REGULATORY WORK-SHARING INITIATIVE IN AFRICA

ZaZiBoNa, Past, Present and Future

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FOREWORD

The *pursuit of health* is one of mankind's oldest strivings, and the *right to health* is now enshrined as one of our generation's recognised human rights. Health, though, at an individual level, is the result of many factors interacting well at a systemic level.

A quality health care system requires quality practitioners interacting with patients in quality environments using quality medical products. A health system with quality practitioners and quality clinics and hospitals but without access to quality medical products is not a quality health care system. The people relying on such a health care system suffer and are denied their right to health.

The quality assurance of the medical products available to our health care systems is the role of national medical products regulatory agencies. Yet the ability of every national regulatory authority to assure the quality of the medical products in its jurisdiction is woefully lacking globally.

Even absent a pandemic, most agencies find the challenge of medical products regulation daunting. Thousands of medical products come onto the global market annually, but few agencies have the capability to assess these products thoroughly. The WHO has estimated that only one-quarter of its member states have agencies with at least a "stable, well-functioning, and integrated regulatory system". In most countries, underfunded and understaffed agencies struggle to meet basic regulatory tasks, let alone respond to a pandemic. Even more mature and better funded agencies find that they sometimes lack the resources they need to meet expectations.

One solution to this challenge: strengthening *reliance-based regulatory pathways* in which agencies rely on the extensive reviews and inspections conducted by trusted counterparts or decide to pool their resources to perform joint product assessments and inspections to better inform their own regulatory decision-making. Such reliance-based regulatory decision-making is now a 21st-century "best regulatory practice," enshrined in the WHO's "Good Reliance Practices" guideline.

In this book, Drs Sithole, Salek and Walker present an in-depth history and analysis of the efforts of national regulatory authorities in the southern African region to join together and pool their resources in a systematic and sustained way to help procedurally optimise and make more scientifically robust their oversight of proposed new medical products for their people. It is a success story many are trying to emulate in various parts of the world. But like all such efforts, there are always process improvements that need to be considered. Drs Sithole, Salek and Walker offer their perspective on approaches the leaders of the ZaZiBoNa initiative could consider, which could further improve their programme and their abilities to assure quality medical products in their individual national health care systems.

I hope many of the leaders of national regulatory authorities globally read Drs Sithole, Salek and Walker's work and integrate the successes of the ZaZiBoNa programme into their own – realising the truth of the old African proverb: *If you want to go fast, go alone, if you want to go far, go together!*

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PREFACE

The role of regulatory authorities in the health system is to ensure the quality, safety and efficacy of medical products. It is acknowledged that regulatory authorities are at times faced with challenges in executing this mandate. Challenges, such as limited resources and technical capacity, which may lead to delayed access to medical products by patients. To address these challenges, regulators are 'joining hands' and collaborating in areas such as the assessment of medical product applications and inspection of manufacturing plants. In addition, regulators are implementing reliance on the work or decisions of other regulators.

One such collaboration is the Southern African Development Community's collaborative medicines registration initiative, ZaZiBoNa. This initiative has been in existence since 2013, however, the last evaluation of the initiative was conducted in 2016. At the time, the initiative had a membership of only the four founding members and a few products had gone through the process. The ZaZiBoNa has since grown and all 16 SADC countries are members (9 active, 5 non-active and 2 observers). More products have been assessed and the number of applicants that have used the procedure has increased presenting an opportune time for the formal evaluation of the performance and regulatory review system.

This was achieved through a series of studies which culminated in the development of a number of recommendations. Robust individual member country processes contribute to a more effective and efficient ZaZiBoNa; therefore, the gaps in the regulatory review processes of the participating countries were identified and solutions proposed to strengthen these processes. Recommendations for the improvement of the current model of the ZaZiBoNa initiative were also made to address the challenges identified with the initiative particularly those around a lack of central tracking and coordination. The implementation of these recommendations will result in an immediate improvement to the effectiveness and efficiency of the initiative whilst a longer term solution is considered. Lastly, a new model, namely a centralised procedure has been proposed as well as the legal framework that would enable this and the additional considerations that need to be made by the decision makers in the member countries in order to implement this new model.

One of the authors has over 13 years of experience working with the regulatory authority in Zimbabwe and as such has an extensive knowledge of the regulatory environment in ZaZiBoNa. The other two authors have, over the past three decades, worked closely with the pharmaceutical industry, mature regulatory agencies and

those in the emerging economies to provide guidance and validated tools in order to enhance regulatory performance.

The authors were encouraged to produce this research in a format that would be accessible by a wider audience as this vital piece of work has provided some recommendations which are key to the success of the ZaZiBoNa initiative in its next phase. It is hoped that this work will aid in bringing transparency to the ZaZiBoNa process encouraging the pharmaceutical industry to use the procedure. In addition, we hope that these studies together with the methodologies and tools used as well as the recommendations made, may be of value to other regional harmonisation initiatives serving as a blue print for enhancing the regulatory review process and patients' access to new medicines.

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CHAPTER 01

OVERVIEW OF THE ZaZiBoNa INITIATIVE

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SUMMARY

- The Southern African Development Community (SADC) collaborative medicines registration initiative (ZaZiBoNa) is a successful regional work sharing initiative on the African continent.
- Statistics of the work carried out by the initiative are available in the literature but there has not been a critical review of the process including an analysis of factors contributing to the success of the initiative or conversely those negatively affecting performance.
- The aim of this chapter was to review the history of the ZaZiBoNa initiative as well as reflect on what had been realised in its eight years of operation and what still needed to be achieved.
- Statistics, meeting records, terms of reference and various unpublished documents associated with this initiative were reviewed and the literature publicly available was also included in this review.
- The initiative has grown from the 4 founding members to all 16 countries in SADC participating in different capacities
- Over 333 products had been assessed and 54% of these received a positive recommendation while the remaining 46% received a negative recommendation or were withdrawn from the process. Ninety four and a half per cent of these products were generics, 4% were biological / biosimilars and 1.5 were new chemical entities. Forty-eight GMP inspections and 30 desk reviews had been conducted
- This initiative had achieved an annual median time to recommendation of 13 months or less since its inception for all the years excluding 2018.
- Antivirals for systemic use followed by antibacterials for systemic use and agents acting on the renin angiotension system were the top 3 pharmacological classes of products submitted to the initiave.
- The successes of the ZAZIBONA initiative could be attributed to leadership commitment, a clear vision and governance structure providing direction, and a clear, documented operating model, processes and objectives defined from the onset of the initiative.
- Closure of the gaps identified in the submission process, review templates, tracking and differences in implementation of the ZaZiBoNa recommendation in the participating countries will further strengthen this initiative.
- The ZaZiBoNa initiative played an important role in improving the regulatory review processes in the individual participating countries, but its success also depended on the very same country processes.

- In view of its mutualistic relationship, there was a need to assess the regulatory review process of the initiative as well as the individual participating countries using established and validated tools and the outcomes to be compared. Such an approach would enable the identification of differences which may be hindering the performance of the initiative.
- In addition, an evaluation of the regulatory review process of the SADC MRH implementing agency, Medicines Control Authority of Zimbabwe, needed to be conducted as it is the coordinating country for the ZaZiBoNa initiative. Furthermore the comparison of the coordinating country's process with mature agencies of comparable size would serve as a benchmark that other countries in the region could use to measure themselves and from which to learn.
- Although some feedback on the performance of the initiative has been sought from applicants through stakeholder meetings in the past, there had not been a comprehensive and structured evaluation of the work sharing programme to inform its future direction. Therefore, there is a need to evaluate the initiative's operational effectiveness and efficiency.

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INTRODUCTION

The regulation of medicines makes a contribution to public health by ensuring that medicines are safe, effective and of good quality. The capacity to regulate medicines varies across the African continent with all countries having either a regulatory agency or a unit within the ministry responsible for health dealing with issues relating to the regulation of medicines except Sarhawi Republic (Ndomondo-Sigonda, 2017). The WHO reports that many of the regulatory authorities for medical products on the African continent are under-resourced affecting the availability of medical products to the population (WHO, 2019a). Countries in Africa, along with other low to middle income countries of Asia and Latin America, bear a significant proportion of the global burden of disease (de-Graft Aikins et.al, 2010). The continent is also faced with the threat of substandard and falsified medicines (Roth et.al, 2018) due to weak regulatory systems. To address this, a great deal of work has been carried out to strengthen regulatory systems in Africa. One of the responses to address weak regulatory systems was the formation of the African Medicines Registration Harmonisation (AMRH) initiative which encouraged harmonisation of the fragmented regulatory systems in the continent.

The AMRH is a programme of the African Union established in 2009 and implemented as part of the Pharmaceutical Manufacturing Plan for Africa (PMPA) to address challenges faced by national medicines regulatory authorities (NRAs) in Africa. These include ineffective legislative frameworks, long registration times and inadequate technical capacity (NEPAD, 2016). Pharmaceutical companies have cited country specific requirements as a barrier to medicines registration and supply in Africa (Narsai, 2012). Another goal of the AMRH is to reduce differences in regulatory requirements between countries encouraging a harmonised regional approach as opposed to a country specific approach (Ndomondo-Sigonda, 2017). The AMRH works through regional economic communities (RECs), for example, the East African Community (EAC), the Economic Community of West African States (ECOWAS) and the Southern African Development Community (SADC) (Ndomondo-Sigonda et.al, 2018; Caturla Goñi et.al, 2016)**.** (Figure 1.1). There are five RECs recognised by the African Union (AU) and it should be noted that a number of countries belong to more than one regional economic block (Ndomondo-Sigonda et.al, 2018). Through the work of the AMRH, some of the RECs have developed regional policies and guidelines for the regulation of medicines, and reduced timelines for registration. Seventeen countries have adopted or adapted the African Union (AU) model law (Ndomondo-Sigonda, 2019). The AMRH was also responsible for establishing a task force to develop a legal and institutional framework for the establishment of

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the African Medicines Agency (AMA) which is expected to address the challenges faced by the African continent in medicines regulation.

Whilst a great deal of success has been realised by the regional medicines harmonisation initiatives, a gap exists in knowledge of the effectiveness and efficiency of these initiatives as well as the alignment of the regulatory review processes and resources of the individual participating countries. It is important to fill this gap as lack of information on the procedure makes it challenging for applicants that want to submit products to these initiatives. In addition, any existing ineffectiveness and inefficiencies result in delayed access to quality assured medicines by patients. Sigonda et.al (2018) recommended that a critical review of these joint review processes be undertaken to evaluate the efficiency and effectiveness as well as the decision-making processes at a country level. This research, therefore, aims to evaluate the regulatory review process of ZaZiBoNa, the Southern African Development Community (SADC) Collaborative Medicines Registration initiative (ZaZiBoNa), and that of the participating countries with the goal to enhance the evaluation process and operating model thereby improving patients' access to life-saving medicines.

THE ZAZIBONA INITIATIVE
History and Inception

The Southern African Development Community (SADC) is a regional economic community on the African continent consisting of sixteen countries. The 16 countries are Angola, Botswana, Comoros Islands, Democratic Republic of Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Eswatini, United Republic of Tanzania, Zambia, and Zimbabwe (SADC, 2019a) (Figure 1.1). Countries in the SADC region have varying regulatory capacities (Dube-Mwedzi et.al, 2020; Kamwanja et.al, 2010: Sithole et.al, 2021a; Sithole et.al 2021b). In 1999 the SADC Protocol on Health was developed to which the Heads of State or Government agreed in Article 29 that member states shall 'cooperate and assist one another in the harmonisation of procedures of pharmaceuticals, quality assurance and registration' (SADC, 1999). The Protocol on Health came into force in 2004 after the launch of the Pharmaceutical Programme which was intended to address the issue of uneven access to affordable, safe and good quality medicines in the region. At that time the prevention and treatment of diseases of public health priority were hindered by a lack of standardised legislation on medicines use (SADC, 2019b). The Pharmaceutical programme is implemented through the SADC Pharmaceutical Business Plan which is reviewed and renewed periodically. One of the strategic priority areas for the 2015 –

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2019 period was the strengthening of regulatory capacity by supporting and actively encouraging joint inspections and registrations among Member States (SADC, 2015).

