11-1-2021

Herbal Medicines Registration Process for Zimbabwe Overview of the Process

Jannet Usai
Purdue University, jusai@purdue.edu

Z Ekeocha
Purdue University, zekeocha@purdue.edu

S Byrn
Purdue University, sbyrn@purdue.edu

K Clase
Purdue University, kclase@purdue.edu

Herbal Medicines Registration Process for Zimbabwe Overview of the Process

J. Usai[1], Z. Ekeocha[2], S. Byrn[3], K. Clase[4]

ABSTRACT

Unregistered traditional medicines pose a huge public health threat as the safety and efficacy of these products is unknown. The issue this study addresses is the inadequate regulatory measures for herbal medicines in Zimbabwe. This project was done to describe the current registration process of traditional medicines in Zimbabwe, and to identify the gaps and opportunities they present to improve the regulatory landscape. Regulations and laws governing the registration of herbal medicines in the country and published research on legislation of herbal medicines were reviewed. Two parallel regulatory bodies both registering and controlling the sale of herbal medicines were identified. The Medicines Control Authority of Zimbabwe (MCAZ) and the Traditional Medical Practitioners Association (TMPA) both derive their authority to regulate from the ministry of health and were established through the act of parliament which gives these authorities power to regulate the quality and sale of traditional medicines without giving a prescriptive way of doing it. The registration process, and product evaluations for the two authorities are different. While the MCAZ has a clearly defined registration process, the TMPA does not. However, MCAZ has not been very successful in registering local products with the majority of the registered herbal products being imports and only 2% of total registered products being local herbs. As a recommendation, there is need for collaboration between the regulatory bodies for consistence in quality of herbal products on the market and to improve registration of local herbal products. Developing monographs for local herbs commonly used in the country will also assist local manufacturer to fulfill the quality requirements and successful compilation of dossiers for product registration.

KEYWORDS

Herbal medicines, herbal medicine legislation, registration process, herbal markers

[1] jusai@purdue.edu; Biotechnology Innovation and Regulatory Science (BIRS) Center; Agricultural and Biological Engineering, Purdue University
[2] zekeocha@purdue.edu; Medical Missionaries of Mary; Biotechnology Innovation and Regulatory Science (BIRS) Center, Purdue University
[3] sbyrn@purdue.edu; Biotechnology Innovation and Regulatory Science (BIRS) Center; Industrial and Physical Pharmacy, Purdue University
[4] kclase@purdue.edu; Biotechnology Innovation and Regulatory Science (BIRS) Center; Agricultural and Biological Engineering, Purdue University

DEFINITION OF TERMS

Herbal medicines**: T**hese are medicines of plant origin used for treatment, diagnosis or management of disease and other ailments in humans. They contain processed or raw plant materials from one or more plants. Herbal medicines can also be referred to as traditional medicines or complementary medicines (WHO, 2005).

Traditional medicine: It is the combination of skills, knowledge and practices grounded on cultural experiences, theories and beliefs applied in the management of health (WHO, 2005).

Regulation: The building structure for execution of policies and proposes a method for registering herbal products.

1. INTRODUCTION

The use of herbal products medicines in Africa is a common practice. About 80% of people on the African continent depend on herbal medicines for their primary health care needs (WHO, 2005). This has been attributed to easy accessibility, low cost and a longstanding history of effectiveness and safety. Use of herbal medicines forms the origin of medicine with many conventional drugs originating from plant source (Pal & Shukla, 2003). Some drugs are plant-based, such as Aspirin (from the willow bark), digoxin (from the fox glove), quinine (from the Cinchona bark). However, there have been major safety issues arising from the use of unregistered traditional medicines whose safety and efficacy have not been evaluated. In Zimbabwe traditional medicines represent the biggest single group of poisoning cases (23%), with the majority of patients being children younger than 5 years old (53%) (Nhachi & Kasilo, 1992). A high mortality rate has been associated with poisoning from traditional medicines (Tagwireyi et al., 2002). Severe adverse events from herbal supplements have shown the harm associated with unregulated herbal medicines (Maphosa et al., 2013) as these medicines may be contaminated with poisonous chemicals, heavy metals and endogenous toxins. Herbal medicines prepared from extracts of plants such as Euphobia, Solanum and Datura species have been found to contain toxic agents (Tagwireyi et al., 2002). It is against this background that regulation and quality assurance standards are pivotal in promoting access to safe and efficacious traditional medicines. However development and enforcement of policy and regulations for herbal medicines is a challenge in African (WHO, 2019).

The current global market for herbal products is 60 billion and is expected grow at CAGR of 7.2% (Carvalho, 2020). Multinational companies have also gained interest in the market for herbal medicines (Mukherjee & Houghton, 2009). Herbal products form an important part in primary health care. However, product assessment and quality assurance of these products are a huge stumbling block in product development. As the demand and use of herbal medicines is increasing globally, more public health concerns associated with safety of these products are emerging. A number of challenges hinder improved regulation of herbal medicines. These include absence of efficient quality control in the production processes, absence of good distribution practice within the supply-chain including traceability, lack of proper identification of botanical species, and no characterized markers or active constituents (Mukherjee & Houghton, 2009).

