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Compliance to GMP guidelines for Herbal Manufacturers in East Africa: A Position Paper

V. Kwesiga¹, Z. Ekeocha², S. Byrn³, K. Clase⁴

ABSTRACT

With the global increase in the use of traditional and complementary remedies for the prevention and treatment of illness, the quality and safety of these medicines have become a significant concern for all regulatory authorities. Herbal medicines are the most commonly used form of traditional and complementary medicines in the world and the efficacy and safety of herbal medicines, like conventional medicines, largely depends on their quality from planting to harvesting, preprocessing and final processing.

Due to the inherent complexity of herbal medicines, often containing an array of active compounds, the primary processing of herbal medicines has a direct influence on their quality. Quality concerns are the reason why the medicines regulatory agencies insist that manufacturers of medicines strictly follow Good Manufacturing Practices since it is an essential tool to prevent instances of contamination, mix-ups, deviations, failures and errors. However, a strict application of GMP requirements is expensive and would drive the prices of the manufactured products up. As a result, a maturity level grading of facilities is proposed as a way of justifying the costs incurred for manufacturers desiring to reach a broader market and investing in continuous improvement.

36 Good Manufacturing Practice (GMP) inspection reports of local herbal manufacturers conducted by National Drug Authority were analyzed to establish the type and extent of deficiencies to GMP requirements for local herbal manufacturers in Uganda. The different GMP chapters and related sub-parameters constituted the variables used for the analysis of conformity to requirements. The primary outcome variable was the conclusion regarding compliance or noncompliance of the inspected local herbal manufacturing facility. GMP parameters that were frequently defaulted by local herbal manufacturers and the corresponding frequencies were identified. The Pearson Chi-square test was applied independently on each category to find the association that existed between conformity and the questions in each category.

Only 22% (8) of the 30 inspected facilities were found to comply with GMP requirements, as per National Drug Authority (NDA) guidelines; while the majority of the facilities, 28 (78%), were found not to comply. Of the facilities inspected, 25 were undergoing GMP inspection for the first time. A total of 1,236 deficiency observations were made in the 36 inspection reports reviewed for the study. The mean for all deficiencies was 34.3, and the standard deviation was 15.829. 91.5% of the facilities did not have mechanisms for a record of market complaints; 80.9% did not meet documentation requirements; 78.9% did not have quality control measures in place, and 65.7% did not meet stores requirements.

By encouraging a culture of self/voluntary improvement through the introduction of listing of manufacturers based on a maturity level grading, the National Drug Authority will improve the Herbal Medicines sector as per the mandate of improving the herbal medicine industry. Also, increased sensitization of all relevant stakeholders regarding the requirements for GMP should be intensified.

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1. INTRODUCTION

1.1. Historical Perspectives of Traditional Medicines

Traditional and complementary remedies have been deeply embedded in the lifestyle of ancient peoples and have been employed in the prevention and treatment of illness (Lemonnier, 2017). Traditional and complementary medicine is a vital health resource in the prevention and treatment of chronic diseases of the ever-ageing world populations (World Health Organization, 2019b). Natural products have provided good medicinal leads in search of new medicinal compounds. Several well-known medicines that are currently in use are derived from plant sources such as Artemisinin, Quinine, Vincristine and Aspirin. The most frequent sources of traditional medicines are herbal, but animal and mineral materials are also sources. Mahomoodally considers Africa to be the cradle of humankind due to its abundant biological and cultural diversity, especially regarding differences in healing practices (Mahomoodally, 2013).

1.2. EAC Potential for the Development of Traditional Medicine

East Africa will greatly benefit from investing in the development of its traditional medicine as a source of foreign exchange earnings and as an alternative to contemporary medicine in solving the public health challenges that the region is currently tackling. (East African Community, 2017) As of 2008, the traditional medicines global market stood at about USD 83 billion annually and continues to increase. (East African Community, 2017) Indeed, with about 40,000 to 45,000 species of plants with a potential for development, only 5,000 species have been used medicinally. With such biodiversity, Africa has great potential that is still unutilized and waiting to be discovered (Mahomoodally, 2013). However, the most significant danger to this enormous potential is the rapid loss of most of these natural plant habitats as a result of human activities. With very high rates of deforestation reported at 0.7% per annum, there is a need to regulate the preservation of these species (FAO, 2006). Besides, there has been a rapid loss of valuable traditional knowledge due to lack of permanent documentation of these remedies in Africa (Mahomoodally, 2013).

The World Health Organization (WHO) policy on traditional medicine aims to facilitate countries to develop strategies to make traditional medicine part

of their national health care systems (World Health Organization, 2013). However, previous works in other countries and healthcare fields reveal many challenges facing this proposed integration of traditional medicine into mainstream national health care systems (Kayombo et al., 2007).

Like the WHO policy on traditional medicines, the Uganda National Health Policy 2015 provides for maximization of the benefits of Traditional and Complementary Medicines (TCM) and protection of the public against their possible adverse effects. The achievement of this objective depends on establishing and operationalization of an appropriate structure to promote, coordinate and monitor the implementation of multi-sectoral traditional and complementary medicines activities in Uganda (MOH, 2015).