The ZaZiBoNa collaborative medicines registration initiative was founded in 2013 by four countries namely Zambia, Zimbabwe, Botswana and Namibia with technical support from the World Health Organisation (WHO) Prequalification Team (CIRS, 2017; Gwaza, 2016; MCAZ, 2019). The initiative has been supported by partners such as the United Kingdom Department of International Development (DFID) which funded the Southern African Regional Programme on Access to Medicines and Diagnostics (SARPAM), WHO, SADC, African Union Development Agency-NEPAD, Bill and Melinda Gates Foundation and the World Bank. The acronym ZaZiBoNa was derived from the first two letters of the four founding countries i.e ZAmbia, ZImbabwe, BOtswana and NAmibia (WHO, 2019b). The name ZaZiBoNa has been maintained even though the initiative has grown to more than just the four founding countries because it has a special meaning in one of the local languages in Zambia (Nyanja) which is 'to look to the future' (WHO, 2019b). The initiative was formed to address common challenges faced by the countries, for example large backlogs of pending products, high staff turnover, long registration times, inadequate financial resources and limited capacity to assess certain types of products such as biologicals and biosimilars. Acknowledging these common challenges, the heads of agencies agreed to develop a work sharing arrangement to meet the following objectives which included 'a reduced workload,

Figure 1.1. Map of the Southern African Development Community (SADC) region

reduction in timelines to registration, the development of mutual trust and confidence in regulatory collaboration and to provide a platform for training and collaboration in other regulatory fields' (CIRS, 2017; Gwaza, 2016; ZaZiBoNa, 2013). In establishing these objectives, the ZaZiBoNa initiative sought to make efficient use of limited resources to ensure the timely access to quality-assured medicines by the public in the SADC region whilst at the same time building regulatory capacity of the national regulatory authorities (NRAs).

The first assessment session was held in Windhoek, Namibia in October 2013 and this marked the beginning of the collaborative initiative which looked at products common to the four countries which were already pending in the backlog initially but expanded over time to products submitted prospectively. In 2014, the ZaZiBoNa initiative was formally endorsed and adopted by the SADC Ministers of Health (SADC, 2014). Since then, the initiative has grown and all the 16 SADC member countries are participating either as active, non-active participants or observers based on their internal capacity to conduct assessments and inspections (Sithole, 2019; Sithole 2021b). The ZaZiBoNa initiative was later absorbed by the SADC Medicines Registration Harmonisation (MRH) project launched in 2015 which was being funded by the World Bank for the period 2018 - 2021. In addition to strengthening and expanding areas of technical cooperation among member states' national regulatory authorities (NRAs) through initiatives such as ZaZiBoNa, the SADC MRH project also has the following objectives to: to ensure that at least 80% of member states have NRAs that meet minimum standards; to ensure regional harmonization of medicines regulatory systems and guidelines; to facilitate capacity building of medicines regulatory authorities in member states through implementation of quality management systems (QMS); develop and implement national and regional integrated information management systems (IMS); and facilitate decision making and sharing of knowledge among member states and stakeholders' (SADC, 2011). Various activities are ongoing currently to fulfil these objectives, for example, most SADC countries have conducted self-benchmarking or formal benchmarking of their regulatory systems using the WHO global benchmarking tool (GBT) (Sillo, 2019). Regional guidelines for variations, biosimilars and labelling are under development to add to the existing SADC guidelines and an audit of skills in the region using the WHO global competence framework for regulators was conducted.

Legal Position

The ZaZiBoNa initiative is not a legally constituted regulatory initiative hence it does not make decisions on the registration or rejection of products (Gwaza, 2016).

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Participation is based on the signing of a memorandum of agreement entitled "the NRA Agreement to Participate" by interested countries. However, a condition for active member status is the availability of legislation enabling or mandating registration in the participating country, registration guidelines equivalent to the SADC Medicines Registration guidelines or the WHO guidelines and in-house capacity to conduct assessments and good manufacturing practices (GMP) inspections (ZaZiBoNa, 2013; SADC, 2014). In view of this legal status, the ZaZiBoNa initiative does not at present allow for the centralised submission of dossiers or payment of fees directly. It operates in an advisory capacity and provides recommendations on the quality, safety and efficacy of products. This arrangement has the advantage of allowing rapid buy in from participating countries as they do not lose their revenue or sovereign decision-making ability. However, some of the challenges presented later in this chapter stem from a lack of a centralised procedure for submission of applications for registration and the communication of questions/queries with applicants.

Organisational Structure

The Heads of Agencies serve as the governance structure for the initiative (Gwaza, 2016; ZaZiBoNa, 2015a) and they report to the SADC Regulators Forum and SADC Health Ministers while the SADC MRH coordinator reports to the Heads of Agencies. The assessors and inspectors each have a coordinator who reports to the SADC MRH project coordinator. The assessors and inspectors from each country are represented by a country focal person. The assessment coordinator, GMP inspections coordinator and SADC MRH project coordinator are seconded by the Medicines Control Authority of Zimbabwe (MCAZ) as the SADC MRH implementing agency. The organisational structure is presented in Figure 1.2.

Participating Countries

The participation in this initiative is voluntary and any SADC country wishing to participate submits an application/request to join to the Heads of Agencies.

Countries participate in the work sharing initiative either as active or non-active members. To be granted active member status, a country should have legislation mandating the registration of medicines as well as in-house capacity to perform assessments or GMP inspections as previously stated. Countries that do not meet these criteria are granted non-active member or observer status as they do not actively contribute to the assessment of registration dossiers and/or GMP inspections. The determination of the applicable status for countries is made by the Heads of Agencies. The countries in SADC that are active members of ZaZiBoNa as well as the year they joined the initiative are presented in Figure 1.3.

Figure 1.2. Organisational Structure of the SADC collaborative medicines registration initiative (ZaZiBoNa)
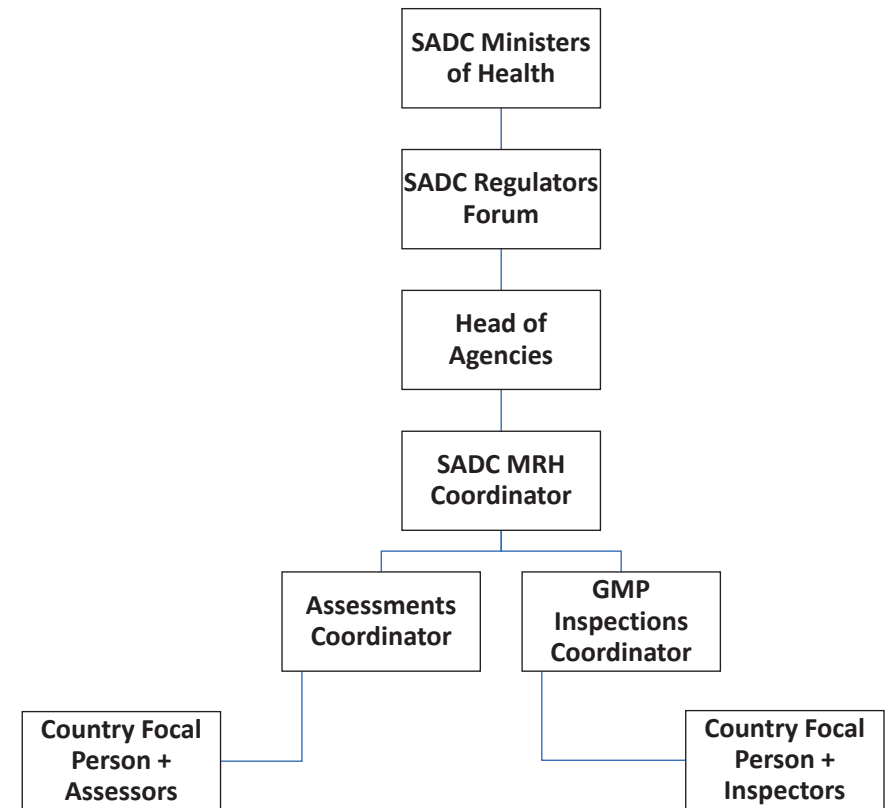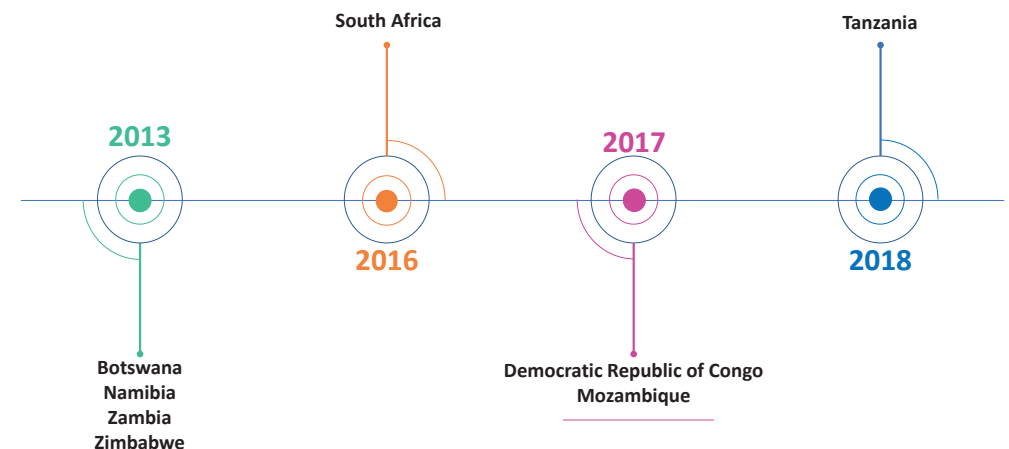

Figure 1.3. Countries participating in ZaZiBoNa as active members and the date of joining the initiative

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Angola, Seychelles, Swaziland, Madagascar and Comoros Islands participate in the initiative as non-active members while Lesotho and Mauritius participate as observers.

Scope of Products Assessment

The following products are eligible for assessment under the ZaZiBoNa initiative, all essential medicines, medicines used in the treatment of the ten priority disease conditions for SADC (i.e HIV/AIDS, tuberculosis, malaria, acute respiratory infections, diarrhoea, diabetes, pneumonia, cardiovascular, cancer, obstetrics, gastroenteritis and colic), reproductive health products, products included in the List of UN Commission for Live-Saving Commodities for Women and Children (Gwaza, 2016; ZAZIBONA, 2013). Requests can be made for consideration of medicines that do not fall under the stated criteria but are important from a public health perspective.

The WHO prequalified products are not eligible for consideration under ZaZiBoNa as most SADC countries are participating in the WHO prequalification collaborative registration procedure (WHO, 2019c) in which countries rely on assessments and inspections conducted by the WHO prequalification team (PQT) enabling registration in 90 days after the verification process is completed. However, the WHO SRA collaborative registration procedure can be used to accelerate assessment of products already approved by globally recognised regulatory agencies such as the European Medicines Agency (Caturla Goñi, 2016; Vaz A, 2022; Luigetti, 2016; WHO, 2019d).

Operating Model

Assessments

Assessment sessions/meetings are held quarterly in the participating countries on a rotational basis meaning that each country will at some point host an assessment session. A country hosting the assessment session is responsible for covering meeting expenses and that is how countries contribute to the initiative. SADC, WHO PQ, ICH and EMA guidelines are used for the assessments.

There is no centralised submission of dossiers to ZaZiBoNa, therefore the following steps are followed for a registration application to be assessed by the initiative (ZaZiBoNa, 2015b) (Figure 1.4).

