Regulation of medical devices in Europe and Africa

A thesis submitted in partial fulfilment of the requirements of the award of

Doctorate in Pharmacy

GLORIA DUSABE

Department of Pharmacy

University of Malta

2020

Acknowledgement

I would like to express my sincere gratitude to my supervisor Prof Anthony Serracino-Inglott. I would also like to thank Prof Lilian Azzopardi and all the staff at the Department of Pharmacy of the University of Malta. I express my gratitude to the Malta Medicines Authority and also extend my gratitude to the Heads of the National Regulatory Authorities and the respondents that contributed to my research. I would also like to thank my parents Prof David and Mrs Elizabeth Ndungutse, my husband Steven Wesley, my siblings, relatives and friends for the unwavering support they rendered to me as I pursued the Doctorate in Pharmacy programme. I would also thank the National Drug Authority of Uganda for granting me study leave to pursue this programme.

Abstract

The spectrum of medical device regulation worldwide is diverse. The safety of the patient takes centre stage whenever updates are made to any regulation. In Europe, the Medical Device Directives were reviewed due to scandals like the one that involved leaking silicone breast implants that contained a different grade of silicone than was initially approved. This led to the development of the Medical Device Regulation (EU 2017/745-MDR), which due to the corona virus pandemic will come into force in May 2021 and not May 2020. Africa does not have a standard medical device regulation. Many countries in Africa do not have country specific medical device regulations and implement varied regulatory practices.

The purpose of this study was to evaluate the regulations and guidelines for medical devices in Europe (Germany and Switzerland) and five countries in Africa, namely, Uganda, Kenya, Tanzania, Rwanda and Ghana with the aim of identifying gaps and proposing strategies for improvement.

A questionnaire was administered to 15 regulatory officers and a key informant guide used to interview 5 key informants. Questionnaires were self-administered and the key informant interviews conducted via telephone, skype and face to face. Data analysis of audio interviews, transcripts and notes based on qualitative thematic content was conducted and reviewed for consistency for qualitative data. Questionnaires were used to carry out quantitative data triangulation of the interviews.

Challenges reported by the participants included inadequate staff numbers which was common to all the African authorities, existence of an imbalance between pre-market approval and post market surveillance with more emphasis being placed on pre-market activities. Neglect of post market surveillance due to lack of funds to conduct related

activities. Perception on the robustness of the medical device regulation was mixed, for example, Tanzania reported that the regulatory system is not robust enough to guarantee medical device safety, effectiveness and quality as inspection of manufacturing facilities is not done and the approach applied was based on the pharmaceutical regulatory framework.

The African countries that took part in this study have undertaken several measures including formulation of regulations where none exist, revisions to medical device regulations to cater for advances in technology and categories of medical devices not taken into consideration at the time the regulations were developed, recruitment of qualified staff and a harmonization drive through the Pan African Harmonisation Work Party to develop a standard regulation for medical devices.

The results of this study provide a current picture and better understanding of the status of medical device regulations and guidelines applied in Europe and the selected African countries. Regulation of medical devices in Africa is limited and the participating African countries were at different maturity levels with respect to existence of medical device regulation, guidelines and actual practice. Out of the 5 African countries that participated, 3, namely, Kenya, Rwanda and Uganda lacked regulations. The absence of a regulatory framework for medical device regulation in the 3 countries implies that the scope of regulation is ill defined. Harmonisation efforts for medical device regulation are in the early stages implying that the development of a standard regulation lacks a defined timeline.

This thesis could contribute to advances in medical device regulation as the results demonstrated that the ground is fertile for the development of regulations where none exist, can contribute towards harmonization efforts and aid in adoption of improvements

in regulation where they exist. This will bolster regulatory efforts and contribute towards patient access to safe and effective medical devices of good quality.

Key words: Medical Device Regulation; Medical devices; Europe; Africa

Table of contents

LIST OF TABLES

LIST OF APPENDICES

DEFINITIONS

ISO 13485: "A standard designed to be used by organizations involved in the design, production, installation and servicing of medical devices and related services. It can also be used by internal and external parties, such as certification bodies, to help them with their auditing processes [1]."

Medical device: "Any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of: diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, alleviation of or compensation for an injury, investigation, replacement, modification, or support of the anatomy or of a physiological process, supporting or sustaining life, control of conception, disinfection of medical devices, providing information by means of in vitro examination of specimens derived from the human body; and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means[2]."

[1] International Organization for Standardization. Popular Standards. [cited May 28,2020]. Available from URL: https://www.iso.org/
[2] World Health Organisation. Definitions. [cited May 28,2020]. Available from URL: https://www.who.int/medical_devices/full_deffinition/en/

Notified Body: “An organisation that has been designated by an EU member state (the designating authority) to assess whether manufacturers and their medical devices meet the requirements set out in legislation[3]. ”

[3] Medicines & Healthcare products Regulatory Agency, [cited May 28,2020]. Available from URL:https://www.gov.uk/government/publications/notified-bodies-for-medical-devices/notified-bodies-for-medical-devices

LIST OF ABBREVIATIONS

BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
CE	Conformité Européenne
EAC	East Africa Community
EU	European Union
EUDAMED	European Database of Medical Devices
GHANA FDA	Ghana Foods and Drug Authority
GHTF	Global Harmonisation Task Force
IMDRF	International Medical Device Regulator's Forum
ISO	International Organization for Standardization Organisation
IVD	In Vitro Diagnostics
MD	Medical Device
MDD	Medical Device Directive
NB	Notified Body
NDA	National Drug Authority Uganda
PAHWP	Pan African Harmonisation Working Party
PPB	Pharmacy and Poisons Board Kenya
Rwanda FDA	Rwanda Food and Drug Authority
Swissmedic	Swiss Agency for Therapeutic Products

TMDA	Tanzania Medicine and Medical Devices Authority
UDI	Unique Device Identifier
WHA	World Health Assembly
WHO	World Health Organisation

Chapter 1

Introduction

1.1 Background

Given the role medical devices play in patient care, standards are a necessity for medical device manufacturers to follow prior to medical devices being placed on any market (McAllister and Jeswiet, 2003). Regulation provides the basis upon which quality is incorporated into medical devices during manufacture (Anuja and Goyal, 2008).

The World Health Organisation (WHO) is continually prompting harmonised medical device regulations through a range of initiatives. One such initiative in Bangkok, Thailand, reported that of the 194 WHO member states, 58 countries had a medical device regulatory structure; another 58 had partial regulatory structures in place and 78 were either in the process of establishing a regulatory structure or did not have one in place[4].

"In May 2007, a resolution on health technologies was adopted by the World Health Organisation World Health Assembly (WHA 60.29) which set out the framework for an unprecedented focus on health technologies, specifically on medical devices. As a follow up to this resolution, resolution 67.20 regarding regulatory system strengthening for medical products which stated that effective regulatory systems are an essential component of health system strengthening and contribute to better health outcomes was adopted in 2014.[5]"

[4] Kelly L. Harmonisation of Regulation-Challenges and benefits. Proceedings of the First Global Forum on medical devices conference; 2010 Sep 9-11; Bangkok, (TH). World Health Organisation; 2010. [cited march 6, 2019]. Available from URL: http://www.who.int/medical_devices/00_co_chair_brief_noboru_takamura_reg.pdf.

[5] World Health Organization. WHO Global Model regulatory framework for medical devices including in vitro diagnostic medical devices. World Health Organisation; 2017. [cited February 2, 2020]. Available from URL: https://www.who.int/medical_devices/publications/global_model_regulatory_framework_meddev/en/

The WHO Global Model Regulatory Framework for Medical Devices including In-vitro Diagnostics (IVD) medical devices is intended to act as a guide to WHO member states that plan on setting up regulatory frameworks for medical devices and those with regulatory frameworks in place that would like to better the structures in place that regulate the quality and safety of medical devices placed on their markets. The model recommends a stepwise approach to regulating the quality, safety and performance of medical devices and recommends that the regulatory oversight should increase with the medical device's potential to cause more harm to the user. Effective and efficient regulation based on sound legal and policy and good regulatory practices contributes to public confidence in medical devices." (WHO, 2017)

A global collaboration between Canada, Japan, United States of America and the European Union led to the formation of the Global Harmonization Task Force (GHTF) whose aim was to harmonise regulation pertaining to medical devices.

The GHTF evolved into the International Medical Device Regulators Forum (IMDRF) in 2011 whose aim was to discuss future directions in medical device regulation harmonization. The International Medical Device Regulators Forum is a voluntary group of medical device regulators from around the world who have come together to build on the strong foundational work of the Global Harmonization Task Force on Medical Devices (GHTF), and to accelerate international medical device regulatory harmonization and convergence. This forum is made up of regulators from Australia, Brazil, Canada, China, the European Union, Japan, the Russian Federation and the United States of America[6]. McNerney and Peeling stated that, "International Medical Device regulators forum meetings can be attended by regulators from Africa, Asia and

[6] International Medical Device Regulators Forum. About IMDRF. [cited April 20,2020]. Available from URL: http://www.imdrf.org/

Latin America and manufacturers associations; WHO and Life Sciences Innovation Forum of the Asia-Pacific Economic Community are observers."

Patient management is progressively involving the use of medical devices (Sorenson and Drummond, 2014). Depending on use, medical devices can have positive or negative effects on patients and must be regulated within an up to date regulatory framework that is developed around the unique features of medical devices (Garber, 2010). Medical devices are either active implantables, general medical devices or in vitro diagnostics (McNerney and Peeling, 2015). Medical devices consist of a wide variety of simple and sophisticated medical devices (Mori, Ravinetto and Jacobs, 2011) like pace makers and prosthetics that have varied uses (Chen et al, 2017).

The global north and global south display variances in regulatory oversight of medical devices in terms of scope and definition (Kaushik et al, 2010). Medical device regulation worldwide is diverse and has been the driver for different harmonisation groups which have emphasised the necessity for a uniform technical document for manufacturers, to facilitate receipt of approvals when submissions are made in different countries (Lamph 2012), and improve access to much need medical devices across the socio-economic spectrum.

Manufacturers must register medical devices with the regulatory authorities of the countries in which they intend to market these products. In order for medical devices to be placed on the market of a country, the regulations on medical devices in the country must be followed and the requirements complied with by the manufacturer.

A regulatory structure provides the different regulatory authorities with the mandate to implement policies pertaining to medical devices (McNerney and Peeling, 2015). Protection of patients and users is the motive of regulation on medical devices.

Availability of substandard medical devices and their use is a consequence of poor regulation (De Maria et al, 2018).

1.2 Regulation of Medical Devices in Europe

1.2.1 Medical Device Directives

European Union member states have successfully developed a harmonised regulatory framework for medical devices (Kedwani et al, 2019). The Medical Device Directives consisting of the Active Implantable Medical Device Directive (AIMDD 90/385/EEC), the Medical Device Directive (MDD 93/42/EEC) and the In Vitro Diagnostic Medical Device Directive (IVDMDD 98/79/EC), provides the structure upon which medical devices are regulated in Europe. In Europe, medical devices are grouped into 4 risk based classes, namely, Class I, Class IIa and IIb and Class III (French-Mowat and Burnett, 2012).