Likewise, the National Drug Authority (NDA), established by the National Drug Policy and Authority Statute in 1993, is mandated to encourage and facilitate research and development of herbal medicines in the country. Section 41(1) of the National Drug Policy and Authority (NDP/A) Act, Cap. 206 states that “The National Drug Authority shall encourage research by persons carrying on research and development in herbal and other medicines and, where appropriate, take such medicines into production as a component of the drug supply” (National Drug Policy and Authority Act, 1996).

1.3. Good Manufacturing Practices in Herbal Medicine Manufacture

The inherent complexity of the composition of herbal medicine, consisting of tens of compounds, along with the number and small quantity of well-defined active ingredients, make Good Manufacturing Practices an essential tool to assure the quality of herbal medicines. The WHO recognizes that the production and primary processing of herbal medicines critically determines the quality of the finished product (World Health Organization, 2007).

Good manufacturing practices are those control measures that ensure which products are produced and controlled in conformance with quality standards fitting to their intended use and as required by the marketing authorization (PIC/S, 2013; World Health Organization, 2011). The manufacturing process is the critical step required to ensure the quality of all

medicinal products, including herbal medicines.

It has been demonstrated that when manufacturers of medicines adopt GMP controls, they produce medicines with the expected identity, strength, quality and purity (U.S. Food & Drug, 2020). Manufacturers are expected to buy and use quality raw materials for the production of medicines. They are also expected to establish standard operating procedures to be meticulously followed during production with no process steps skipped. They should have systems to detect and investigate product quality deviations and maintain reliable testing laboratories. The reason why regulatory bodies demand strict adherence to these practices is to prevent instances of contamination, mix-ups, deviations, failures and errors (PIC/S, 2013; World Health Organization, 2013).

1.4. Adverse Drug Reactions Due to Herbal Medicines

The public generally believes that herbal medicines are very safe and devoid of adverse effects because they are found in nature. However, studies have shown that herbs are capable of producing many undesirable reactions. Ekor demonstrated that some of these herbal remedies had caused severe injuries, life-threatening conditions and even death. Many irrefutable cases of poisoning as a result of intake of herbal remedies have been reported in the literature (Ernst, 2002). Auerbach et al. (2012) reported an association between traditional herbal medicine use and the development of liver fibrosis among study participants in Uganda (Auerbach et al., 2012). In most countries, manufacturers or importers sell herbal medicines and related products into the market without any mandatory safety or toxicological evaluation. Since very few people using herbal medicines inform their primary care physicians, many adverse drug reactions likely go unrecorded (Ozioma & Okaka, 2019).

There are direct and indirect causes of adverse events arising from the use of herbal medicines. Some herbs have been shown to have intrinsic toxicity at the usual therapeutic dosage, or in overdose. Other adverse drug reactions are caused by contamination with toxic metals, other adulteration or by substitution of herbal ingredients or improperly produced products (Zhang et al., 2012) and wrong indications and herb-drug interactions (Zhang et al., 2015).

1.5. Substandard and Falsified Products

WHO and other international organizations have recognized the circulation of substandard and falsified medicines as a global problem affecting all medicines, medical consumables, lifestyle products, as well as herbal medicines. Ernst has reported an increase in the rate of adulteration of herbal medicine with extraneous chemical substances or banned drugs (Ernst, 2002).

Herbal medicines are adulterated with undeclared drugs/chemical substances, together with being substituted with non-drug components and other foreign non-drug materials. Some manufacturers have been found culpable for intentional adulteration (Xu, et al., 2019). Between 2007 and 2016, Tucker reported that 776 dietary supplements marketed for sexual enhancement, weight loss or muscle building in the United States of America contained unapproved pharmaceutical ingredients (Tucker et al., 2018).

The National Drug Authority surveyed herbal products claimed to enhance sexual activity in the central division of Kampala to isolate and identify adulterants. A total of 49 samples was randomly collected and screened for the presence of adulterants. 75% of imported herbal products contained unreported added conventional medicine, whereas the prevalence of adulteration for locally manufactured herbal products was 49% (National Drug Authority, 2020b). These reports show the high rate of counterfeiting of these products due to the lack of rigorous checks as compared to conventional medicines.

1.6. Study Justification

Although adherence to Good Manufacturing Practices (GMP) is a crucial step in ensuring the quality of herbal medicines, conforming to GMP requirements requires investment from manufacturers. It is estimated that small manufacturers would have to incur 7.2% of annual income to establish and maintain GMP requirements which eventually impacts on the affordability of the medicines (InstantGmp, 2002). Therefore, strict adherence to all parameters in standard GMP guidelines may not help the National Drug Authority achieve its mandate of encouraging research and development of herbal medicines.

The overall objective of the study was to determine compliance with GMP guidelines for herbal manufacturers in Uganda. The aim was to determine the common areas of deficiency of local herbal

manufacturers and propose a risk-based framework for maturity grading of local herbal manufacturers.

2. METHODOLOGY

2.1. Research Design

The study used a literature review research design through an assessment of existing Good Manufacturing Practice inspection reports for local herbal manufacturers in Uganda conducted by National Drug Authority. The study was both descriptive and analytical. The descriptive approach focused on the quantitative aspect of the study that involved obtaining information regarding the parameters of GMP evaluated as provided for in the GMP guideline currently in use for inspection of local herbal manufacturers. The analytical part evaluated the current practice compared with other NRAs. Adaptation of these GMP parameters to the country's situation and level of sophistication of the majority of the local manufacturers were made in order to realize the mandate of NDA in improving the standards of locally manufactured herbal medicines.