1. The applicant submits the same application for registration (dossier) including payment of the appropriate fees to each participating country in which they wish to market their product. At this stage, the applicant also expresses interest for their product to be assessed 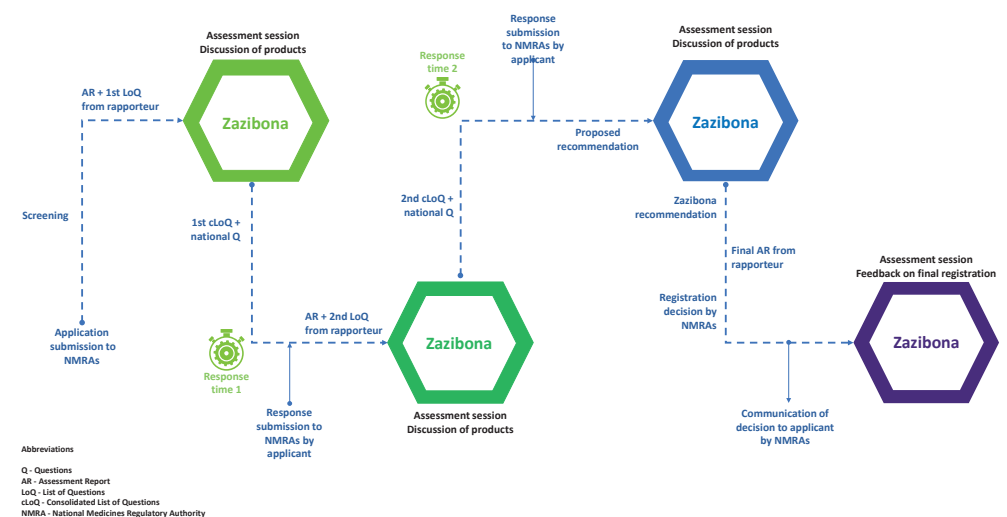by ZaZiBoNa. At present, the dossier must be submitted to at least two (2) active countries to be eligible for consideration under ZaZiBoNa.

2. The assessments coordinator assigns one country to conduct the first review (rapporteur) and a second country to conduct second review (co-rapporteur) of the product. The WHO is responsible for performing a quality assurance check of the final reports generated by the rapporteur and co-rapporteur

3. Upon request, the applicant submits a signed letter of consent to the rapporteur to allow consideration of their product under the initiative. The applicant is informed of the countries participating in the initiative before giving consent.

4. Assessments are carried out in the countries before discussion at the quarterly assessment sessions.

5. Once the assessment is complete, usually after two cycles, a recommendation on the quality of the product is made to countries who then make the final decision on registration or rejection of the product after consideration of any country specific requirements.

Good manufacturing practices (GMP) inspections

At present, the ZaZiBoNa GMP inspections are conducted on a cost recovery basis to support product registration. Capacity building for participating member states is supported by development partners. The WHO PQT guidelines are used for inspections and GMP site visits are conducted four times a year i.e once a quarter.

Figure 1.4. The ZaZiBoNa review process

Abbreviations

Q - Questions
AR - Assessment Report
LoQ - List of Questions
cLoQ - Consolidated List of Questions
NMRA - National Medicines Regulatory Authority

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Two manufacturing facilities are inspected during each visit therefore a total of 8 inspections are conducted in a year.

Sites in well-resourced markets like the USA, EU, Australia, Japan and Canada are normally exempt from GMP inspections. Desk reviews may be conducted instead of actual inspections for sites that would have been inspected by stringent authorities and the WHO PQT. The scheduling of inspections and the coordination of inspectors from different countries is carried out by the SADC MRH implementing agency MCAZ. The team inspecting one site is, normally, comprised of three people, a lead inspector, a co-inspector and an observer, each from a different country. The lead and co-inspector roles are rotated among the participating countries that have competent GMP inspectors (Dengu, 2019). The following steps are followed for a manufacturing site to be inspected under ZaZiBoNa;

1. The assessments coordinator liaises with the GMP inspections coordinator for products that have been assessed and the sites requiring inspection
2. The GMP inspections coordinator liaises with the manufacturer to schedule an inspection and quote the applicable inspection fees
3. The GMP inspections coordinator assigns a lead inspector and co-inspector from the countries to which the product has been submitted and in accordance with the pre-agreed inspectors' rotational calendar
4. An inspection is conducted and a final report is prepared in consultation with the rest of the inspectors in ZaZiBoNa. A final compliance status is reached collaboratively after submission and consideration of corrective and preventive actions (CAPAs)
5. The final decision is then communicated to the assessment coordinator for consideration when the final recommendation is made for the product.

Financing

The initiative is funded through contributions from participating countries, GMP inspection fees and support from partners such as, SADC, United Kingdom Department of International Development (DFID) funded Southern African Regional Programme on Access to Medicines and Diagnostics (SARPAM), World Health Organisation (WHO), Bill and Melinda Gates Foundation, AUDA NEPAD agency and World Bank. The initiative has adopted a frugal financial model which will ensure sustainability in the future even in the absence of partner support. It was important for the Heads of Agencies from the onset that countries invest in the initiative themselves before speaking of partner support.

Timelines and statistics
Assessments

The initiative has been in operation now for eight years. As of 31 December 2021, 36 assessment sessions and twenty training sessions have been held. The Heads of Agencies have held two meetings every year. A total of 333 applications have been assessed and of these, 283 have been finalised and 50 are pending. Fifty-four per cent (153) of the applications finalised received a positive recommendation whilst the remaining 46% received either a negative recommendation or were withdrawn from the process before conclusion. Withdrawal could be initiated voluntarily by the applicants or by the initiative when the applicant fails to provide a response within the stipulated time. Three hundred and fifteen (94.5%) of the applications received were generics while 5 (1.5%) were innovator products/new chemical entities and 13 (4%) were biologicals/biosimilars.

When classified according to the WHO Anatomical Therapeutic Classification (ATC) system's second level, that is, active ingredients according to pharmacological or sub-therapeutic group, the highest number of applications were received under the following five groups: antivirals for systemic use (16%); antibacterials for systemic use (12%); agents acting on the renin-angiotensin system (11%); antineoplastic agents (10%); and antiepileptics (7.2%) (Figure 1.5).

The target median time to a recommendation / scientific opinion is 9 months (inclusive of the manufacturer / applicant's time to respond to queries). The actual performance for the years 2014 to 2021 is displayed in Figure 1.6.

The times displayed are inclusive of the time taken by the applicants to respond to queries. The times displayed do not include the time taken in countries with the dossier i.e before assessment under ZaZiBoNa or the time taken by countries to register or refuse a product after the ZaZiBoNa recommendation is given. In 2014 the median time to recommendation was 5 months (3–11.6 months), in 2015 it was 9 months (4.3–16.05 months), in 2016 it was 9 months (5–24 months), in 2017 it was 9 months (4–24 months), in 2018 it was 18 months (5–40.4 months), in 2019 it was 12 months (5.1– 26.55 months), in 2020 it was 13 (1–32 months) and in 2021 it was 6 months (4 – 12 months) (Figure 1.6). The long timelines in 2018 and 2020 can be attributed to challenges highlighted later in this chapter and a limitation on resources due to the Covid-19 pandemic, respectively.

Figure 1.5. Products received by the ZaZiBoNa initiative (2013-2021) classified using the WHO Anatomical Therapeutic Classification (ATC) system (2nd level)
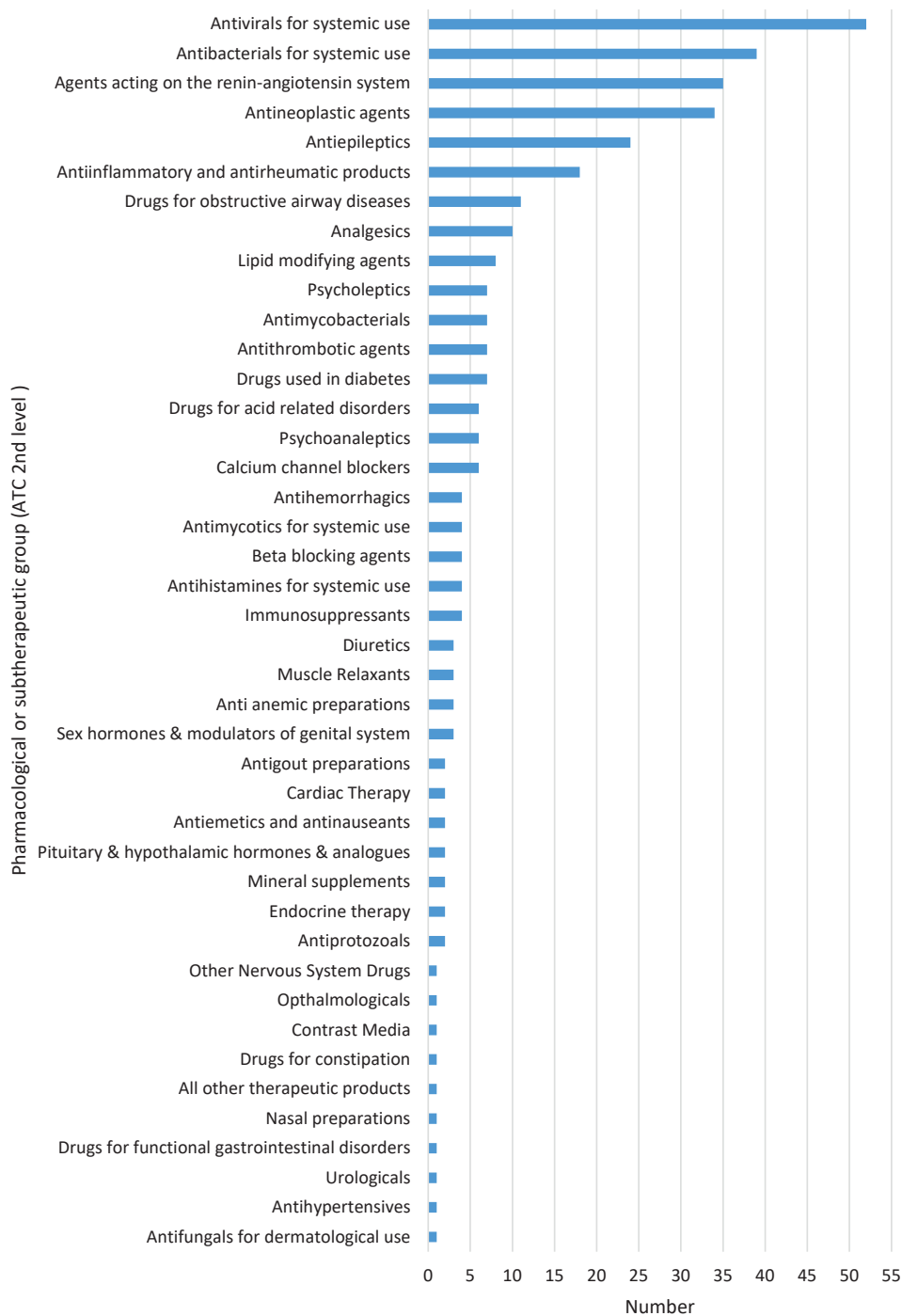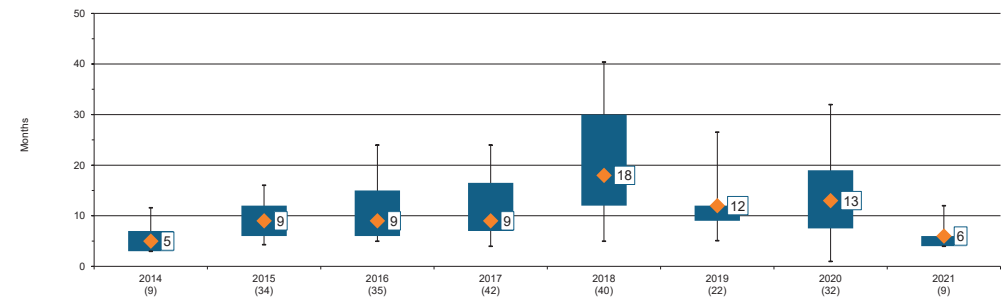

Figure 1.6. Trend in median time to recommendation (2014-2021)

Data are shown for applications that were given a recommendation (positive and negative) between 2014 and 2021 (inclusive)

(n) = number of products given a recommendation.
◆ = Median. Box: 25th and 75th percentiles. Whiskers: 5th and 95th percentiles.

