REVIEW OF MEDICINE REGISTRATION SYSTEM IN TANZANIA

Mr. SUNDAY KISOMA

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SUPERVISOR: DR KENECHUKWU OBIKEZE

CO-SUPERVIOR: MR RAFIK BAPOO

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Abstract

Introduction

Registration of medicines is an essential function of the national medicine regulatory system of any country. Since the start of the medicine registration system in Tanzania in early 2000s, no systematic review has been carried out to document the status of the system and its impact on availability and access to quality assured medicines to the people of Tanzania.

Objectives

The study was aimed at reviewing the medicine registration system in Tanzania as implemented by the Tanzania Food and Drugs Authority in order to come up with status of the medicine registration system implemented in Tanzania, and evaluate how the system contributes to the availability and access of essential medicines, particularly those needed to support the essential medicines lists and standard treatment guidelines.

Methods

A descriptive cross sectional survey was used to review the system for registration of medicines in Tanzania before and after implementation of CTD guidelines. The study involved the review of medicine registration system for the period of one year prior to and two years of implementation of CTD guidelines (July 2015 – June 2017) and data on a total of 250 medicines which were received, reviewed and approved during this study period was reviewed.

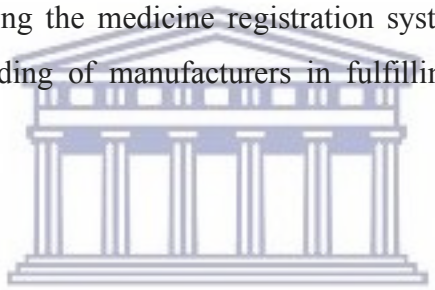
Results

Tablets were the most commonly registered dosage forms across the study period and India and China were the most dominant suppliers of active pharmaceutical ingredients as well as finished products registered in Tanzania. Alarmingly, a decreasing trend was observed in terms of registration of medicinal products which are prescribed in the Standard Treatment Guidelines. Results of this study have also revealed that generic medicines are still the predominant type of medicines with all the medicines (100%) registered between the year 2015 – 2017 being generic medicines and between 94 – 100% of those registered medicines from chemical medicines category. Only 4% of medicines were indicated for use in pediatrics', with the majority of the medicines (71%) indicated for the use in both children

and adults. Conformance of manufacturers with requirements for registration of medicines was low in the areas of synthesis and manufacture of active ingredients as well as control of quality while with respect to finished products, the majority of deficiencies were observed in the choice of container closure systems followed by stability testing. Introduction of CTD guidelines has had a positive impact on registration timelines, review timelines have decreased from above 400 days to as low as just above 200 days.

Conclusion

Findings of this study have highlighted the status of medicine registration system in Tanzania. Despite the implementation of CTD guidelines by TFDA, similar patterns in parts of medicinal products dossiers with deficiencies have been noted across the study years. The observed deficiencies demonstrate a weakness in the preparation of marketing authorization applications on the side of the applicants. It is recommended that findings of this study should be used in strengthening the medicine registration system in Tanzania, particularly with respect to capacity building of manufacturers in fulfilling medicine registration and GMP requirements.



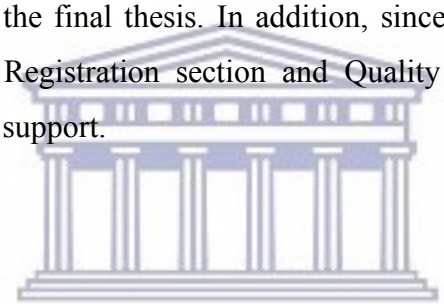
DECLARATION

I hereby certify that this material which I now submit for assessment on the programme of study leading to the award of M.Sc. Pharmacy Administration and Policy Regulation 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.

Signed: Sunday Kisoma Dated: 1/08/2019

ACKNOWLEDGEMENTS

I wish to extend my sincere thanks to almighty God for granting me good health and right mindset in conceptualizing and successfully carrying out this study and finally producing the mini thesis. Second I thank my family, my lovely wife Florence Urio and my daughter Darla Upendo Kisoma for all the support that they have given to me throughout my studies for this MSc degree programme. Despite overwhelming responsibilities and family commitments, they have always encouraged me to continue pursuing this programme and carry out the dissertation. Last but not least I wish to sincerely thank the Management of Tanzania Medicines and Medical Devices Authority (TMDA) for funding this degree programme, giving me time to undertake the modules required for this degree programme and allowing me to use their database for the final thesis. In addition, sincere thanks goes out to all my colleagues within Medicine Registration section and Quality Management Unit for their encouragement and everyday support.



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LIST OF ABBREVIATIONS

API	:	Active Pharmaceutical Ingredient
CTD	:	Common Technical Documentation
EU	:	European Union
FPP	:	Finished Pharmaceutical Product
GMP	:	Good Manufacturing Practice
ICH	:	International Council on Harmonization
NRA	:	National Medicine Regulatory Agency
STG	:	Standard Treatment Guidelines
TFDA	:	Tanzania Food and Drugs Authority
USA	:	United States of America

CHAPTER ONE

INTRODUCTION

Medicines are substances specifically recognized by an official Pharmacopeia and Formulary that are approved for use to treat, diagnose, cure or prevent a disease or disorder. According to Tanzania food, drugs and cosmetics act (2003), a medical substance induces changes to the function or structure of the patient's body. Based on the nature and function of the medicines it has long been recognized that medicines are among the highly regulated products and they are not ordinary consumers' products. In most instances, consumers are not in a position to make decisions about when to use medicines, which medicine to use, how to use them and to weigh potential benefits against risks as no medicine is completely safe, without professional advice from healthcare professionals (Rago *et al*, 2008).

Health budgets in the developing countries are generally small, when compared to developed countries, and 30-40% of the total health budget is spent on medicines and other medical supplies (Kazeem, *et al*, 2011). Considering the small amount of funds available for drugs in these poor countries, it is desirable that countries and international donor communities purchase medicines including essential medicines that are of acceptable quality, safety and efficacy

The regulation of medicines is crucial to the health and safety of the public since it is the tool that ensures that medicines of high quality are manufactured, stored and distributed in the given country. High quality ensures safety and efficacy of the respective medicines and hence ensures protection and promotion of public health.

Medicines regulation involves a range of related activities including interactions with various stakeholders with different economic, social and political motives. This makes the implementation of regulation by National Medicines Regulatory Agencies (NRAs) both politically and technically challenging in many parts of the world. Minimum regulatory functions include licensing of the manufacture, import, export, distribution, promotion and advertising of medicines; assessing the safety, efficacy and quality of medicines;, inspecting and surveillance of manufacturers, importers, wholesalers and dispensers of medicines; and issuing marketing authorization for individual products. Other important functions involve

controlling and monitoring the quality of medicines on the market, controlling promotion and advertising of medicines, monitoring safety of marketed medicines including collecting and analyzing adverse drug reaction reports, and providing independent information on medicines to professionals and the public (Rago *et al*, 2008).

The importance of regulating medicines comes from the fact that the use of ineffective, poor quality, harmful medicines can result in therapeutic failure, progression of disease conditions, and development of resistance to most lifesaving medicines and sometimes death (WHO, 2003). Money spent on ineffective, unsafe and poor-quality medicines is wasted whether by patients, insurance companies or governments. Therefore, countries have set up medicines regulation systems which involves medicines registration, inspection of manufacturing facilities where the respective medicines are manufactured and tested and post marketing surveillance for safety and efficacy of the respective medicines.