2.2. Study Population

The study focused on reports generated from GMP inspections of local herbal manufactures in Uganda. The study population included all manufacturers who had undergone GMP inspection by the time this study was conducted. A total of 36 reports were included in

the analysis. All completed GMP reports of previous inspections of local herbal manufacturers in Uganda were obtained from the NDA repository and included in the study.

2.3. Data Collection Methods

The secondary data for this study was obtained from the completed GMP inspection reports. Variables were identified by the different aspects contained in the National Drug Authority GMP inspection checklist containing the different GMP parameters considered by the GMP inspectors. The data obtained from these reports were collected using a Microsoft Access database designed for this purpose. The different GMP inspection reports were coded to enable quicker cross-referencing of data captured in the database to ensure the validity of data captured. The outcomes of the inspection exercise were also captured in the same Access database.

2.4. Reliability of the Research Instruments

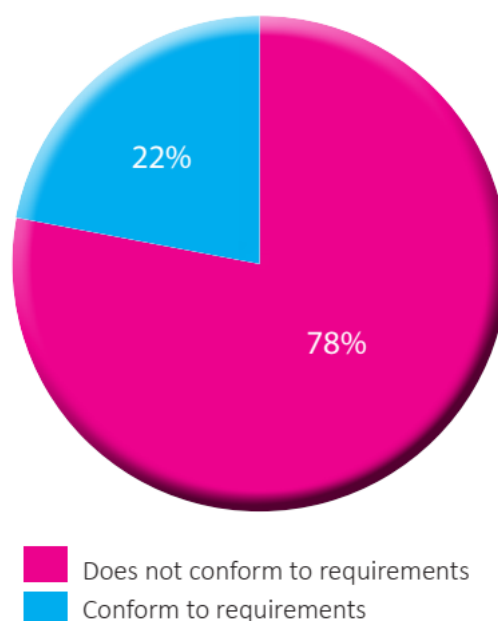
Cronbach's alpha was used to test the internal consistency of the checklist used to assess GMP for local herbal manufacturers which was the basis for the reports included in the study. It was found that the tool was highly reliable (Cronbach's alpha=0.95).

2.5. Data Analysis

The primary outcome variable was the conclusion regarding compliance or noncompliance of the inspected local herbal. Different activities carried out by inspected facilities included cultivation of medicinal plant materials, manufacture of herbal medicine, packaging and importing. Their frequencies were determined using SPSS/20. The GMP inspection checklist titles/chapters were used to identify the GMP parameters that are frequently defaulted by local herbal manufacturers. These constituted the measures of conformity and are categorized into nine groups including;

- Premises
- Location and surroundings
- Stores
- Sanitation and hygiene
- Machinery and equipment
- Documentation
- Market complaints
- Production area
- Quality control.

Figure 1: Rate of Compliance to Good Manufacturing practices (GMP) requirements by Local herbal manufacturers in Uganda



Activity	Inspection reports associated with the activity		
	Yes, n (%)	No, n (%)	Total
Cultivation of medicinal plant materials	10 (27.8)	26 (72.2)	36
Collection and storage of medicinal plant material	23 (63.9)	13 (36.1)	36
Manufacture of herbal medicine	32 (88.9)	4 (11.1)	36
Packaging	24 (66.7)	12 (33.3)	36
Importing	5 (13.9)	31 (86.1)	36
Laboratory testing	2 (5.6)	34 (94.4)	36

Table 1: Activities carried out by facilities

Pearson Chi-square test was applied independently on each category to find the association that existed between conformity and the GMP parameters within each category.

The significant factors were selected and subjected to binary logistic regression to determine their relationship with non-conformity. The primary outcome of this model was “not conform=1” and “conforms=0”. Crude odds ratios (core) and p-values with a statistical significance of 0.05 were presented at the bivariate level. A multivariable logistics regression was used to determine independent variables significantly associated with non-conformity, adjusting for related factors and potential confounders. Based on the likelihood-ratio (LR), a stepwise forward selection was used to find significant variables, retaining those variables with p-values < 0.2. The adjusted odds ratios and their p-values were reported. The conclusions on the significance of the relationships were based on a 5% level of significance.