GMP inspections

As of December 2021, 48 manufacturing sites have been inspected and 30 desk reviews conducted. An inspection of one clinical research organisation (CRO) was conducted with technical assistance from the WHO. The number of desk reviews performed increased significantly because physical inspections could not be carried out due to travel restrictions imposed as a result of the Covid-19 pandemic. In addition to the inspection of manufacturing facilities, policy meetings for managers are held annually, GMP technical working group meetings are held quarterly and inspectors' meetings are held bi-annually (Dengu, 2019). The time taken from the start of a GMP inspection to conclusion after review of the corrective and preventive action (CAPA) is approximately 90 days.

Successes

The story of ZaZiBoNa is a story of leadership commitment, determination, consistency and ownership. A number of lessons have been learnt along the way as the initiative seeks to continuously improve. The statistics presented are a testament that work sharing is possible and that it is being conducted successfully. Through ZaZiBoNa, registration has been much shorter than it would normally take in most of the individual countries (Keyter et.al, 2018; Sithole et.al 2020, Sithole et.al 2021b). The initiative is meeting its objectives to reduce the time to registration, build capacity of countries, share limited resources for maximum output and build trust among regulators by creating a platform for information sharing. The initiative has created guidelines for assessors, various templates, for example, a specific template

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for the review of batch manufacturing records, and standard operating procedures (SOPs) for assessments and GMP inspections including desk reviews to harmonise the quality of work produced.

Challenges

Although the initiative has had successful outcomes, a number of challenges have also been identified in the past few years since its inception (Mahlangu, 2018).

Country processes

As previously described, each country makes a sovereign decision on the registration or rejection of a product once the technical assessment of a product is completed and a recommendation made at ZaZiBoNa (Gwaza, 2016). A gap in the completion of the process at a country level previously identified during stakeholder consultation was that query letters were either not sent or sent late resulting in applicants receiving communication at different times from different countries for the same product (Mahlangu, 2018, ZaZiBoNa, 2017). The effect of this was that the time to a recommendation was longer than the targeted time. This has been a challenge as applicants lose out on the major benefit of having dossiers assessed by the initiative which is to gain access to various markets at the same time (ZAZIBONA, 2019). This challenge has largely been as a result of differences in the regulatory review processes of participating countries as well as the lack of clarity on the process to be followed at a country level for ZaZiBoNa products i.e how to submit dossiers to the programme and follow up in the different countries to which the product would have been submitted.

Tracking systems

Another gap identified was that in some instances the applicants were not responding to queries on time thereby lengthening the total time to recommendation and by extension registration (ZaZiBoNa, 2017). This gap points to a lack of adequate automated tracking systems in participating countries and this is because most of the countries are using manual records and tracking systems.

Regulatory review times

Countries in the ZaZiBoNa initiative face the common challenge of long registration review times due to an increasing volume of applications received, significant backlogs (Keyter, 2018), an inadequate number of assessors, inadequate financial resources and limited capacity to assess certain types of products e.g biological / biosimilars (Sithole et.al, 2021a; Sithole et.al, 2021c; Gwaza, 2016).

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Review templates

Although the ZaZiBoNa initiative currently mainly focuses on generics and has review templates for quality and bioequivalence, Gwaza (2016) recommended expansion of the current model to include reviews of new medicines for diseases endemic to Africa. The European Medicines Agency (EMA) provided a training on biosimilars to ZaZiBoNa in 2018 and a gap identified as a result of the training was the need to develop templates for assessment of Biosimilars, Biologicals and New Chemical Entities (NCEs) (ZaZiBoNa, 2018).

Submission process

Submission of applications to ZaZiBoNa is not centralised and the process is not clearly detailed in some agencies which has been challenging for applicants. In addition, country specific requirements such as labelling are problematic for applicants. However, a regional guideline on labelling is currently under development. Some applicants submit different dossiers to countries when the requirement of the work sharing initiative is that the same dossier should be submitted to all countries in which registration is sought.

## ELEMENTS OF PROGRESSIVE REGULATORY PROCESSES
Standardised Templates

Historically, regulatory agencies have used some form of documents to record their review. Such a document has often been referred to as a checklist and often offering limited information. More recently, regulatory authorities involved in the evaluation of new medicines have recognized that to have a structured, systematic approach incorporated into an assessment template offers major advantages in order to support their decision as well as ensuring transparency. Transparency, consistency and uniformity in the assessment of medicines and decision-making are the hallmark of a mature and progressive regulatory process. There is now an ever greater need for a universal standardized template as increasingly there is a move towards collaboration and regulatory agencies will be relying on one another's review processes and outcome. Currently regulatory agencies may make different decisions despite having the same data on new medicines submitted to their authority. This leads to increased pressure to improve agency transparency and accountability and therefore requires them to establish an appropriate structured and systematic approach to the assessment of such products to facilitate the review (Walker et.al, 2015).

Benefit-Risk Assessment

The use of a systematic, structured and transparent approach for the benefit-risk assessment of new medicines is in line with Good Review Practices (WHO, 2015). The implementation of a documented benefit-risk assessment framework would give confidence to the decision of the regulator to either reject or approve new medicines. There is a consensus regarding the importance and need for benefit-risk assessment by regulators, the pharmaceutical industry as well as patients, however the methodologies proposed for conducting benefit risk assessment vary (Mt Isa, 2016). Various frameworks exist and have been used in well-resourced regulatory authorities for the benefit-risk assessment of medicines. The EMA published a reflection paper on benefit risk assessment and subsequently developed a framework which they entitled the EMA PrOACT-URL. The USFDA performs a structured benefit-risk assessment as part of their approval process (5-step framework). In addition, the pharmaceutical industry developed a benefit-risk framework called the PhRMA BRAT (Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team) and the BRAIN (Benefit-Risk Assessment in New and Old Drugs) (Mt-Isa, 2016; Walker et.al, 2015). The Universal Framework for the Benefit-Risk Assessment of medicines (UMBRA) (Figure 1.7) was developed by the Centre for Innovation in Regulatory Science (CIRS) in conjuction with regulators and the University of Hertfordshire (Walker et.al, 2015) and subsequently tested by 4 regulatory authorities that made up the Consortium on Benefit Risk Assessment (COBRA) (McAuslane, 2017) which later the acronym was changed to ACSS. Such an approach described above provides a consistent, transparent and systematic methodology which has shown to be of value in a work sharing environment (McAuslane, 2017).

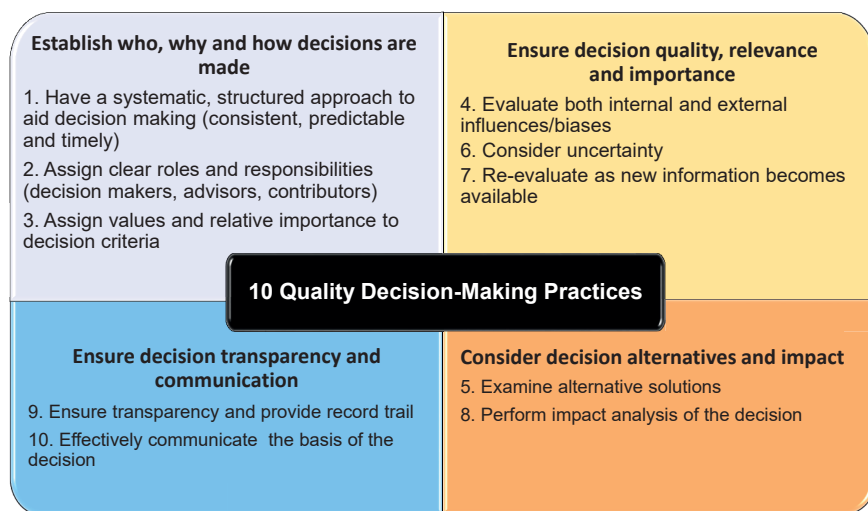**Figure 1.7. UMBRA Benefit-Risk Framework**
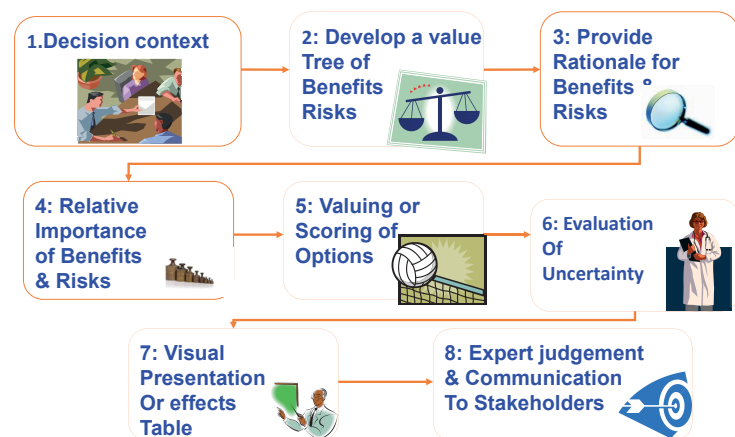
DISCUSSION

Differences in the regulatory review process in countries can hinder the performance of a work sharing initiative. There is a need to evaluate the regulatory review process in ZaZiBoNa as well as the review processes in the individual participating countries using established and validated tools and to compare the outcomes. This will support the standardisation of country processes enabling improvement and capacity building where required. In addition to identifying the differences in the processes in countries currently participating in the ZaZiBoNa initiative, the review of regulatory processes will enable low to middle income countries (LMIC) to benchmark with similar countries in terms of processes, resources and capacity, something which has not been possible to do in the past (Gwaza, 2016).

The use of manual tracking systems in the countries is a major contributor to protracted timelines for registration. Ideally, tracking should be automated and carried out in real time. The use of available tracking tools through adoption or adaptation will make it possible to track deadlines for response to queries and enable countries to report both the time taken by the applicant (clock start) as well as the time taken by the agency (clock stop). Another advantage is that countries will be able to accurately and regularly report and publish statistics of their performance against target timelines. This transparency will aid achievement of one of the goals of the SADC MRH programme which is for member states to attain either maturity level 2 or 3 using the WHO Global Benchmarking Tool depending on the current capacity of the agency.

Due to the high cost of biologicals and an increasing burden of non-communicable diseases like cancers in low to middle-income countries, especially in sub-Saharan Africa, there is a growing demand for biosimilars (Bennett, 2018). Consequently, there is an increase in the number of applications for the registration of biosimilars received in ZaZiBoNa countries and most of these are not approved anywhere else in the world except in the country of origin. With the majority of patients paying for medication out of pocket, biosimilars provide an opportunity to dramatically reduce drug acquisition costs. This is likely to help improve patient access in countries where exposure to originator compounds is heavily restricted in part by price (Barker, 2018). However, many oncologists in the SADC region are reluctant to consider biosimilars as a treatment option for their patients and the same has been observed with oncologists in Europe (Weise, 2012). Access to unbiased information on registered biosimilars is important for physicians to make informed and appropriate treatment choices for their patients (Weise, 2014). ZaZiBoNa countries should explore developing a structured, formalised and quantitative approach to benefit-risk assessment,

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Figure 1.8. The ten quality decision-making practices

Establish who, why and how decisions are made	Ensure decision quality, relevance and importance
1. Have a systematic, structured approach to aid decision making (consistent, predictable and timely) 2. Assign clear roles and responsibilities (decision makers, advisors, contributors) 3. Assign values and relative importance to decision criteria	4. Evaluate both internal and external influences/biases 6. Consider uncertainty 7. Re-evaluate as new information becomes available

10 Quality Decision-Making Practices

Ensure decision transparency and communication	Consider decision alternatives and impact
9. Ensure transparency and provide record trail 10. Effectively communicate the basis of the decision	5. Examine alternative solutions 8. Perform impact analysis of the decision

including the assignment of relative importance to benefit and risk considerations. The enhanced benefit risk assessment framework could serve as a template for product reviews, as well as a vehicle for explaining the basis for ZaZiBoNa's regulatory decisions in product approvals. This in turn will encourage greater transparency and public availability of non-confidential regulatory information (for example, decisions, review reports and/or summaries, review processes) in line with the Good Review Practices. A common approach to benefit risk decision making is mandatory in facilitating any work-sharing model (McAuslane, 2017). Other Good Review practices such as quality decision making should also be explored using the ten quality decision-making practices (Figure 2.7) as a standard to improve decision making practices by the assessors as well as in the member countries of the initiative.

