regard to medicines registration procedure

Among 47 technical representative who indicated to know the importance of medicines evaluation, only 12 (25.53%) could explain correctly the importance of medicines evaluation "that is to ensure quality, safety and efficacy of medicines in the country

Since the outcome variable was binary, that is, whether the applicant had high compliance or Low, logistic regression was performed. Simple logistic regression was performed to obtain the unadjusted estimates and the investigator led stepwise regression was used to come up with the best fit model. Table 4.2 shows the unadjusted estimates from a simple logistic regression

Table 4.2 unadjusted estimates from simple logistic regression

Predictor	***Odds Ratio***	***P - value***	***95% CI***
Profession of applicant			
Pharmacist	1(Ref)	NA	NA
Scientist	16.2	0.066	(1.39, 188.89)
Position of applicant			
Pharmacist-in-charge	1(Ref)	NA	NA
Quality assurance manager	11.4	0.053	(0.97, 134.54)
Professional training adequate for dossier review			
No	1(Ref)	NA	NA
Yes	3.75	0.041	(0.13, 4.27)
Received training for dossier preparation			
No	1(Ref)	NA	NA
Yes	4.96	0.009	(2.00, 9.61)

At univariate level, the three variables that were statistically significant were knowledge on medicines registration, those who responded on professional knowledge being adequate for dossier

review before submission and those who received in-house training in dossier preparations. The rest of the variables were not statistically significant as their p values were more than 0.05. the selected variables were considered to be the predictors of compliance levels in medicine registration. Table 4.3 below, shows the factors associated with compliance levels in medicine registration

Table 4.3 Factors associated with compliance levels in medicine registration

Predictors	**Unadjusted estimates**			**Adjusted estimates**		
	Odds Ratio	**P – value**	**95% CI**	**Odds Ratio**	**P - Value**	**95% CI**
Knowledge on medicine registration						
Low	1(Ref)	NA	NA	1(Ref)	NA	NA
High	6.24	0.026	(1.39, 188.89)	17.52	0.032	(1.23, 248.79)
Received training for dossier preparation						
No	1(Ref)	NA	NA	1(Ref)	NA	NA
Yes	16.21	0.015	(14.05, 20.16)	17.91	0.002	(14, 22.24)
Professional training adequate for dossier review						
No	1(Ref)	NA	NA	1(Ref)	NA	NA
Yes	10.21	0.015	(07.05, 20.16)	13.91	0.002	(11, 22.24)

4.3 Time taken for dossier registration

Only 4 (8.51%) Local Technical representatives agreed with time taken of Twelve to Eighteen (12 to 18) months stipulated in the guidelines and service charter for medicines registration to be followed. Among the respondents, 19 (40.42%) disagreed and 27 (57.45%) strongly disagree with time taken for dossier registration. This indicates that the time taken for dossier registration is longer than that stipulated in the guidelines; which was 18 months.

4.4 Challenges of medicines registration encountered by local technical representative

In the study, 70.21%(33/47) of the clients said there was delayed response in acknowledging receipt of submissions, rejecting or approval of submissions by ZAMRA. 14.89%(7/47) said that there were too many re-submissions required from them without proper guidance on how ZAMRA wants it to be done and 14.89%(7/47) complained that ZAMRA officers were not available to attend to their queries as the emails and letters were not responded to. Figure 4.2 below is a pie chart showing the challenges faced by clients in medicine registration.