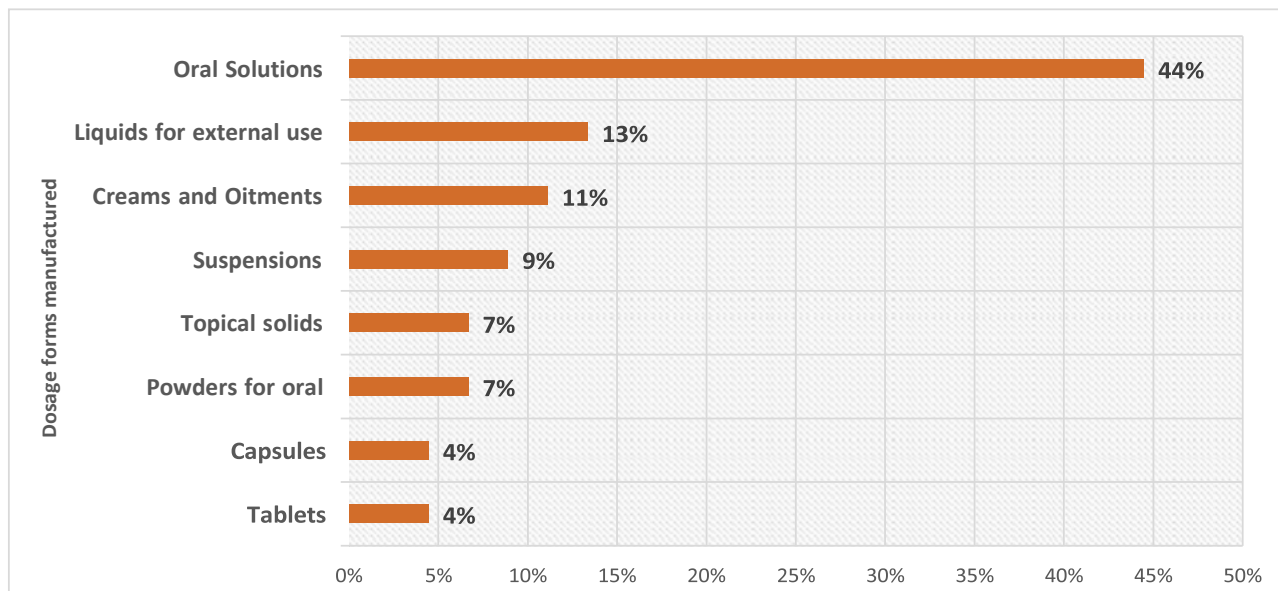
3. RESULTS

The National Drug Authority had inspected thirty local herbal manufacturing facilities by the time of the review. Of these, 69.4% of facilities were being inspected for the very first time. Only 23% (7) of the inspected facilities fulfill the requirements for compliance to GMP specifications as per National Drug Authority guidelines. In comparison, the majority of the facilities 77% (23) do not comply with the requirements, as shown in Figure 1.

Overall, the most frequently carried out activity by the facilities was the manufacturing of herbal medicine (n=32, 88.9%), followed by packaging (n=24, 66.7%) and collection and storage of medicinal plant material (n=23, 63.9%) as shown in Table 1. The least carried out activity was laboratory testing (n=34, 94.4%), followed by importing (n=31, 86.1%) and cultivation of medicinal plant materials (n=26, 72.2%) as summarized in Table 1.

Oral solution dosage forms were manufactured in 44% of inspected facilities, followed by liquids for external use in 13% of inspected sites. Creams and ointments were third at 11%. Results for other dosage forms covered in the inspection are shown in Figure 2. In addition, results show that only 27.8% of surveyed reports correspond to facilities engaged in cultivation of the raw materials used for the production of the herbal medicines. Evidence needs to be gathered to demonstrate whether the manufacturers of the raw materials (API) adhere to Good Agricultural Practices. These manufacturers would have to be certified to conduct this cultivation process according to the set requirements to facilitate traceability. It is also not clear whether the local herbal manufactures

Figure 2: Dosage forms manufactured by the local herbal manufacturing facilities



have contracts with raw material suppliers.

3.1. Deficiencies Observed in the Review

1,236 deficiencies were observed in 36 inspection reports reviewed. The average number of deficiencies was 34.3 per report, with a standard deviation of 15.829 deficiencies. 91.5% of the facilities did not have mechanisms for record of market complaints. There was an 80.9% rate of noncompliance to

P=0.042), as summarized in Table 2.

Firms with no suitable weighing areas for materials were approximately eight times more likely not to conform to GMP standards (aOR=7.71, P=0.012). Firms with no appropriate weighing scales were approximately nine times more likely not to conform to GMP standards (aOR=9.21, P=0.0002). Firms whose scales were not calibrated regularly were