Regulation of medicines is a national responsibility and it is carried out by the Ministry of Health, and in many countries the role is assigned to the National Medicine Regulatory Agency. According to the World Health Organization, national medicine regulatory agencies contribute to protecting and promoting public health by ensuring that medicines are of the required quality, safety and efficacy. They also ensure that health professionals and patients have the necessary information to enable them to use medicines rationally, that medicines are appropriately manufactured, stored, distributed and dispensed, that illegal manufacturing and trade is detected and adequately sanctioned, that promotion and advertising is fair, balanced and aimed at rational drug use and that access to medicines is not hindered by unjustified regulatory work.

Registration of medicines is an essential function of the national medicine regulatory system of any country, and is also known as product licensing or marketing authorization. In principle, all medicines that are marketed, distributed and used in the country should be registered by the national competent regulatory authority. The process of registration includes the scientific evaluation of product to ensure that it meets the criteria for safety, efficacy and quality.

CHAPTER TWO

LITERATURE REVIEW

The primary aim of medicine regulation and in particular medicine registration is protection of the public's health. However, Al-Essa *et al*. (2015) who reviewed medicine regulatory systems in the gulf region revealed that regulation is often perceived as an obstacle to the availability of medicines in national or regional markets. This view has placed a significant demand on regulators to accelerate reviews and evaluations to approve new medicines in the shortest possible time and to expedite the review and ensure continuous safety and efficacy of the marketed medicine.

The evaluation process has often been perceived as lengthy and it is often cited as one of the major factors affecting access to essential medicines especially in developing countries. A report published by Management Sciences for Health (2017) highlighted that in developing countries, new chemical entities, generic medicines, new fixed-dose combination products, and innovative new products, including important antimalarials and antiretroviral medicines for HIV/AIDS are subject to prolonged registration times compared to other categories of important medicines.

In Tanzania, the registration of medicines is a legal requirement prescribed in Section 51 of the Tanzania, Food, Drugs and Cosmetics Act 2003; Cap 219. The act mandates the Tanzania Food and Drugs Authority (TFDA) to register all medicines before they are allowed to circulate on the Tanzania market with the conditions for registration of medicines specified as: compliance of manufacturing sites with GMP requirements, proven safety, efficacy and required quality and whether the availability of the medicine applied for registration is of public interest (TFDA 2013).

The medicines registration process as implemented by TFDA since its establishment in the year 2003 involves the following sequential steps: receiving of applications, evaluation of scientific data submitted to demonstrate quality, safety and efficacy of the medicine, conducting quality control tests of medicine samples submitted, conduction of inspection of manufacturing facilities to verify compliance to good manufacturing practice standards (GMP) and eventually approval and issuance of certificates of registration.

Since the start of the medicine registration system in 2003, the TFDA has registered more than 5300 medicinal products, many of which are generic products manufactured by both foreign and domestic manufacturers. According to TFDA's ten years' anniversary report (2013), there has been an overall increase in the number of registered medicines every year.

Currently registration of medicines in Tanzania is carried out through the implementation of CTD guidelines for registration of medicines as harmonized with other partner states within the East African Community (EAC). These harmonized guidelines were adopted by TFDA with effect from 1st July 2015 as part of the Harmonization process within the EAC Partner States. In the process of development of Harmonized EAC guidelines, ICH CTD and WHO documents were used as templates in an attempt not to deviate from the world's major regulators, international standards as well as best regulatory practices.

Despite its usefulness, the medicine registration system has for long been cited as a technical barrier to the access of essential medicines especially in resource limited countries. As is the case in other developing countries, the medicine registration system of Tanzania has not been significantly studied to identify the spectrum of factors that affect the performance of the respective systems despite various reports of these systems functioning below the optimum requirements. In addition, the contribution of the medicine registration systems to the availability and access of essential medicines, lists and standard treatment guidelines have not been clearly explored in the context of developing countries, particularly the African context.

Different regulators in the world have established different timelines for the assessment and approval of medicines based on intuition. In addition different assessment practices and pathways have been designed in order to make medicine registration systems more efficient. A study by Reem *et al*. (2015) conducted to study medicine registration timelines in Gulf countries revealed varying medicine registration timelines across the respective countries. In that study, it was also demonstrated that there was a significant reduction in the timelines because of harmonization and application of alternative mechanisms such as parallel approvals and fast track application routes.

Moreover, it is recognized that among regulators that, timely completion of assessments and approval of medicines requires the cooperation of the manufacturers in fulfilling the requirements, including submission of medicine registration applications that are compiled

according to the requirements. Studies by Ortega *et al*. (2014) and Worku *et al*. (2012) demonstrated deficiencies in the fulfillment of medicines registration requirements in the dossiers of API and FPP submitted for assessment in WHO Prequalification programme respectively. From the studies, the authors recommended the need for continued capacity building of local generic manufacturers, further development of pharmacopoeia monographs and promotion of development of generic products as well as new guidelines.

Since the start of medicine registration system in Tanzania in the early 2000s, no systematic review has been carried out to document the status of the system. Thus, evidence on the actual contribution of medicines registration systems to the availability of essential medicines in this country has not been well documented, and the actual time taken to register medicinal products have not been well characterized. In the absence of a systematic review of the system, it is also currently not possible to determine the contribution of the manufacturers with regards to facilitation or hindrance of access to medicines in Tanzania from the regulatory point of view.

This study was aimed at reviewing the medicine registration system in Tanzania as implemented by Tanzania Food and Drugs Authority. The expectation from the study was to evaluate the status of the medicine registration system implemented in Tanzania, particularly on the way that the system contributes to the availability and access of essential medicines. The broad objective of this study was to review the system for registration of medicines in Tanzania. Specifically the study was aimed at assessing; trends in registration of medicines in Tanzania in line with Tanzania Essential Medicines Lists and standard treatment guidelines, conformance of applicants for registration of medicines to technical requirements for registration and timelines for registration of medicines in Tanzania.

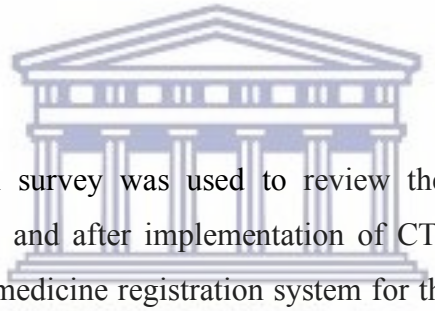
It is expected that the findings of this study will better inform all stakeholders on the current status and provide recommendations for further improvements of the system. The findings of this study will also provide baseline information on medicines registration systems in the context of developing countries.

CHAPTER THREE

METHODOLOGY

3.1 Study Area

The study was conducted within the Directorate of Medicines and Complementary Products in the Tanzania Food and Drugs Authority. The directorate hosts the Section for Registration of Human and Veterinary Medicines Registration, the section carries out evaluation and registration of Human and Veterinary medicines, maintains medicine registers and manages the lifecycle of registered medicines including post-registration amendments (variations) and renewal of registrations.



3.2 Study Design

A descriptive cross sectional survey was used to review the system for registration of medicines in Tanzania before and after implementation of CTD guidelines. Therefore, the study involved the review of medicine registration system for the period of one year prior to and two years post implementation of CTD guidelines (July 2015 – June 2017).

3.3 Study data

The data was obtained from the medicine application database, the medicine registration database and medicine registration assessment reports repositories. The medicine registration database used at TFDA is managed through the web based Management information system (MIS) that is used for management of medicine registration applications as well as in other support functions. The database contains administrative information, brand and generic names, information on active pharmaceutical ingredients, dosage forms, routes of administration, and information on manufacturers of both APIs and FPPs. The database also includes registration numbers as well as product validity information.