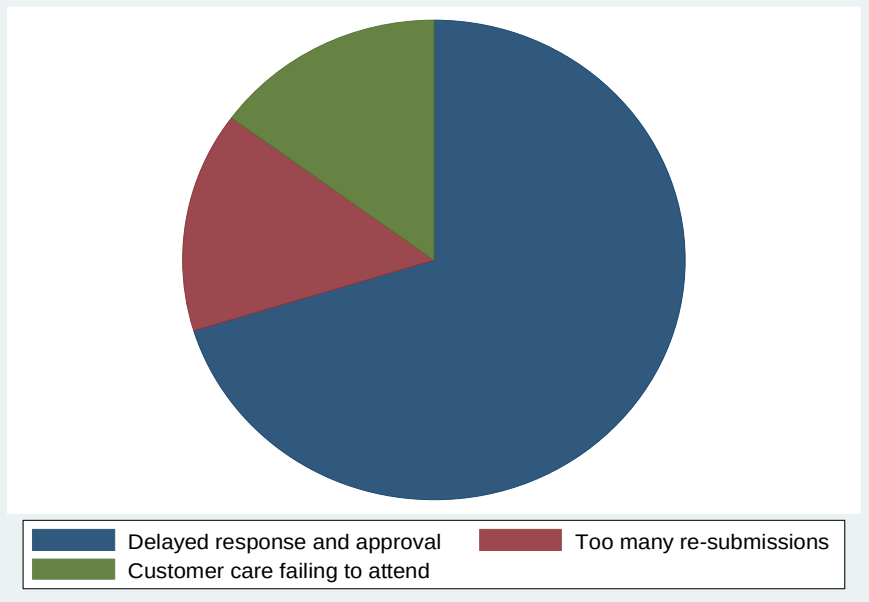

Figure 4.2 Challenges faced by clients in medicine registration.

4.5 Assessment of quality of dossiers undergoing evaluation with respect to the registration guidelines

A retrospective review of applications received for Two consecutive years were obtained (2018 and 2019. In total, 940 dossiers application were retrieved and assessed. In 2018, out of 589 applications received, 350 (59.42%) applications were evaluated and the remaining 239 (40.57%) were not evaluated. Among the evaluated applications, only 51 (21.33%) were registered, 188 queried, 3 rejected and 66 application had status not determined. In 2019, out of 351 applications received, 180 (51.28%) were evaluated and the remaining 171 (48.72%) were not evaluated. Among the evaluated applications, only 28 (16.37% were registered, 102 queried, 7 rejected and 34 had their status not determined.
Taken together, out of the 940 applications which were received for the period of two years, 79 (8.40%) applications were registered, 10 (1.06%) were rejected, 290 (30.85%) queried and 100 (10.6%) had their status not determined. Out of 530 dossiers which were evaluated, more than half (54.70%) of them were either rejected or queried. This is an indication that the quality of submitted dossiers is not adequate .
As per the Client Service Charter it is specified that for a normal type of dossier, the evaluation is supposed to take a minimum of Eighteen (18) months. In this study, 100 applications had no status remarks indicating that they were not yet evaluated indicating that such dossiers would take more than three years to be evaluated.

Table: 5. Proportion of human medicine applications received in 2010 and 2011 and their status as on April 2013

Year	New dossier applications received	New applications evaluated	New dossier applications not evaluated	Final Remarks after evaluation			
				approved	Queried	Rejected	Status not indicated
2018	**589**	**350 (59.42%)**	**239 (40.57%)**	**51 (21.33%)**	**188**	**3**	**66**

2019	**351**	**180 (51.28%)**	**171 (48.72%)**	**28 (16.37%**	**102**	**7**	**34**
Total	**940**	**530**	**410**	**79**	**290**	**10**	**100**

CHAPTER FIVE

5.0 DISCUSSION

The is the study conducted in Zambia on challenges of regulatory requirements on medicines registration in Zambia. The study focused on the local based pharmaceutical companies who are local technical representative. The study also had intended of assessing the knowledge of pharmacist in-charge who are involved in medicines registration. Many issues regarding registration of medicines have been revealed through this study. The study involved 47 technical representatives of companies specifically from abroad which was equivalent In addition, a total of 940 applications which were received in 2018 and 2019 were reviewed to determine the time taken for evaluation of a dossier, number of dossiers registered or rejected as per December 2021.

