Importation and distribution of unregistered medicines in the public sector: similarities, differences and shared challenges among Southern African Development Community (SADC) countries

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Abstract

Background

The purpose of the study was to assess the requirements for approval of the importation of unregistered medicines for use in the public sector in the Southern African Development Community (SADC) countries.

Methods

The study reviewed the legal provisions and requirements to be fulfilled when importing unregistered medicines for the public sector in SADC countries relative to two comparators drawn from countries with stringent regulatory systems through extant document analysis. The relative implementation index score was calculated and used to measure the level of implementing legal provisions and requirements to be fulfilled. Analysis was performed using the STATA software package.

Results

Approximately 13 out of 16 SADC countries had a relative implementation index below 50%. The aggregated implementation index across all SADC countries was 44%, ranging from 4% to 54%, while the two comparators had a relative implementation index of 81% and 85%, respectively.

Conclusion

Implementing the minimum requirements for importing unregistered medicines for the public sector was deficient compared to the jurisdictions with stringent regulatory systems, and wide implementation gaps also existed within the SADC region.

Background

The use of medical products such as pharmaceuticals, biologicals including vaccines, blood products, and medical devices, including in vitro diagnostics, is essential in the healthcare system (1, 2). Every country should ensure an adequate supply of safe, efficacious, good quality, and affordable medical products to promote public health (3). Effective regulatory systems ensure that the medical products meet the recommended standards to protect and promote public health(4, 5). All countries globally are encouraged to have effective and efficient National Regulatory Authorities (NRAs)(6). However, at least 30% of the existing NRAs have constrained capacity to perform core regulatory functions (7, 8).

Medical products are allowed for use after the respective NRAs approve them. The requirements to obtain such approval differ among NRAs based on their regulatory capacity(9, 10). This regulatory review process requires a considerable amount of time and adequate skilled personnel, impacting the availability of registered medicines(9, 11).

According to World Health Organization (WHO), Africa has 54 NRAs with varying capacities, but most cannot perform the critical regulatory functions. The WHO report estimates that only 30% of NRAs among its Member States can effectively and efficiently regulate medical products in their countries(12).WHO and its Member States require that medical products be registered; this involves the regulatory review of the quality, safety and efficacy data before approval for marketing (10, 11, 13). Unregistered medicines are medical products that have not undergone evaluation and/or approval by the respective NRA in a specific jurisdiction to determine compliance with established requirements for quality, safety, and efficacy and compliance with the national or regional regulation and legislation as applicable. This medical product may or may not have obtained the relevant authorization from the NRA in the source market (14, 15). There is evidence to demonstrate that unregistered medicines are associated with an increased incidence of adverse drug reactions and that despite advances in medicine regulation and guidance from professional organizations, the use of unregistered medicines (16, 17)in at-risk populations has not reduced (18, 19). Moreover, the impact of unregistered medicines is greater in low and middle-income countries due to the less mature regulatory systems and financial and human capacity constraints.

Ineffective delivery of quality healthcare services has led to shortages of medicines worldwide, including the Southern African Development Community (SADC) (20–23). Medicines shortages can be worsened in the absence of functional NRAs, exposing the public to potentially unsafe medical products. Medicines shortages can also be caused by changes in pharmaceutical manufacturers' marketing strategy, supply chain challenges, unexpected surges in demand, production-related issues, global pandemics such as Ebola and Covid-19, and natural disasters such as cyclones, among others (20, 21, 24). These factors create a vacuum for the availability of the medicines approved by the NRAs, leading to the demand and the use of medicines that have not undergone regulatory review approval. Therefore, the importation and distribution of unregistered medicines is a global phenomenon that is often necessary to bridge supply chain gaps, and this is expected to continue into the foreseeable future.

To objectively assess each NRA and create an opportunity for strengthening regulatory systems, WHO developed a Global Benchmarking Tool (GBT) (9). The GBT assesses the strengths and weaknesses in the various regulatory functions and scores the system in terms of maturity levels (ML), ranging from 1 to 4.(2, 18) In addition, the GBT assesses the availability of legal provisions, policies, manuals, guidelines, Standard Operating Procedures (SOPs), infrastructure, and availability of adequate and skilled personnel, which are all critical factors for effective regulation of medicines(2, 13, 16).

The use of unregistered medicines is expected to continue for the foreseeable future, raising concern globally, as documented in previous studies(25). Of concern is that unregistered medicines' quality, efficacy, and safety remains unknown to the importing countries. Therefore, to safeguard public health, the approval processes for importing and distributing unregistered medicines should be robust to mitigate the potential risk posed by such exemptions from the normal registration processes required to protect public health. The potential increase in the risk of adverse medical events or lack of therapeutic effect is also a cause for concern with unregistered medicines(25, 26).