1.2.2 Certification process

Notified bodies are organisations that are accredited and have been given the mandate by the European Commission to impose the medical device directives on manufacturers and to issue the Conformité Européenne (CE) mark to medical devices that successfully meet all the set out requirements in the directives. Manufacturers are at liberty to choose a notified body that handles a particular medical device class to make a submission of technical documents. All class II and class III medical devices must undergo an assessment by Notified Bodies in order to be certified (Chen et al., 2017) in addition to a review of the quality management system of the manufacturer being conducted. Receipt of a Conformité Européenne (CE) mark is an indication that a medical device meets the required safety and functional parameters stated by the manufacturer. The CE mark permits the marketing of the medical device in all European Union member states (Kramer, Xu and Kesselheim, 2012).

Contingent on medical device class, a declaration of conformity can be made by the manufacturer in the case of class I devices, or a submission of a technical documentation made for assessment to a notified body for classes II and III medical devices for safety data evaluation given the risk categorisation of these 2 types of medical devices. If the Notified Body determines that the information submitted is sufficient, a conformity certification is issued and a CE mark affixed on the medical device by the manufacturer, following which the device is placed on the European market. The manufacturer is obliged to report any adverse events related to the medical device to the competent authorities in the event that any such event occurs.

1.2.3 Medical Device Regulation (EU 2017/ 745-MDR)

In 2002, the Medical Device Expert Group set up by the European Commission, reviewed the Medical Device Directives and documented its findings[7].

The European Parliament developed the Medical Device Regulation (EU 2017/ 745-MDR), as a result of the weakness that were inherent in the Medical Device Directives, and that were compounded by the silicon breast implant scandal (Donawa and Gray, 2012), and the regulation of new health technologies (Donawa and Gray, 2012; Kedwani, 2019). The Medical Device Regulation (EU 2017/ 745-MDR), was passed by the European parliament and European Commission in May 2017 (Migliore, 2017) and is concurrently being applied with the Medical Device Directives.

[7] Zaid Al Nassir. The European MDR: Impetus, Impacts and Current status. Med Device Online [Internet]. 20202 Jan [cited 2020 Feb 19]. Available from https://www.meddeviceonline.com.

In place of the 3 core directives of the Medical Device Directive are 2 regulations of the Medical Device Regulation (EU 2017/745-MDR) that will govern new health technologies and ensure that the European public is protected[8]. The 2 regulations are the Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on In-vitro diagnostic devices and a transition period has been permitted until May 2021. The Medical Device Regulation (EU 2017/745-MDR) is more detailed on the scope of medical devices regulated and the responsibilities of the manufacturers and competent authorities[9].

The Medical Device Regulation (EU 2017/745-MDR) is binding for all European Union member states while the Medical Device Directives had to be transposed into national law by every member state (Zaid, 2020).

Among the changes introduced by the Medical Device Regulation (EU 2017/745-MDR) is the need to improve transparency by requiring manufacturers to publish summaries of safety and clinical performance which must be updated annually for high risk devices (Fraser et al, 2018). The new regulations further require manufacturers to conduct validation studies and to conduct clinical studies to prove the benefit to the end user. The new medical device regulation requires more clinical evidence demonstrating clinical benefit of devices for high-risk devices (Byrne, 2019).

Eikermann et al, 2013 decried the insufficiency of the assessment process leading to the assignment of the Conformité Européenne (CE) mark under the medical device directives. The process which is undertaken by the Notified Bodies was reported to lack

[8] European Commission. Internal market, Industry, Entrepreneurship and SMEs. [cited April 15, 2020]. Available from URL: https://ec.europa.eu/growth/sectors/medical-devices_en

[9] European Medicines Agency. Medical devices legislation. [cited May 20, 2020]. Available from URL: https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices

transparency, ridden with bias towards manufacturers, did not require submission of evidence demonstrating medical device performance and safety parameters by manufacturers and put no demands on manufacturers to conduct post market studies for devices placed on the market.

1.2.4 Regulation of medical devices in Africa

Africa is characterised by differences in political, social, religious and economic status. All the 54 countries on the continent are members of the African Union (AU). Africa lacks a standard directive or regulation that regulatory authorities on the continent can refer to with respect to developing regulations for medical devices. The majority of these countries have structures in place to regulate pharmaceuticals but lack regulatory frameworks and the requisite human resource capacity to regulate medical devices. Many of the countries in Africa do not have regulations in place or implement varied medical device regulatory practices. For African countries with regulatory frameworks, constraints limit the effectiveness of the regulatory structures to guarantee medical device safety, quality and performance.

Some African countries have made strides and developed regulations and guidelines to cater for the local context. For example, the Pharmacy and Poisons Board in Kenya requires importers to support applications for Medical Devices with conformity certificates in order to obtain import authorization (Saidi and Douglas, 2019) and the Tanzania Medicines and Medical Devices Authority is mandated with regulating all medical devices on the Tanzanian market[10] and performs risk based assessment of medical device applications based on the Tanzania Food, Drugs and Cosmetics act (Cap 219) regulations 2015 under section 122 (1) (c) (e). Ghana utilises the guidelines for

[10] Tanzania Medicines & Medical Devices Authority. Acts. [cited April 8, 2019]. Available from URL: https://www.tmda.go.tz/pages/acts

registration of medical devices, document number FDA/MDD/GL-01 revision 02 that is aligned to the Public Health Act 2012, Act 851 part 7.

Due to inadequate resources, the regulation of medical devices in Uganda, Kenya, Tanzania and Rwanda is not a primary area of focus for the different regulatory authorities (Rugera et al, 2014; McNerney and Peeling, 2015).

Regulatory control of medical devices and diagnostics is weak across the East African Community (EAC) with efforts to control the quality of imported products largely confined to national disease programs for pathogens. A draft proposal at the EAC secretariat aims to enhance medical device capacity and collaborative mechanisms to facilitate access to safe and effective devices and IVDs[11].

For this study, the medical device regulatory profile for 5 of the 54 countries is the point of interest. Appropriate control of the regulatory cycle for medical devices is key to ensuring quality, safety and performance. Poor regulatory oversight or lack of a regulatory framework compromises responses to emergencies arising from faulty and questionable medical devices.

Different countries have tailored lists of requirements for applicants to comply with prior to issuance of marketing authorization for medical devices. Reliance on WHO certification or authorisations issued by stringent regulatory authorities are taken into consideration by many African regulatory authorities when assessing submissions. Tanzania for instance took the initiative to build its medical device regulation capabilities

[11] East African Community Regional Project Proposal on Strengthening and Harmonization of the Regulation of Medical Devices and Diagnostics: The EAC Secretariat; 2015 January.

with the help of partners like the World Health Organisation (McNerney and Peeling, 2015).

In order to enable patients on the African continent to access reasonably priced medical devices of good quality, a voluntary working group known as the Pan African Harmonisation Working Party (PAHWP) was set up in 2012 to facilitate the process of generating uniform regulation for the African continent (McNerney and Peeling, 2015). The PAHWP aims to review the different aspects of regulation such as medical device classification, technical documentation format, studies on medical device functionality, quality management system inspections and postmarketing surveillance of medical devices. The goal of the review of the different regulatory aspects is to facilitate harmonisation efforts for medical device regulation across Africa[12] in order to facilitate access to affordable medical device by the African population.

Low and middle income countries have the potential and promise of providing markets for medical devices from the developed world countries (Malkin, 2007). The increased visibility and application of medical devices in patient care requires that regulations pertaining to their safety, quality and performance are in place and enforced given that they present varied risks to the end-users.

Strict regulations are essential for management of the different risk categories of medical devices in order to ensure safety and effectiveness which are vital to human health. Medical devices have distinct features from medicines and require a regulatory framework that is specifically tailored to manage this uniqueness (Rugera et al, 2014). According to De Maria et al, the responsibilities of the manufacturers need to be clearly

[12] Update on Regional Harmonization of Diagnostic Regulation in Africa, Rosanna W Peeling. [cited February 28, 2020]. Available on URL: https://www.who.int/hiv/amds/202

stated in legislation making reference to technical requirements. Inefficiencies in the medical device regulations can hinder access to much needed medical devices or can result in markets being flooded with substandard medical devices. Evidence of poor technical performance (Bimenya et al, 2003), counterfeits, poorly labelled devices and generation of inconsistent results (Gillet et al, 2010) are some of the challenges associated with the use of medical devices in Africa. The regulation of medical devices in Africa is in its infancy to curtail the importation and use of substandard devices (Lamph, 2012).

1.3 Aim

The aim of this study is to evaluate the current regulations and guidelines for medical devices and to assess the challenges faced by regulators in Europe and selected African countries, namely, Uganda, Kenya, Tanzania, Rwanda and Ghana with an emphasis of identifying and proposing strategies improvement.

1.4 Research questions

1. What is the current status of medical device regulation in Europe and the selected African countries of Uganda, Kenya, Tanzania, Rwanda and Ghana?
2. What measures are currently undertaken by Europe and the selected African countries to guarantee medical device safety, effectiveness and quality?
3. What are the challenges faced by Europe and the selected African countries in medical device regulation?
4. How robust are the current regulations for medical devices in Europe and the selected African countries?

1.5 Study objectives

1.5.1 General objective

To evaluate the current regulations and guidelines for medical devices and to assess the challenges faced by regulators in Europe and selected African countries, namely, Uganda, Kenya, Tanzania, Rwanda and Ghana with an aim of identifying and proposing strategies of improvement.

1.5.2 Specific objectives

1. To determine the current status of medical device regulation in Europe and the selected African countries of Uganda, Kenya, Tanzania, Rwanda and Ghana?
2. To assess measures currently undertaken by Europe and the selected African countries to guarantee medical device safety, effectiveness and quality.
3. To document the challenges faced by Europe and the selected African countries in medical device regulation.
4. To assess the robustness of the current regulations for medical devices in Europe and the selected African countries.

This study aims to evaluate the regulations and guidelines for medical devices in Europe and five selected countries in Africa, namely, Uganda, Kenya, Tanzania, Rwanda and Ghana in order to determine the current status of regulation, identify existing gaps and propose strategies of improvement.

Chapter 2

Methodology

2.1 Introduction

This chapter describes the design and approach applied to achieve the objectives and address the research question.

The chapter covers the overall research design, study tools, study participants, research setting, sampling procedure, data collection procedures and data analysis.

2.2 Research design

A cross-sectional study was conducted since data collection was at one point in time. The study design was cross sectional in that it collected data at one point in time, and adopted both qualitative and quantitative strategies of data collection.

Data was collected using structured questionnaires, key informant interview guides and desk review of regulations, guidelines and literature.

This design was deemed appropriate for this study because it is relatively cheap and would provide a current picture of the regulatory landscape in selected European countries of Germany and Switzerland and the selected African countries of Uganda, Kenya, Tanzania, Rwanda and Ghana within a short period of time of study that would be in line with the study timeframe. The study was conducted from August to October 2019.

The qualitative approach was applied through key informant interviews to explore the factors that influence regulation of medical devices while the quantitative approach utilised questionnaires to assess the various factors that influence medical device regulation. Questionnaires were administered to regulatory officers and a key informant guide used to interview key informants.

. The questionnaire was selected for use in this study because it would facilitate the collection of data in a short period of time, with a certain degree of impartiality and at a low cost.