The increasing demand, the rising economic value and adverse effects of herbal products have prompted health ministries to develop laws that will ensure safe use of these products (Alostad et al., 2018). Some countries like Austria, France and Germany have legislated well-defined registration systems for herbal products (Fan et al., 2012), while other nations are still struggling to develop and enforce laws on regulation of herbal medicines. The absence of registration and evaluation of herbal products has detrimental effects on public health. In some markets, such as the US for example, herbal medicines are regulated under dietary supplements and are not required to undergo premarket evaluation by the FDA. Reports of counterfeit herbal products and adverse events from these products have been observed (Fan et al., 2012). In the US, dietary supplements and herbal medicines accounted for 15.5% of hepatotoxicity events (Fontana et al., 2009). A 2013 study in Toronto analyzed 44 herbal products from US and Canada markets. This study found that less than 50% of the products contained the herbal medicine on the label claim; and more than 50% of the supplements had extra ingredients not mentioned on the label (Newmaster et al., 2013). Therefore, it is crucial for nations, where herbal medicines are consumed, to design a registration system for herbal medicine products and ensure that they are evaluated for quality, efficacy and safety before they go to the market. However this is the primary difficulty in registering of herbal medicines because of the chemical complexity of herbs. The registration process must be simple and should not delay product registration. The registration process must specify product evaluation criteria which includes safety, efficacy and quality. The evaluation criteria should

also include stability testing, packaging and labeling.

Quality is the standard of a medicinal product measured against purity, its identity and product content. It can be influenced by the production process, other chemical, biological and physical properties. Quality control is the process of ensuring quality of the finished product. Botanical identification and verification is the initial step in quality assurance, it ensures that the right plant and the correct part/s is used. The manufacturer is expected to provide: Latin binomial and vernacular names, plant part/s used for the product, and a comprehensive description for plant production and harvest conditions in accordance to in-country good agricultural practice (WHO, 2000). For identity most regulatory authorities rely on local herbarium.

Assessment of herbal medicines is very difficult due to chemical complexities of the product. For most herbal drugs, the active ingredient is unknown, making assay/content evaluation challenging (Bandaranayake, 2006). Markers compounds are commonly used in content or assay of herbal products. These are chemical constituents of herbal products which are chosen for quality control purposes to ensure product consistency and assist in assay. The marker may or may not have therapeutic effect. The European Medicines Agency (EMA) defines markers elements as chemical elements, or a group of constituents, used for quality control purposes of herbal products regardless of their therapeutic effect. Markers are very important in quality control. They aid in ensuring content uniformity and product standardization in herbal products. Choice of markers is based on chemical stability, how easy it is to analyze, cost and time of analysis, relation to product efficacy and quality/stability. (Mukherjee & Houghton, 2009). Ideally a herbal product chemical marker should be a trait constituent and must be therapeutically significant however for most herbal products therapeutic components are unknown. Though markers may not have pharmacological activity, their presence in the plant material is set, with specific chemical attributes (Bandaranayake, 2006). Srinivasan classifies markers into four group as shown in table 1 based on their chemical attributes. The constituents of the marker chemicals is directly affected by any slight change in the quality of the herbal material.

Therefore, the quantitative and qualitative analysis of marker compounds is a reliable quality control protocol.

Table 1. *Classification of marker elements (Srinivasan., 2006)*

Classification	
Active principles	Known therapeutic effect
Active markers	Contribute to therapeutic effects
Analytical markers	No therapeutic or pharmacological importance. They aid in positive identification
Negative markers	Possess toxic or allergenic properties. A stringent limit of these markers maybe specified.

Published herbal monographs in pharmacopeias play a crucial role in quality control of herbal products. They set the quality control standards for both the manufacturers and the regulators. They help define the minimum quality standards and purity requirements that form the basis for qualitative evaluation and assessment of herbal product for market approval. While some countries have developed pharmacopeia monographs to aid in the registration of herbal medicines: British pharmacopeia, European pharmacopeia and the Indian pharmacopeia (Mukherjee & Houghton, 2009), some countries have not. Where there are no published pharmacopeial monographs, analytical procedure development and method validation are the manufacturer's responsibility (Bandaranayake, 2006). A significant variation of pharmacopeial in quality standards and plant specific parameters has been noted among different countries. This may be attributed to varying chemical constituents of the plants due to climate and environmental variations. For a country with establish herbal monographs, quality standards for the indigenous herbs are well defined and the information is made readily available for manufacturers and regulators, which goes a long way in improving herbal medicines registration. This project will investigate how Zimbabwe's regulatory

authority is setting standards for quality evaluation and what technical documents exist to aid manufacturers in quality control.