For the purpose of assessing conformance of applicants with medicine registration requirements, medicine assessment reports for the studied applications were obtained from

the repositories for assessment reports. Questions raised by the assessors found in the sections of the assessment reports were counted and number of questions were entered into data collecting tool.

3.4 Sample size

During the review period, a total of 2700 applications for registration of human medicines were received, out of which 250 were registered. Out of the medicinal products registered in the review period, 137 were of applications received before the implementation of CTD and 113 were of applications received after the implementation of CTD guidelines. Therefore, the study involved the review of the registration process of all 250 human medicines that were received, reviewed and registered during the study period.

3.5 Sampling technique

Convenience sampling was used in which all the 250 applications for registration of medicines that were received, reviewed and registered between July 2014 and June 2017 were included in the review.

3.6 Data Collection

3.6.1 Data Collection Tool

A special data collection tool (**Annexure I**) was used to collect the required information on the medicine registration applications to be included in the study. The tool was divided into four major parts of which Part A was intended at collecting general and administrative information about the studied applications, Part B was used to capture the information on trends in applications and registration. Part C was used to collect information on deficiencies observed during assessment of the applications and Part D was used to capture the information about registration timelines including regulator's time and applicant's time.

3.6.2 Pre-testing of Tool

The data collection tool was tested for suitability and usability on 10 intended applications to be reviewed. It was then amended, refined and reviewed before commencement of the actual data collection process.

3.6.3 Data collection procedure

Two (2) research assistants were trained on the objectives and methodology of the study and they used the data collection tool to collect the data from the identified data sources within the Human and Veterinary Medicines registration section at TFDA Headquarters. The entire data collection activity was done in the month of August 2017 and it was closely monitored and supervised by the investigator.

3.6.4 Quality control of data collection

Electronic copies of the filled in data collection tools were collected from the research assistants and checked for correctness and consistency by the investigator.

3.7 Data Analysis

The data from the tool was entered in Microsoft excel program and analyzed by current versions of Microsoft excel software for means and proportions. Conformance of the applicants with the requirements of medicines registration as prescribed in the guidelines for submission of applications for registration of medicinal products was evaluated based on the extent to which data submitted in medicinal products dossiers did meet the requirements at the first round of assessment. To achieve this, assessor's comments/questions were reviewed and tallied on each of the quality parts of the active pharmaceutical ingredient (API) and quality of the finished pharmaceutical product (FPP).

3.8 Ethical Considerations

Permission to conduct the study and use the data was sought from TFDA management and research assistants were made to fill in confidentiality undertakings which were kept in the relevant file at TFDA. Efforts were made to ensure that no proprietary information or trade secrets contained in the source data were included in the final report.

CHAPTER FOUR

RESULTS

4.1. General information

4.1.1 Types of dosage forms registered

Tablets were the most registered type of dosage form of medicines compared to other dosage forms registered in Tanzania. The second most registered type of dosage form was solutions for injections and external/topical preparations. There was a general trend with respect to pessaries and suppositories registered during the study period (2014 – 2017) where the data show very little or no registration of this type of dosage forms.

Table 4.1 Trends in proportions of different types of dosage forms of medicines registered over the course of review period.

Dosage form/type	Percentage registered per year				
	2014	2015	2016	2017	Overall
Tablets	47	52	41	47	48
Capsules	8	0	10	0	6
Solution for Injection	9	20	10	13	13
Dry powder for Injection	8	0	7	13	6
Dry powder for oral suspension	7	6	7	0	6
External/Topical preparations	5	7	10	7	7
Pessaries	1	0	0	0	0
Suppositories	1	0	0	0	0
Syrups	1	1	0	1	1
Nasal drops	1	0	3	0	1
Eye/ear drops	2	7	7	13	5
Inhalers	3	0	0	7	2
Solutions for Infusions	5	6	3	0	5
Emulsion for Injections	1	0	0	0	0
Granules	1	0	0	0	0

4.1.2 Distribution of registered medicines based on country of supply of active ingredients

At an overall contribution of 53% over the four years period, India was the number one contributing country of the active pharmaceutical ingredients used to manufacture the studied medicines followed by China (14%) and Switzerland (6%). Notably none of the API supplies used to manufacture the medicinal products included in the study had been sourced from Tanzania and the African continent in general (see figure 4.1).

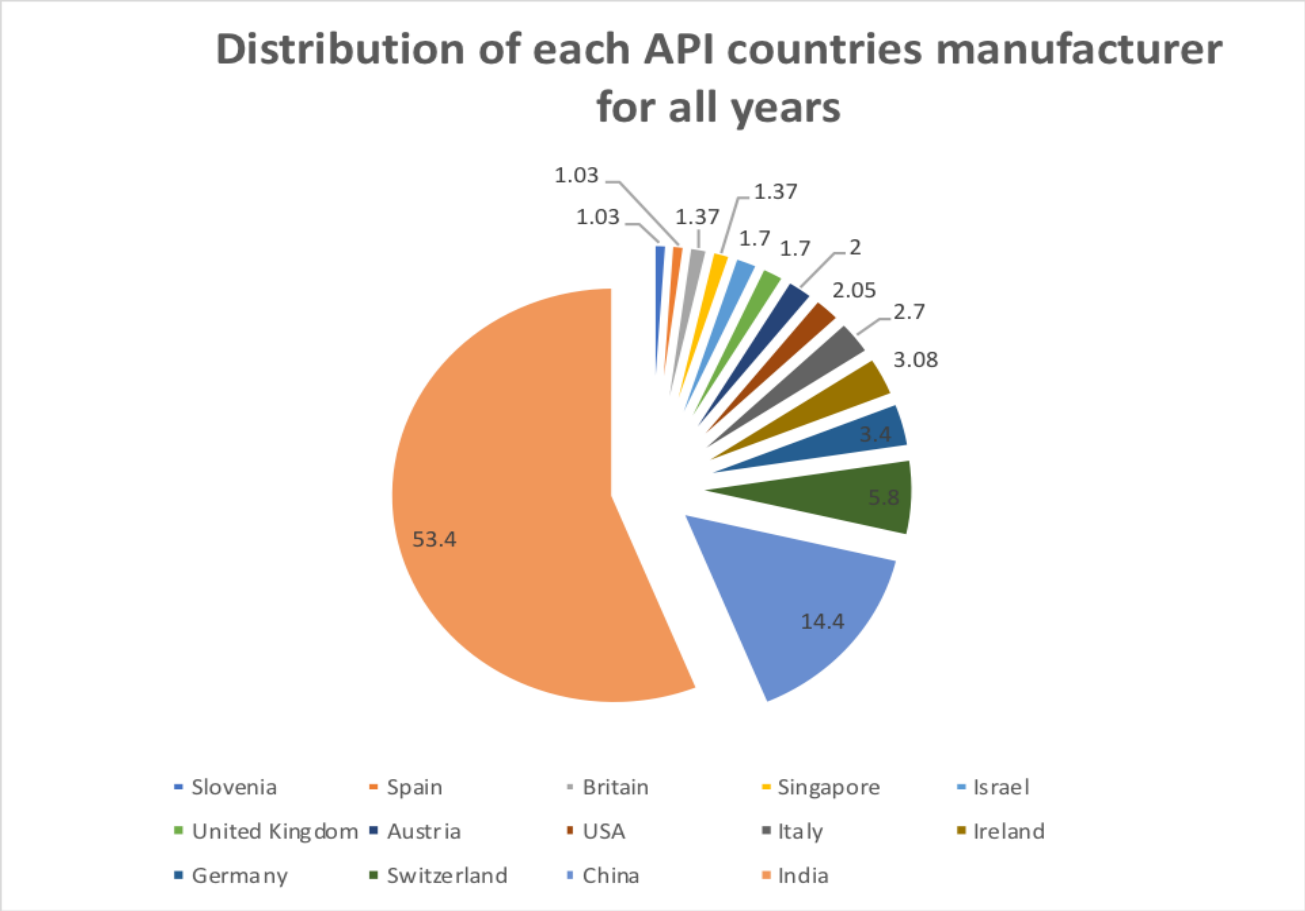


Figure 4.1: Distribution of country of origin of suppliers of active pharmaceutical ingredients (APIs) used to manufacture the reviewed medicines