2.3 Study population

The target population was regulators from regulatory authorities in Germany and Switzerland and the African countries of Uganda, Kenya, Tanzania, Rwanda and Ghana that were selected for this study. A total of twenty regulators were invited through the Heads of authorities to participate in this study. The sample consisted of 5 key informants and 15 regulatory officers who were administered with questionnaires. The key informants who held managerial positions and the regulatory officers were members of staff in the respective regulatory authorities of Germany, Switzerland, Uganda, Kenya, Tanzania, Rwanda and Ghana. One key informant was interviewed per country for Uganda, Kenya, Tanzania, Rwanda and Ghana.

Questionnaires were administered to 1 regulator from Germany, 1 from Switzerland, 3 from Uganda, 2 from Kenya, 3 from Ghana, 4 from Tanzania and 1 from Rwanda.

The key informants possessed in depth knowledge of the medical device field and were chosen to provide information with regards to the regulation of medical devices in the different countries. The regulators who self-administered the questionnaires provided responses to the different aspects of regulation based on day to day experience.

Participants were all involved in medical device regulation.

Inclusion criteria

1. Regulators working with regulatory authorities, involved in medical device regulatory activities with 3 or more years of working experience in medical device regulation.

Exclusion criteria

1. Regulators working with regulatory authorities, involved in medical device regulation with less than 3 years of working experience in medical device regulation.

2.4 Research setting

The research setting consisted of regulatory authorities involved in medical device regulation in Europe namely, Germany and Switzerland and the selected African countries of Uganda, Kenya, Tanzania, Rwanda and Ghana. The regulatory authorities that participated included; Federal Institute for Drugs and Medical Devices (BfArM), Swiss Agency for Therapeutic Products (Swissmedic), Ghana Foods and Drug Authority (Ghana FDA), Pharmacy and Poisons Board Kenya (PPB), Rwanda Food and Drug Authority (Rwanda FDA), Tanzania Medicine and Medical Devices Authority (TMDA) and National Drug Authority Uganda (NDA).

2.5 Sampling

The purposive and simple random sampling were applied for Africa. Purposive and simple random sampling were applied to obtain the study sample.

The sample size of the study was twenty regulators; two regulators from European countries of Germany and Switzerland and eighteen combined from the African regulatory authorities of Uganda, Kenya, Tanzania, Rwanda and Ghana.

The sample size for the qualitative aspect of the study was set at 5 key informants, that is 1 key informant per regulatory authority that participated from Africa. The targeted key informants for Germany and Switzerland were not available for interviews at the time the study was conducted. The key informants from Ghana, Kenya, Rwanda, Tanzania and

Uganda provided in depth answers to the regulation of medical devices in the respective countries. Convenience sampling was applied to obtain the sample for the key informants.

The sample size for the quantitative aspect was 15 respondents who consented to participate in the study. These included 1 regulator from Germany, 1 from Switzerland, 3 from Uganda, 2 from Kenya, 4 from Ghana, 3 from Tanzania and 1 from Rwanda. These respondents provided responses to different questions that touched on the regulatory aspects of medical device regulation, namely, classification of medical device, format of technical documentation, assessment, inspection of quality management systems and post market surveillance.

Selection was based on the participants' daily line of work being medical device regulation in the respective country regulatory authority and experience which was set at 3 years because it was assumed that a regulator would have grasped the different aspects of medical device regulation by the 3year mark.

Heads of authorities were contacted and a request submitted seeking permission to conduct the study at the respective regulatory authorities. The Heads of authorities identified the staff that would participate in the study and these were recruited in the study after giving consent. An information sheet bearing a consent statement was included in the study tools for the participant's consideration.

All 20 study participants were invited to participate through the Heads of authorities who approved the request for permission to conduct the study at the respective authorities.

2.6 Study area

Table 1: Population statistics April 2020

Country	**Population**
Germany	83,783,942[13]
Switzerland	8,645,757[14]
Ghana	30,500,000[15]
Kenya	53,771,296[16]
Rwanda	12,893,526[17]
Tanzania	59,414,877[18]
Uganda	41,246,829[19]

[13] Worldometer. Germany population. [cited May 11, 2020]. Available from URL: https://www.worldometers.info/world-population/germany-population/
[14] Worldometer. Switzerland population. [cited May 11, 2020]. Available from URL: https://www.worldometers.info/world-population/switzerland-population/
[15] Worldometer. Ghana population. [cited May 11, 2020]. Available from URL: https://tradingeconomics.com/ghana/population/
[16] Worldometer. Kenya population. [cited May 11, 2020]. Available from URL: https://www.worldometers.info/demographics/kenya-demographics/
[17] Worldometer. Rwanda population. [cited May 11, 2020]. Available from URL: https://worldpopulationreview.com/countries/rwanda-population/
[18] Worldometer. Tanzania population. [cited May 11, 2020]. Available from URL: https://www.worldometers.info/world-population/tanzania-population/
[19] Uganda Bureau of Statistics. Uganda population status. [cited May 11, 2020]. Available from URL: https://www.ubos.org/

2.7 Data collection methods and tools

This study used both key informant interviews and a questionnaire to collect data from the Germany, Switzerland, Uganda, Kenya, Tanzania, Rwanda and Ghana. Literature on medical device regulation was also reviewed for Europe.

A self-administered questionnaire with open- and close-ended questions was emailed to the other 15 respondents. It had questions on the different regulatory functions of inspection, assessment, vigilance and post market surveillance.

Key informant interviews were conducted via skype and telephone and face to face with the key informants selected to participate in the study.

Questionnaire

The questionnaire had questions on assessment, inspection, vigilance, post market surveillance, training and harmonisation.

The questionnaire was selected for use in this study because it would facilitate the collection of data in a short time frame, with a certain degree of impartiality and at a low cost.

Key informant interview

The key informant interview guide questions were administered to 5 key informants who held senior positions in the medical device departments in the regulatory authorities that participated in the study. This facilitated collection of rich data given that the key informants had the freedom to provide their views on the questions that were open ended in nature and relevant to the research objectives. The questions that were posed to the key informants were relevant to the research objectives and were used to collect data on the

regulation of medical devices in the 5 African countries that were selected to take part in this study.

Key informant interviews were applied to obtain the views and opinions of experts regarding regulation of medical devices in the respective countries.

The questionnaire and key informant interviews used were appropriate for this research because they facilitated the collection of data and opinions from the different regulators in order to obtain answers to the research questions.

Validity and reliability

Validity and reliability tests were undertaken to ensure that the data generated was reliable, complete, accurate and reproducible using the same method.

Validity

In order for the research instrument to measure the intended purpose, consultations with the academic supervisor were done to check the consistency and relevance of the items in the tool in the context of the research. The research tool was validated by a panel of regulatory experts and approved by the academic supervisor.

Reliability

The questionnaire was pre-tested, reviewed by a panel of 4 regulatory experts and based on the feedback, questions were refined to make them clear. None of the experts were involved in the research study.

2.8 Data collection

2.8.1 Procedures

Ethical approval was obtained from the Faculty Review Ethics Committee (FREC) of the University of Malta prior to commencement of data collection (Refer to appendix I).

A copy of the letter seeking permission and information sheet and (see attached appendix I and II) to conduct research were emailed to the Heads of regulatory authorities in Germany, Switzerland, Uganda, Kenya, Tanzania, Rwanda and Ghana in September 2019. The different Heads of regulatory authorities identified the staff that would participate and emailed the contact details to the researcher.

The questionnaire was validated by a panel of four experts with the aim of testing the appropriateness of the questions, re-designing and improving the clarity of the questions.

To rule out selection bias, the Heads of the regulatory authorities selected the respondents that met the inclusion criteria who would participate in the research and shared the contact details with the researcher.

Following receipt of permission from the different Heads of regulatory authorities, the respondents were contacted via email and telephone and referred to the instructions on the first page of the respective study tools. Participants were issued with an information sheet, then briefed about the study, relevant information about the study was disclosed, comprehension of the information provided assessed through posing of questions on the study following which participants voluntarily consented to participate in this research by signing the consent statement or by word of mouth. This study did not involve collection of human materials or use of interventions.

Following acceptance to participate in the research, questionnaires to be self-administered were sent to the respective emails, and key informant interviews conducted via Skype and telephone from August 2019 to October 2019.

2.8.2 Plan for data collection

The researcher checked and ensured during the data collection period that the questionnaires were filled in completely and accurately and that the information provided was logical.

A data entry format was developed and the information collected keyed into the form with the relevant code.

The questionnaires were stored to maintain integrity and confidentiality.

2.9 Data management and analysis

Questionnaires responses were entered into Epidata version 4.4.2.1 with programmed quality control checks. Epidata version 4.4.2.1 was selected because it can be programmed to have logic checks that facilitate easy data entry and double data entry. The data was then exported to Microsoft excel and STATA 14.0 for data analysis. Key informant interviews conducted in English were audio recorded, transcribed, and reviewed by the researcher. The notes that were taken during the interviews were reviewed. All data was stored electronically in password protected computers and cloud storage.

Quantitative data was presented using frequencies, proportions and tables.

Qualitative data involved analysis of audio interviews, transcripts, and key interview notes which were reviewed several times for consistency and analysed based on qualitative thematic content with meaning units identified. The meaning units were then condensed, coded and put into categories from which themes emerged. Manual analysis blended with Open-code software was used. Open code software helped to organize the transcripts into a format to analyse, identify meaning units, assign codes, categories and themes. Quotes from the interviews were presented in line with the themes generated for

the different objectives. The principal investigator used the questionnaires to carry out quantitative data triangulation of the interviews.

2.10 Ethical considerations

The principal investigator applied for and obtained ethical approval from the Faculty Review Ethics Committee of the University of Malta prior to conducting the research.

Permission was sought from Heads of regulatory authorities in Germany, Switzerland, Uganda, Kenya, Tanzania, Rwanda and Ghana to interview relevant staff for the study.

An information sheet was shared with the study following which they were briefed about the study, relevant information about the study was disclosed and comprehension of the information provided assessed following which participants voluntarily consented to participate in the study.

Chapter 3

Results

3.1 Introduction

This chapter presents the findings on regulation of medical devices in Europe and Africa. The findings are presented according to the study objectives. The results were generated from a total of 20 regulators who were involved in work related to medical device regulation in 2 regulatory authorities in Europe and 5 regulatory authorities across Africa.

Study population description

Five heads of medical device departments were interviewed as key informants and 15 regulatory officers administered with the questionnaire. The study population consisted of 7 females and 13 males. The response rate to the questionnaire items was 98% and to the key informant interviews 100%.

Table 2: Population characteristics

Characteristic		**N**
Sex	Female	7
	Male	13
Total		20
Age range	30-34 35+	4 16
Education level	Bachelors	8
	Postgraduate	12
Work experience	3 years 3+ years	5 15

Objective 1 of this study was to determine the current status of medical device regulation in the two selected countries of Europe Germany and Switzerland, and the selected African countries of Uganda, Kenya, Tanzania, Rwanda and Ghana.

In Europe, regulation for medical devices exists in the form of the Medical Device Directive, which consists of three core directives for safety regulations and marketing of medical devices. The Medical Device Regulation (EU 2017/745) was subsequently developed and came into force in May 2017.