To our knowledge, the legal provisions and requirements set by each NRAs in SADC when approving the importation and distribution of unregistered medicines, similarities, differences, robustness, and challenges remain unknown as the processes are not usually published; hence no opportunity for knowledge sharing and or transfer. The objectives of this study were to review and determine the level of implementing the legal provisions and requirements for the importation of medicines across the SADC NRAs. The study provides baseline data for creating a regional guideline for good practices when importing unregistered medicines to protect public health. The identified gaps can be included in the institutional development plans for each NRA to enhance the regulatory systems within the region.

Method

Sample

SADC has 16 Member States. The legislative instruments and guidelines from 15 SADC countries, namely Angola, Botswana, Comoros, Democratic Republic of Congo (DRC), Eswatini, Lesotho, Madagascar, Malawi, Mozambique, and Namibia, Seychelles, South Africa, Tanzania, Zambia, and Zimbabwe, were included in the analysis. No response or data was obtained from Mauritius.

Source of data

The study reviewed the legislative provisions and the requirements for the approval of importation and distribution of unregistered medicines by 15 SADC NRAs, and two comparators drawn from developed settings. Convenient selection of the two comparators was applied in this study. These two reference-NRAs are also listed as WHO-listed authorities, i.e., considered stringent regulatory authorities by WHO(27). Data on the provisions and the requirements for the approval of importation and distribution of unregistered medicines were extracted from the legislation (laws and regulations) and guidelines of the NRAs by the researchers. Additionally, 15 independent reviewers drawn from each of the NRAs were tasked to review legislative provisions and the requirements for the approval of importation and distribution of unregistered medicines from their respective NRAs. A set of 18 parameters adopted from the WHO guideline on import procedures of medical products was used in the review process (19). The themes were based on good regulatory practices for marketing authorization as detailed in WHO guidelines (28). The parameters were measured on a 4-point scale based on the GBT: no formal approach (ML 1); reactive approach (ML 2); well-functioning and integrated regulatory systems (ML 3) and regulatory systems operating at an advanced level of performance and continuous improvement" (ML 4) (2,18).

Statistical analysis

A Relative Implementation Index (RII) was used to assess the level of implementation of the legislative provisions and the requirements for the approval of importation and distribution of unregistered medicines, overall, for the NRAs, across each parameter, and for each of the NRAs. The $RII = \sum W / (A * N)$, where W is the weighting given to each indicator (ranging from 1 to 4), A is the highest weight (i.e. 4 in

this case), and N is the total number of indicators assessed(29). All data analysis was carried in the STATA software package.

Results

Implementation of legislative provisions and guidelines

Most of the NRAs had legal provisions for importing unregistered medicines. The level of implementation of the recommended standards is approximately 73% for importing unregistered medicines, 58% for receiving donations, and 54% for the use of standard operating procedures and guidelines.

Implementation of the requirements for assessing the quality of imported medicines

Implementing the requirements for obtaining good manufacturing practice (GMP) approval was estimated to be 53%, 23% for pre-distribution analysis, 36% for batch specific data such as certificate of analysis, and 33% for pre-distribution inspection across the NRAs.

Implementation of the requirements for assessing the efficacy and safety of imported medicines

The requirement for registration in the country of origin or recognized jurisdictions was estimated to be 33% across the NRAs, 54% for implementing post-market surveillance and 14% implementation level for requirements for specific dosage forms and product-specific data. The level of implementing the requirement for product brochures containing chemical, pharmaceutical, pre-clinical pharmacological and toxicological data and, where applicable, human or animal pharmacological and clinical data with the medicine concerned was estimated to be 28% across the NRAs. Similarly, a 24% implementation level was noted across NRAs for supply history.

Implementation of other additional requirements

Assessing if a registered alternative or the registered option has not been imported in the past six months occurs in 48% of the NRAs, and 16% require a dossier to be submitted. Only 12% implementation level was observed on the requirements for inclusion in the essential medicines list (EML), and 27% implementation of requirements for a justification for an unregistered medicine. The level of implementing the requirement for restriction to emergencies, disease outbreaks, neglected disease and shortages was estimated to be 22% across the NRAs.

Implementation level by country

The overall level of implementation of the legal provisions for the importation of medicines across all the NRAs in SADC was estimated to be approximately 44%, ranging from 4% to 55%, while that for the comparators Canada and the United Kingdom was estimated to be approximately 81% and 85%, respectively (Figure 1).