4.1.3 Distribution of registered medicines based on country of manufacture

Medicinal products registered between the year 2014 – 2017 were from manufacturers located in a total of 27 countries. Out of these, India was the leading country with 54% of finished products originating from this particular country followed by Germany which contributed 5.6% of the finished pharmaceutical products. Other countries that had significant contributions to the number of medicinal products registered include Tanzania which contributed 4% of all medicinal products, Austria (2.6%), Kenya (3.3%), United States of America (2.6%) and Slovenia which contributed 3.3%. The United Kingdom, Belgium and Bangladesh had the least number of registered medicines with each one of the countries contributing around 1% of all registered medicines (see figure 4.2).

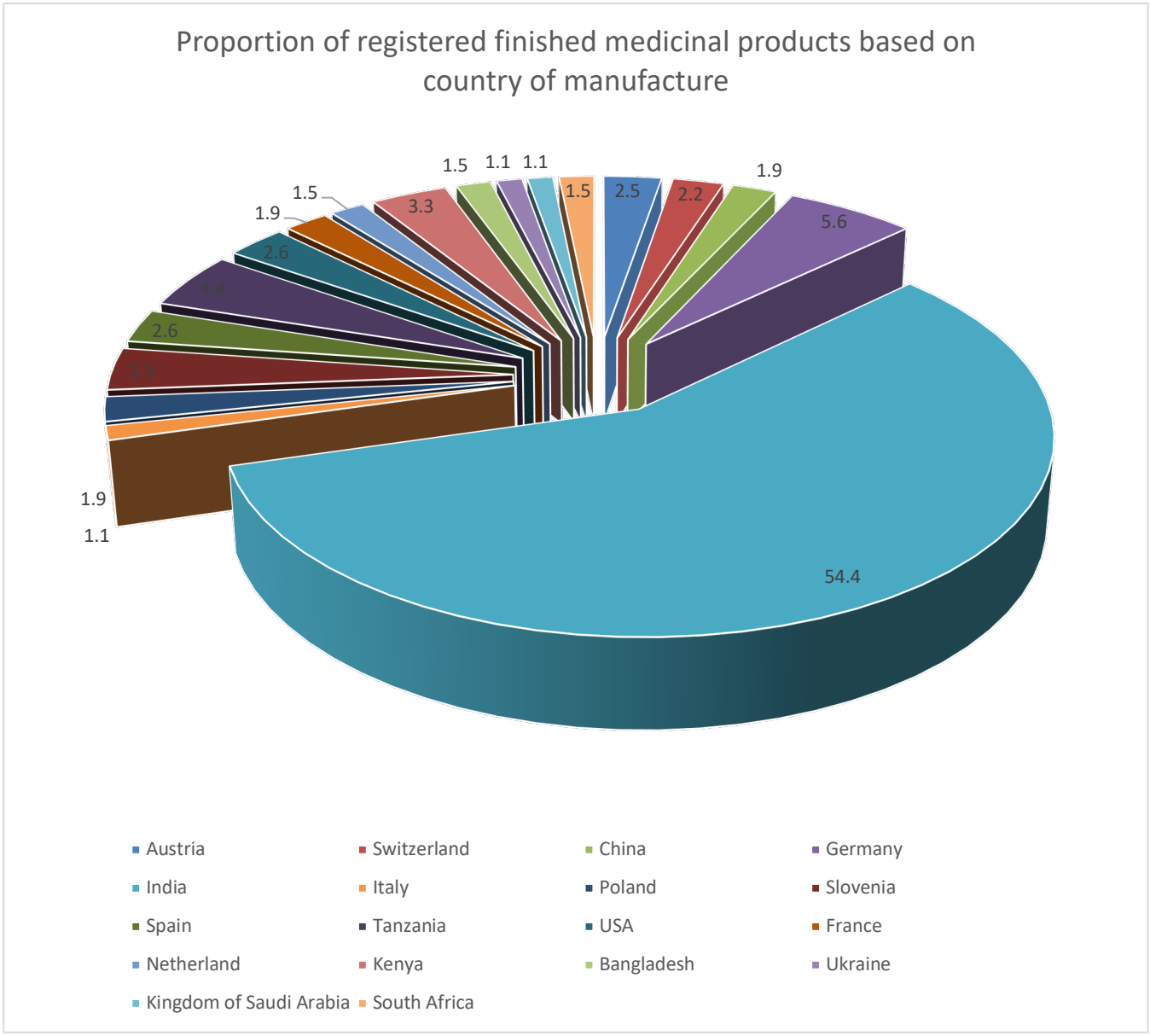


Figure 4.2: Distribution of registered medicines based on the country of manufacture

4.1.4 Distribution of registered medicines based on availability in standard treatment guidelines

The products were also assessed with respect to their availability on the standard treatment guideline (STG). In 2014, 60% of the medicinal products registered were also available in the standard treatment guidelines (STG) for Tanzania and 40% were not in the STG document. In 2015, 41% of the registered medicinal products were in the STG and 59% were not, whereas in 2016, only 11% of the registered medicinal products were on STG and 89% were not in the STG. For the period of January to June 2017 all medicinal products granted registration were not listed in the standard treatment guidelines for Tanzania.

4.1.5 Registration based on type of medicine and proportions registered

Generic medicines made up 89% of the medicinal products registered in 2014, while in the subsequent years of study period (2015 -2017) all the registered medicinal products (100%) were generics. There was a decreasing trend in number of medicinal products registered over the years during the study period with 54% of the medicines registered in 2014, followed by 28% in 2015, 13% in 2016 and only 5% of the medicinal products registered in 2017.