In Germany, the procedures for market access of medical devices are mainly defined and harmonized on a European level and applied by the Notified Bodies. The Federal Institute of Drugs and Medical Devices is not involved in market access of medical devices.

Information received from the Federal Institute of Drugs and Medical Devices (BfArM) of Germany stated that one of its main tasks in the medical devices area is the collection and scientific assessment incident reports for medical devices according to the current German ordinance referred to as the Ordinance on the Medical Device Safety Plan (MPSV), in future according to the Medical Device Regulation (EU 2017/745).

Federal Institute of Drugs and Medical Devices (BfArM) reports on serious incidents according to the MDD/MPSV currently respectively the Medical Device Regulation (EU 2017/745) in future. The Federal Institute of Drugs and Medical Devices can only recommend corrective actions as in Germany due to the federal structure the competencies for market surveillance and enforcement are with the regional authorities known as Landesbehörden.

Switzerland was transposing the medical device regulation (EU 2017/745) into its national laws. Switzerland is integrated into the European Union system and has adopted

compliance assessment and certification based on bilateral agreement. With respect to complaints pertaining to medical devices, Swissmedic systematically collects and evaluates reports, implements necessary corrective actions in a risk-based manner while monitoring implementation. Swissmedic enforces corrective actions to restore the correct status and conformity if a medical device does not conform.

Table 3.1: Elements of current status of regulation and compliance in Europe and Africa

Element of compliance	**Europe** N=2		**Africa** N=5				
	Germany	**Switzerland**	**Ghana**	**Kenya**	**Rwanda**	**Tanzania**	**Uganda**
Regulation present	✓	✓	✓	×	×	✓	×
Guidelines available			✓	✓	×	✓	×
Compliance oversight	×	×	✓	✓	×	✓	×
Training	×	×	✓	✓	×	✓	✓
Reporting			✓	✓	×	✓	✓
Monitoring			✓	✓	×	✓	✓

Data collected from the regulatory authorities of Germany, Switzerland, Tanzania, Ghana, Kenya, Rwanda and Uganda was analysed using descriptive statistics to obtain frequencies, percentages, proportions and tables.

In Kenya, guidelines on submission of documentation for registration of medical devices including in-vitro-diagnostics (IVDs) dated May 2018[20] are applied when assessing technical documentation submitted for registration of medical devices. In Tanzania, the Tanzania Food, Drugs and Cosmetics act (Cap 219) regulations 2015 under section 122 (1) (c) (e) is applied to submitted medical device technical documentation. Ghana utilizes the guidelines for registration of medical devices, document number FDA/MDD/GL-01 revision 02 that is aligned to the Public Health Act 2012, Act 851 part 7[21], while Uganda and Rwanda do not have legislation in place regulating medical devices.

Key informants highlighted the following reflections;

> ***KI from Tanzania, 2019***-*"In 2015 and 2017, our regulations were revised to include all medical devices and In Vitro Diagnostics respectively. The current regulations address all the key functions like legal provisions for import and export, Post Marketing Surveillance and pharmacovigilance, registration and*

[20] Pharmacy and Poisons Board. Medical Device Guidelines. [cited May 23, 2020]. Available from URL: pharmacyboardkenya.org › files › file=Final Guidelines.

[21] Ghana Food and Drugs Authority. Guidelines & Forms. Medical Devices, Cosmetics and Household chemical substance. [cited May 23, 2020]. Available from URL: https://www.fdaghana.gov.gh/cosmetics.php

licensing of premises, donations, special importation of unregistered medical devices."

KI from Ghana, 2019- *"All our regulations and guidelines work well and are freely accessible from the website."*

KI from Kenya, 2019-*"…We have working guidelines. The control of import, Listing of Class A medical devices, Registration of Class B, C, D also has been well established. The post market surveillance of products in the market is robust and working".*

KI from Rwanda, 2019-*"…. we do not have approved regulations and guidelines on medical devices."*

KI from Uganda, 2019-*".. We do not have guidelines specific to medical devices in the country. We use the ISO regulations and Standards for this and use the United States Pharmacopoeia for the sutures and syringes"*

Objective 2 of this study was to assess measures currently undertaken by Europe and the selected African countries to guarantee medical device safety, effectiveness and quality.

In Europe, the MDR (EU 2017/745) makes it a requirement for manufacturers to assign each medical device which has been certified as fit to be sold on the European market a unique identifier clearly indicating it on all labels (Wagner and Schanze, 2018).

A procedure termed the scrutiny procedure has been introduced with the MDR (EU 2017/745) and it requires that Notified Bodies generate a Clinical Evaluation Assessment Report which through the European commission is shared with a panel of experts for

scientific opinions concerning high risk medical devices in categories III implantable devices and class IIb (Wagner and Schanze, 2018).

The requirements for post market surveillance have been increased with manufacturers obligated to collect post marketing clinical data and to submit periodic safety update reports to EUDAMED for public access (Byrne, 2019).

Prior to receipt of approval, pre-market controls such as provision of clinical evidence for devices under the high risk category are a requirement with the MDR (EU 2017/745). Manufacturers of devices similar to those already on the market have to demonstrate parity to those on the market (Byrne, 2019).

Manufacturers will submit safety and clinical performance summaries and annual reports to the European Union database of medical devices (EUDAMED) for medical devices in the high risk category. The public will have access to this information in the future (Byrne, 2019).

Patient compensation mechanisms have been introduced in the MDR (EU 2017/745) in the event that patients are issued defective devices. It requires manufacturers to budget resources to reimburse affected patients when the need arises.

The respondents from the African regulatory authorities reported the various measures currently in place to ensure adequate regulation of medical devices. Importantly, in countries where the regulations and guidelines were absent, steps were in advanced stages of formulating, harmonizing and operationalizing them. In countries where regulations and guidelines were present, revisions, staff recruitments, inspection and evaluation of medical devices, trainings, testing of medical devices, and post market surveillance were being implemented.

The respondents also highlighted ongoing partnerships in training between their respective countries as key for the integrated review of medical devices in Africa.

a) Formulation of regulations and guidelines

The following respondents stated although not available, they are being drafted.

> ***KI from Uganda, 2019*** *-"We drafted a bill to address medical device regulation that is before the parliament of Uganda. It has however taken nine years before its approval. The Uganda National Bureau of Standards has drafted guidelines for use in in regulating sutures, we plan to use them later. A draft document for regulation of surgical instruments has been drafted too although it does not cover everything"***.**

> ***KI from Rwanda, 2019*** *-"We are working on Rwanda FDA regulation and guidelines on medical devices and In Vitro Diagnostics"***.**

b) Revision of guidelines

Where guidelines were present, regulatory bodies undertook regular revisions, and increased pre- and post-market vigilance. Tanzania and Ghana have taken steps in this direction as illustrated below;

> ***KI from Tanzania, 2019*** *- "We have undertaken a continuous process with regulatory measures revised from time to time. We revised our regulations in 2015 to include all medical devices, and in 2017 to incorporate IVDs and lab agents. We are also balancing efforts between pre and post marketing, plus leveraging reliance on other authorities to hasten Marketing Authorization"*

KI from Ghana 2019 *- "In 2018, we revised our guidelines to include the specifics regarding donations of medical devices"*

c) Recruitment of well qualified staff

Staff with various qualifications have been recruited by 4 of the 5 African regulatory authorities to handle medical device related activities. The staff numbers for the four regulatory authorities are; Ghana (6), Uganda (9), Kenya (14) and Tanzania (22) respectively.

The different countries had staff with varying levels of educational training in order to meet the needs of the tasks. Ghana has staff with backgrounds in Biomedical Engineering, Pharmacy and Science background; Tanzania has staff with backgrounds in Pharmacy, Biomedical engineering, Chemistry, Microbiology and Medical Laboratory Sciences. Kenya has staff with chemistry and pharmacy backgrounds while Uganda has pharmacists and chemists.

d) **Inspections and Evaluations**

The Ghana Food and Drug Administration and the Tanzania Medicines and Medical Devices Authority conduct inspections of the medical device manufacturing facilities according to the ISO 13485 international standard and country specific regulations and guidelines.

During evaluation of applications for of medical devices and inspection of manufacturing sites, the regulators in the above 2 African regulatory authorities reported that certifications and approvals as shown in (Table 2) are accepted:

Table 2: Recognized approvals for medical devices in Ghana, Tanzania, Kenya and Uganda.

	International standard		
Country	CE mark	Stringent Regulatory Authority (SRAs) e.g USFDA, Health Canada, Pharmaceuticals and Medical Devices Agency Japan	WHO
Kenya	✓	✓	✓
Uganda	✓	✓	✓
Tanzania	✓	✓	✓
Ghana	X	✓	✓

✓ acceptable without additional regulations

X not acceptable unless it complies with "in country" guidelines.

Manual submission of dossiers and relevant documents is the commonest mode of receipt of applications for approvals of medical devices. Only Uganda had a combined manual and electronic submission platform.

e) Training

Personnel at the regulatory authorities have been trained in some basics in evaluation of medical devices in their countries. This is highlighted by the key informants from the respective countries below;

> ***KI from Kenya 2019***- *"…. Diverse training, in the areas of ISO 13485certification, desk reviewing of medical devices; risk based classification, conformity assessment and also combination medical devices".*

> ***KI from Ghana 2019***- *"...Our staff have had both in house and abroad trainings in evaluation of dossiers in order to know what to look for during assessment"*

Additional trainings are also scheduled for all staff in emerging areas of importance in medical device regulation.

> ***KI from Kenya 2019***- *"...The trainings are scheduled to be undertaken depending on the areas of need that have been identified. The current training rota focuses on areas of new development."*

> ***KI from Tanzania 2019***- *"Training is a continuous process based on identified needs. The resources for training are available but the main challenge is where the training should be done. TMDA sends personnel to Thailand, WHO, USFDA, Turkish FDA. Condom testing training is also conducted once a year at the TMDA by UNFPA"*

KI from Ghana 2019- *"In Ghana, the process is continuous and expected to work in conjunction with other partners."*

KI from Uganda 2019- *"We have annual trainings on the use of condoms by suppliers. We have had staff trained in the United States of America, Europe, Ghana in addition to attending local, regional and international meetings for exposure"*

f) Partnerships in training

The countries have made south-to-south and north-south collaborations to foster training and knowledge sharing.

KI from Uganda 2019- *"We have trained other staff from Rwanda and Seychelles in some components of device regulations like condoms. In Uganda, we have also sent our members to participate in select ISO technical committees and also visited Ghana for further training"*

KI from Ghana 2019- *"The training is not adequate at any time. It is a continuous process since regulations are dynamic. Trainings are planned in conjunction with WHO and other organizations that train for example in the USA"*

g) Harmonization of guidelines

There are ongoing efforts in the countries to harmonize their guidelines with existing regional and intercontinental regulatory blocks. This is illustrated by the quote below:

KI from Kenya 2019- *"We are part of the EAC regional block which is undertaking harmonization efforts for medical devices including IVD (In Vitro Diagnostic) devices."*

KI from Ghana 2019- *"We are part of Pan Africa Harmonization Working Party (PAHWP). The framework for this is in the early stages of development."*

Even in cases where the guidelines are in development, the responsible parties are also linked to regional blocks to ensure harmonized outputs. For example, Rwanda is working with a new continental entity on this as shown by the quote below:

KI from Rwanda 2019-*"Yes, we are working on harmonization through Pan African Harmonization Working Party now called African Medical Device Forum (AMDF) but it is still new and they are working on ToRs (Terms of Reference) of this forum"*

h) Testing of medical devices

There is routine in-country testing of medical devices in some of the study countries. For example:

KI from Uganda 2019- *"...There is a unit at the Directorate of laboratory services responsible for testing of medical devices. At this facility, we carry out routine testing of gloves, syringes and condoms."*

i) Post market surveillance

All of the respondents (18) from the five African countries confirmed that the regulatory authorities undertake some form of post market surveillance of the approved and cleared medical devices. It was reported that post market surveillance was not comprehensive.