Effective medicines registration requires the medicines regulatory authority to have adequate number of qualified staff to perform medicines evaluation and registration. The staff, specifically evaluators, should be knowledgeable enough to provide the required technical assistance. WHO (2010) reported that authorization of medicines for sale in a country should be based on a scientific assessment of their safety, efficacy and quality and this is considered the core function of the regulatory authority. The same applies with regards to local technical representative for companies who applies for medicines registration. The study findings revealed that most of the Local technical representative 35 (74.47%) are qualified pharmacists and had received training formal. However, out of 47 representative only 12 were categorized as being compliant to medicines registration procedures and this is an indication that majority of staff involved in medicines registrations do not have the required expertise for dossier screening for completeness before submission.

The findings of this study also revealed that majority (61%) of the pharmacist in-charge had low knowledge on medicines registration concept. This observation has also been reported in a study which was conducted in Uganda by Moran et al (2010). In the later study it was revealed that pharmacy schools do not provide specific training in regulatory affairs, thus limiting the usefulness of graduates to medicines regulatory authorities (MRAs). These findings are also supported by the results of the situation analysis

conducted in Mozambique by WHO (2007). In that study, it was reported that there was lack of staff in terms of quantity and quality for the whole pharmaceutical sector.

ZAMRA guidelines has defined registration process to take a minimum of 18 months. However, it has been observed that the registration process goes beyond the stipulated timeframe. The finding from this study show that majority (97.87%) of local technical representative indicated that the time taken for registration of their applications is much longer than 18 months. This is also supported by the retrospective data analysis of the applications received in 2015, in which out of 940 applications, 410 applications had their status not yet determined as by April 2021. In other word, products of these applications would take more than three years to be registered in Zambia. These findings are similar to those reported by Narsai et al (2010) among local and multinational companies based in South Africa, indicating that registration timelines did vary between one and three years

Luck of robust information management system was mentioned as one of the challenges for effective dossier evaluation and registration. This challenge was reported by local representative representatives of foreign applicants. , . Similar findings were reported by Hill and Johnson et al (2010) indicating that competent MRAs should not only have sufficient scientific capacity to carry medicines registration but also an effective system of tracking application that would employ appropriate use of information technology. Similar findings were reported by Ratanawijitrasin and Wondemagegnehu (2002) in 10 WHO member states indicating that the time taken to assess and register a product should be long enough to ensure medicines are effectively assessed for safety, efficacy and quality.

The findings of this study suggest that more than half of the applications submitted in 2018 and 2019 were either rejected or queried. This is an indication that most manufacturers do not compile their dossier with regard to the countries specification. These findings might suggest that the personnel involved have limited knowledge on dossier preparation and/or the quality of the products submitted for registration do not meet the requirements. These findings are similar to those reported by WHO pre-qualification programme indicating that there are more quality, safety and efficacy related deficiencies in generic dossiers submitted and this was found to be the main reasons for delay in registration of products or rejection (Worku et al, 2012)

A study conducted by Handoo et al. (2012) also reported that, the primary challenge encountered by many countries is the submission of medicines dossiers that do not comply with registration requirement.

CHAPTER SIX

6.1 **Conclusions**

This study has found that medicines registration process in Zambia is faced with a number of challenges and reviews specific challenges from local technical representatives perspective.

The registration of medicines takes longer time than what has been stipulated in the guidelines. The prolonged registration is contributed by mainly due to poor compliance to medicines registration requirements. Limited knowledge observed among the pharmacist in-charge working in the pharmacies dealing with medicines registration contributes to their delay due to submission of poorly prepared medicine dossiers. If this problem is identified earlier it would certainly reduce the number of queries and rejection, thereby shortening registration process .