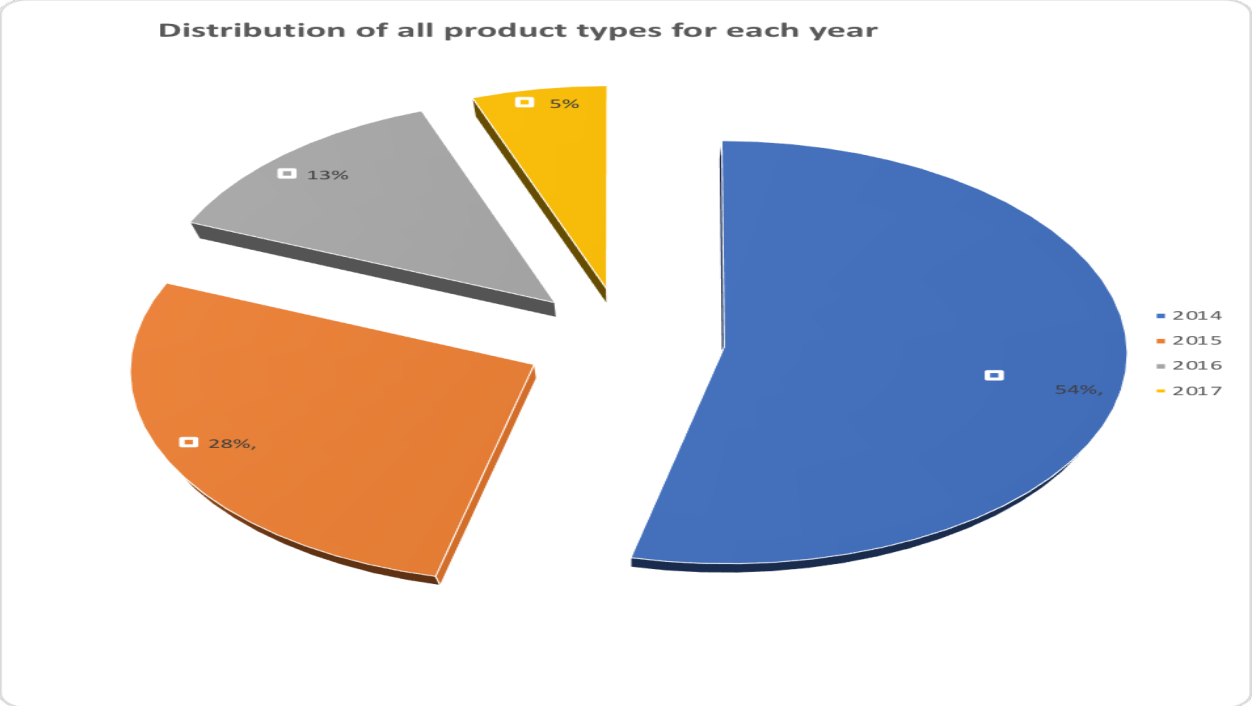


Figure 4.3: Distribution of registered medicines based on year of approval

4.1.6 Registration based on category of medicine

Generally four major categories of medicinal products were registered between 2014 – 2017, these categories were chemical drugs, vaccines, immunological products and biosimilars.

Table 4. 2: Distribution of registration of these four categories of medicines across the study period

Category of Drug Product / Year	Percentage registered per year			
	2014	2015	2016	2017
Chemical	97	97	94	100
Vaccine	0	1.5	6	0
Immunological	0	0	0	0
Biosimilar	3	1.5	0	0

The overwhelming majority of registered medicines over the study period were chemical medicines with vaccines and Biosimilars constituting a small minority. During the study period, no Immunological medicines were registered. Notably all the medicines registered up to June 2017 were chemical medicines.

4.1.7 Registration based on intended age group

With regards to intended age group for which the medicines are registered, the majority of the medicines registered in the year 2014 were indicated for both adults and children (53%) with 40% indicated only for adults (40%), and 7% indicated for pediatric age groups only.

In the year 2015, only 1% of medicinal products registered were specifically indicated for the use in children while products indicated for both age group were as many as 93% of the products. The rest were those indicated for adults only. The data shows that from the year 2016 and up to June 2017 none of the medicinal products registered were indicated for the use in children only. In 2016, 11% of registered medicines were indicated for adults only while up to June 2017, only 7% of the registered medicines were indicated for adults only. Rest of the products in these years were for the use in both adults and children.

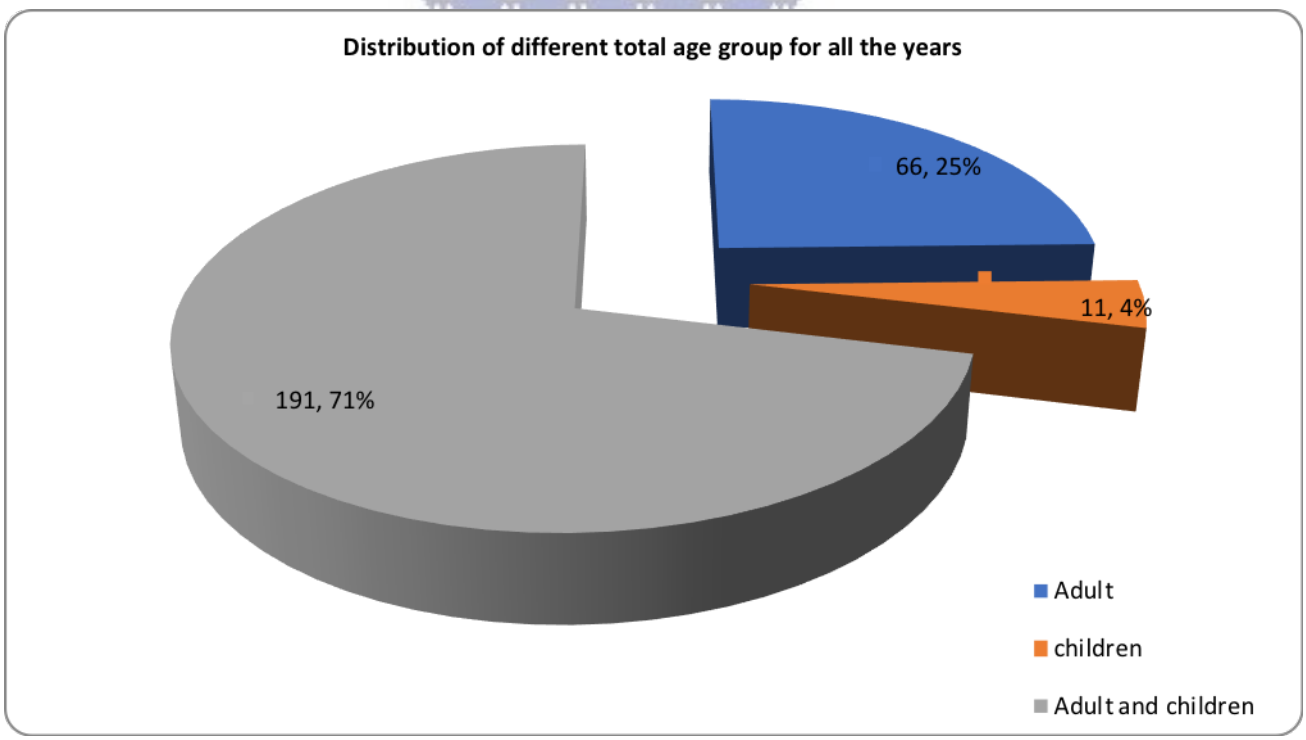


Figure 4. 4: Distribution of medicines registered by indicated age group.

4.2 Conformance of the applicants with medicine registration requirements

4.2.1 Conformance on requirements for quality of active pharmaceutical ingredients

For the dossiers which were submitted and registered in the year 2014, the majority of the deficiencies (67%) were in the nomenclature and properties of the API, 25% of the deficiencies were in the manufacture of the API, and 8% were in the characterization of potential impurities in the API (table 3).

In the year 2015, 24% of the deficiencies were in container closure system followed by the stability studies on the API (17%) and 14% of deficiencies were on control of critical steps and intermediates (table 3). In 2016, 36% of all the deficiencies were on analytical procedures and validation, followed by 24% on the API manufacturing process (narrative, flow diagrams and control of intermediates and critical steps) and 10% were on nomenclature and properties of the API (table 3).

For medicinal products which were registered up to June 2017, 28% of all the deficiencies were from description of API manufacturing process, 24% were from API specification and analytical procedures and validation and 12% were from the nomenclature and properties of the API (table 3).

Table 4.3: Proportions of nonconformances with medicine registration requirements for API across the study period

API dossier section	Percentage number of questions across CTD sections			
	2014	2015	2016	2017
3.2.S.1	67	5	10	12
3.2.S.2.1	25	2	0	0
3.2.S.2.2	0	4	24	28
3.2.S.2.3	0	12	0	0
3.2.S.2.4	0	14	7	0
3.2.S.3.1	0	0	5	0
3.2.S.3.2	8	3	5	4
3.2.S.4.1&4.5	0	7	2	24
3.2.S.4.2 &4.3	0	1	36	24
3.2.S.4.4	0	2	3	0
3.2.S.5	0	9	5	0
3.2.S.6	0	24	5	4
3.2.S.7	0	17	5	4

4.2.2 Conformance on requirements for quality of finished pharmaceutical products

On compliance of medicine registration requirements for finished pharmaceutical products, in the year 2014, more than 33% of the deficiencies were observed on the data to demonstrate suitability of the container closure system, 17 % of the deficiencies were from stability of FPP and 10% of the deficiencies were from control of quality of the finished pharmaceutical products (i.e. specifications, analytical procedures including validation as well as batch analyses) (see table number 4).