Objective 3 was to document the challenges faced by Europe and the selected African countries in medical device regulation.

From review of literature, the following challenges were noted as being faced by Europe in the regulation of medical devices:

Data from notified bodies pertaining to devices that have been issued approval and thus a CE mark are largely unavailable to the public and pave the way for subsequent generations of the devices to deviate from the initial specifications (Thompson et al, 2011).

Some experts have also pointed out that the regulations governing medical devices are not stringent with respect to the assessments conducted by the notified bodies on safety and efficacy (Storz-Pfennig, 2013).

Another flaw in the European regulations is that manufacturers are still given the leeway to determine and alter the purpose of a medical device prior to receipt of approval from competent authorities (Storz-Pfennig, 2013).

There was a challenge of an ineffective certification process through the notified bodies as demonstrated by the Poly Implant Prothese (PIP) breast implant scandal. “The process is inconsistent, opaque and operates in the interest of manufacturers. It requires insufficient evidence of efficacy of the devices and no long term follow-up of patients.” (Eikermann et al, 2013).

Manufacturers tend to submit incomplete evidence on device safety and efficacy for high risk medical devices and new technologies to Notified Bodies which issue certificates of conformity for the medical devices without spelling out the responsibilities on the conduct of post marketing studies (Storz-Pfennig et al, 2013).

Inconsistent application of the medical device directives across countries as they are not as binding as regulations was common. Directives could not be implemented immediately and so had to be contextualised to the legislation of each country (Zaid, 2020). Directives had to be adapted to a country's national laws while a regulation is binding to all member countries[22].

According to the European Commission, "Problems with diverging interpretation of the existing rules as well as certain incidents -e.g. with breast implants and metal hips - highlighted the weaknesses of the current legal system and damaged the confidence of patients, consumers and healthcare professionals in the safety of medical devices[23]."

[22] Eisenhart. S. Emergo, 26 April 2016. [Internet]. Whatever happened to the ASEAN Medical Device Directive? [Cited 28 Feb 2020]. Available: https://www.emergobyul.com/blog/2016/04/whatever-happened-asean-medical-device-directive.

[23] Commission E. New EU rules to ensure safety of medical devices. European commission—Fact Sheet. 2017. [cited 15 Jan 2020]. Available: https://ec.europa.eu/commission/presscorner/detail/en/MEMO_17_848

Lack of post-marketing clinical follow-up data which would provide data on the actual use of devices on the market. Pane et al stated, “Valuable data on long-term effectiveness and safety of devices” was thus not available from the manufacturers.

There was a problem of device traceability arising from the absence of an identifier code that would facilitate tracking of a defective device to its source as and when the need arises after the device is placed on the market and to also identify patients that might have been issued the defective devices (Byrne, 2019).

The approach applied by the notified bodies during the assessment of medical device applications is not transparent as it does not permit interested parties to access information on how approvals were issued for high risk medical devices (Thompson et al, 2011; Byrne, 2019).

Under the medical device directives and prior to the introduction of the requirement of the new medical device regulation to provide ‘implant cards’ for patients (European Commission, 2017) bearing information that is easily understandable to the patient, there was a general lack of information on implantable devices.

Poor patient compensation mechanisms in the event that patients ended up with defective devices as manufacturers were not taking on this liability and there were no sufficiently robust mechanisms in place to cater to this.

The African countries participating in this study face challenges of delays in establishment of regulatory bodies, lack of cooperation from partner government authorities, limited funding, insufficient staff numbers, fast changing technology, inadequate training, interpretational gaps and poor adherence to guidelines and regulations. The key informants highlight the following:

a) Lack of or delay in establishment of regulations and /or regulatory bodies by country authorities

In Rwanda where the regulations and guidelines were absent, the institutional framework establishing the regulatory bodies was absent.

In Uganda, an institutional framework is in place but there have been delays in establishment of medical device regulations. This is highlighted by the reflections of the key informants from Rwanda and Uganda:

> ***KI from Rwanda 2019 -****"…we have no guidelines because the Rwanda FDA (Food and Drug Authority) was not yet established and the Ministry of Health which was in charge was overwhelmed to carry out all products regulatory functions including medical device registration…"*
>
> ***KI from Uganda 2019****- "There is no enabling law to facilitate the regulation of medical devices in Uganda. It causes a lot of back and forth for the last 9 years leading to lengthy discussions."*

b) Lack of cooperation from other government sectors.

In Uganda, there have been delays in fast tracking the medical devices bill due to disagreements between government agencies like the Ministry of Agriculture and the Ministry of Health. The reflection from the Ugandan key informant summarizes the situation:

> ***KI from Uganda 2019****- "The bill to regulate medical devices has stalled because the Ministry of Agriculture would like to take over the food components and veterinary drugs which are components of the National Drug Authority Act."*

c) Inability to match the regulations to the fast changing technology and changing scope of medical device regulations

The respondents reported that with the development of fast changing technologies, the regulatory techno-vigilance has not matched up to this demand in their countries. This is ascribed to inadequacy of the required skillsets and tools to carry out the vigilance as illustrated below:

> ***KI from Kenya 2019*** *- "…no measures have been put in place at the moment because the skill sets and tools required are not yet available."*

In Tanzania, the available guidelines are not yet fully tailored to medical devices and in some cases are inadequate.

> ***KI from Tanzania 2019****- "..We realized that medical devices are unique and need to have a framework tailored to them. We are using the medicinal product regulation approach for vigilance of medical devices"*
>
> ***KI from Tanzania 2019****- "The guidelines are also more biased on the side of premarketing, making them less robust in regards to safety, effectiveness and performance. They also do not provide for tracking of the medical devices."*

d) Insufficient numbers of trained human resources

Majority of the countries namely Tanzania and Kenya with established regulatory bodies for medical device evaluation have few trained staff for work. Only Ghana had adequately trained staff in medical device regulation.

KI from Kenya 2019 *-"We do not have enough numbers of staff to handle the entire workload. This is a significantly large area of development that requires to be understood".*

The key training gaps identified by the key informants included latest innovations in medical devices technology, hands on training, pre- and post-market surveillance.

e) Interpretational gaps

KI from Uganda 2019*- "…Since the current law is not clear on the regulation of medical devices, it restricts the scope of regulation. Therefore, the current available documents can be interpreted differently by implementers."*

f) Funding

There are insufficient funds for the agency to carry out its activities

KI from Tanzania 2019*- "The post market surveillance program under our docket requires a lot of funds which are currently insufficient."*

g) Poor adherence to regulations.

KI from Tanzania 2019*- "… Some importers do not adhere to all the regulations because of financial risks which causes delays in processing their permits…."*

Objective 4 was to assess the robustness of the current regulations for medical devices in Europe and the selected African countries.

Several authors have commented on the medical device directives and how they are not robust enough to sufficiently regulate all kinds of medical devices on the European market. Critics have pointed out the scandals that followed the approval of metal to metal hip implants and the recalls that ensured resulting in many patients undergoing surgeries that could have been avoided had the right checks and balances been in place (Cohen, 2012).

Cohen and Billingsley stated that, "UK Medicines and Healthcare Products Regulatory Agency (MHRA) was unable to provide even the most basic data on how many high risk devices—those implanted inside the body—were currently in use, and refused to say what data had been submitted by manufacturers because this was deemed commercially confidential."

For example, Storz-Pfennig et al stated that, "A growing number of examples, including metal on metal hip implants and breast implants, show the harm that can result from new devices and procedures being introduced without a rigorous assessment of their safety and efficacy. This has led to the wide acceptance that the system for regulating medical devices, particularly in the European Union (EU) is flawed."

Manufacturers still have the liberty to define and change the purpose of devices they manufacture without competent authority approval (Storz-Pfennig et al, 2013). This places the manufacturers in a position of power which makes it more difficult to regulate medical devices.

With regards to robustness, the key informants from the 5 African regulatory authorities commented as illustrated by the quotes below;

a) Perceived robustness

The interviewed officers from 2 of the countries participating in this research, namely, Ghana and Kenya, perceived their guidelines to be robust.

KI from Kenya 2019 - *"…. the regulations in place are robust to handle medical devices. For example, in Kenya, the control of import, Listing of Class A medical devices, Registration of Class B, C, D is also well established. The post market surveillance of products in the market is robust and working".*

Two of the participating key informants (Ugandan and Tanzanian), perceived their respective regulations not to be robust enough based on the current process. This is highlighted by the statements below;

KI from Uganda 2019 - *"There are some areas like registration of devices, follow up of device use, validation which we are unable to do. We only rely on testing the devices which is a small component of the whole regulation process"*

KI from Tanzania 2019 - *"The regulatory framework needs to be customized to medical devices as they are varied and unique. We also need to balance the efforts between pre and post market surveillance"*

KI from Tanzania 2019- *"The system is not robust to guarantee safety, quality and effectiveness as we rely on testing and do not conduct inspection of manufacturing plants."*

Chapter 4

Discussion

4.1 Regulatory status of medical devices in Europe and Africa

Interest in medical devices has increased in the last decade but gaps in regulation in the different regions of the world still exist. Various researchers have demonstrated increased interest in regulation of medical devices in Europe as shown by the many studies undertaken in this area (French-Mowat and Burnett, 2012; Lamph, 2012; Byrne, 2019; Kedwani et al, 2019).

In Europe, the Medical Device Regulation (EU 2017/745) was developed as a result of the gaps in the Medical Device Directives and scandals resulting from poor regulation of medical devices. The gaps that needed to be regulated included medical devices resulting from advances in technology, regulatory functions like post market surveillance, preclinical and post approval data on medical device performance, the assessment process of high risk devices by Notified Bodies and accountability of all players in the medical device supply chain. The introduction of new measures to further protect patients and ensure that safe, effective and quality medical devices are made available to patients are at the core of the Medical Device Regulation (EU 2017/745) that will come in force in May 2021 and not May 2020 due to the Corona Virus pandemic.

Germany consists of 16 federal states that have regional regulatory authorities referred to as Landesbehörden. The Federal Institute of Drugs and Medical Devices is not involved in market access activities of medical devices nor in inspections/audits but conducts risk assessment for incident reports for medical devices on the market. Depending on the outcome of the assessment, BfArM makes a recommendation to the regional authority who have the mandate to implement the recommendations. The Medical Device Regulation (EU 2017/745) is expected to show more harmonization across the European

Union. Note that although harmonization is good in principle, some countries do still require to have some specific guidelines to manage logistical problems.