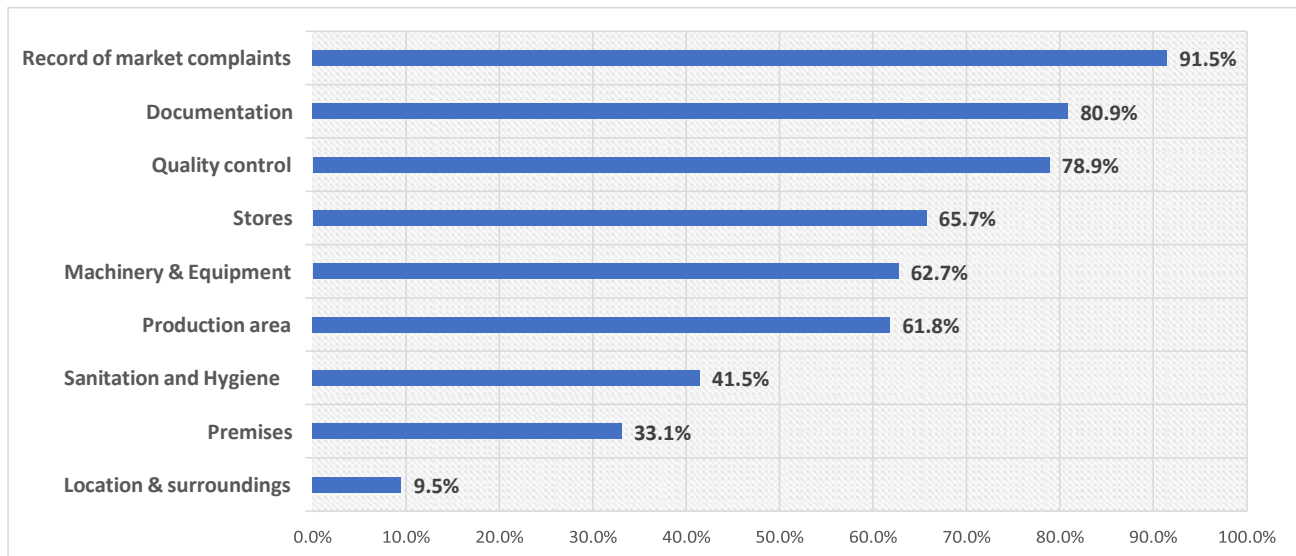


Figure 3: Rate of nonconformance to GMP requirements per inspection parameter

documentation requirements, 78.9% noncompliance to quality control requirements and 65.7% rate of noncompliance to requirements for stores, as shown in Figure 3. These results indicate that very few products manufactured by the local manufacturers would meet any international standards since the three key control areas: stores, production and quality control areas have the highest deficiencies.

3.2. Logistic regression results

Logistics regression results are summarized in Table 2. Firms without adequate space for equipment, materials and movement of personnel were approximately five times more likely not to conform to GMP standards (aOR=4.81, P=0.001). Firms whose premises were not constructed to allow adequate cleaning, good sanitation and hygiene practices were seven times more likely not to conform to GMP standards (aOR=7.12, P=0.041). Firms whose premises had no logical flow of activities, material and personnel were two times more likely not to conform to GMP standards (aOR=2.31, P=0.002). Firms whose raw materials or ingredients were not identified, inspected and tested before processing were six times more likely not to conform to GMP standards (aOR=6.14,

approximately eight times more likely not to conform to GMP standards (aOR=8.31, P=0.031). Firms whose area for weighing was not frequently and adequately cleaned were five times more likely not to conform to GMP standards (aOR=5.61, P=0.028). Firms with no straightforward and illustrative procedure listing the required basic personal hygiene practices were approximately seven times more likely not to conform to GMP standards (aOR=5.61, P=0.001). Firms with no running water for handwashing after use were approximately 12 times more likely not to conform to GMP standards (aOR=11.91, P=0.021).

Firms whose personnel were not protected from contact with toxic irritants and potentially allergenic plant materials using adequate protective clothing were approximately nine times more likely not to conform to GMP standards (aOR=8.81, P=0.031). Firms whose batch manufacturing records were not kept for all batches were five times more likely not to conform to GMP standards (aOR=5.31, P=0.0016). Firms whose record of sale and distribution of each batch of alternative medicines were not maintained were 12 times more likely not to conform to GMP

standards (aOR=12.31, P=0.031) as shown in Table 2.

Firms whose production area was not adequate to carry out production activities were eight times more likely not to conform to GMP standards (aOR=8.05, P=0.041). Firms whose personnel do not wear protective gear were six times more likely not to conform to GMP standards (aOR=6.21, P=0.045). Firms whose final products were not sampled batch-wise for quality testing before being released were nine times more likely not to conform to GMP standards (aOR=9.21, P=0.003). Firms with no quality control laboratory were 13 times more likely not to conform to GMP standards (aOR=13.01, P=0.014). Firms whose final product was incorrectly labelled, including the expiry date, were eight times more likely not to conform to GMP standards (aOR=8.51, P=0.031) as summarized in Table 2.

4. DISCUSSION AND PERSPECTIVES

4.1. Demographics

The facilities included in the study mostly manufactured oral solutions (44%), followed by liquids for external use (13%) and then creams and ointments (11%). Figure 2 shows that most of the herbal medicines produced by local manufacturers in Uganda are intended for ingestion. This corresponds to a report by Kumadoh and Ofori-Kwakye (2017) that identified oral solutions, also known as decoctions. These solutions were prepared by boiling the herb in water for a specific time. They were the most common dosage forms produced by his study group in Nigeria. These preparations usually were recommended to be used immediately within 24 to 48 hours. (Kumadoh & Ofori-Kwakye, 2017) However, Kumadoh notes that the proliferation of large-scale production has led to increased shelf-life for herbal products without review of stability data. (Kumadoh & Ofori-Kwakye, 2017) The absence of stability data and the generic expiry dates of 1-3 years poses a risk to patients who buy these products as the products may have deteriorated and contained unidentified breakdown products not intended for consumption. (European Medicines Agency, 2007) It is important to note that the herbal preparations manufactured and sold in Uganda are subject to a simplified registration process called "notification". Stability data for local herbal remedies is not required for submission before approval for sale is granted.

4.2. Rate of Compliance to GMP Guidelines

GMP is aimed at ensuring that products are produced and controlled according to required quality appropriate to their intended use and as approved by the marketing authorization. For the 30 facilities inspected, only 23% (7) facilities were considered to fulfill the requirements for compliance with GMP guidelines for herbal manufacturers in Uganda. In contrast, the majority of the facilities, 77% (23), did not comply with the requirements.