Discussion

To our knowledge, this is the first study to explore the regulations and requirements for the importation of unregistered medicines and receiving donations in the SADC region. Thirteen out of the 15 SADC NRAs were estimated to be below 50% implementation level compared to above 80% for the two reference NRAs. All the SADC NRAs had a score of less than 60%. The wide-ranging implementation index scores also confirm the varying regulatory capacities within the region. Our results show that the SADC countries have not fully implemented most of the expected risk-based requirements for approving requests for importing unregistered medicines. The legislation and guidelines in these countries were not meeting minimum requirements set out in the WHO guideline on import procedures for medical products. Such procedures included risk-based testing, an inspection of consignments, among others (19).

Our study focused on the regulation of unregistered medicines, an area often neglected and not fully addressed in ongoing efforts to strengthen regulatory systems. Nonetheless, the results are consistent with previous reports; for example, the estimates that only 30% of NRAs among its Member States can effectively and efficiently regulate medical products in their countries(30). The results are also consistent with other studies that observed that legal frameworks lacked or were fragmented in most African countries (2)(2, 6). Additionally, some studies have shown that implementing medicines control regulation on the importation, use, and reporting of adverse drug reactions in developing countries is by far still too low compared to the levels in high-income countries (31, 32). As a result, inadvertently, NRAs in SADC, or similar settings, allow the importation of medicines whose quality is unknown and not being assessed.

SADC is a region with diverse countries across several dimensions, for example, population sizes, geographical sizes, the size of the pharmaceutical market, economic levels, and regulatory capacities. The study, therefore, encompassed many different factors, and results can be generalized to countries in Africa or similar settings. The GBT is considered a well-established tool through a robust process and applied globally. Therefore, the indicators used in the study are considered fairly validated. The basis for requirements used in the study was the requirements in WHO guidelines on import procedures of medical products, requirements for obtaining marketing authorization, and those set out by ML4 NRAs.

Given that unregistered medicines should be imported under exceptional circumstances and in some cases during emergencies, it may not always be feasible to implement all the requirements for granting marketing authorizations. Nonetheless, even in those circumstances, there remains a need to assess the medicines' quality, efficacy, and safety to protect public health based on a risk-based approach. Therefore, the results are based on comprehensive parameters that were considered sufficient to reflect the implementation of the regulatory function for exemptions.

Analysis of legislation and guidelines is fairly robust and objective; however, interpretation of the results should contextualize the different legislative systems across the countries and implications at the operational level when implementing the legislation provision in practice. Therefore, further studies analysing data on the importation of unregistered medicines and practices among the regulators are

required. In other words, the implementation index values alone may not directly indicate public health risk for individual countries. Other factors should be considered, for example, the extent to which unregistered medicines are supplied in the public sector, the supply chain of such unregistered products, and the quality assurance mechanisms implemented by the procurement agencies. For instance, United Nations Agencies and other international organizations largely procure WHO-prequalified products or products approved by WLAs. Therefore, while these products may be unregistered in the SADC NRAs, their quality, safety and efficacy are known and established (29, 30)

Conclusion

Implementing the standard guidelines for importing unregistered medicines in SADC is still very low, with an overall implementing index of 44% compared to the reference NRAs with index values above 80%. The region is heterogeneous, with a wide range among the NRAs. The low implementation levels of recommended standards for unregistered medicines increase the risk of potentially exposing the population in the region to unsafe medical products of variable quality and effectiveness. The SADC countries should learn from other NRAs and implement a risk-based and more robust process for regulating unregistered medicines.

Declarations

Ethics approval and consent to participate

The study obtained approval to carry the study from the Joint Research Ethics Committee (JREC) For the University of Zimbabwe, Faculty of Medicine and Health Sciences (FMHS) and Parirenyatwa Group of Hospitals (PGH), (JREC – JREC/148/2021). Each participant provided informed consent to participate in the study. The study was performed while observing good clinical practices and in accordance with the Helsinki declaration.

Consent for publication

Not Applicable.

Availability of data and material

The study is yet to publish the data to the public. However, the data can be available upon request and approval from the corresponding author.

Competing interests

The authors declare that there is no conflict of interest.

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No funding was used for this study.

Authors' Contributions

A.N and L.G. were involved in conceptual development. A.N, B.N., I.M. and L.G. were involved in full proposal development. A.N and B.N were involved in data collection, management and analysis. A.N, B.N and L.G were involved in the interpretation and discussion of results. A.N and B.N were involved in coming up with the draft manuscript. All the authors have read and approved the manuscript.

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Figures

Figure 1

Relative Implementation Index (%) by country including examples of comparators from developed settings