Research on regulation of medical devices in Africa is limited. Regulation is weak (Kedwani et al, 2019) and generally not well defined in many of the African countries. According to Lamph, 2012, the level of underdevelopment of regulation presents a weakness that can be exploited. Studies that have been conducted have noted the weaknesses inherent in the regulatory arena in the East African regional block of which Uganda, Kenya, Tanzania and Rwanda are members (Rugera et al, 2014). In agreement with Rugera et al, 2014, Uganda, Kenya and Rwanda currently do not have sufficient capacity to adequately regulate medical devices. The results of this research concur with the East African Community Regional Project Proposal on Strengthening and Harmonization of the Regulation of Medical Devices and Diagnostics, 2015, which reported that regulatory control of medical devices and diagnostics is weak across the East African Community. Contrary to the findings of Rugera et al, 2014 who stated that, "medical device regulation was a neglected area", Tanzania which has revised its medical device regulations twice in the last 5 years and hired more staff to build capacity has not neglected medical devices. The presence of weak or nonexistent medical device regulation makes the markets in Uganda, Kenya and Rwanda vulnerable to medical devices of poor quality and questionable performance. It also increases the possibility of these countries becoming fertile grounds for dumping medical devices that are obsolete or not suitable for low and middle income settings. This is demonstrated by a World Health Organisation alert that was sent out regarding the existence of fake Covid 19

testing kits on the world market and an article on the same problem in the Daily Monitor newspaper [24] in Uganda.

The implementation of international references and standards like Pharmacopoeia and ISO standards by Uganda is an indicator of the acknowledgement of the need to regulate the quality of the medical devices that are on the market following receipt of authorization from the National Drug Authority.

The results demonstrated different maturity levels with regards to existence of medical device regulations, guidelines and actual practice. The implication is that there are countries that have covered a lot of ground in this area and that have invested resources to develop the medical device regulatory framework in place and to a level that facilitates regulation of medical devices, and those that do not have a regulatory framework in place. The latter are bound to face a multitude of challenges regulating medical devices on the respective markets and managing new technologies that are emerging every other day, and that could ultimately end up in the respective country markets as a result of being patient needs.

The absence of regulations makes it difficult for regulatory authorities to trace the end-users as there is no requirement on importers to register the devices that have been imported and for doctors and other health professionals to keep record of the patients who purchase these devices. This affects tracing activities in the event that faulty devices are reported and need to be recalled from the market. The regulatory authority's efforts are

[24] Abet T. Covid-19: Government on alert as fake test kits hit market. Daily Monitor. 2020 April 03.

hampered with respect to the creation of post marketing surveillance systems which are key in ensuring that safe devices that perform as claimed by the manufacturer are available to the public.

The constraints faced by some of these countries further hinder proper regulation as most of the limited resources are dedicated to the regulation of pharmaceuticals. Successful drafting, development and implementation of the developed regulations in all countries for which none exist will contribute towards the establishment of a regulatory framework that regulates medical devices for all regulatory functions.

The creation of the Pan African Harmonization Working Party (PAHWP) in Africa and the drive to develop a set of regulations that will govern medical devices on the continent demonstrates the important role that medical devices play in public health. The activities of the PAHWP should help streamline medical device regulatory processes across the continent once a regulatory framework on medical device regulation is developed and implemented. This will pave the way for African countries that do not have medical device regulations to have a reference point to regulate the medical devices in the respective markets and to close loopholes that could be exploited to the detriment of the public. The PAHWP medical device regulatory framework will enable African countries that have advanced in the regulation of medical devices to make amendments that will further strengthen the processes that are already in place as the continent strives to create a single regulatory authority.

Efforts to implement measures that would guarantee that medical devices meet the specifications set for safety, effectiveness and quality are being implemented. The breast implant and metal on metal hip prothese scandals were a water shade moment in the regulation of medical devices in Europe. These events provided the impetus towards the

revision of the Medical Device Directives in order to cater for advances in technology and introduce mechanisms that would provide better protection for patients and enhance safety.

The gaps that were observed in the medical device directives drove the European Council to review the medical device directives. The European Council refined the requirements in the Medical Device Directives and introduced several measures that have to be adopted by different stakeholders.

Under the Medical Device Directives, medical devices approved by the Notified Bodies (NB) were not required to bear a Unique Device Identifier (UDI). The Medical Device Regulation makes it a requirement going forward for manufacturers to assign and label all medical devices that are to be placed on the European market with a unique alpha numerical number (Wagner and Schanze, 2018). This is to facilitate traceability of medical devices in Europe and to enhance patient safety with regards to faulty, substandard and counterfeit products. Previously, medical devices in the European market did not bear a Unique Device Identifier. This scenario presented risks to patients when faulty and defective medical devices in the high risk category ended up on the market or an adverse event was reported for high risk medical devices. It also made it difficult for regulatory authorities to trace and link the medical devices to particular manufacturer(s) in order to effect recall procedures and for corrective and preventive actions to be undertaken at the manufacturing site.

The introduction of the scrutiny procedure by the Medical Device Regulation and involvement of experts in the pre-approval process of high risk medical devices introduces another layer of protection for patients, as it involves persons with expertise in different medical fields in the pre-approval process, who are engaged to provide

valuable opinions on the medical devices. The scrutiny undertaken by the teams of specialists puts in check the Notified Bodies, which previously made unilateral decisions, since the opinion of the experts needs to be taken into consideration prior to issuing certification to high risk medical devices for placement on the European market.

The requirement for manufacturers to submit post marketing clinical data and periodic safety reports (Byrne, 2019) will result in provision of more information on the performance of all high risk category medical devices and adverse events associated with them, which will be beneficial to end-users and physicians. Regulators will be updated on the performance of approved medical devices and this will facilitate recommendations to manufacturers to provide corrective and preventive actions when the need arises. The information archived in European Union database of medical devices (EUDAMED) will strengthen vigilance of medical devices in Europe and build the public's confidence in the medical devices on the market and the regulatory processes.

Clinical evidence from the pre-market period will be taken into consideration during assessment of submitted information by Notified Bodies as it will provide a performance trail on high risk medical devices. This provision of the MDR (EU 2017/74) will provide assessors with data that will enable informed decisions to be made during the certification process. This requirement will buffer end users from being sold medical devices of questionable performance and quality as such medical devices will require manufacturers to provide justification for not providing pre-clinical data prior to receipt of approval. This requirement will also apply to manufacturers of devices similar to those already on the market as information that demonstrates equivalency of the medical device to medical devices on the market must be submitted for assessment.

The promotion of transparency by the Medical Device Regulation through the European Union database of medical devices (EUDAMED) will build the confidence of the public

in the regulatory processes followed to approve medical devices and in the medical devices on the European market. Provision of information on the performance of medical devices during the post approval period by manufacturers that will be available and accessible to the public in EUDAMED will further keep Notified Bodies and manufacturers in check as safety will be factored into assessments and medical device manufacture.

Regulations provide a framework within which authorities can conduct activities related to medical devices. The formulation of medical device regulations by countries that do not have them presents an avenue through which the scope of medical device regulation can be defined. Uganda and Rwanda have started on the process of medical device regulation formulation. This is an indicator that the regulatory authorities acknowledge the need to regulate medical devices as the number imported into the different countries increases and yet no binding and specific checks such as regulations are in place to control quality, safety and performance of medical devices. On completion of this process, medical devices on the market will have to comply with the requirements laid out in the regulations of the different African countries as there will be guidance available to manufacturers and other players in the medical device supply chain upstream and downstream.

Insufficient staff numbers are a chronic problem in all regulatory authorities of the five African countries. This could be due to different reasons like a scarcity of resources and a lack of adequate numbers of qualified people to handle medical devices. Sufficient numbers of qualified staff are necessary to adequately regulate medical devices. In response to the growing need to regulate medical devices, recruitment of adequately qualified staff is being undertaken by all countries that participated in this study. Staff recruited include Biomedical engineers, Pharmacists, Chemists and Microbiologists. The

increased staff numbers will enable the regulatory authorities to deploy staff for the different regulatory functions to ensure that different types of medical devices in the respective countries meet the standards set for quality, safety and performance that are a necessity for patient safety.

Assessment of Quality Management Systems of medical device manufacturing facilities based on ISO 13485 guidelines is performed by the regulatory authorities of Uganda, Ghana and Tanzania. The application of an internationally accepted standard such as the ISO 13485 by the 3 countries reflects an understanding of the need to apply uniform standards as it excludes bias in the inspection process which could arise if each country applied its own standard, and promotes the aspect of reliance on the approvals issued by the different regulatory authorities.

The challenges impeding regulation of medical devices are diverse and will require diverse remedies in order to be rectified. Absence of a regulatory frameworks has hindered the regulation of medical devices. This in turn has created a gap in that the scope of regulation is undefined and the regulatory authorities lack the mandate to regulate medical devices on the market. This scenario compounds the work that regulatory authorities must conduct as they do not have a reference for guidance for actions to be undertaken to regulate medical devices. The implication is that substandard and counterfeit medical devices could find their way onto the markets and the regulatory authorities would neither be in position to prosecute the culprits nor institute regulatory actions.

The regulations that the African regulatory authorities have were developed years ago to cater for the types of medical devices that existed at the time of drafting the regulations.

Advances in technology and innovations meant that a mismatch between advances in technology and existing regulations would eventually crop up. This could have arisen because the advances in technology of the future had not been taken into consideration by the legislators at the time of drafting the regulations. This gap in legislation has created a grey area for new medical devices that are not catered for by the active regulation. This scenario makes the job of the regulatory authorities harder, as the medical devices might be urgently issued with authorizations to get them onto the market. Regulatory decisions like these might over look aspects of patient safety and are compounded by the inadequate human resource capacity to conduct post market surveillance.

There is an inadequate number of qualified human resources across all the regulatory authority medical device departments. This inadequacy could be as a result of medical devices not being a priority area, the absence of suitably qualified persons or the lack of resources to recruit the requisite staff. This inadequacy in staff numbers result in insufficient regulation of medical device related activities and a backlog of applications that causes delays in issuance of approvals for medical devices.

Insufficient funding is faced by all the African regulatory authorities that participated in this research. Lack of funding could be as a result of inadequate budget allocation to medical device regulatory activities or inadequate revenue collection by the regulatory authority resulting in available funds being allocated to other areas considered to be more important. Inadequate funds hamper all regulatory functions associated with medical devices leading to poor oversight over most medical devices on a country's market.

Robustness of any regulation is key to the achievement of the objectives it is intended to achieve. In line with a study conducted by Storz-Pfennig et al, 2013, weak regulations are bound to be exploited by stakeholders whose main concern is profit. Focus on pre-market activities by regulators translates into weak post marketing regulation of medical devices.

in agreement with Cohen, 2012, medical devices of questionable quality end up flooding markets as a result of non-robust regulations. This poses risks to patients as the regulatory oversight is thin or absent and can be exploited by manufacturers to their own benefit (Cohen and Billingsley, 2012).

Of the two African countries that have medical device regulation, Tanzania reported that the regulations were not robust enough as they did not cater to all types of medical devices in addition to have been developed based on the regulatory framework for pharmaceuticals. Given the unique characteristics of medical devices, a regulatory framework that incorporates the characteristics of medical devices is required in order to facilitate proper regulation. Its absence creates circumstances in which proper regulation is hindered because the guidance provided by the regulation is not tailored to suit medical devices.