The majority of manufacturers rely solely on the experience of the lead herbalist to ensure that the product is sufficiently produced. Large scale production requires scale-up and validation of smaller traditional processes, which are the experience of the lead herbalist. This poses a risk of magnifying errors arising from scaling up runaway processes that affect the quality of the finished products. As a result, these products cannot comply with intra and inter batch organoleptic, or chemical consistency tests like powder fineness, foreign matter and aflatoxin content. Therefore, patients will be exposed to different quantities and contents of the drug possibly resulting in overdose or under-dose.

4.3. Non-conformances

Overall, 1,236 deficiencies were made in the 36 inspections reviewed for the study. The number of deficiencies per facility averaged 34.3 ± 15.8 deficiencies. This is a very high level of deficiencies observed per facility, with almost half the parameters inspected being identified as nonconformances. One reason for this high level of nonconformance observations seen in the reports reviewed may have been the high cost required for implementation and maintenance of GMP requirements in a resource-limited setting. Typically, small manufacturers would have to incur 7.2% of annual income to establish and maintain these requirements (InstantGmp, 2002). With rudimentary techniques of manufacture and low incentives for venture capital investments, it is difficult for small manufacturers to afford this high level of investment.

Also, a lack of knowledge of GMP requirements could have been a factor in explaining these results since 69.4% (25) reports reviewed in the research were for first-time inspections. Only 31.6% of reports were for subsequent inspections. The National Drug Authority has just finalized the implementation of a

GMP inspection framework within the organization. Training of inspectors to conduct inspections and education of herbal manufacturers regarding the regulator's expectations has begun NDA.

4.4. Most Relevant Areas of Deficiency

Among the parameters inspected for Good Manufacturing Practices, absence of mechanisms for recording of market complaints, noncompliance to documentation requirements, quality control requirements and requirements for stores had significantly more noncompliant GMP observations than other parameters. 91.5% of the facilities did not have mechanisms for record of market complaints. According to the WHO, all product complaints, and potentially defective products, should be carefully investigated to identify the root cause according to written SOPs; and the corrective action should be taken. This is an essential aspect of GMP because the review of complaints could reveal that the product was actually defective and that regulatory action needs to be taken. In addition, this presents a learning opportunity for the manufacturer to improve the product. When defects are detected, measures are put into place to ensure that they do not recur, hence saving money that would otherwise be used to withdraw or rework the product.

There was an 80.9% rate of noncompliance to documentation requirements. The requirement for documentation aims to define the specifications and procedures for all materials and manufacturing process and quality control. Documentation requirements ensure that all employees know what to do and when to do it and ensure that before release of a batch for sale, authorized persons have all the information necessary to release or reject the batch. Documents provide records of an audit trail that will permit investigation in case of product failure or product-related complaints. (National Drug Authority, 2020a) Quality control ensures that relevant tests are carried out and that materials are released for use, or sale only after ascertaining that their quality complies with the requirements. There was a 78.9% noncompliance to quality control requirements.

A 65.7% rate of noncompliance to requirements for storage areas was observed in the study. Storage areas are expected to have sufficient capacity to allow orderly storage of materials and products, with proper separation and segregation. Sufficient storage

areas ought to be provided, controlled, monitored and recorded, as required for manufacturing and control task.

4.5. Most Relevant and Scientific Associations

Significant correlations were observed between failure to comply with these 4 of the 9 categories of GMP parameters (independent variables) and failure to comply with GMP requirements (dependent variable outcome). These include production areas, preparation of materials for production, personnel issues, and quality control deficiencies.

Among the parameters inspected for Good Manufacturing Practices for production areas, lack of adequate production space (aOR=4.81, P=0.001), designs which do not allow for adequate cleaning (aOR=7.12, P=0.041) and logical flow of materials (aOR=2.31, P=0.002) were significantly more critical in predicting failure to comply with GMP requirements. Unsuitable (aOR=7.71, P=0.012) and dirty weighing areas (aOR=5.61, P=0.028), together with inappropriate (aOR=7.71, P=0.012) and uncalibrated weighing scales (aOR=9.21, P=0.0002), were significantly more critical in predicting failure to comply with GMP requirements among GMP parameters related to the preparation of materials for manufacturing of products.

Likewise, among the parameters inspected for Good Manufacturing Practices affecting personnel issues, lack of running water for handwashing (aOR=11.91, P=0.021), lack of protection of workers from toxic materials (aOR=8.81, P=0.031) and absence of protective gear (aOR=6.21, P=0.045) were significantly more critical in predicting failure to comply with GMP requirements. For parameters affecting documentation, the issues most significantly predicting failure to comply with GMP include lack of traceability mechanisms like keeping of batch records (aOR=5.31, P=0.0016), and lack of sale and distribution records (aOR=12.31, P=0.031). Lastly, among the parameters inspected for Quality Control, lack of proper quality control mechanisms like the batch-wise sampling of finished products (aOR=9.21, P=0.003), lack of QC laboratory (aOR=13.01, P=0.014) and incorrect labelling of finished products (aOR=8.51, P=0.031) were significantly more important in predicting failure to comply with GMP requirements.