It has been proposed that the RECs, for example ZaZiBoNa, will serve as technical working groups under the African Medicines Agency responsible for assessing new chemical entities (NCEs) being launched in Africa for the first time as well as complex products such as biologicals and biosimilars. Implementation of the proposals made above will help to identify any gaps or areas needing improvement to enable the initiative to efficiently execute this mandate.

CHAPTER 02

REGULATORY REVIEW PROCESS OF THE SOUTHERN AFRICA DEVELOPMENT COMMUNITY MEDICINE REGISTRATION HARMONIZATION (SADC MRH) IMPLEMENTING AGENCY ZIMBABWE (MCAZ)

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SUMMARY

- Unlike high-income countries, there is limited information in the public domain on the regulatory review/assessment systems and performance of LMIC
- The aims of this study were to assess the current regulatory review process of the Medicines Control Authority of Zimbabwe (MCAZ), identify key milestones and target timelines, evaluate the overall performance from 2017–2021, identify good review practices, evaluate the quality of decision-making processes, and identify the challenges and opportunities for improvement.
- Data identifying the milestones and overall approval times for all products registered MCAZ from 2017 – 2021 were collected and analyzed.
- The MCAZ successfully implements three types of review models in line with international standards by conducting a full review of quality, safety, and efficacy data for generics and biosimilars not approved by a reference agency, an abridged review for products approved by a reference agency and a verification review for World Health Organization prequalified products under the collaborative registration procedure.
- The majority of applications approved during the study period were generics manufactured by foreign companies followed by NCEs, biologicals/biosimilars and generics manufactured by local companies. All approved NCEs, biologicals and biosimilars were sponsored by foreign companies and there were no locally sponsored NCEs, biologicals or biosimilars.
- The longest median approval time observed during the study period was 844 calendar days for biologicals/biosimilars in 2017. The shortest median approval time observed was 239 calendar days for NCEs in 2019.
- The highest number of products approved during the study period was 195 in 2018 for foreign generics, 31 in 2017 for NCEs, 14 in 2021 for biologicals/biosimilars and 13 in 2019 for local generics. The lowest numbers were seen in 2020 across all product categories except for local generics which was lowest in 2018.
- Guidelines, standard operating procedures, and review templates were in place and the majority of indicators for good review practices were implemented. Although quality decision-making practices were implemented there was no formal framework in place.
- Overall, the results of this study demonstrated that the target timelines set and communicated by the authority to stakeholders and previously thought to be realistic and achievable, were no longer being met with the current resources available. Therefore there is a need for an urgent intervention to prevent a further increase in the timelines

- Recommendations made such as the review of available human resources, separation of agency and company time when setting and measuring targets, review of the templates and benefit-risk framework used for abridged review and the development of a decision-making framework, present opportunities for an enhanced regulatory review process.

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RECOMMENDATIONS

The following opportunities for system/process improvement were identified from this study:

- The adequacy of human resources available to review products as well as the ability of the authority to retain staff with key competencies and expertise should be evaluated.
- The authority should consider mainly the agency time when setting target timelines and measuring performance but the timeframe for the applicant's responses should only be extended if there is a good rationale as this affects the overall approval time.
- Applications should be placed in different queues according to the review type, for example, products requiring full review should have a separate queue from products eligible for abridged or verification review.
- The MCAZ should, where possible, pursue formal agreements with chosen reference agencies to facilitate the sharing of unredacted assessments reports or alternatively to encourage manufacturers to use the recently published WHO collaborative procedure to facilitate the accelerated registration of products approved by mature regulatory agencies (WHO, 2018)
- The authority should consider improving the recently implemented electronic tracking system to allow applicants to track the progress of their applications in line with good review practices.
- Since there is no formal decision-making framework in place, a study should be conducted, using validated tools, to ascertain the decision-making practices in the agency. The results of the study could then be used to close any gaps identified
- The current templates and the benefit-risk framework used for abridged reviews should be evaluated and compared with those of comparable or reference agencies to determine if there is need for improvement.

INTRODUCTION

Zimbabwe and the National Medicines Regulatory Authority

Zimbabwe is a landlocked country with a gross domestic product (GDP) of 18 billion USD and a population of 14.8 million in 2020 (World Bank, 2021). The country is bordered by South Africa, Namibia, Zambia, Botswana and Mozambique (IMF, 2017). The regulation of medicines began in 1969 through an Act of Parliament, the Drugs and Allied Substances Control Act of 1969 (Chapter 15.03) (MCAZ, 2022a). The Medicines and Allied Substances Control Act was promulgated in 1997, creating an autonomous agency independent of the fiscus, the Medicines Control Authority of Zimbabwe (MCAZ). The MCAZ's chemistry laboratory is prequalified by the World Health Organization (WHO, 2020a) and accredited by the Southern African Development Community Accreditation Services (SADCAS, 2022).The MCAZ has a robust quality management system, which resulted in the ISO 9001 certification by the Standards Association of Zimbabwe in 2019 (SAZ, 2022). The MCAZ offers training to regulators on the continent and as a result is designated as a Regional Centre of Regulatory Excellence (RCORE) for medicines evaluation and registration, clinical trials authorization, and quality assurance and control by the African Union's Development Agency New Partnership for Africa Development (AUDA - NEPAD) (MCAZ, 2022b). In addition, the MCAZ is a founding member of the ZAZIBONA collaborative medicines registration initiative and is also responsible for coordinating the Southern African Development Community (SADC) Medicines Registration Harmonization (MRH) project as the implementing agency (Sithole, 2020). The SADC MRH project aims to build the regulatory capacity of member states in various areas including supporting agencies to be assessed using the WHO Global Benchmarking Tool and to implement measures to close the gaps identified.

WHO assessment of regulatory authorities

Various countries or jurisdictions have legislation mandating the regulation of medical products to ensure their quality, safety and efficacy (Rägo, 2008). The capacity to regulate medical products varies widely and traditionally, countries that were members or observers of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) were regarded as having stringent regulatory authorities (SRAs) (WHO, 2019d). However, the World Health Organization (WHO) has recently made a proposal to use the term WHO listed authorities for authorities previously referred to as SRA and any additional authorities based on assessments using the Global Benchmarking Tool (GBTs) (WHO, 2019d; WHO, 2021b, WHO, 2022). This tool allows for the objective evaluation of national regulatory

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systems, as agreed by WHO Member states in the World Health Assembly Resolution 67.20 on Regulatory System Strengthening for medical products (WHO, 2014). The GBT evaluates the overarching national regulatory system as well as the following functions that make up the regulatory system; registration and marketing authorization, market surveillance and control, regulatory inspection, vigilance, licensing establishments, clinical trial oversight, laboratory testing and NRA lot release (WHO, 2021b). The WHO has begun the process of evaluating the regulatory systems of countries including low-and-middle income countries (LMICs). One of the outcomes of the assessments using the GBT is the development of an Institutional Development Plan, which identifies gaps as well as the activities and resources required to strengthen the regulatory system. As of March 2022, 16 of the 55 countries in Africa had undergone formal benchmarking by the WHO while 33 had conducted self-benchmarking (Sillo, 2022). Self-benchmarking is required before formal benchmarking by the WHO. For a variety of reasons, the remaining six countries have not begun the process of benchmarking. The goal of countries is to achieve maturity level 3 status which represents 'a stable, well-functioning and integrated regulatory system' (WHO, 2019d). Tanzania was the first African country to attain maturity level 3 status in 2018, followed by Ghana in 2020, then Nigeria and Egypt in 2022 (WHO 2019e; WHO, 2021c; WHO, 2022). The Medicines Control Authority of Zimbabwe was formally benchmarked in August 2021 and is in the process of developing corrective and preventive actions (CAPA) to address the shortcomings identified during the assessment. Regulatory reviews fall under the marketing authorization function of the GBT.

Unlike high-income countries, there is limited information in the public domain on the regulatory review/assessment systems and performance of LMIC (Gwaza, 2016). Evaluation of the regulatory review systems of a number of high-income and upper middle-income countries, for example, Saudi Arabia, Jordan, Turkey, and South Africa are available in the literature (Alsager et.al, 2015; Al Haqaish et.al, 2017; Ceyhan et.al, 2018; Keyter et.al, 2019) However, it appears that there are few published assessments of the regulatory review systems in LMIC in Africa. The aim of this chapter therefore was to evaluate the current regulatory review process in Zimbabwe, identifying challenges and opportunities for growth and improvement.

STUDY RATIONALE

As MCAZ is the implementing agency of the SADC MRH project, the gaps or areas for improvement identified in this study have the potential to strengthen the agency's coordination of the ZaZiBoNa initiative. In the absence of sufficient information regarding the regulatory processes of LMIC in the public domain, the findings of this study will serve as a benchmark for other countries in the SADC region as well as LMIC in the rest of Africa and beyond.

STUDY OBJECTIVES

The main objectives of this exploratory study were to:

1. Assess the current regulatory review process in Zimbabwe
2. Identify the key milestones and target timelines in the review process
3. Evaluate the overall performance for the review models as well as the different product types approved by the Authority during the period 2017 to 2021
4. Evaluate how the quality of the process of decision making is built into the regulatory review process of medicines
5. Identify the challenges and opportunities for an enhanced regulatory process in Zimbabwe, with a view to expediting patients' access to life-saving medicines

METHODS

Data collection process

A questionnaire technique (McAuslane, 2009) was used to identify the key milestones and activities associated with the review processes and practices within the MCAZ. The questionnaire was initially completed by a senior assessor, reviewed by the division's management and verified by the Director General in 2019. To aid agencies achieve the goals of regulatory efficiency, the Centre for Innovation in Regulatory Science (CIRS) developed a unique regulatory-strengthening tool entitled Optimising Efficiencies in Regulatory Agencies (OpERA). The OpERA project was initiated in 2013 based on requests from regulatory agencies, and the objectives of this program are to provide benchmarking data that can be used to define performance targets and focus ongoing performance improvement initiatives; accurately compare the processes used in the review of new medicines marketing authorizations; encourage the sharing of information on common practices in order to learn from others' experiences and encourage the systematic measuring of the processes that occur during the review of new medicines marketing authorization (CIRS, 2020).

The questionnaire consists of 5 parts (McAuslane, 2009; CIRS 2020). *Part 1: Organization of the agency* documents the information on the structure, organization, and resources of the agency.

Part 2: Types of review models identifies different types of review model(s) used for the scientific assessment of medicines in terms of the data assessed and level of detail

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by the agency, as well as how the agency might rely on the results of assessments and reviews carried out by a reference agency.

Part 3: Key milestones in the review process documents information on the key milestone dates, using the on-line OpERA tool and maps the process of assessment starting from receipt of the dossier, validation/screening, the number of cycles of scientific assessments including the questions to the sponsor/applicant, expert registration committee meetings to the final decision on approval or refusal of a product for registration. A standardized process map embedded in the questionnaire was based on the experience of studying established and emerging regulatory authorities.

Data were collected for new chemical entities (NCEs), biologicals, and biosimilars, and generics registered by the Zimbabwean NRA during the period 2017–2021. These data were sourced directly from the division within the Authority responsible for the regulatory review process.

Part 4: Good review practices (GRevP) evaluates how quality is built into the regulatory process by examining activities that have been adopted to improve consistency, transparency, timeliness, and competency in the review process.

Part 5: Quality decision-making processes explores the quality of agency decision-making practices and whether measures are in place to ensure that quality decisions are made around the data during the registration process.

Models of Regulatory Review

There are three models for the scientific regulatory review of a product that can be used by regulatory authorities (McAuslane, 2009) and these are;

1. the verification review (type 1) which requires prior approval of a product by two or more reference or competent regulatory authorities allowing the agency relying on such assessments to employ a verification process to validate a product and ensure it conforms to the previously authorized product specifications.
2. the abridged review (type 2) which involves an abridged evaluation of a medicine taking into consideration local factors and environment, with the pre-requisite of registration by at least one reference or competent regulatory authority.
3. the full review, type 3A, which involves the agency carrying out a full review of quality, safety and efficacy, but requires that the product has previously been

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reviewed by an agency for which there is a CPP or type 3B which involves an independent assessment of a product's quality, pre-clinical as well as clinical safety & efficacy, but which has not been evaluated by any previous agency

RESULTS

The results will be presented under five major headings which are organisation of the agency, types of review models, key milestones in the review process, good review practices and quality decision-making processes.