Table 2. *Common herbal medicines contaminants (WHO, 2007)*

Chemical contaminants	
Heavy metals	Mercury
	Lead
	Cadmium
	Arsenic
	Chromium
Microbial contaminants	
Micro-organisms	Fungi
	Parasites
	Bacteria
Residual organic solvents	
	Methanol
	Acetone
	Ethanol

It is very difficult to produce a 100% pure herbal product; the product is often contaminated. Table 2 shows possible contaminants for herbal products. Common contaminants can be classified as chemical contaminants, microbial contaminants and residual solvents used in the production or extraction processes. Herbal medicines should be evaluated for contamination and should not exceed specified limits set bey the national regulatory authorities. Quantitative and limit test can be used to evaluate the level of contamination. The choice of test for determination of contaminants is determined by the nature of the impurity and the type of sample to be analyzed. Regulatory authorities can choose to use either quantitative or limit tests based on this consideration. Procedures used to determine toxic metal contamination should meet the national and regional regulatory requirements and they should be relevant. The best strategy in quality control is to abide by the pharmacopeal definition of purity, identity and content. Table 3 shows examples of proposed limits on heavy metal contamination.

Table 3. *Proposed limits on heavy metal contamination (WHO,2007)*

	Mercury	Lead	Chromium	Arsenic	Cadmium
Malaysia (mg/kg)	0.5	10		5	
Thailand (ppm)		10		4	0.3
Singapore (ppm)	0.5	20		5	
Canada (mg/day)	0.02	0.02	0.02	0.01	0.006
WHO recommendation (mg/kg)		10			0.3

There is a great need for the product registration system to control labeling of herbal medicines, as it is the primary and, sometimes the only, source of information about the product from the manufacturer to the consumer. The quality of information presented about the herbal product is equally important as product quality. Properly labeled products reduce the incidence of inappropriate drug use and adverse drug events (Bandaranayake, 2006). WHO (2010) recommends the labelling information to include

1. Name of the product
2. Indication of use
3. Storage conditions
4. Expiry date or product shelf life
5. Contraindication and any other warnings
6. Directions of use,
7. Manufacturer, packer or distributor's name and address,
8. Quantity per dosage unit

9. List of any other ingredients and additive.

A Singapore study identified labeling inconsistency, false label claim and missing important product information as problems commonly encountered in herbal medicine labeling (Yee et al., 2005). Some of the labeling shortcomings identified during herbal product registration included:

1. For most products imported from Asia, the products were not labeled in English. In some instances, the English translation on crucial product information (product indication and dosage, for example) did not match the original text.
2. Batch number and expiration date were not stated and, in some cases, unrealistically long shelf life stated without scientific justification.
3. Inadequate information was provided on primary ingredients or any other controlled substances.
4. Ingredients were improperly named.
5. Quantity of active ingredient was not stated.
6. Directions of use were not properly presented and some deviated from what was approved in the country of origin and the standard formulary.
7. False or exaggerated therapeutic claims were made. The claims were prohibited in the country of origin.
8. Information on contraindications and side effects of the herbal product were not provided (Yee et al., 2005).

In relation to medicines, safety can be defined as the probability of not causing trauma when used as prescribed. Efficacy is the ability to produce a medical benefit. When evaluating whether the herbal product is safe and effective, the therapeutic indication has to be considered. A herbal product is only useful if it is both safe and effective (Moreira et al., 2014). In some European countries safety and efficacy evaluation of herbal medicines can be based on proof of longstanding history of product use and traditional experiences while other countries may require a form of clinical studies. In US herbal medicines are only recognized as safe when they meet modern medicine standards, in which case they can be registred as a drug. Otherwise they are not considered medicines and regulated as dietry supplements. A longstanding history of product use, defined as a period of use from 20 to 30 years, although it varies between cultures, experience is key in evaluating safety and efficacy of herbal products. It considers:

- evidence of longstanding history and experience of product use;
- indications the product was used for;
- historical and ethnographic background of the product.

A herbal product is considered safe if there is documented evidence of traditional use without any reported adverse events and there are no restrictive regulatory requirements for such a product (WHO, 2000). A thorough literature review of all available information about the plant medicine should be conducted. This should include original research articles, oral evidence and references. Available review articles and monographs should be analyzed too (Ameh et al., 2010). Table 4 summaries documentation of safety based on experience.

Table 4. *Documentation of safety based on experience (Ameh et al., 2010)*

Condition	Action needed
No toxicological data exist	Assess risk based on documented evidence of traditional use and experience (for a period of at least 20yrs) without any reported adverse events. Period of drug use must be considered.
Some toxicological data exist	Document condition/s treated, figure of treated patients and place of treatment.
There is toxicity	Try to show relation to dose administered.
There is potential for misuse	Document all misuse and dependence cases.
There is no proof of Long term tradition use.	Toxicological studies should be done.

The key points for assessment of efficacy of a herbal medicine are:

1. Are the product ingredients, and their phamacodynamic properties well defined? What is the link with the observed clinical outcomes?
2. Is the therapeutic application for the product specified? What proof supports the indications of use? There is need to thoroughly look at the evidence that supports the therapeutic claims.
3. Clinical evidence for products without established long-term traditional use (Ameh et al., 2010).