6.2 Recommendations

From this study a number of recommendations are given to improve the registration process of medicinal products in Zambia. They are classified into educational, managerial and regulatory approaches

i **Educational Approach**

Pharmaceutical Society of Zambia, ZAMRA should and Schools of pharmacy in the country should review pharmacy training curriculum for undergraduate course to include regulatory issues particularly in the area of medicines registration.

ii **Regulatory Approach**

ZAMRA should consider adopting reliance procedures with reliable regulatory Authorities to significantly reduce registration timelines. Improve the information management system to improve tracking of applications.

Another challenge mentioned by the applicants was lack of adequate personnel to clear backlog of dossiers and the Authority should ensure employing more staff to clear the backlog.

The study focused on the local technical representative, therefore a study should be conducted to identify challenges from the regulator perspective.

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APPENDICES

APPENDIX I: BUDGET

Material Needed	**Quantity required**	**Unit Cost (ZMW)**	**Total cost (ZMW)**
Proposal typing, printing and binding	04	500.00	2000.00
Flash disk (4GB)	01	100.00	100.00
Ethics approval	01	2000	2000.00
Typing and printing of questionnaires	150	10.00	1500.00
Fuel	250 liters	21.70	5425.00
Final report typing printing and binding	04	500.00	2000.00
Total		3131.70	13,025.00

APPENDIX II: ACTIVITY SCHEDULE

Activity/Timeframe	January	March	April	May
Proposal writing				
Data collection/ Data analysis				
Report writing				

APPENDIX III: INFORMATION AND CONSENT FORM

PARTICIPANTS INFORMATION SHEET

Title of the research

Challenges of the regulatory requirements on medicines registration in Zambia- perceptions of locally based pharmaceutical companies.

Introduction.

Please read this information sheet carefully and feel free to ask questions.

This research is being conducted by Sakeni Hadebe a Master of Science in Public Health Student at the University of Zambia school of Public Health. I wish to invite you to take part in a study aimed at assessing the challenges experienced by locally based pharmaceutical companies when applying for medicines registration in Zambia.

This information leaflet is providing you with information that will help you to decide if you would like to participate in this study. You should fully understand what is involved before consenting to take part. You should only agree to take part in this study only if you are completely satisfied with all the procedures involved.

About the study

This study is meant to understand the challenges experienced by locally based pharmaceutical companies when applying for medicines registration in Zambia.

Results from this study may help in the formulation of strategies within ZAMRA to meet its registration timelines. Smooth and timely registration could increase the number and quality of registered medicines and therefore increase competition among registered medicines. This could eventually lower prices, increase availability and affordability of essential medicines in the country.

What is needed

To participate in this study, you will firstly be asked to sign a consent form. This form is to show that you have understood what this study is about and have accepted to answer to the questions related to the study being undertaken. The researchers will ask you questions using a questionnaire regarding the challenges experienced by locally based pharmaceutical companies when applying for medicines registration in Zambia.

This process of completing the questionnaire shall take about 30 minutes**.**

Procedures

If you are comfortable and willing to participate in this study, you will be given a questionnaire to complete which will take about 30 minutes. No name will be included in the questionnaire and the typed documents.

Risks

We do not expect you to have any problems because of your participation in this study. However, some information we may learn from you may be personal, emotional and may compromise your privacy. We would like to assure you that the information we will get from you will not be shared with anyone outside the research team

Benefits

The study may help both locally based pharmaceutical companies and ZAMRA in the formulation of strategies to meet its registration timelines. Smooth and timely registration could increase the number and quality of registered medicines and therefore increase competition among registered medicines. This could eventually lower prices, increase availability and affordability of essential medicines in the country.

Data be collected

Data will be collected using a structured questionnaire. All the responses will be written on the questionnaire that will be used as a data collection tool.

Protecting data confidentiality

We have put up steps to protect the information we will get from you. Firstly, only members of the study team will be able to see the information. Secondly, we will not put names on any information collected from you. Instead, we will use numbers for identification. Thirdly, we will destroy all hard copy questionnaires. Soft copy data will be stored on a password protected computer in a locked office for a minimum of 5 years.