4.2 Limitations

- The sample size was small and therefore not representative of the African continent but fairly representative of the East African region.

4.3 Recommendations

- Further research should be conducted on the effectiveness of the MRD (EU 2017/745) as relates to the requirements introduced for the different stakeholders.
- Research on the types of medical devices in circulation in the markets of Kenya, Rwanda and Uganda to determine whether they meet the minimum set standards.
- Research on the knowledge attitudes and practices of importers of medical devices in Kenya, Rwanda and Uganda.
- Promotion of twinning programs and collaborative training should be undertaken between countries whose medical device regulatory framework is already established and those where it is weak or absent.

- The results of this study cannot be generalised to all African countries. Further research should be conducted for all countries on the African continent to determine the status of regulation of medical devices and the challenges and measures put in place by the different regulatory authorities.

4.4 Conclusion

Regulation of medical devices in Africa is limited. The results of the study demonstrated different maturity levels with respect to existence of medical device regulation, guidelines and actual practice in the countries that participated. The varied existence of medical device regulation presents potential for loopholes to be exploited by the industry, resulting in medical devices of questionable quality, safety and performance being placed on the African market.

4.5 Dissemination of results

- Abstracts were accepted for poster presentation at the 80th International Pharmaceutical Federation (FIP) World Congress of Pharmacy and Pharmaceutical Sciences that was scheduled to take place in September 2020 in Seville, Spain and the 12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology that was scheduled to take place from 23-26 March 2020 in Vienna, Austria.
- Copies of dissertation will be shared with regulatory authorities that participated.
- Publication of results in a recognized peer reviewed journal.

REFERENCES

Altenstetter C. Medical device regulation in the European Union, Japan and the United States. Commonalities, differences and challenges. Innovation: The European Journal of Social Science Research. 2012 Dec 1;25(4):362-88.

Bimenya GS, Nzarubara GR, Kiconco J, Sabuni S, Byarugaba W. The accuracy of self-monitoring blood glucose meter systems in Kampala Uganda. African health sciences. 2003;3(1):23-32.

Bowen RA, Adcock DM. Blood collection tubes as medical devices: the potential to affect assays and proposed verification and validation processes for the clinical laboratory. Clinical biochemistry. 2016 Dec 1;49(18):1321-30.

Byrne RA. Medical device regulation in Europe-what is changing and how can I become more involved? Euro Intervention: journal of Euro PCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2019 Oct 20;15(8):647.

Chen YJ, Chiou CM, Huang YW, Tu PW, Lee YC, Chien CH. A comparative study of medical device regulations: US, Europe, Canada, and Taiwan. Therapeutic innovation & regulatory science. 2018 Jan;52(1):62-9.

Cohen D, Billingsley M. Europeans are left to their own devices. BMJ. 2011 May 14;342:d2748.

Cohen D. How a fake hip showed up failings in European device regulation. BMJ. 2012 Oct 24;345:e7090.

De Maria C, Di Pietro L, Lantada AD, Madete J, Makobore PN, Mridha M, Ravizza A, Torop J, Ahluwalia A. Safe innovation: On medical device legislation in Europe and Africa. Health Policy and Technology. 2018 Jun 1;7(2):156-65.

Donawa M, Gray R. The breast implant scandal and European medical device regulation. GMP Rev. 2012;11:2-4.

Eikermann M, Gluud C, Perleth M, Wild C, Sauerland S, Gutierrez-Ibarluzea I, Antoine SL, Demotes-Mainard J, Neugebauer EA. Commentary: Europe needs a central, transparent, and evidence based regulation process for devices. BMJ. 2013 May 7;346:f2771.

Fiedler BA, Ferguson M. Overview of Medical Device Clinical Trials. In Managing Medical Devices Within a Regulatory Framework. Elsevier. 2017 Jan 1:17-32.

Fraser AG, Butchart EG, Szymański P, Caiani EG, Crosby S, Kearney P et al. The need for transparency of clinical evidence for medical devices in Europe. The Lancet. 2018 Aug 11;392(10146):521-30.

French-Mowat E, Burnett J. How are medical devices regulated in the European Union? Journal of the Royal Society of Medicine. 2012 Apr;105(1_suppl):22-8.

Garber A. Modernizing Device Regulation. New England Journal of Medicine. 2010;362(13):1161-1163.

Gillet P, Mukadi P, Vernelen K, Van Esbroeck M, Muyembe JJ, Bruggeman C et al. External quality assessment on the use of malaria rapid diagnostic tests in a non-endemic setting. Malaria journal. 2010 Dec;9(1):359.

Heneghan C. The saga of Poly Implant Prosthèse breast implants. BMJ 2012; 344:e306.

Kedwani M, Schröttner J, Baumgartner C. Analysis of regulatory requirements of medical devices and in-vitro diagnostics worldwide for the development of an efficient procedure of registration for manufacturers of medical products. Current Directions in Biomedical Engineering. 2019 Sep 1;5(1):609-12.

Kramer DB, Xu S, Kesselheim AS. Regulation of medical devices in the United States and European Union. The New England journal of medicine. 2012;366(9):848-55.

Lamph S. Regulation of medical devices outside the European Union. Journal of the Royal Society of Medicine. 2012 Apr;105(1_suppl):12-21.

Malkin RA. Barriers for medical devices for the developing world. Expert review of medical devices. 2007 Nov 1;4(6):759-63.

McNerney R, Peeling RW. Regulatory in vitro diagnostics landscape in Africa: update on regional activities. Clinical Infectious Diseases. 2015 Oct 15;61(suppl_3):S135-40.

Migliore A. On the new regulation of medical devices in Europe. Expert Review of Medical Devices. 2017;14(12):921-23.

Mori M, Ravinetto R, Jacobs J. Quality of medical devices and in vitro diagnostics in resource-limited settings. Tropical Medicine & International Health. 2011 Nov;16(11):1439-49.

Niederländer C, Wahlster P, Kriza C, Kolominsky-Rabas P. Registries of implantable medical devices in Europe. Health Policy. 2013 Nov 1;113(1-2):20-37.

Pane J, Francisca RD, Verhamme KM, Orozco M, Viroux H, Rebollo I, Sturkenboom MC. EU postmarket surveillance plans for medical devices. Pharmacoepidemiology and drug safety. 2019 Sep;28(9):1155-65.

Rugera SP, McNerney R, Poon AK, Akimana G, Mariki RF, Kajumbula H, et al. Regulation of medical diagnostics and medical devices in the East African community partner states. BMC health services research. 2014 Dec 1;14(1):524.

Saidi T, Mutswangwa CT, Douglas TS. Design Thinking as a Complement to Human Factors Engineering for Enhancing Medical Device Usability. Engineering Studies. 2019 Jan 2;11(1):34-50.

Saini KS, Kaushik A, Anil B, Rambabu S. Harmonized medical device regulation: need, challenges, and risks of not harmonizing the regulation in Asia. Journal of Young Pharmacists. 2010 Jan 1;2(1):101-6.

Shah AR, Goyal RK. Current status of the regulation for medical devices. Indian journal of pharmaceutical sciences. 2008 Nov;70(6):695.

Sorenson C, Drummond M. Improving medical device regulation: The United States and Europe in perspective. The Milbank Quarterly. 2014 Mar;92(1):114-50.

Storz-Pfennig P, Schmedders M, Dettloff M. Trials are needed before new devices are used in routine practice in Europe. BMJ. 2013 Mar 18;346:f1646.

Tarricone R, Torbica A, Ferre F, Drummond M. Generating appropriate clinical data for value assessment of medical devices: what role does regulation play? Expert review of pharmacoeconomics & outcomes research. 2014 Oct 1;14(5):707-18.

Thompson M, Heneghan C, Billingsley M, Cohen D. Medical device recalls and transparency in the UK. BMJ. 2011 May 14;342:d2973.

Valerio M, Emberton M, Eggener SE, Ahmed HU. The challenging landscape of medical device approval in localized prostate cancer. Nature Reviews Urology. 2016 Feb;13(2):91.

APPENDICES

APPENDIX I: ETHICS APPROVAL

L-Università ta' Malta

Faculty of
Medicine & Surgery

University of Malta
Msida MSD 2080, Malta

Tel: +356 2340 1879/1891/1167
umms@um.edu.mt

www.um.edu.mt/ms

Ref No: **FRECMDS_1819_050**

Tuesday 23rd July 2019

Ms Gloria Dusabe
Chequers Court, Flat 5
Triq Lorenzo Gatt,
Birkirkara.

Dear Ms Gloria Dusabe,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

Regulation of medical devices in Europe and Africa

The Faculty Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Professor Pierre Mallia
Chairman
Research Ethics Committee

APPENDIX II: LETTER OF REQUEST FOR INSTITUTIONAL APPROVAL

LETTER OF REQUEST FOR INSTITUTIONAL APPROVAL TO ACCESS PARTICIPANTS FOR THE RESEARCH TITLED: "REGULATION OF MEDICAL DEVICES IN EUROPE AND AFRICA"

TO WHOM IT MAY CONCERN

This is to introduce to your institution, Ms. Gloria Dusabe, a Doctorate in Pharmacy student. She is conducting research for her Doctorate thesis titled **Regulation of Medical Devices in Europe and Africa** as part of the requirements of the Doctorate in Pharmacy programme at the University of Malta.

The aim of this research is to evaluate current regulations and guidelines for medical devices and to assess the challenges faced by regulators in Europe and selected African countries (Uganda, Kenya, Tanzania, Rwanda and Ghana) with the aim of identifying and proposing areas of improvement.

The researcher will utilise questionnaires and key informant interviews to generate data from participants in your institution in addition to conducting a desk review of the regulations and guidelines where available. The data generated from this research will shed light on the current practices, identify gaps in regulation and enable the generation of recommendations related to the regulation of medical devices.

Your participation in this research is valuable and will lead to a greater understanding of medical device regulation.

Please contact me if you have any questions.

Thank you.

Ms. Gloria Dusabe

APPENDIX III: INFORMATION SHEET

Information sheet

Title of project: Regulation of Medical Devices in Europe and Africa
Affiliating institution: University of Malta
Academic supervisor: Prof Anthony Serracino Inglott

Purpose of research
The purpose of this research is to evaluate the current regulations and guidelines for medical devices and to assess the challenges faced by the regulators in Europe and selected African countries namely, Uganda, Kenya, Tanzania, Rwanda and Ghana, with the aim of identifying and proposing areas of improvement.

What participation involves and expected duration

Participation in this research is voluntary and you can withdraw at any time, without giving reasons.

It involves the completion of a self-administered questionnaire and interviews for key informants in the different regulatory agencies. The self-administered questionnaire will take 30 minutes to complete and 45 to 60 minutes for the key informant interview.

The key informant interview will be conducted by the Principal investigator via phone on the number provided in the contact details below. Participants will be given the option of either conducting a skype interview or being called via the phone numbers they will provide. The interview will last between 45 to 60 minutes. An audio recorder that will only be accessible to the investigator will be utilized to record the interview. The audio recorder will be kept under lock and key when not in use, that is, recording interviews or transcribing data.

All the data collected for this study will be stored for a period of 1 year following which it will be destroyed.