The evaluation criteria for efficacy recommends that both the therapeutic and pharmacodynamics effects and the active ingredient be named or specified if known. The global requirements for proof of effectiveness can be less stringent for herbal products used to treat minor ailments or for prophylaxis, considering the history of traditional use. Documented experiences from traditional practitioners and physicians should be considered (WHO, 2000). For most regulatory authorities for example Brazilian National Health surveillance agency and EMA safety and efficacy is evaluated based on evidence of long term use. If a product fits in the definition of long standing traditional use data from clinical or pre-clinical studies is not a prerequisite to obtain approval for commercialization (Moreira et al., 2014).

In response to the growing threat of unsafe traditional medicines, studies have been done to build on identity, pharmacological properties of various plants and to document the traditional knowledge on effective herbs and their use in an attempt to preserve traditional knowledge (Maroyi, 2013). Research has also been done to identify toxicity associated with traditional medicines. These studies all point to the need of effective regulatory systems that adequately assess and evaluate all traditional medicines to ensure provision of quality, safe and effective traditional products in the country. In 2010 the Zimbabwe parliament health committee recommended the creation of a regulatory framework, as well as guidelines, for traditional medicines. World Health Organisation (WHO) has been advocating and promoting the need for access to safe, effective and quality herbal medicines (WHO, 2013).

An efficient and effective registration system of traditional medicines is key in ensuring safety, quality and effectiveness of traditional medicines. In its 2014-2023 strategy for traditional medicines, WHO endeavors to strengthen quality control, promote safe, correct use and efficacy of traditional medicines by controlling traditional products and practices (Qi, 2013). To achieve this goal, product registration is key (Qi, 2013). Regulation of traditional medicines presents a number of challenges. Studies have been done to analyze the registration process of these products in various countries to try and improve product regulation. These include a case study on Bahrain and Kuwait traditional medicine registration systems and policy implementation (Alostad et al., 2019) and Global perspective of traditional medicines regulation and variations between countries (Fan et al., 2012). These studies examined the regulatory framework with emphasis on the registration process in an effort to improve regulation of herbal products.

However due to variations in traditional medicine practices in various cultures, herbal medicines regulatory challenges and experiences are not the same. Therefore there is a need to study the registration process of herbal medicines in Country A with a background of the unique cultural beliefs and practices of traditional medicines in the country.

About 80% of people in country A use herbal products for their primary health care needs. In spite of the support and efforts towards regulation of herbal medicines, there are still a huge number of unregistered herbal medicines used in the country, presenting a huge public health problem of safety and quality. This project aimed to discover the challenges and obstacles affecting the registration of herbal products in the country.

Key concepts

Table 5. *Reasons for increase in unregistered herbal products in the market of Zimbabwe*

1. There are no adequate laws and regulations
2. The registration process is not well defined
3. Manufacturers and wholesalers are finding the registration process difficult to follow
4.There is no surveillance of traditional medicines in the market by regulatory authorities to enforce the law

2. METHODS

The following document were reviewed:

1. 2019 complementary medicines register for Zimbabwe to come up with:
    - Registrations trends
    - Total number of complementary medicines registered
    - Imported herbs versus local herbals
    - Country and manufacturer of the registered herbal medicine.
2. The guidelines on document submission for herbal medicine registration in Zimbabwe to determine the herbal medicines registration process, product evaluation criteria, labeling requirements, and prohibited indications.
3. Published research on traditional medicines
4. WHO guidelines on registration of traditional medicines were also analysed and compared to the country registration process to identify gaps.
5. The Traditional Medical Practitioner's Act Chapter 27 and the Complementrary Medicines Regulations medicines regulations.

3. RESULTS AND DISCUSSION

Two regulating bodies were identified: the Medicines Control Authority of Zimbabwe (MCAZ) and the Traditional Medical Practitioners Association (TMPA). Both authorities derive their power to regulate from the act of law, MCAZ from statutory instrument 97 of 2015 and the TMPA from Traditional medical practitioners act chapter 27:14. The two are not interrelated. The major differences of the two authorities are highlighted in Table 6. MCAZ has a well-documented registration process shown in Figure 1. No published registration process for TMPA was identified.

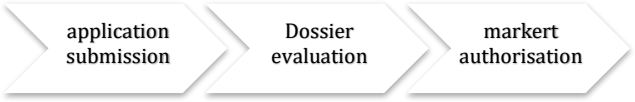

Figure 1. MCAZ herbal products registration process

For the registration process in Zimbabwe a complete application consists of

1. Dossier
2. Application fees
3. Product samples, submitted in their original container as intended for the patient. The sample should be labeled as it will be on the final product.
4. Completed C.M 1 form.
5. Declaration by the applicant

The samples should be accompanied by a copy of certificate of analysis, product specifications and analytical methods. The applicant should provide reference standards, degradation products and related impurities for a full monograph analysis. The samples should be labeled as the final product planned for the market.