How will confidentiality and anonymity be ensured for the study?

What you will write is confidential and only the researchers would be able to have access to the information you will provide. You will not be identified by name in any research data or any reports to come out of the research. No individual information will be reported on. Any data will be reported in an aggregate way. Information will remain as confidential as the law allows.

What happens if you do not want to participate or decide to leave the interview early?

You are free to decide whether you want to take part in this study, and you are free to leave at any point during the interview. You are also free not to answer any questions that you are not comfortable with and this will not bring any problem to you. If you wish to withdraw, data will be deleted at your request. You are free not to answer certain questions they may deem personal or otherwise without penalty.

Thank you for taking time to read the information sheet.

Your willingness to participate in this study is greatly appreciated.

Who to call for questions or problems?

You can call the principal investigator;
If you have any matter which you feel is not adequately explained in this leaflet, do not hesitate to phone the principal investigator**, Sakeni Hadebe.**

Sakeni Hadebe
University of Zambia School of Public health,
P.O. Box 50110,
Lusaka

0979 575678

Email; sakenihadebe@gmail.com.

You can also call or contact the University of Zambia, Biomedical Research Ethics Committee (UNZABREC) office of the School of Medicine, University of Zambia, if there are questions about your rights. You can contact the UNZABREC if you have not been treated fairly or if you have other concerns. The UNZABREC contact information is:

The Chairperson
Biomedical Research Ethics Committee
School of Medicine
P.O.BOX 50110, Lusaka.
Telephone No: 211256067
Email: unzarec@unza.zm

CONSENT TO PARTICIPATE

I have been fully informed of the purpose of the study. The benefits, discomforts, risks and confidentiality and I agree to participate willingly. I further understand that if I take part in this study, I can withdraw at any time without having to give an explanation. Taking part in this study is purely voluntary. I also understand that I am free not to answer certain questions they may deem personal or otherwise without penalty.

The opportunity to ask questions about the research was given and I have been answered to my satisfaction

I therefore agree to participate in this study

I…… (Names) hereby called the respondent understands the

guidelines of this study and I agree to take part in the study

Signed/thumb print……. Data……. (Participant)

Signed/thumb print_____ Date_____ (Witness)

You will be given a copy of this information to keep for your records.

THANK YOU.

QUESTIONNAIRE: LOCAL TECHNICAL REPRESENTATIVES OF MANUFACTURERS (APPLICANTS) OR PHARMACIST-INCHARGE

TITLE: CHALLENGES OF THE REGULATORY REQUIREMENTS ON MEDICINES REGISTRATION IN ZAMBIA- PERCEPTIONS OF LOCALLY BASED PHARMACEUTICAL COMPANIES.

Code No ……... Name of the institution……..

Location……Date: …….

SECTION I:

1. Gender:

a) Male
b) Female

2. Your profession:

a) Pharmacist

b) Medical Doctor

c) Veterinary Doctor

d) Others specify .....

3. Your position

a) Director

b) Pharmacist in charge

SECTION II: *Please tick when necessary the answer of your choice*

4. What are your daily activities

_____

_____

5. How long have you been working in the same position?

a) 0-1 year

b) 2-5 years

c) 6 -10 years

d) Above 10 years 6.

How many companies do you represent in Zambia? _____ (*in numbers*) and where are they located

a) Europe,
b) Africa
c) Asia
d) Others specify _____

7. How many dossiers have you submitted at ZAMRA for registration? _____ (*in numbers*) and among them how many have been registered?

a) 0-10

b) 11-20

c) Above 20

8. Is the time allocated for medicine registration process convenient?

a) Strongly agree

b) Agree c) Undecided

d) Strongly disagree

d) Disagree

Question 9, 10, 11, 12, 13, 14, 15 and 16 should be answered by the regulatory affairs pharmacist/personnel.