Part I: Organization of the agency

The MCAZ is an autonomous agency established in 1997 as a successor to the Drugs Control Council and the Zimbabwe Regional Quality Control Laboratory. The MCAZ regulates medicinal products for human and veterinary use as well as medical devices and diagnostics. The scope of control of medical devices is currently limited to gloves and condoms, but will increase once the medical devices regulations, which have been developed, are approved. The MCAZ scope of activities includes issuing of marketing authorizations/product licenses, post-marketing surveillance, laboratory analysis of samples, clinical trial authorization, regulation of advertising, site inspections/visits, import and export control, and licensing of premises and persons responsible for the manufacture, supply, distribution, storage, and sale of medicines.

The MCAZ currently has 143 full-time personnel including management, technical, and administrative staff. Twenty full-time reviewers are dedicated to assessing applications for marketing authorization/product licenses for synthetic and biological products, of whom 3 specialize in the review of biological products. As the MCAZ does not receive many applications for registration of biological products, the 3 reviewers also assess chemical/synthetic products (small molecules). The majority of the staff reviewing marketing authorization applications are pharmacists and some of them have post-graduate qualifications. However, no physicians are engaged in the regulatory review process for issuing marketing authorizations.

This section of the results has addressed objective 1 (to assess the current regulatory review process) and objective 5 (to identify the challenges and opportunities for an enhanced regulatory process, with a view to expediting patients' access to life-saving medicines).

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Part II: Types of review models used in Zimbabwe

The MCAZ carries out all three types of established regulatory review models (McAuslane, 2009), although there are some differences in the requirement of the number of approvals by a reference agency. The verification (type 1) review is used only for WHO prequalified (PQ) products through the WHO Collaborative Medicines Registration Procedure (CRP), and this is typically for foreign generic medicines (WHO 2019b). This type of review is enabled because WHO shares unredacted assessment reports for PQ products with the manufacturer's consent and WHO GMP inspection outcomes are also available.

Reviews involve ensuring that the product approved by the WHO PQ is the same as that submitted to the MCAZ and reviewing country-specific requirements such as labeling. Post-approval changes are communicated to the MCAZ by WHO PQ. The target timeline for this route is 90 calendar days (Table 2.1).

The abridged (type 2) review is used for products approved by at least one reference authority; for example, the European Medicines Agency, Medicines and Healthcare Products Regulatory Authority, United States Food Drug Administration, Australian Therapeutic Goods Administration, Health Canada, Japanese Pharmaceuticals and Medical Devices Agency and other mature agencies in Europe. This is the primary route for NCEs and biologicals. Generics and biosimilars approved by a reference

Table 2.1. Target timelines for the MCAZ review process

Milestone / Process	Target
Acknowledgement of receipt	30 calendar days
Screening/Validation	60 calendar days
Acknowledgement/Screening/Validation	90 calendar days
Scientific assessment (per review cycle)	60 calendar days
Sponsor response time (per review cycle)	60 calendar days
Scientific Assessment + Sponsor Response	120 calendar days
Expert Committee procedure	No target time
Authorization procedure	60 calendar days
Full review (Normally several cycles)	480 calendar days
Abridged review	270 calendar days
Verification review (WHO CRP)	90 calendar days
Expedited Review/Fast Track	180 calendar days
ZAZIBONA Review + Country Approval	270 + 90 calendar days
Emergency Use Authorisation	14 calendar days

agency will also go through the abridged route. However, the MCAZ does not have any formal agreements in place with any of these reference agencies to facilitate the sharing of unredacted assessment reports, therefore public assessment reports are used instead. The target timeline for this route is 270 calendar days (Table 2.1).

A full review (type 3A) of quality, safety and efficacy is conducted for products not approved by any reference agency and these products are usually generics and biosimilars. For generics, the chemistry, manufacturing and control (CMC) and bioequivalence are reviewed sequentially whilst for biosimilars the quality, non-clinical and clinical data are reviewed in parallel. The target timeline for this route is 480 calendar days (Table 2.1). ZaZiBoNa products undergo a full review; however, they are placed in their own queue with a target timeline of 270 days for ZaZiBoNa review and 90 days for country approval. A type 3B review which involves an independent assessment of pre-clinical (safety) and clinical (efficacy) is not usually conducted except in a public health emergency, for example, the review of Covid 19 vaccines.

An expedited/fast track review is also conducted. Applications are placed at the front of the queue but can be assessed using any of the above types of review (1, 2, or 3) depending on the product. Applications from local manufacturing companies and products for unmet medical needs are also given a priority review. The target timeline for this route is 180 calendar days (Table 2.1). As a result of the Covid 19 pandemic, the MCAZ recently implemented the Emergency Use Authorisation procedure to ensure availability of critical medicines and medical products in a public health emergency. The target timeline for this procedure is 14 calendar days (Table 2.1).

Data requirements and assessment

At present, the Certificate of Pharmaceutical Product (CPP) is legally required for registration in Zimbabwe for all three review types, as this is used as evidence of registration in the country of origin and to confirm similarity of the product being submitted to Zimbabwe with the one that is approved in the country of origin. The requirement for the CPP may be waived at the time of submission of the application but the CPP must be submitted prior to registration. The legislation is in the process of being reviewed to remove this requirement. Evidence of compliance with good manufacturing practices (GMP) for both the active pharmaceutical ingredient and finished pharmaceutical product manufacturers, product samples, copies of the labeling, and a full dossier (modules 1-5) are required for all review types. A detailed assessment of the data is carried out and the relevant assessment reports prepared. The MCAZ performs benefit-risk assessments during the abridged review of NCEs and

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biologicals, as well as during a full review of biosimilars taking into account differences in medical culture/practice, ethnic factors, national disease patterns, and unmet medical needs. As previously stated, the Authority does not access internal assessment reports from other authorities except from the WHO through the collaborative registration procedure. However, publicly available reports such as European Public Assessment Reports and those from other reference/recognized agencies are used during the review process.

This section of the results has addressed objective 1 (to assess the current regulatory review process) and objective 5 (to identify the challenges and opportunities for an enhanced regulatory process, with a view to expediting patients' access to life-saving medicines).

Part III: Key milestones in the Zimbabwe regulatory review process

The regulatory review process and authorization of medicines are performed within the Evaluations and Registration division of the MCAZ, and this is depicted in Figure 2.1 including the milestones and timelines. This is a simplified representation of the main steps in the review of applications. The map represents the review and authorization of a product that goes to approval after one review cycle. It often takes a minimum of three review cycles before the review of a product is finalized. In addition, the map, does not include steps such as the submission of representations to the 'Administrative Court' within a specified period to appeal against the refusal of an application.

Scientific assessment

The start of the scientific assessment is formally recorded. Scientific data are separated into quality, safety, and efficacy for review and these are assessed sequentially by one assessor when it is a generic medicine. However, the sections may also be assessed in parallel by different assessors when it is a biosimiliar medicine. At present, the primary scientific assessment is carried out by the Authority technical staff although in the past external assessors have been engaged under contractual agreement to work within deadlines set by the agency. Peer-reviewed assessment reports and recommendations are discussed by the external expert panel *Registration Committee,* which makes the final decision on registration or refusal of a product. The target timeline for each cycle of scientific assessment is 60 calendar days.

Questions to applicant (sponsor)

There is an opportunity for applicants to hold meetings with the agency staff to discuss questions and queries that arise during the assessment and a record is

generated during these meetings. Technical advisory meetings are also provided to local pharmaceutical manufacturers upon request, however unlike other jurisdictions, no fee is charged for these meetings. Questions are collected into a single batch after each review cycle and only sent to the applicant after the Registration Committee has made its decision. The applicant is allowed 60 calendar days to respond after each review cycle; however, due to manual tracking and requests for extension to the deadline, company time can exceed this target time. The scientific review ceases while questions are being processed by the sponsor; that is, a *clock stop* is applied; however, this time is not excluded when median approval time is calculated in practice as well as in this study.

Expert committee

The Registration Committee, which includes representatives from the disciplines of pharmacy, medicine, public health, toxicology, pharmaceutical science, biotechnology, and academia, meets once a month and makes decisions on registration or refusal of a product after the review of the scientific data by assessors. There is no target time limit for the Committee procedure. A letter communicating the Committee's decision is prepared and questions communicated to the applicant/sponsor with a 60-day deadline. Responsibility for the decision lies with the Registration Committee, which uses a consensus process for decision making, and the MCAZ is mandated to follow its decisions.

The criteria for granting or refusing a marketing authorization/registration relate only to the assessment of scientific data on quality, safety, and efficacy and is not dependent on a pricing agreement or on sample analysis. In some cases, sample analysis may be done in parallel with the scientific review, but for the majority of applications the analysis is carried out post-registration. Information in the summary of product characteristics (SPC) is reviewed and for generics this is expected to be similar to that of the reference/innovator SPC. Compliance with local labeling requirements; for example, pharmacological classification, is also a requirement for registration. Before a product is authorized, the manufacturing site must be deemed GMP compliant by the MCAZ inspectorate and this can be based on an onsite visit or a desk review where there is a GMP inspection by a recognized regulatory authority. The sponsor/applicant is informed of the authority's intention to approve the registration as well as any conditions of approval before the authorization is issued. At that stage, the sponsor is given 30 calendar days to respond. It can take approximately 60 calendar days from receiving a positive scientific opinion to issuing a certificate of registration (Table 2.1).

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Figure 2.1. Regulatory review process map for Zimbabwe showing target times in calendar days
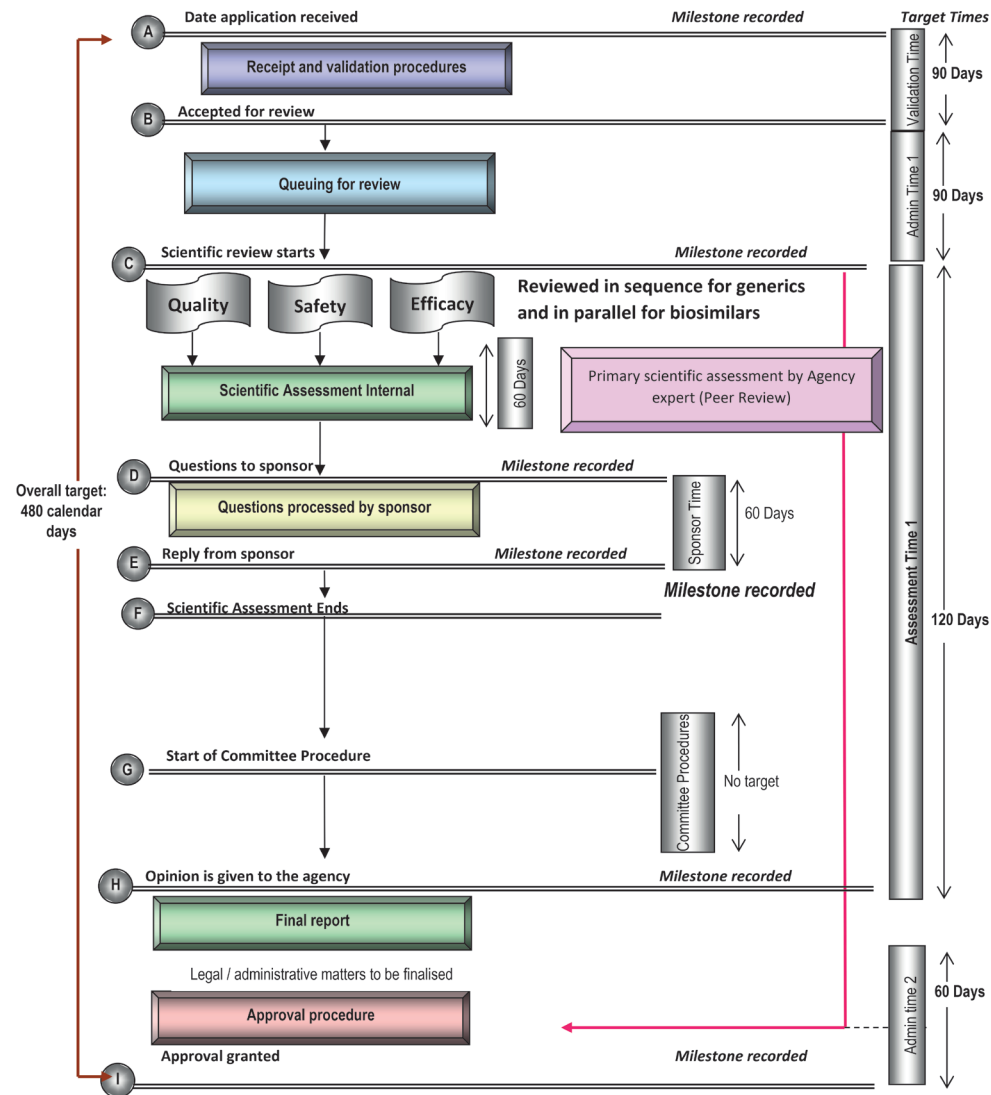

[The map represents the review and authorization of a product that goes to approval after one review cycle – the additional two cycles would add another 120 calendar days resulting to 480 as target review time].