MCAZ evaluators assess the dossier while inspectors evaluate company conformance to current Good Manufacturing Practices (GMP). Any company manufacturing herbal medicines is required to adhere to some cGMP standard. The applicant is required to provide supporting evidence which demonstrates their compliance. The inspectors may conduct GMP inspection before product registration. Analysists test the samples supplied. When a product meets all the regulatory requirements it is then registered as either a complementary medicine for general sale or pharmacy complementary medicine. Products registered as pharmacy complementary medicines can only be sold in a pharmacy. There are no restrictions on sale of complementary medicines general sale.

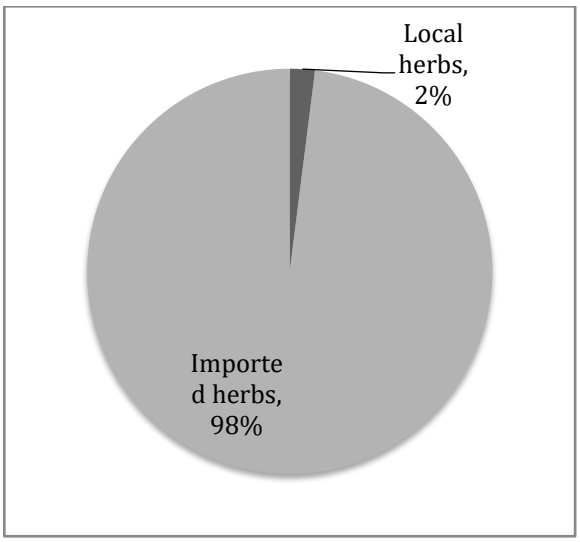

Figure 2. Compares registered local herbal products vs Imported herbal products

Table 6. *Comparison of the Herbal medicine registration Process of TMPA and MCA in Zimbabwe*

TMPA	**MCA**
The practitioner has to be registered as a member of the TMPA before they can sell their products	No affiliation to anybody or association is required
No defined registration process	A clearly defined registration process
No clearly laid out evaluation procedure for effectiveness, safety and quality	Detailed evaluation procedure for safety, effectiveness and quality
Products are sold through herbal drug stores	Products are sold in registered retail pharmacies
Derive the authority to regulate traditional medicines from the Traditional Medical Practitioners Act chapter 27.14	Mandated by the ministry of health through statutory instrument to regulate all complimentary medicines

MCAZ registers herbal medicines as complementary medicines. According to the December 2019 complementary register, there were 195 complementary products registered by the MCA with the majority being imported product (98%) and a very small percentage (2%) were local herbs, as shown in Figure 2. Therefore this process is not addressing the health risk posed by the local products, which are the bulk of the herbal products being consumed in the country.

MCAZ regulates all complementary medicines except those compounded, dispensed and administered by the practitioners in their practices at their premises. Some regulatory agency follow a two-tier system for herbal medicines registration. This is a risk based approach allowing early market authorizat for products containing low risk ingredients and manufactured in accordance with GMP. These products are mainly used for health maintains and health enhancement or self-limiting conditions (Fan et al., 2012). European Medicines Agency (EMA), Australian Complementary Medicines Registration Agency and Brazilian Regulatory Authority have a two-tier registration processes for herbal medicines. In contrast to other regulatory authorities with two-tier registration processes, a risk based registration process, all the MCAZ registered herbal products follow the same process highlighted in Figure 1. Considering that in developed countries, stricter guidelines affect well-established herbal products manufacturers, in Africa it is the traditional medical practitioners who will have to comply with these regulations. Thus, there is a need to minimize the registration requirements, while having the best possible impact on protecting consumers (Ngcobo et al., 2012). Reduction in bureaucracy by introducing a risk-based approach based on risk assessment and intended use might aid in improving local registrations. An example of this is the Brazil approach where herbal medicines are classified into two categories: herbal medicines and traditional herbal medicines. Herbal medicines are registered after providing proof of safety and effectiveness, through clinical and non-clinical trials. Traditional herbal medicines are registered through known history of traditional use. While herbal medicines have to be registered before marketing, traditional medicines can be notified. Notification is simple market authorization process meant to reduce bureaucracy in registration of herbal products manufactured by GMP compliant authorized companies, following a well laid out technical procedure. For a traditional medicine to qualify for notification it has to be in the Brazilian Herbal formulary and preparation must have a quality assurance monograph in an official pharmacopeia (Carvalho et al., 2018). MCAZ may consinder the risk-based approach in their registration process for herbal medicines as a way of promoting registration of indigenous herbs. This will allow early market access to local herbal products that have a low risk to the public.

The MCAZ evaluation for herbal medicines is based on quality, safety and effectiveness. Safety and efficacy evaluation is evidence-based. Toxicological and clinical studies are not a prerequisite if the product is used for the same known indication. Clinical studies are required for new indications. The process used to evaluate safety and efficacy of herbal medicines by MCAZ was compared to the evaluation process used by other regulatory authorities (Table 7). Some regulatory authorities such as EMA define traditional use as a documented period of use of 30 yrs with at least 15 years of use in the European union. Unlike other regulatory authorities like EMA, MCAZ does not have a defined period of use as a prerequest for product registration.