For the year 2015, the highest proportion of deficiencies (26%) were observed from the requirements for demonstration of suitability of container closure system of the FPP followed by deficiencies in stability data (19%) and control of quality of the finished product (specifications, analytical procedures, validation and batch analysis) with 16% of the deficiencies (see table 4). Similarly, for the dossiers submitted and products registered in the year 2016, the highest proportion of deficiencies were observed in the demonstration of suitability of container closure system (13%). These were followed by deficiencies on validation of analytical procedures which contributed 10% of the deficiencies (table 4). In 2017, 31% of the deficiencies were from container closure system information of FPP, 21% were from manufacture information FPP and 14% were from control of the FPP (table 4).

Table 4.4: Proportions of nonconformances with medicine registration requirements for finished pharmaceutical products across the study period

API dossier section	Percentage number of questions across CTD sections			
	2014	2015	2016	2017
3.2.P.1	1	3	1	3
3.2.P.2	5	1	0	2
3.2.P.3	10	3	1	21
3.2.P.4	7	9	2	8
3.2.P.5.1	9	20	1	14
3.2.P.5.2	2	1	6	0
3.2.P.5.3	5	5	10	0
3.2.P.5.4	5	7	5	5
3.2.P.5.5	1	0	9	0
3.2.P.6	1	8	9	8
3.2.P.7	33	26	33	31
3.2.P.8	16	16	13	3
Bioequivalence	4	2	10	5

4.3 Medicine registration timelines

Registration timeline is the measure of time taken from the day that an application for registration of a medicinal product is lodged to the day that the product is registered and issued the marketing authorization in Tanzania. Overall registration timelines were calculated to include the total amount of time the application has spent in the registration process in TFDA and the time the application has stayed with the applicant where additional data has been requested.

For applications that were submitted and registered in the year 2014, median registration time from the time that the application is submitted to the time that the product is granted registration was 401 days. A decrease in the median registration time was observed in the other consecutive study periods, with the median registration time in 2015, 2016 and 2017, 397, 362 and 217 days respectively. Figure number 4. 5 below shows the trends in median registration time over the years for medicine registration applications falling within the study period.

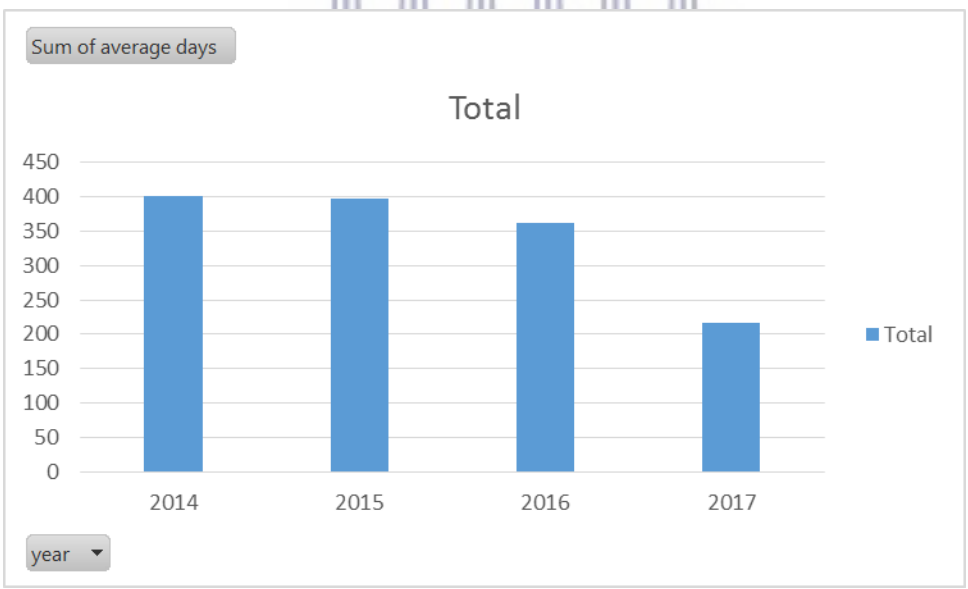


Figure 4.5: Trend in registration timelines (days) across the years in study period

CHAPTER FIVE

DISCUSSION

Tablets were by far the most common registered dosage form, followed by solutions for injections and dry powder for injections. This observation is consistent across medicines registered in all four years of the study period, and correlate with the recommendations in Standard Treatment guidelines for Tanzania where tablets are the most preferred treatment options for most disease conditions (MOHCDGEC, 2017). With such assured market, most registrants would be attracted to registering the most preferred dosage form of their medicine which is tablets.

The study findings also indicates a bias towards medicines manufactured outside the country with India accounting for 54% of all medicines registered within the study period and only 4% locally manufactured in Tanzania. A report published by Businessworld (2018) indicated that currently India holds the third position in global pharmaceutical exports amounting up to 20 billion dollars. Findings of this study probably reflect from the fact that the standard treatment guidelines for Tanzania advocates for the use of generic names in prescribing and dispensing of medicines in the country, this in turn promotes the use of generic medicines which are mainly obtained from India as the main supplier of generic medicines. In addition, a report from BMI Research on Tanzania Pharmaceuticals and Healthcare (BMI, 2016) revealed that more than 90% of medicines circulating in the market in Tanzania were imported from overseas and majority of which were from India. These were consistent with findings of this study.

Regardless of the country of manufacture of the finished pharmaceutical products, India and China were the leading sources of active pharmaceutical ingredients used in the medicines registered within the study period. This was consistent with the report on Market assessment on tools for U.S exporters (2016) which reported that most of the affordable active pharmaceutical ingredients and excipients used for finished products in the United States are manufactured in India and China. Several factors are known to contribute to this, including relatively low production costs, good government policies towards manufacturing and export business, as well as the availability of a large pool of skilled workers in these countries (Goldar & Parida, 2017).

From findings of this study, there was a clear shift in the trends in the registration of medicines as compared to the medicinal products proposed in standard treatment guidelines and essential medicine lists. These findings suggest that medicine selection and usage in developing countries may be influenced by other factors in addition to often static standard treatment guidelines. This finding indicates the need for regular updating of standard treatment guidelines so that they match the pace of advances in science and technology as well as public health needs. Registration of medicinal products that have been proposed in the standard treatment guidelines would ensure that all medicines registered in Tanzania have undergone rigorous risk/benefit analysis, health technology assessment and consideration on relevance to public health to enable full realization of the benefits as well as protection of public health. In many parts of the world including major and experienced jurisdictions such as those in the USA and United Kingdom, registration of medicines is not tied to its status in standard treatment guidelines. This allows innovation in disease areas in addition to those covered in treatment guidelines.

Study findings have also revealed an overall high proportion of registered medicines being generics in the first year of study and all registered medicines as generics in the subsequent three years of the study. This re-affirms the preeminent position of generics in drug regimens in resource-limited countries such as Tanzania and is in line with emphasis on generic prescribing and dispensing that is advocated in the standard treatment guidelines of Tanzania (MOHCDGEC, 2018). Some of the advantages of using generic names in the prescribing of medicinal products include cost effectiveness, and the reduced potential for confusion when prescribing. A study by Manisha Das *et al*, (2017) aimed at evaluating the experience and attitude of patients who were consuming generic drugs reported no statistically significant difference in perception of quality and effectiveness among the patients who used generics and branded products, hence the use of generic medicines is well justified.