Approved products and review times
Classification of approved products

From 2017-2021, 81% of approved products were submitted by foreign companies. The majority of applications approved during the study period were generics manufactured by foreign companies followed by NCEs, biologicals/biosimilars and generics manufactured by local companies (Figure 2.2). In 2017, 73% of the products approved were generics (foreign), 17% were NCEs, 6% were biologicals/biosimilars and 4% were generics (local). In 2018, 86% of products registered were generics (foreign), 9% were NCEs, 3% were biologicals/biosimilars and 2% were generics (local). In 2019, 82% of products registered were generics (foreign), 9% were biologicals/biosimilars, 5% were generics (local) and 4% were NCEs. In 2020, 83% of products registered were generics (foreign), 11% were generics (local), 4% were NCE and 2% were biologicals/biosimilars. In 2021, 79% of products registered were generics (foreign), 10% were biologicals/biosimilars, 7% were NCEs and 4% were generics (local). The highest number of products approved during the study period was 195 in 2018 for generics (foreign), 31 in 2017 for NCEs, 14 in 2021 for biologicals/biosimilars and 13 in 2019 for generics (local). There was a decreasing trend in the number of NCEs approved over the study period. All approved NCEs, biologicals and biosimilars were sponsored by

Figure 2.2. Number of approved products (2017 – 2021) classified into total, generics (foreign), generics (local), new chemical entities, and biologicals/biosimilars
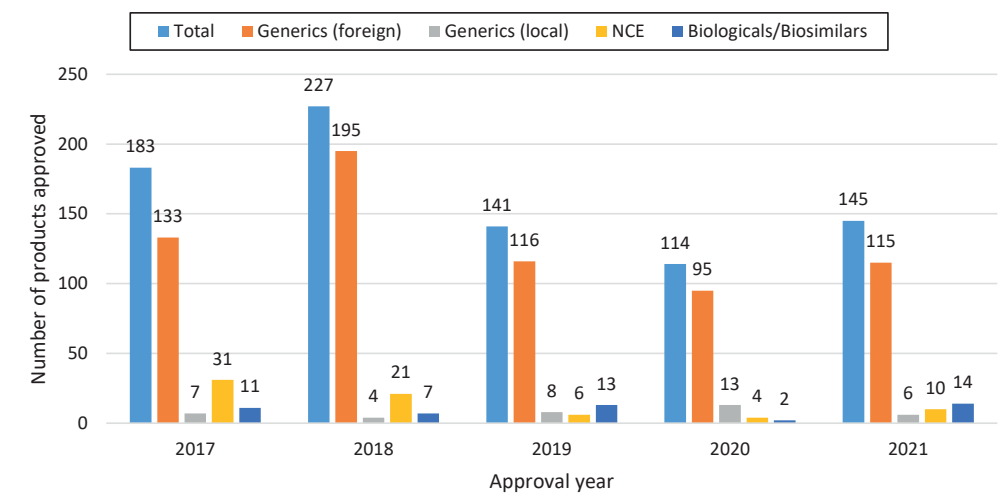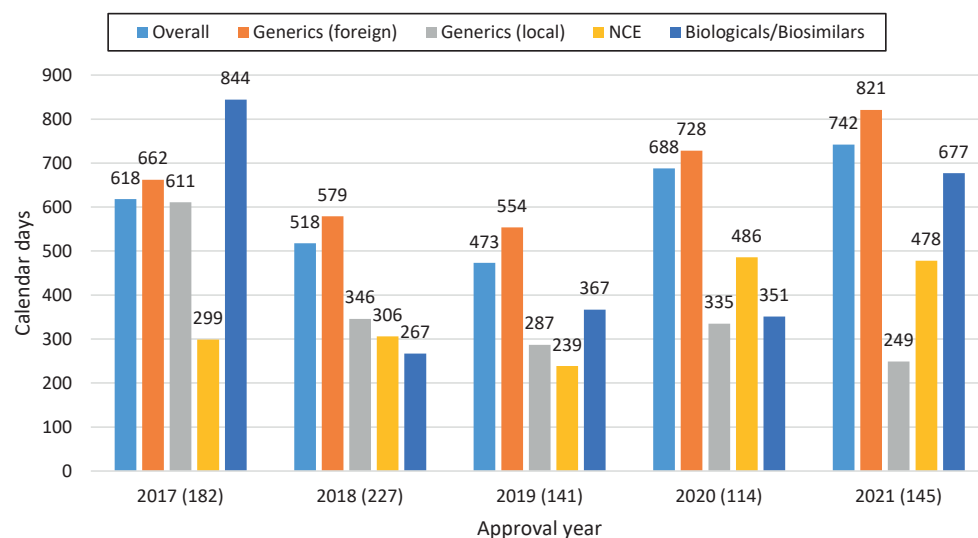

Review times for different product types

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foreign companies, there were no locally sponsored NCEs, biologicals or biosimilars. The lowest numbers were received in 2020 across all product categories except for generics (local) which was lowest in 2018.

It is significant that there was an improvement in review times in the first three years of the study period for all categories of products, however in the last two years the review times increased (Figure 2.3). The median overall approval time for all products was initially reduced from 618 calendar days (n = 183) in 2017 to 518 days (n = 227) in 2018 and 473 days (n = 141) in 2019 before increasing to 688 days (n = 114) in 2020 and 742 days (n = 145) in 2021. The median approval time for generics (foreign) was initially reduced from 662 calendar days (n = 133) in 2017, to 579 days (n = 195) in 2018 and 554 days (n = 116) in 2019 before increasing to 728 days (n = 95) in 2020 and 821 days (n = 115) in 2021. The median approval time for local generics initially halved from 611 calendar days (n = 7) in 2017 to 346 days (n = 4) 2018; 287 days (n = 8) in 2019 then increased to 335 days (n=13) in 2020 before decreasing again to 249 days (n=6) in 2021. The median approval time for NCEs initially remained relatively constant at 299 calendar days (n = 31) in 2017, 306 days (n = 21) in 2018 and 239 days (n = 6) in 2019 but in the last two years increased to 486 days (n=4) in 2020 and 478 days (n=10) in 2021. The median approval

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time for biologicals/biosimilars was initially reduced from 844 calendar days (n = 11) in 2017 to 267 days (n = 7) in 2018, 367 days (n = 13) in 2019, 351 days (n=2) in 2020 before increasing to 677 days (n=14) in 2021. The longest median approval time observed during the study period was (844 calendar days) for biologicals/biosimilars in 2017. The shortest median approval time observed was 239 calendar days for NCEs in 2019.

An improvement in review times was observed across all review models in the first three years of the study period before an increase in the last two years (Figure 2.4). The median approval time for full review (used for generics and biosimilars not approved by a reference authority) initially decreased from 727 days (n = 142) in 2017, to 612 days (n = 174) in 2018 and 624 days (n = 105) in 2019 before increasing to 728 days (n=98) in 2020 and 806 days (n=133) in 2021. The median approval time for abridged review (used for NCEs, biologicals, generics and biosimilars approved by a reference authority) initially decreased from 298 days (n=35) in 2017 to 274 days (n=36) in 2018 and 272 days (n=29) in 2019 before increasing to 486 days (n=9) in 2020 and 596 days (n= 4) in 2021. The median approval time for verification review (used for WHO PQ products under the CRP) decreased from 185 days (n = 5) in 2017, to 164 days (n = 17) in 2018, 126 days (n = 7) in 2019, 109 days (n = 7) in 2020 and 125 days (n = 8) in 2021. The highest median approval time was 806 days (n = 133) in 2021 for products that had a full review and the shortest was 109 days (n = 7) in 2020 for products that had a verification review. In general, the median approval time for verification review was the shortest throughout the study period, followed by abridged review then full review. Products were approved in less than half the time taken for full review under abridged review except in the last two years where abridged review took approximately three-quarters of the time for a full review. Throughout the study period, verification review took a quarter or less of the time taken for a full review.

This section of the results has addressed objective 1 (to assess the current regulatory review process), objective 2 (to identify the key milestones and target timelines in the review process), objective 3 (to evaluate the overall performance for the review models as well as the different product types approved by the Authority during the period 2017 to 2021) and objective 5 (to identify the challenges and opportunities for an enhanced regulatory process, with a view to expediting patients' access to life-saving medicines).

Part IV: Good review practices: Building quality into the regulatory process

The following quality measures were evaluated.

Figure 2.3. Median approval times (inclusive of applicants' time) (2017 – 2021) for all products (overall), generics (foreign), generics (local), new chemical entities, and biologicals/biosimilars

Comparison of review times for different models

Figure 2.4. Median approval times (inclusive of applicants' time) (2017 – 2021) for different review models; that is, overall, full review, abridged review and verification review (World Health Organization WHO Collaborative Medicines Registration Procedure)
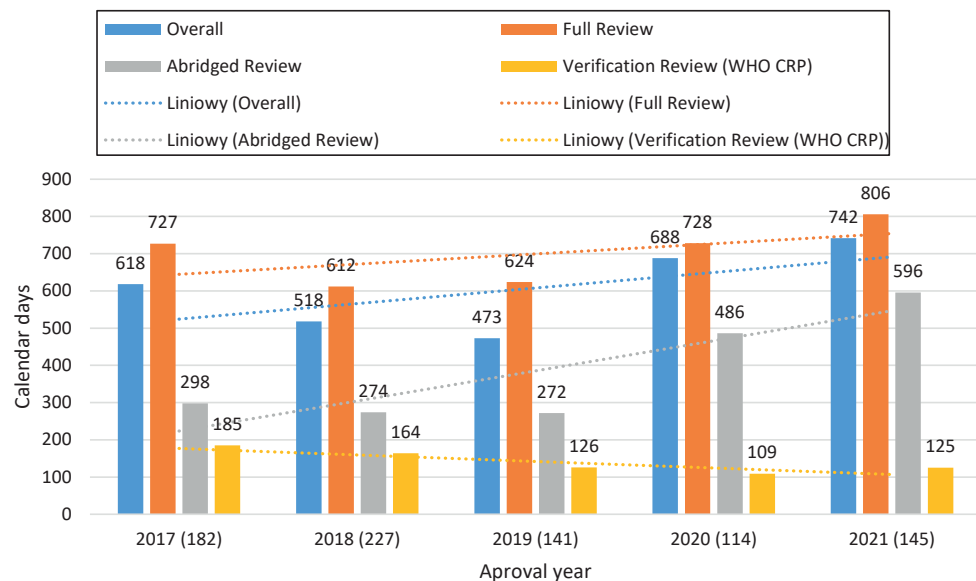
General measures used to achieve quality

GRevPs have been implemented by the agency, using WHO PQ as a standard, including the use of guidelines, standard operating procedures, assessment templates and screening checklists (Table 2. 2). These documents are not available to the public except the guidelines and the applicant's screening checklist, which are available on the MCAZ website www.mcaz.co.zw. The MCAZ top management has endorsed and formally adopted an internal quality policy that gives direction related to the quality of the review process. The agency produces an assessment report in English, which undergoes a process of internal peer review before consideration by the Registration Committee. A Registration Committee preparatory meeting serves as a quality assurance check before reports are taken to the Committee. Applicants / sponsors do not get a full copy of the assessment report and a redacted assessment report is not published on the website. Other tools used to build quality into the assessment process are the availability of the following platforms for communicating with applicants/ sponsors and obtaining their feedback: procedures for submitting complaints by applicants/sponsors; annual stakeholder meetings; individual client meetings; and liaison meetings with stakeholders such as associations of pharmaceutical manufacturers, retail pharmacists, and pharmaceutical wholesalers.