Table 7. *Comparison of registration process of herbal medicines in Zimbabwe by MCAZ and other countries regulatory authorities (Fan et al., 2012; Ngcobo et al., 2012)*

Requirements for registration	EMA	TGA Australia	WHO Guidelines for registration of traditional medicines in Africa	MCAZ guidelines for complementary medicines registration
Pharmaceutical quality	Raw materials specified by botanical identification. Quality prerequisites similar to conventional medicines	Identify all the ingredients used in product formulation. Identify the part/s of plant used and any processing done prior product manufacturing Provide a summary of the production process.	Characterization of plant raw materials, stating the part/s used. Quantitative and qualitative analyses of the final herbal product. Purity test to exclude toxic metal and microbe contaminants.	Botanical identification by herbarium of the country of origin. Qualitative and quantitative tests of plant materials. Purity tests to exclude toxic metal and microbe contaminants.
Safety	Based on documented evidence of safe traditional use. To included information on safe use in pregnancy and lactation. Mention probable interactions with other drugs.	Evaluation based on evidence of safe traditional use. Manufacturer to provide information on safety of product in pregnancy and lactation. To include herbal ingredients and any probable interactions with other drugs	Botanical certification of plant material; literature search for biological data. Toxicological studies are a must.	Botanical identification by herbarium of country of origin. Evidence based, no clinical trials toxicological studies if the product has proven safe traditional use and will be used for the same indication, same dosage form and dose.
Therapeutic efficacy	Evaluation based on evidence of long standing use and experience.	Evaluation based on historical evidence of long standing use. Evidence from clinical studies is required when there is no history or enough evidence of traditional use.	Evaluation depends on the type of indication for use and traditional medical practitioners and physicians experiences. Data from clinical trials required to support new indications.	Evaluation depends on the type of indication for use and traditional medical practitioners and physicians experiences. Clinical data is needed when the product is used for a new indication, in the absence of documented evidence.

Labeling and packaging	Product should be clearly labeled and easy to read by the targeted users and should have a package insert with all the required information on product use, indication, dosage, storage conditions, shelf-life, batch number and contraindications.	Product should be clearly labeled, with all the required information according to Australian TGA 1989. labeling guidelines	Packaging and labeling requirements are part of GMP and quality control	Similar to conventional medicines.

In Zimbabwe evaluation of the quality of traditional medicines is based on three pillars: identity, purity and content. The MCAZ quality control test requirements include test for heavy metals, microbial contamination and adulteration. For identification MCAZ relies on the herbarium of the country of origin of the herb. The manufacturer or applicant has to submit a certificate of identity from their local herbarium.

Globally quality control of herbal medicines still remains a challenge, as sometimes the active ingredients might be unknown or there may be multiple ingredients. This is more often the case for herbs that are not thoroughly studied, especially most African herbs. An applicant or manufacturer is to submit monograph specifications and tests performed, according to their chosen pharmacopeia, or submit their in-house validated methods for assay. As there are no national monographs or pharmacopeia for herbals in country A, developing inhouse tests for quality control can be challenging, especially for local manufacturers. Globally in the registration process, quality seems to be most difficult even with well-established and experienced manufactures and regulators (Fan et al., 2012). Monographs play a critical role in the registration process of herbal medicines. They help establish quality control standards by defining identity, quality, strength, and purity standards of the herbal product. Development of herbal monographs were they do exist would benefit both the regulators and local manufacturers in ensuring quality herbal product registrations (Qu et al., 2014). It was observed that the majority of the products (93.5%) registered by MCAZ are imported from countries with developed national herbal medicines compendiums and pharmacopeias, which makes it easier for foreign manufacturers with access to compendia and pharmacopeia to comply the information required by the authorities. An example is the British herbal compendium, which has monographs for herbs. Monographs start with definitions and synonyms and the botanical information, followed by a detailed description of the established herbal constituents. It also provides information on quality control and references assay methods. This is critical in evaluation of herbal products (Bradley, 2006).

Table 8. Comparison of Technical standards and developments in herbal medicines regulations (Fan et al., 2012; Sahoo, Manchikanti, & Dey, 2010)

Country	**Herbal drug registration system**	**National monograph**	**Pharmacopeia**	**Percentage of Products registered in Zimbabwe**
Bangladesh	Exist	Does not exist	Bangladesh national formulary on Unani and Ayurvedic medicines	4%
India	Exist	Does not exist	Ayurvedic pharmacopeia of India and Unani pharmacopeia of India	34%
United Kingdom	Exist	British herbal compendium	British herbal pharmacopeia	11.20%
USA	Exist	USP herbal medicine compendium	USP pharmacopeia	16.20%
Zimbabwe	Exist	No	No	1%

Table 8 summarises the resources and technical documents in Zimbabwe versus other selected countries whose products are registered with the MCAZ. India, the biggest importer of herbal medicines to country A, has the highest product registration 34% and does have national formulary, compendium and a pharmacopeia for herbal medicines. Australia, United Kingdom and the US also have these national resources. Local manufacturers in Zimbabwe might struggle to fulfill the requirements for the country's registration process, due to limitations on the avalibe resources. There are no local herbal monographs.