The observed trend of majority of registered medicines being chemical medicines (97%) was contrary to what is observed in developed countries. Report on global biological market size and market (April 2018) indicated that approximately 50% of all new molecules approved in the USA were from the biological group of molecules. Increase in prevalence of noncommunicable and chronic diseases in these countries has been cited as

a major factor for the observed trend. It is also forecasted that during the period of 2018 to 2026 there will be around 800 new biologicals approved, with biologicals accounting for approximately 25% of the total pharmaceutical market in 2016 (reference conversion newsletter).

Despite documented an increasing prevalence of noncommunicable and chronic diseases in Tanzania (Mayinge et al, 2011), the decreasing trends in registration of biological medicines over the study years observed in this study could be attributed to the high costs of biological medicines compared to the low purchasing capacity of individuals and the governments as it has been documented in the report from Health24 (2018) and the study from Erasmus L (2015). To address this challenge, Tanzania is on the verge of publishing for the first time the regulations aimed at facilitating the registration and availability of orphan medicines in the country. When approved and implemented, the likelihood is that the trend would be reversed, and an increase in the number of biological medicines made available for those patients in need.

A trend towards the decrease in the registration of medicinal products intended for use in children was observed, and this seems to undermine the efforts made by the World Health Organization and other international organizations in bringing up the agenda of the development of pediatric only medicine formulations. Starting around the year 2012, these efforts had shown promising outcomes due to the fact that manufacturers in the European Union and USA have started formulating medicinal products that are indicated for exclusive use in pediatric age groups, however somehow manufacturers of these medicines have not considered their registration in Tanzania. The findings of this study did show an opposite trend to the trend seen in the European Union where the ten years report published in 2017 did show an overall increase in the approval of medicines for children in many therapeutic areas, most notably rheumatology and infectious diseases (EU, 2017). However, the same trend was seen in medicines for diseases which shows biological differences between adults and children, particularly rare diseases.

Results on conformance of manufacturers to medicine registration requirements regarding the quality of the active pharmaceutical ingredients are consistent with the study by Isabella Ortega *et al*, (2014) where it was concluded that the most frequent critical deficiencies were related to how the specific manufacturing process and the key materials used, in particular the API starting material, impact the API impurity content.

In this study, the number and pattern of APIMF deficiencies did not change over time during the study years, which may be attributed to the fact that due to their low volumes of purchase and need for cheaper APIs most generic manufacturers are not able to obtain information on the quality of the APIs from respective manufacturers. Instead the materials are mostly obtained from vendors who would most of the time may be in possession of very limited and/or old data on open parts of the DMFs. As a result, the major areas such as synthesis and manufacture of the API and specifications and control of the API have been shown to have high proportions of overall deficiencies in across the years.

With regards to the findings on the deficiencies in the FPP part of the studied applications, parts of the dossiers with overall highest proportions of findings over the years reflects the parts of the dossiers which are of critical importance to medicine evaluators and GMP inspectors. The section on manufacturing and process control of the FPP is much more scrutinized to ensure consistency of future production batches and specifications are more scrutinized to ensure accuracy in testing and validity of analytical methods, in addition specifications are viewed as a contractual document between the manufacturer and the regulators. Therefore increased scrutiny on these sections may explain why these sections of the submitted application dossiers have been found to have the higher proportion of deficiencies compared to other parts of the dossiers. The observed results are also consistent with the study by Zeleke *et al*, (2014) which reported that more deficiencies were from the areas of specifications of active pharmaceutical ingredients, development pharmaceutics, manufacturing methods and finished pharmaceutical products specifications.

Notably, in all the years, the majority of deficiencies were observed from the sections on container closure systems of the finished product. This observation could be explained by the overall low GMP capacity among the manufacturers of finished pharmaceutical products from developing countries. A working paper from the Centre for Pharmaceutical Public Health Policy (2007) highlighted how GMP is perceived among manufacturers in India and Nepal and how these manufacturers perceive international GMP standards as being more stringent and restricting them from accessing international markets for their pharmaceutical products.

A gradual decrease in the time taken to register medicinal products as measured as time taken between the submission of the application for registration to the time the product obtains registration was observed. This could be attributed to the introduction of the CTD format for the compilation of applications for registration of medicines in Tanzania and in many other parts of the world. As documented by Mozlon (2010), the introduction of CTD influences the content of the review by imposing a consistent order of information and data, which results in shaping both the conduct of the review and the presentation of the results of the review, and hence promoting good review practices and increased efficiency.

The observed trend in registration could also be attributed to an overall improvement in regulatory performance at the Tanzania Food and Drugs Authority which was catalyzed by the introduction of automated systems in the processing of medicine registration applications, GMP inspections and other support activities. Improvement in overall regulatory performance of TFDA have also been demonstrated from the findings of Benchmarking of TFDA regulatory systems by the World Health Organization in may 2018 where TFDA had attained the Maturity Level 3 of its national medicine regulatory system pending clarification of few areas.

CHAPTER SIX

CONCLUSION

Findings of this study have for the first time highlighted the status of the medicine registration system in Tanzania. It is clear that to some extent the system is capable of supporting the standard treatment guidelines of the country by making quality assured medicines available and by supporting the use of generic medicines. However, registration of biological medicines as well as medicines intended specifically for use in pediatric patients is on the decrease with no sign of reversal of the situation, and this could negatively impact the public health, particularly in the era of the increase in prevalence of noncommunicable diseases and chronic disease conditions in Tanzania.

Despite the implementation of CTD guidelines on application for registration of medicinal products and strengthening of GMP inspections function by the TFDA, similar patterns in parts of medicinal products dossiers with deficiencies have been noted across the study years. These patterns were visible in both active pharmaceutical ingredient and finished pharmaceutical products part of the dossier. The high proportion of deficiencies identified still demonstrates weaknesses in the preparation of marketing authorization applications on the side of the applicant, furthermore, with regards to data on the quality of active pharmaceutical ingredients, special consideration needs to be made in ensuring that finished product manufacturers are in control of the quality of the active pharmaceutical ingredients that they use in their final dosage forms.

The study has also revealed that initiatives made to strengthen the medicine registration system has produced positive results in terms of a decrease in overall timeline for registration of the product from the time that an application is made. Though the timeline in the final year of the study seems to be lower compared to other years where studied medicines were sampled, the timeline is still above the requirement of the clients' service charter (2016) that has been established between TFDA and its clients. The observation could have been better if there was mechanism in place for tracking the exact time that the application stays with TFDA and the time taken by the applicant to address comments from the assessors. This therefore calls for establishment of robust medicine registration database that is capable of tracking registration timelines.

REFERENCES

Al-Essa, R. Al-Rubaie, M. Walker, S. and Salek, S. (2015). *Regulatory Review Times in the Gulf Region. Pharmaceutical Regulatory Environment*. Switzerland: Adis, pp (65-78)

Al-Essa, R. Al-Rubaie, M. Walker, S. and Salek, S. (2015). *Pharmaceutical Regulatory Environment: Challenges and Opportunities in the Gulf Region.* Switzerland: Adis. pp

BMI Research, (2016). *Tanzania Pharmaceuticals and Healthcare report, BMI Research, June 2016.*[online] Available at: http://theconversation.com/biologics-the-pricey-drugs-transforming-medicine-80258 [Accessed 15 Oct 2018]

Das, M. Choudhury, S. Maity, S. Hazra, A. Pradhan, T. Pal, A. and Roy. R. (2017). *Generic versus branded medicines: An observational study among patients with chronic diseases attending a public hospital outpatient department***.** J Nat Sci Biol Med. 8(1) pp(26–31)

Diego, I. Fake, A. Stahl, M. and Rago, L. (2014). *Review of Quality Deficiencies Found in Active Pharmaceutical Ingredient Master Files Submitted to the WHO Prequalification of Medicines Programme,* Journal of Pharmacy & Pharmaceutical Sciences : a Publication of the Canadian Society for Pharmaceutical Sciences, Societe Canadienne des Sciences Pharmaceutiques 17(2), pp (169 - 186).