9. Do you think your professional training has adequately prepared you to review dossiers for registration purpose?

a) Yes

b) No

10. Have you received any training on dossier preparation and compilation for registration purpose?

a) Yes

b) No 68

If yes, explain where and for how long?

_____

_____

11. Do you know the importance of carrying out medicine evaluation in the country?

a) Yes

b) No If yes, please explain

_____

_____

12. Do you know the information that are required to be submitted before dossier can be evaluated?

a) Yes

b) No If yes, please explain

_____

_____

13. Do you know what medicine registration process is?

a) Yes

b) No If yes, please explain

_____

_____

14. Do you know which information are required to be submitted in the dossier for generic products?

a) Yes

b) No

15. If the answer for Q 14 above is Yes, please mention at least four (4) categories of information required

a. _____

b. _____

c. _____

d. _____

16. Are you aware of the importance of carrying out post marketing surveillance of medicines?

a) Yes

b) No If yes, please explain

_____

_____

17. What challenges do you encounter during medicines registration process?

i)_____

ii)_____

iii)_____

iv)_____

18. In your opinion what should the ZAMRA management do in order to efficiently and effectively improve the process?

_____

_____

_____

xxxxxxxxxxxxx *Thank You* xxxxxxxxxxxxxxx

APPENDIX IV: MEDICINES APPLICATIONS STATUS FORM

Year	**New dossier applications received**	**New applications evaluate**	**New dossier applications not evaluated**	**Final Remarks after evaluation**			
				approved	Provisional approved	Rejected	Status not indicated
2018							
2019							
Total							

APPENDIX V: DELIVERABLES (DISSEMINATION PLAN)

PURPOSE	Challenges of the regulatory requirements on medicines registration in Zambia- perceptions of locally based pharmaceutical companies.
AUDIENCE	1. Health professionals 2. Policy makers 3. Public health institutions and pharmaceutical companies 4. Researchers 5. Other key stakeholders
USES	1. Provide relevant information to help in the formulation of strategies within ZAMRA to meet its registration timelines. 2. Identify major challenges faced by applicants when applying for medicines registration in Zambia. 3. Help locally based pharmaceutical companies comply with medicines registration requirements. 4. Improve availability of quality
CONTENT SCHEDULE	1. Flexible content schedule as and when needed 2. Content will be published in the established journal and also through scientific conference presentations to key stakeholders

APPENDIX VI: APPROVAL LETTERS

UNIVERSITY OF ZAMBIA
BIOMEDICAL RESEARCH ETHICS COMMITTEE

Telephone: +260 977925304
Telegrams: UNZA, LUSAKA
Telex: UNZALU ZA 44370
Fax: + 260-1-250753
Ridgeway Campus
P.O. Box 50110
Lusaka, Zambia
E-mail: unzarec@unza.zm

Federal Assurance No. FWA00000338 **IRB00001131 of IORG0000774** **NHRAR-REC No 2021-05-0002**

6th March, 2023

Your REF. No. 3617-2023

Mr. Sakeni Hadebe,
University of Zambia,
Institute of Distance Education,
School of Public Health,
P.O Box 32379,
Lusaka.

Dear Mr. Hadebe,

RE: CHALLENGES OF REGULATORY REQUIREMENTS ON MEDICINES REGISTRATION IN ZAMBIA- PERCEPTIONS OF LOCALLY BASED PHARMACEUTICAL COMPANIES (REF. NO. 3617-2023)

The above-mentioned research proposal was presented to the Biomedical Research Ethics Committee on 5th March, 2023. The proposal is **approved**. The approval is based on the following documents that were submitted for review:

a) **Study proposal**
b) **Questionnaires**
c) **Participant Consent Form**

APPROVAL NUMBER : REF. 3617-2023

This number should be used on all correspondence, consent forms and documents as appropriate.