MCAZ is restrictive in product claims for herbal medicines. It has a list of prohibited medicinal claims which include: cardiovascular indication (e.g. hypertension and hypotension), HIV-AIDS, cancer, sexual transmitted infections, tuberculosis, diabetes, kidney stones, prostate gland disorders, rheumatoid arthritis, infantile diarrhea, epilepsy, Parkinson′s disease and meningitis. Evidence has shown effectiveness and wide use of herbal medicines on some of the prohibited indications, such as sexual transmitted infections. Sexual transmitted infections are one of the primary reasons people consult traditional medical practitioners in country A, as there are plants that have been shown to be effective therapy (Maroyi, 2013). This could be a deterrent for registering such local herbal products. To promote registration of these products, MCAZ could allow registration of these products based clinical trials or document clinical evidence.

4. CONCLUSION

Regulation of herbal medicines in Zimbabwe is still in its infancy stage and there is a need to build on the already established structures and efforts of MCAZ. While the well-defined registration process is able to register imported herbal products in the country, it is missing the local herbs, which is what the bulk of the population are consuming. Collaboration between the MCAZ and the TMPA will improving local herbal medicines legislation. While TMPA has wealthy of knowledge and experience with use of herbal medicines and the practice of traditional medicine they may benefit from the experience and expertise of MCAZ in control and regulation of medicines. MCA has expertise and experience in legislation of medicinal products. They ensure compliance to quality control standards and good manufacturing practice. Jointly the two bodies can effectively regulate the sell of herbal

medicines, learning from each other's unique knowledge and expertise in herbal medicines use and production.

All herbal medicines registered by MCAZ follow the same procedure. There is a need for a risk-based approach in product registration. MCAZ could emulate other regulatory authorities and consider a more simplified approached for their local traditional medicines, based on intended use and the toxicological profile of the herb. This will reduce bureaucracy, thus saving time for the regulators and improve registration of local herbal products.

There is no local herbal medicine compendium to define the quality standards, tests and specifications for local herbs, therefore the manufacturers of local herbal medicines developed their own methods and specifications to prove product consistency and quality which could be a huge task, considering the expertise and knowledge of most traditional practitioners. There is a need for developing herbal medicines compendium and a pharmacopeia for the country's herbal medicines with monographs. This will assist in setting up quality standards that are achievable by local manufacturers.

5. RECOMMENDATIONS FOR NEXT STEPS

There is a need for collaboration between the two regulatory bodies; together they can achieve more and learn from each other. The MCAZ may benefit from the practice of other regulatory authorities by applying a risk-based approach in regulation of low risk local herbal products to create a more simplified process.

Development of monographs, compendiums for local herbs by Zimbabwe will assist in setting quality standards which are internationally acceptable. The compndiums will be a guide for the local manufacturers to produce quality herbal products which are safe and efficacious. It will make it easier for them to follow in order to compile the required information for dossier submissions.

REFERENCES

Alostad, A. H., Steinke, D. T., & Schafheutle, E. I. (2018). International comparison of five herbal medicine registration systems to inform regulation development: United Kingdom, Germany, United States of America, United Arab Emirates and Kingdom of Bahrain. *Pharmaceutical medicine, 32*(1), 39-49.

Alostad, A. H., Steinke, D. T., & Schafheutle, E. I. (2019). A qualitative exploration of Bahrain and Kuwait herbal medicine registration systems: policy implementation and readiness to change. *Journal of pharmaceutical policy and practice, 12*(1), 32.

Ameh, S. J., Obodozie, O. O., Inyang, U. S., Abubakar, M. S., & Garba, M. (2010). Current phytotherapy-A perspective on the science and regulation of herbal medicine. *Journal of Medicinal Plants Research, 4*(2), 072-081.

Bandaranayake, W., M. (2006). *Morden phytomedicine, turning medical plants into drugs*. In I. Alamad, F. Qil, & M. Owasis (Eds.), *Quality control screening, toxicity and regulation of herbal drugs* (pp. 25-34).

Bradley, P. (2006). British herbal compendium. Volume 2: a handbook of scientific information of widely used plant drugs. *British herbal compendium. Volume 2: a handbook of scientific information of widely used plant drugs.*

Carvalho, A. C. B., Lana, T. N., Perfeito, J. P. S., & Silveira, D. (2018). The Brazilian market of herbal medicinal products and the impacts of the new legislation on traditional medicines. *Journal of Ethnopharmacology, 212*, 29-35. doi:https://doi.org/10.1016/j.jep.2017.09.040

Carvalho, J.C.T., Market analysis on traditional medicine-2020. *Herbal Medicine: Open Access,* 6(2).

Fan, T.-P., Deal, G., Koo, H.-L., Rees, D., Sun, H., Chen, S., . . . Chan, K. (2012). Future development of global regulations of Chinese herbal products. *Journal of Ethnopharmacology, 140*(3), 568-586. doi:https://doi.org/10.1016/j.jep.2012.02.029

Fontana, R. J., Watkins, P. B., Bonkovsky, H. L., Chalasani, N., Davern, T., Serrano, J., . . . Group, D. S. (2009). Drug-induced liver injury network (DILIN) prospective study. *Drug safety, 32*(1), 55-68.