Table 2: Criteria for assigning maturity level (This model is adopted from WHO Global Benchmarking Tool (GBT))

Maturity Level	Risk Rank	Description
Maturity Level 1 (ML1)	High	All GMP parameters that are ranked HIGH risk would constitute the Maturity Level 1 (ML1) and are considered essential for being listed at all after assessment. Omitting any if these requirements constitutes a high risk to the final consumer since this cannot guarantee a good and consistent quality product.
Maturity Level 2 (ML2)	Medium	All GMP parameters ranked as MEDIUM risk would constitute the Maturity Level 2 (ML2), with an evolving quality management system that partially performs essential GMP functions as regards Herbal products.
Maturity Level 3 (ML3)	Low	All GMP parameters ranked as LOW risk would constitute Maturity Level 3 (ML3), with a stable and functioning GMP system

Discovery of the leading GMP deficiencies is a crucial step for regulatory authorities to identify the root causes of medicines-related issues and prioritize when allocating resources to improve the industry. It is useful to adopt an annual review on common GMP deficiencies to identify high-risk GMP areas for training, and identifying the GMP inspections to high-risk facilities. (PIC/S., 2013)

4.6. Framework for Maturity Level Grading

The World Health Organization developed the Global Benchmarking Tool (GBT) used to objectively evaluate regulatory systems. The GBT also incorporates the concept of ‘maturity level’ or ML (adapted from ISO 9004), allowing WHO and regulatory authorities to assess the overall ‘maturity’ of the regulatory system on a scale of 1 (existence of some elements of the regulatory system) to 4 (operating at an advanced level of performance and continuous improvement). (World Health Organization, 2019a).

A similar framework has been developed and is proposed for use during the evaluation of compliance of Good Manufacturing Practices for local herbal manufacturers in Uganda. The purpose is to enable local herbal manufacturers to rise from baseline regulatory compliance to sustained, predictive practices. This maturity level matrix proposed consists of 3 levels including Maturity level 3 (ML3 – the existence of basic elements of the regulatory system), Maturity Level 2 (ML2 – existence of more proactive elements of regulatory systems), and Maturity level 1 (ML1 – the existence of continuous improvement elements of regulatory system as shown in table 2. The maturity level matrix is developed by categorizing all GMP parameters based on risk analysis (probability to cause cross-contamination and mix-ups) and statistical correlation to overall non-compliance to GMP guidelines as shown in table 3.

GMP parameters with low risk would constitute Maturity Level 3 (ML3), with a stable and functioning GMP system. GMP parameters ranked as the medium risk would constitute the Maturity Level 2 (ML2), with an evolving quality management system that partially performs essential GMP functions as regards Herbal products. All GMP parameters that are ranked high risk would constitute the Maturity Level 1 (ML1) and are considered essential for being listed at all after assessment. Omitting any of these ML1 requirements constitutes a high risk to the final consumer and cannot guarantee a good and consistent quality product. See figure 4.

During the inspection, the checklist would be used for assessing each GMP parameter. A maturity level would then be assigned based on the maturity level matrix. The ranking is valid as long as the facility maintains this level of compliance. This ranking would be subject to revision upon subsequent GMP inspections. The list showing maturity level for inspected local herbal manufacturers would then be published on the NDA website.

5. CONCLUSION AND RECOMMENDATIONS

From the results of the review of previous herbal manufacturers’ GMP reports, it is clear that National Drug Authority could do more work to improve the herbal medicines sector in the country, as per its mandate. The number of non-complying facilities would have been higher if strict GMP classification of the criticality of deficiencies was used during the assessments. When conducting inspections, the NDA is also asked to consider the government policy “Buy Uganda Build Uganda.” (Ministry of Trade Industry and Cooperatives, 2014) This is a policy to help indigenous businesses have a fair advantage for their products over imported goods. Therefore,

the regulator, instead of instituting enforcement measures, is called on to help and guide the facility to improve in their production processes when nonconformance observations have been identified. This weakens the effectiveness in enforcing the law, thus allowing room for inferior quality products to circulate on the market. However, if human and financial resources are effectively utilized to train local herbal manufacturers on GMP as well as set up quality control infrastructure and establish quality specifications for the different products and dosage forms, the local herbal sector will greatly benefit and take advantage of the indigenous flora to provide alternative medicines to the population of Uganda.

Substantial improvements of the herbal sector will require intense sensitization of all relevant stakeholders regarding the requirements for GMP and the need to produce scientifically backed and consistent products. Encouraging a culture of self- or voluntary improvement through the introduction of listing local herbal manufacturers, based on a maturity level grading, will further encourage/motivate the local manufacturers to invest resources in order to receive the recognition of the regulator, hence increasing their reputation and business opportunities.

A limitation of the study was the small number of GMP inspection reports for local herbal manufacturers available for review. This reduced the desired research population and, therefore, results may not be

generalizable. It is recommended to conduct a similar analysis in the future to determine the outcomes of analysis and compare those with the current results for similarities or differences.

Integrate all aspects of quality, including Good Agricultural Practices, Good Processing Practices and Good Manufacturing Practices in order to ensure that products meet all pertinent the requirements. Any deviations during the earlier stages of cultivation, production, and manufacturing can adversely affect the quality of the final products.