There will be no monetary disbursement to participants. The duration of data collection is expected to last 2 to 3 months.

Expected benefits and any potential discomfort/risks

Data collected will facilitate better understanding of regulations and challenges faced by regulators with regards to medical devices, aid in making recommendations and generation of short-and long term solutions.

The risks regarding data collected will be safe guarded according to the provisions of the Under the General Data Protection Regulation (GDPR).

Planned use of data collected and dissemination of results

Data collected will be anonymized and stored separately from any codes and personal data to ensure confidentiality. A password controlled folder will be created for storage of questionnaire responses and saved on the principal investigator's personal laptop, back-

up copies will be saved on an external drive and a google cloud that are only accessible to the investigator. Responses from the key informant interviews will be recorded using an audio recorder to which only the investigator will have access. They will be downloaded and stored in a password controlled folder as well. All these devices will be under lock and key when not in use.

The results of this study may be reported/ published and all steps will be taken to protect participant privacy and confidentiality.

Under the General Data Protection Regulation (GDPR) and national legislation that implements and further specifies the relevant provisions of said Regulation, you have the right to obtain access to, rectify, and where applicable ask for the data concerning them to be erased.

Contact details of PI

Gloria Dusabe
+356 99767779
gloria.dusabe.17@um.edu.mt

Consent to take part in research

I voluntarily agree to participate in this research study. The purpose of the study has been explained and I have been given the opportunity to ask questions about the study. I agree to my interview being audio-recorded and have been informed that my information will be treated with utmost confidentiality, my identity kept anonymous and that the information provided will be kept under lock and keep to restrict access by unauthorized persons.

I have read the foregoing information. I have had the opportunity to ask questions about it and my questions have been answered to my satisfaction.

I consent voluntarily to be a participant in this study.

_____ _____

Name and signature of participant Date

_____ _____

Name and signature of researcher Date

APPENDIX IV: QUESTIONNAIRE

SURVEY ON THE REGULATION OF MEDICAL DEVICES IN EUROPE AND AFRICA (UGANDA, KENYA, TANZANIA, RWANDA AND GHANA)

The purpose of this study is to obtain information on the current status of the regulation of medical devices in Europe and five African countries, namely, Uganda, Kenya, Tanzania, Rwanda and Ghana, assess current practices and to document the challenges regulators face during the pre-licensing phase.

For the purpose of this study, a **medical device** has been defined as an instrument, apparatus, implant, in vitro reagent, or other similar or related article, which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or intended to affect the structure or any function of the body and which does not achieve any of its primary intended purposes through chemical action within or on the body.

Instructions

Please complete all the sections of this questionnaire as applicable.

SECTION A

Title:	**Telephone number:**
Organization:	**Email:**
Address:	**Country:**

SECTION B

	Question	Yes	No	NA	Additional comments
1.	Do you have a department responsible for medical devices regulation in your agency?				
2.	Are there regulations/ guidelines pertaining to regulation of medical devices in existence in your country?				
3.	Are these regulations/guidelines applied equally in both the public and private sectors?				
4.	Are the guidelines/ regulations explicit on the procedures to be followed prior to issuance of a marketing authorization for a medical device application?				
5.	What categories of medical devices is your agency currently handling?				

6.	Are there other bodies in your country that play a role in the regulation of medical devices?				
7.	Does your agency conduct good manufacturing practice (GMP) audits for the manufacturing sites of the medical devices prior to issuance of a marketing authorization?				
8.	What aspects are audited during the GMP inspections?				
9.	Does your agency consider approvals by other regulatory agencies? Which ones in particular?				
10.	What resources are utilized to verify approvals issued by reference regulatory authorities that are included in the marketing authorization applications?				
11.	Are the criteria utilized by the notified bodies in the reference regulatory authorities' countries to issue approvals for the medical				

	devices in sync with the criteria in your guidelines/ regulations?				
12.	What method of submission is available to applicants at your agency?				
13.	Do you provide the applicants a format in which they must compile information prior to submission?				
14.	Do you follow the same evaluation process for all medical devices? (**risk based evaluation or not**)				
15.	Briefly describe the evaluation process undertaken by your regulatory authority when assessing a new medical device application.				
16.	What are the approval timelines for the different medical device categories from receipt of an application to approval?				
17.	What standards pertaining to medical devices are acceptable to your agency? For example CE marking, ISO, etc.				

18.	Do you encounter challenges during the evaluation of a marketing authorization application?				
19.	What challenges do you encounter specifically?				
20.	Is a database of the approved medical devices maintained by your agency?				
21.	Does your agency have human resources that are qualified to evaluate the applications submitted?				
22.	What training has been offered to these human resources to facilitate the evaluations that they undertake?				
23.	In your opinion, do you think that the training was adequate or is there need for additional training to be conducted? Explain.				
24.	In your opinion, do you think that the regulations in place are robust to guarantee that the devices on the market are safe, of good quality and effective?				

25.	Do you have any suggestions on how the regulations and guidelines could be improved?				
26.	Are there mechanisms currently in place for harmonization of procedures on medical devices in the economic block to which you belong?				
27.	If yes, how far along is the procedure in no. 26 above?				
28.	Are there controls applied to imports of medical devices?				
29.	If yes, please give details.				

30.	Does your agency conduct post-market surveillance of medical devices?				
31.	Do you have a system in place to track complaints?				
32.	What response procedures are in place to deal with reported complaints?				

APPENDIX V: KEY INFORMATION GUIDE

REGULATION OF MEDICAL DEVICES IN EUROPE AND AFRICA

KEY INFORMANT INTERVIEW QUESTIONS

INSTRUCTIONS: Please respond to the questions below as completely as possible.

Procedure:

Prior to commencement of the interview, the principal investigator will introduce herself and will ask the respondent whether he/she has any questions regarding the research.

The purpose of the interview will then be explained to the respondent.

This is a research study being conducted as part of the requirements of the Doctorate in Pharmacy at the University of Malta. The purpose of this interview is to obtain information on the regulation of medical devices in your country. The information obtained will shed more light on your practices, assist in identifying gaps and enable the generation of recommendations related to the regulation of medical devices.

The interview will last between 45 to 60 minutes.

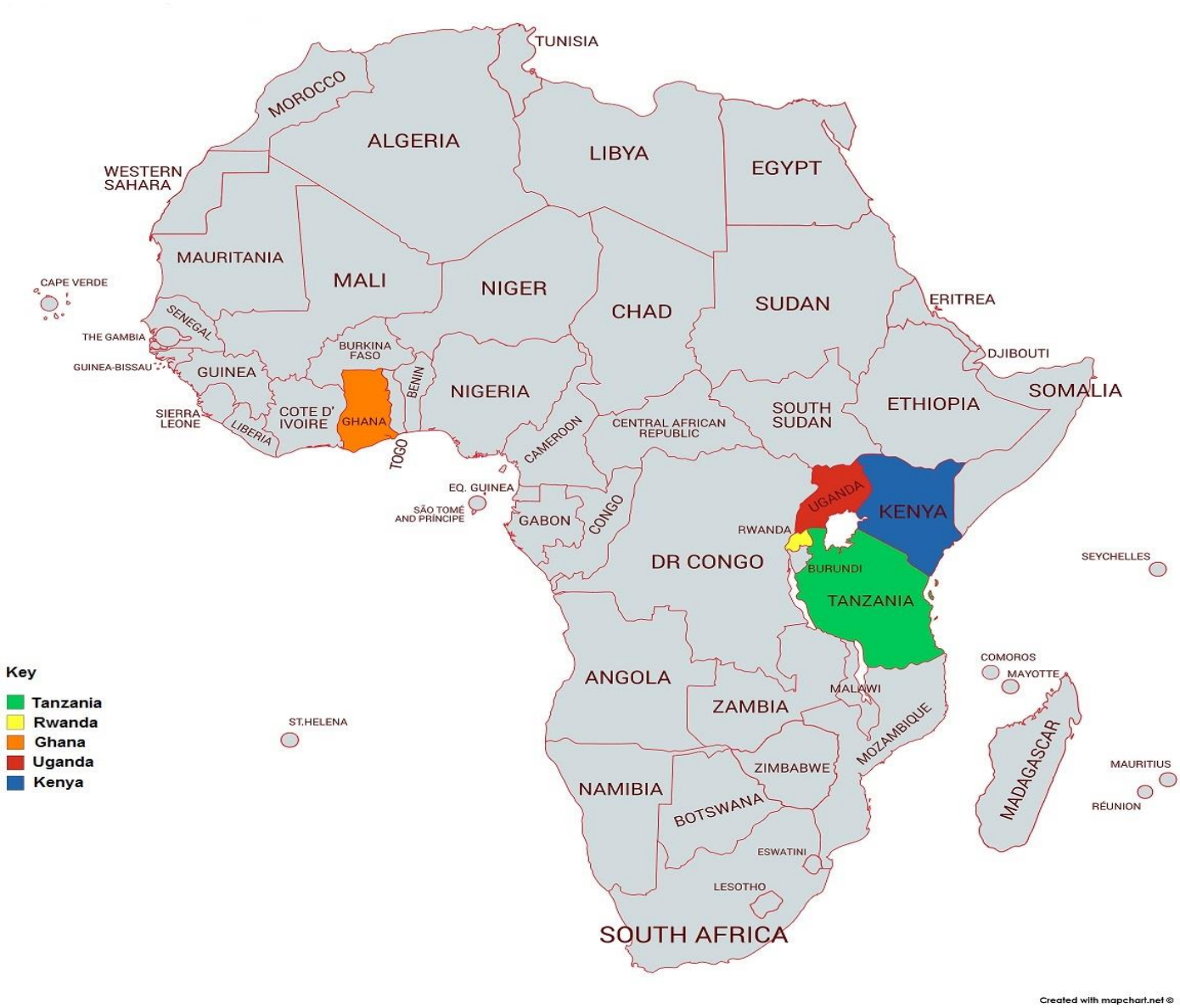
All the information you will provide will be treated with confidentiality and to protect your identity, a serial number will be assigned to your response. Feel free to seek clarification for any question during the course of the interview and let me know if there are questions you prefer not to answer.

Do keep in mind that there are no right or wrong answers. We are interested in obtaining information that will help us understand the regulation of medical devices in your country.

1. Please tell us what aspects of your regulations/guidelines work well.
2. Please identify the primary gaps you have observed in your regulations/guidelines.
3. Have any measures been put in place to tackle the identified gaps?
4. Are there any particular reasons as to why these gaps exist?

5. Do you have any suggestions on how the regulations and guidelines could be improved?
6. In your opinion, do you think that the regulations in place are robust to guarantee that the devices on the market are safe, of good quality and effective
7. Does your agency have human resources that are qualified to evaluate the applications submitted?
8. How many of your staff are assigned to handle medical device evaluations?
9. What training has been offered to these human resources to facilitate the evaluations that they undertake?
10. In your opinion, do you think that the training was adequate or is there need for additional training to be conducted?
11. Are there mechanisms currently in place for harmonization of procedures on medical devices in the economic block to which you belong?

APPENDIX VI: MAP SHOWING STUDY AREA IN AFRICA



Created with mapchart.net[25]

[25] Custom mapchart. Map of Africa. [created May 10, 2020]. Available from URL: mapchart.net