Govindaraghavan, S., & Sucher, N. J. (2015). Quality assessment of medicinal herbs and their extracts: Criteria and prerequisites for consistent safety and efficacy of herbal medicines. *Epilepsy & Behavior, 52*, 363-371. doi:https://doi.org/10.1016/j.yebeh.2015.03.004

Jayaraj, P. (2010). Regulation of traditional and complementary medicinal products in Malaysia. *International Journal of Green Pharmacy (IJGP), 4*(1).

Maroyi, A. (2013). Traditional use of medicinal plants in south-central Zimbabwe: review and perspectives. *Journal of ethnobiology and ethnomedicine, 9*(1), 31.

Moreira, D. d. L., Teixeira, S. S., Monteiro, M. H. D., De-Oliveira, A. C. A. X., & Paumgartten, F. J. R. (2014). Traditional use and safety of herbal medicines1. *Revista Brasileira de Farmacognosia, 24*(2), 248-257. doi:https://doi.org/10.1016/j.bjp.2014.03.006

Mukherjee, P. K., & Houghton, P. J. (2009). *Evaluation of herbal medicinal products : perspectives on quality, safety, and efficacy*. London ; Chicago: Pharmaceutical Press.

Newmaster, S. G., Grguric, M., Shanmughanandhan, D., Ramalingam, S., & Ragupathy, S. (2013). DNA barcoding detects contamination and substitution in North American herbal products. *BMC medicine, 11*(1), 222.

Ngcobo, M., Nkala, B., Moodley, I., & Gqaleni, N. (2012). Recommendations for the development of regulatory guidelines for registration of traditional medicines in South Africa. *Afr J Tradit Complement Altern Med, 9*(1), 59-66. doi:10.4314/ajtcam.v9i1.9

Nhachi, C. F. B., & Kasilo, O. M. J. (1992). The pattern of poisoning in urban Zimbabwe. *Journal of Applied Toxicology, 12*(6), 435-438.

Pal, S. K., & Shukla, Y. (2003). Herbal medicine: current status and the future. *Asian pacific journal of cancer prevention, 4*(4), 281-288.

Qi, Z. (2013). Who traditional medicine strategy 2014-2023. *Geneva: World Health Organization*.

Qu, L., Zou, W., Zhou, Z., Zhang, T., Greef, J., & Wang, M. (2014). Non-European traditional herbal medicines in Europe: A community herbal monograph perspective. *Journal of Ethnopharmacology, 156*, 107-114. doi:https://doi.org/10.1016/j.jep.2014.08.021

Sahoo, N., Manchikanti, P., & Dey, S. (2010). Herbal drugs: standards and regulation. *Fitoterapia, 81*(6), 462-471.

Srinivasan, V.S. (2006). Challenges and scientitic issues in standardization of botanicals and their preparations.United States Pharmacopea's dietary supplement verification program- A public health program. *Life sciences,* 78(18), 2039-2043.

Tagwireyi, D., Ball, D. E., & Nhachi, C. F. B. (2002). Traditional medicine poisoning in Zimbabwe: Clinical presentation and management in adults. *Human & experimental toxicology, 21*(11), 579-586.

WHO. (2000). *General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine*. Retrieved from geneva:

WHO. (2005). *national policy on traditional medicine and regulation of herbal medicines*. Retrieved from geneva:

WHO. (2007). WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues. In. 2007: World Health Organisation.

WHO. (2019). *WHO global report on traditional and complemntary medicine 2019*. Retrieved from geneva:

Yee, S.-K., Chu, S.-S., Xu, Y.-M., & Choo, P.-L. (2005). Regulatory control of Chinese Proprietary Medicines in Singapore. *Health Policy, 71*(2), 133-149. doi:https://doi.org/10.1016/j.healthpol.2003.09.013

Zhang, J., Wider, B., Shang, H., Li, X., & Ernst, E. (2012). Quality of herbal medicines: challenges and solutions. *Complementary therapies in medicine, 20*(1-2), 100-106.

ACKNOWLEDGEMENTS

I would like to thank all of the BIRS guest faculty from global industry and regulatory organizations for generously sharing their professional expertise and providing donated, in-kind time towards building the professional skills and technical capabilities of the students within the BIRS program. I would also like to thank my fellow peers in the BIRS MS student cohort for providing guidance and constructive feedback during the classroom group work and interactive sessions; Abigail Ekeigwe and Mercy Okezue, Purdue ABE BIRS PhD candidates, for their mentorship and input throughout the project; Professor Fran Eckenrode for providing content expertise throughout the review process on this paper; and Lauren Terruso, operations manager for BIRS Center, for all of her efforts on editing multiple iterations of the technical paper draft in preparation for publication. The international component of the Purdue BIRS program was initiated through educational support provided by the Merck Foundation and most recently through a capacity building effort funded by the Bill and Melinda Gates foundation, grant # 41000460.