Erasmus, L. (2017). *Why are biologicals so expensive?* [online] Health24. Available at:https://www.health24.com/Natural/News/why-are-biologics-so-expensive-20170623[Accessed on 16 Oct 2018]

European Union, (2017). *State of Paediatric Medicines in the EU 10 years of the EU Paediatric Regulation* . [online] Brussels: Publisher, p.6 – 7. Available at: https://www.eumonitor.eu/9353000/1/j4nvke1fm2yd1u0_j9vvik7m1c3gyxp/vkish7pex0tr/v=s7z/f=/com(2017)626_en.pdf [Accessed 12 October. 2018]

Goldar, B & Parida, Y. (2017). *Sustaining India's manufacturing sector growth in the face of increasing competition from Chinese imports*. Cambridge University Press. pp 147-174.

ICH (2004). *ICH Harmonized Tripartite Guideline. Organization Of The Common Technical Document For The Registration Of Pharmaceuticals For Human Use (M4).* Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R4_Organisation/M4_R4__Granularity_Document.pdf (Accessed 29 February 2019)

Kazeem, A. Ibrahim, O. Olayinka, A. (2011). *Sources of drug information and their influence on the prescribing behavior of doctors in a teaching hospital in Ibadan, Nigeria*. The Pan African Medical Journal. 9(13).

Management Sciences for Health, (2017) , *Policy and economic issues. Intellectual property and access to medicines,* Chapter 3. Available at: https://www.msh.org/sites/msh.org/files/mds3-ch03-intellectual-property-mar2012.pdf, (Accessed December, 2017)

Mayige M, Kagaruki G, Ramaiya K, Swai A. (2012). *Non communicable diseases in Tanzania: a call for urgent action.* Tanzania Journal of Health Research. Volume 14, number 2, 2-8.

Rago,L. Santoso, B. (2013). *Drug Regulation: History, Present and Future. Drug Benefits and Risks*. International Textbook of Clinical Pharmacology, 2nd ed. Amsterdam: IOS Press. Chapter 6, 66-77.

Research and Markets, (2018) *Global Biologics Market Size, Market Share, Application Analysis, Regional Outlook, Growth Trends, Key Players, Competitive Strategies and Forecasts, 2018 To 2026*. Available at:https://www.researchandmarkets.com/reports/4564281/global-biologics-market-size-market-share on 15/10/2018 [Accessed 15 Aug. 2018]

Tanzania Food and Drugs Authority. (2003) *Tanzania Food, Drugs and Cosmetics Act, Cap 219*. Dar es Salaam: Government Printers.

Tanzania Food and Drugs Authority (2013); *Ten years of regulating food, medicines, cosmetics and medical devices: Milestones attained*. [online] Dar es Salaam: https://www.tfda.go.tz/sites/default/files/10%20Years%20Book%20english.pdf [Accessed September. 2018]

The Centre for International Public Health Policy (2007). *Good Manufacturing Practice in the Pharmaceutical Industry*. Working paper 3, prepared for Workshop on /Tracing Pharmaceuticals in South Asia, 2-3.University of Edinburgh. Available at: http://www.csas.ed.ac.uk/__data/assets/pdf_file/0011/38828/GMPinPharmaIndustry.pdf (accessed on February 2019)

Tripaty, A. (2018) *India Emerges As Top Five Pharmaceuticals Markets Of The World, by, May 2018*.[online] Businessworld. Available at http://www.businessworld.in/article/India-Emerges-As-Top-Five-Pharmaceuticals-Markets-Of-The-World/05-05-2018-148349/[Accessed in October 2018].

U.S. Department of Commerce. (2016). *International Trade Administration | Industry & Analysis (I&A). A Market Assessment Tool for U.S. Exporters*.. Available at https://www.trade.gov/topmarkets/pdf/pharmaceuticals_top_markets_reports.pdf (accessed October 2018)

Worku, W. Gordon, J. Stahl, M. and Rago, L. (2012) *Deficiencies in generic product dossiers as submitted to the WHO Prequalification of Medicines Programme*. Journal of Generic Medicines 9(2) pp, 63–74.

World Health Organization (2003), *Effective medicine regulation: ensuring safety, efficacy and quality*.[online] Geneva. Available at: http://apps.who.int/medicinedocs/pdf/s4921e/s4921e.pdf [Accessed Day Mo. 2018]

Annexure I: Data collection tool

Part A: General and administrative information

s/n	Particular	Response
1	Application's reference number	
2	International non-proprietary name of the product	
3	Dosage form	
4	Strength	
3	Applicant's details"	
	Name:	
	Country:	
4	API (s) manufacturer details	
	Site address	
	Country	
5	API (s) manufacturer details	
	Site address	
	Country	
6	Local technical representative (name and address)	
7	Submission in CTD?	**Yes:** **No:**
8	Templates provided?	QOS: BTIF: Biowaiver form: Not applicable:

Part B: Trends in applications and registration

s/n	Particular	Response
1	Product type	New chemical entity: Generic:
2	Category	Chemical drug: Vaccine: Biosimilar: Immunological product:
3	Therapeutic indication	
4	Intended age group	
5	In standard treatment guideline?	**Yes:** **No:**
6	Indication per STG?	**Yes:** **No:**

Part C: Deficiencies observed in submitted dossiers:

S/n	CTD Section	Number of questions
3.2.S Active Pharmaceutical Ingredient		
1	3.2.S.1	
3	3.S.2.1	
4	3.S.2.2	
5	3.S.2.3	
6	3.S.2.4	
7	3.S.3.1	
8	3.S.3.2	
9	3.S,4.1 & 4.5	
10	3.S,4.2 & 4.3	
11	3.S,4.4	
12	3.S,5	
13	3.S,6	
14	3.S,7	

S/n	CTD Section	Number of questions
3.2.P Finished Pharmaceutical Product		
1	3.2.P.1	
2	3.2.P.2	
3	3.2.P.3	
4	3.2.P.4	
5	3.2.P.5	
6	3.2.P.6	
7	3.2.P.7	
8	3.2.P.8	

S/n	CTD Section	Number of questions
1	Appendices	
2	Production documents	

S/n	CTD Section	Number of questions
Bioequivalence		
1	Study rejected	
2	Study sites	
3	Study protocol and report	
4	Ethics	
5	Wrong comparator product	
6	Bioanalytical methods and analysis	
7	Statistics	
8	Handling of comparators	
9	Dissolution methods	
10	Quality assurance and monitoring	
11	Quality of the Biobatch	
12	Other	

Part D: Review of evaluation of assessment and registration timelines

s/n	Particular	Response
1	Date received	
2	Date first assessed	
3	Date second assessed (assumed to be date of dispatch of communication)	
4a	Date of submission of response(s)	
5a	Date of review of responses (date of second assessment or first assessment)	
4b	Date of submission of response(s)	
5b	Date of review of responses (date of second assessment or first assessment)	
4c	Date of submission of response(s)	
5c	Date of review of responses (date of second assessment or first assessment)	
6	Date of approval	
7	Number of variations since approval	

……End……...