- **APPROVAL DATE : 6th March 2023**
- **TYPE OF APPROVAL : Standard**
- **EXPIRATION DATE OF APPROVAL : 5th March 2024**
  After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the UNZABREC Offices should be submitted one month before the expiration date for continuing review.
- **SERIOUS ADVERSE EVENT REPORTING**: All SAEs and any other serious challenges/problems having to do with participant welfare, participant safety and study integrity must be reported to UNZABREC within 3 working days using standard forms obtainable from UNZABREC.
- **MODIFICATIONS**: Prior UNZABREC approval using standard forms obtainable from the UNZABREC Offices is required before implementing any changes in the Protocol (including changes in the consent documents).

- **TERMINATION OF STUDY**: On termination of a study, a report has to be submitted to the UNZABREC using standard forms obtainable from the UNZABREC Offices.
- **NHRA**: You are advised to obtain final study clearance and approval to conduct research in Zambia from the National Health Research Authority (NHRA) before commencing the research project.
- **QUESTIONS**: Please contact the UNZABREC on Telephone No. +260977925304 or by e-mail on unzarec@unza.zm.
- **OTHER**: Please be reminded to send in copies of your research findings/results for our records. You are also required to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study. Use the online portal: unza.rhinno.net for further submissions.

Yours sincerely,

Sody Mweetwa Munsaka, BSc., MSc., PhD
CHAIRPERSON
Tel: +260977925304
E-mail: s.munsaka@unza.zm

NATIONAL HEALTH RESEARCH AUTHORITY
Lot No. 18961/M, off Kasama Road, Chalala, P.O. Box 30075, LUSAKA
Tell: +260211 250309 | Email: znhrasec@nhra.org.zm | www.nhra.org.zm

Ref No: NHRA00001/21/03/2023 **Date:21st March 2023**

The Principal Investigator,
Mr. Sakeni Hadebe,
University of Zambia, School of Public Health,
Lusaka, Zambia.

Dear Mr Hadebe,

Re: Request for Authority to Conduct Research

The National Health Research Authority is in receipt of your request for ethical clearance and authority to conduct research titled **"Challenges of Regulatory Requirements on Medicines Registration in Zambia- Perceptions of Locally Based Pharmaceutical Companies."**

I wish to inform you that following submission of your request to the Authority, our review of the same and in view of the ethical clearance, this study has been **approved** on condition that:

1. The relevant Provincial and District Medical Officers where the study is being conducted are fully appraised;
2. Progress updates are provided to NHRA bi-annually from the date of commencement of the study;
3. The final study report is cleared by the NHRA before any publication or dissemination within or outside the country;
4. After clearance for publication or dissemination by the NHRA, the final study report is shared with all relevant Provincial and District Directors of Health where the study was being conducted, University leadership, and all key respondents.

Yours sincerely,

National Health Research Authority

Prof Godfrey Biemba,
Director/Chief Executive Office

All correspondence should be addressed to the Director General

In reply, please quote .....

ZAMBIA MEDICINES REGULATORY AUTHORITY

10th March, 2023.

Sakeni Hadebe
The University of Zambia
School of Public Health
P.O.Box 32379
Lusaka

Phone: + 260 978 772 249
Email: director-ide@unza.zm

Dear Sir,

RE: Permission Letter-Regulatory approval for the study-Ref. No. 3617-2023

Reference is made to your letter dated 9th March 2023 on the subject above.

We wish to advise that the Authority has no objection to the request to conduct the study entitled **challenges of the regulatory requirements on medicines registration in Zambia-perceptions of the locally based pharmaceutical companies (Ref No. 3617-2023**

In this regard, you may proceed with the proposed study as approved by the relevant authorities. The Authority is looking forward to the outcome of this study, and therefore you are reminded to share the results of the study accordingly.

Should you have any questions, please do not hesitate to contact the undersigned.

Yours faithfully,

for/ **Zambia Medicines Regulatory Authority**

Makomani Siyanga (Mr)
ACTING DIRECTOR – GENERAL