Additionally, there is a need to balance government priorities of safeguarding the population of Uganda and helping indigenous manufacturers gain an advantage under the Buy Uganda, Build Uganda (BUBU) policy. The government could give protection to companies that are committed to continuous improvement as required by the law and discourage those only wanting to do the bare minimum or produce substandard products that, instead, harm the general public.

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Figure 4: Schematic Model for Development of Risk-Based Herbal GMP Maturity Level Grading

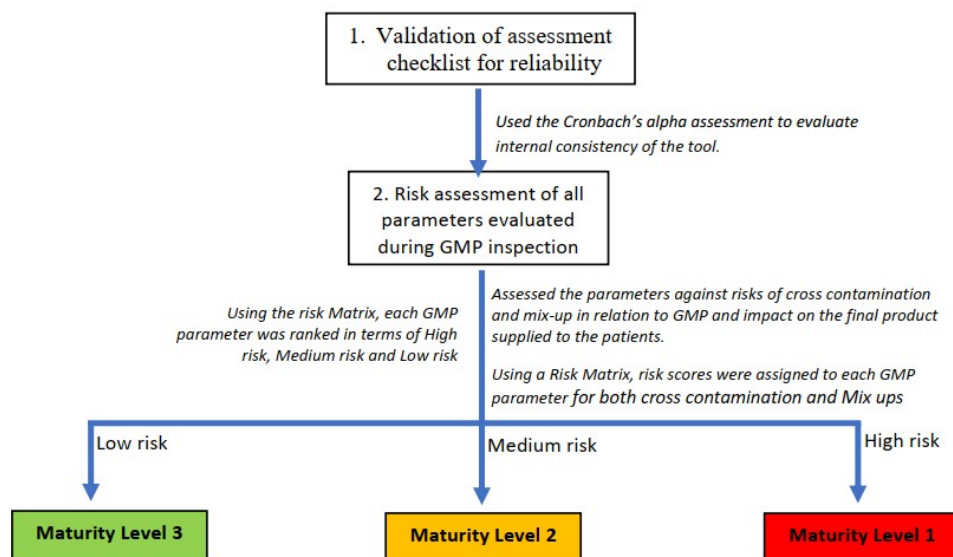


Table 3: Variables significantly associated with noncompliance to GMP guidelines requirements for Herbal manufacturers using multivariate logistic regression

Variables		Crude analysis		Adjusted analysis	
		Crude OR	P-Value	Adjusted OR	P-Value
Is there adequate space for equipment, materials and movement of personnel and materials?	Yes	1.0	-	1.0	-
	No	3.25	0.002	4.81	0.001
Are the premises constructed to allow adequate cleaning and good sanitation and hygiene practices?	Yes	1.0	-	1.0	-
	No	8.71	0.012	7.12	0.041
Is there a logical flow of activities, material and personnel?	Yes	1.0	-	1.0	-
	No	2.41	0.005	2.31	0.002
Are raw materials or ingredients identified, inspected and tested before processing?	Yes	1.0	-	1.0	-
	No	3.25	0.026	6.14	0.042
Are there suitable weighing areas of materials?	Yes	1.0	-	1.0	-
	No	9.15	0.002	7.71	0.012
Does the facility have appropriate weighing scales?	Yes	1.0	-	1.0	-
	No	4.45	0.027	9.21	0.0002
Are scales calibrated regularly?	Yes	1.0	-	1.0	-
	No	7.25	0.042	8.31	0.031
Is the area for weighing frequently and adequately cleaned?	Yes	1.0	-	1.0	-
	No	8.15	0.042	5.61	0.028
Is there a clear and illustrative procedure listing the required basic personal hygiene practices?	Yes	1.0	-	1.0	-
	No	8.25	0.052	6.81	0.001
Do the above facilities have running water for hand washing after use?	Yes	1.0	-	1.0	-
	No	7.95	0.042	11.91	0.021
Are Personnel protected from contact with toxic irritants and potentially allergenic plant materials by means of adequate protective clothing?	Yes	1.0	-	1.0	-
	No	6.25	0.012	8.81	0.031
Are batch manufacturing records kept for all batches?	Yes	1.0	-	1.0	-
	No	3.55	0.012	5.31	0.0016
Is a record of sale and distribution of each batch of alternative medicines maintained?	Yes	1.0	-	1.0	-
	No	8.85	0.007	12.31	0.031
Is the production area adequate enough to carry out production activities?	Yes	1.0	-	1.0	-
	No	6.05	0.042	8.01	0.041
Do all the personnel wear protective gear?	Yes	1.0	-	1.0	-
	No	4.26	0.018	6.21	0.045
Are final products sampled batch wise for quality testing before being released?	Yes	1.0	-	1.0	-
	No	7.65	0.039	9.21	0.003
Does the facility have a quality control laboratory?	Yes	1.0	-	1.0	-
	No	9.23	0.027	13.01	0.014
Is the final product correctly labelled including the expiry date?	Yes	1.0	-	1.0	-
	No	5.17	0.002	8.51	0.031

cOR= Crude Odds Ratio, **aOR**= Adjusted Odds ratio

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