Quality management

The MCAZ has identified quality management to be critical in achieving its values which are customer focus, continuous improvement, integrity and accountability. The Authority strives to be more efficient, to ensure consistency, and to increase transparency. The following activities are undertaken to bring about continuous improvement in the assessment and authorization process: reviewing assessors' feedback and taking necessary action; reviewing stakeholders' feedback through for example satisfaction surveys, complaints, meetings, or workshops and taking necessary action; using an internal tracking system to monitor quality parameters such as consistency, timeliness, efficiency, and accuracy. Internal quality audits such as self-assessments, as well as external quality audits by accredited certification bodies have helped to improve the system. The Authority has a dedicated Quality Unit for assessing and/or assuring quality in the assessment and registration process for medicines. Quality management review meetings are held quarterly to monitor implementation of quality standards across the organization.

Quality in the review and assessment process

Some measures that have been implemented to help improve the quality of applications and the scientific review are publication of various guidelines to assist industry as well as regular feedback to applicants on common deficiencies observed in applications for registration. These are made available through the MCAZ website, industry associations, meetings with stakeholders, and upon request. In addition, pre-application scientific advice has been given mostly to local manufacturers/applicants. Quality is monitored through the minutes of such meetings. The applicant is not given the contact information of the assessor to discuss their application during the review.

However, there is some formal contact to discuss the status of pending products. Meetings are held by appointment on specific days of the week; however, applicants can send emails at any time requesting status updates from the administrative regulatory officer. Phone calls are largely discouraged but may be taken on designated days.

Shared/Joint reviews

The MCAZ is a founding member and active participant of the SADC collaborative medicines registration initiative ZaZiBoNA (MCAZ, 2022a; Sithole, 2020). The MCAZ acts as a rapporteur, performing the first review of a product application or as a co-rapporteur performing the peer review of an application for products assessed by the initiative for which marketing authorization in Zimbabwe is sought. The product application should have been submitted to a minimum of two countries to be eligible

Table 2.2. Status of implementation of good review practices by MCAZ

Indicator	Status	Comments
Quality processes		
Internal quality policy	✓ 🟩	
Good review practice system	✓ 🟩	
Standard operating procedures for guidance of assessors	✓ 🟩	
Assessment templates	✓ 🟩	
Peer review	✓ 🟩	
Dedicated quality department	✓ 🟩	
Scientific Committee	✓ 🟩	
Shared and joint reviews	✓ 🟩	
Transparency and communication parameters		
Feedback to industry on submitted dossiers	✓ 🟩	
Details of technical staff to contact during assessment	✗ 🟥	
Pre-submission scientific advice to industry	✓ 🟩	For local manufacturers
Official guidelines to assist industry	✓ 🟩	
Industry can track progress of applications	✗ 🟥	
Publicly available Summary Basis of Approval	✗ 🟥	
Approval times	✓ 🟩	
Advisory Committee meeting dates	✓ 🟨	Planned to formally implement
Approval of products	✓ 🟩	

🟩 Formally implemented
🟨 Informally implemented
🟥 Not implemented

Table 2.2. (continued)

Indicator	Status	Comments
Continuous improvement initiatives		
External quality audits	✓ 🟩	
Internal quality audits	✓ 🟩	
Internal tracking systems	✓ 🟩	
Review of assessors' feedback	✓ 🟩	
Reviews of stakeholders' feedback	✓ 🟩	
Training and education		
International workshops / conferences	✓ 🟩	
External courses	✓ 🟩	
In-house courses	✓ 🟩	
On the job training	✓ 🟩	
External speakers invited to the authority	✗ 🟥	
Induction training	✓ 🟩	
Sponsorship of postgraduate degrees	✓ 🟩	In the form of study leave
Placements and secondments in other regulatory authorities	✓ 🟩	

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for review under ZaZiBoNa. The WHO carries out quality assurance for all reviews under the initiative. There are formal measures in place to ensure consistent quality during the review under the initiative through the use of guidance documents for assessors, use of common templates for assessment of generic medicines, and the availability of standard operating procedures. With the manufacturer's consent, the agency shares the assessment report with other regulatory authorities for ZaZiBoNA products. The joint reviews have served as a platform for training, particularly assessment of the active pharmaceutical ingredient and biologicals/biosimilars as well as greater exposure to WHO standards of assessments. To date, ZaZiBoNa has contributed 11% of total registrations in Zimbabwe in 2017 and 2019, and 4% in 2018, 8% in 2020 and 6% in 2021 (Sithole, 2019).

Training and continuing education as an element of quality

A formal training strategy and program for assessors is in place which includes training at induction, on-the-job training, internal and external short courses, support for post-graduate degrees, placements/secondments to more established regulatory authorities such as WHO PQ and The Federal Institute for Drugs and Medical Devices (BfArM) in Germany, and mentoring of junior assessors by more experienced assessors including peer review. The MCAZ does not seek direct assistance of more experienced agencies for the development of SOPs and guidelines, however guidelines published by more experienced agencies are referenced, adapted, or adopted during the development of country guidelines. The agency collaborates with other agencies in the training of assessors for example during pre-assessment training sessions at ZaZiBoNA or as co-facilitators for courses offered under the MCAZ RCORE. The MCAZ participates in training offered by WHO and other agencies. Once completed, a system is in place to evaluate the impact of any given training on the individual and on the division. The MCAZ participated in the exercise to determine the level of competence of assessors using the WHO Global Competence Framework for Assessors together with other SADC countries.

Transparency of the review process

Being open and transparent in relationships with the public, professionals, and industry is in line with MCAZ organizational values and is of high priority**.** The MCAZ identified the following top three incentives for assigning resources to activities that enhance the openness of the regulatory system: political will; the need to increase confidence in the system; and the provision of assurance regarding safety measures. Measures to achieve transparency include the provision of details regarding the registration process on the MCAZ website including fees payable for the different pathways and

regular stakeholder meetings to interact with applicants and discuss processes and timelines for approval. In addition, an online register of approved products is available on the website whilst approved, cancelled, refused, and withdrawn products are periodically published in the Government gazette. Although the MCAZ does not share assessment reports with applicants, the listed deficiencies or questions raised during assessment are shared with the applicant, which they are given a period of 60 days to address. When a product is refused registration, the reasons for the refusal are shared with the applicant. Furthermore, detailed statistics are published in the annual reports which the Minister of Health and Child Care presents to the Parliament. Copies of the MCAZ Annual Reports from 2011–2019 are available on the MCAZ website. Customer satisfaction surveys and complaint forms, which are freely available on the website, are used to obtain feedback from applicants on the quality of the review process.

At present, it is not possible for companies to track the progress of their applications, however this is something the Authority plans to do in the future. However, companies can follow the progress of their applications through meetings, e-mail and telephone contact. Currently, a database capable of archiving information on applications in a way that can be searched exists and an electronic tracking system has recently been implemented for internal use only.

This section of the results has addressed objective 1 (to assess the current regulatory review process), objective 4 (to evaluate how the quality of the process of decision making is built into the regulatory review process of medicines) and objective 5 (to identify the challenges and opportunities for an enhanced regulatory process, with a view to expediting patients' access to life-saving medicines).

Part 5: Quality decision-making processes

Although some good decision-making practices are implemented, the MCAZ does not have a validated documented framework in place that forms the basis of the decision to approve or reject an application. The current process in place is based on custom and practice. Assessors use a decision tree to assign relative importance, that is, *critical* or *not critical* to findings, which ensures decisions/recommendations are made consistently regardless of the assessor.

One of the challenges identified is that the agency does not have measures in place to minimize the impact of subjective influences/biases on the agency's decision making for the process to approve or reject an application. In addition, there is no training provided in the area of quality decision making in general and neither is there a formal

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assessment to periodically measure the quality of decision making within the agency and for the process to approve or reject an application. There is, therefore, room for improvement of the authority's decision-making process and the implementation of a framework.

This section of the results has addressed objective 1 (to assess the current regulatory review process), objective 4 (to evaluate how the quality of the process of decision making is built into the regulatory review process of medicines) and objective 5 (to identify the challenges and opportunities for an enhanced regulatory process, with a view to expediting patients' access to life-saving medicines).

DISCUSSION

The MCAZs vision is to be a leading and effective regulatory authority on the African continent. This is evidenced by its adoption of a robust quality management system and the implementation of good review practices in line with international best practice. Historically, the MCAZ has had the challenge of long registration times. Gwaza reported a range of 516 days to 1673 days median time to registration for the years 2003 to 2015 (Gwaza, 2016). To address this challenge, the MCAZ invested in improving and re-engineering its processes using international standards as a benchmark. Management invested financially in the hiring of a dedicated administrative regulatory officer to perform validation of applications thus preventing incomplete applications from clogging the pipeline, hiring of dedicated dossier reviewers and the introduction of one-week off-site retreats to allow assessors to review dossiers without disruptions. Management also invested in the development of an electronic tracking system. The process was also at the time evaluated which resulted in the setting of target times for all key milestones, adherence to the target times, stricter monitoring of deadlines given to applicants to respond to questions and limiting the number of review cycles to three which reduced the time previously spent with the applicant on the same issues when there was no limitation on the number of review cycles. In addition, the use of the abridged review model was extended to generics and biosimilars approved by recognised reference agencies where previously it was only used for new chemical entities and biologicals.

The results of this current evaluation show that the investment was worthwhile as the regulatory review process now incorporates milestones used by leading regulatory authorities globally and in the first three years the time to registration decreased over time. The improvement in the process resulted in a decrease in the overall median approval time to 473 calendar days (15.8 months) in 2019, which is comparable to

the review times of 10 to 16 months achieved for new active substances by mature and better resourced agencies (Bujar, 2017). However, in the last two years the timelines have increased across all product categories except locally produced generic medicines. This can be attributed to various factors such as the Covid-19 pandemic which was at its peak in 2020 forcing organisations to adopt a 'work from home' model due to travel restrictions resulting in loss of time and productivity in the beginning as adjustments were made. Other factors contributing to increased timelines were the loss of critical staff, withdrawal of measures previously implemented to reduce timelines such as retreats and the strain on resources during the expedited review of Covid-19 vaccines.

Performance against set targets

The results of this study show that the authority was meeting the targets set for overall approval time (480 days) and abridged review (270 days) at one point during the study period however this is no longer the case. Although the time taken for approval using the verification review (WHO CRP) is above the target (90 days), it is still very reasonable (125 days in 2021). The time taken for full review is much higher than the target of 480 days (806 days in 2021). Some of the reasons that contribute to a long approval time are a long queue time (the time a product spends in the queue from receipt to the start of the scientific assessment), an inadequate number of experienced reviewers, and numerous requests from applicants for deadline extensions to respond to reviewer questions. The queue time is indicative of the resources available to perform the work and a target of 180 days is too long, reflecting the need for an evaluation of the adequacy of human resources available to review products as well as the ability of the MCAZ to retain staff with key competencies and expertise. Gwaza reported that the authority had a relatively young workforce of assessors/reviewers, two of whom had doctorates at that time in 2014 (Gwaza, 2016); however, when compared with results from the current study conducted five to seven years later, the workforce is still relatively young and the two reviewers with doctorates are no longer a part of the team of reviewers. This points to a problem of high staff turnover and poor skills retention, which needs to be addressed if the queue time and overall timelines are to be improved.

New chemical entities

While generics play an important and critical role in ensuring access to life saving treatment in LMICs, the need for new and innovative medicines cannot be overlooked. Some patients have reported better outcomes with innovator brands compared with generic products (Dunne, 2013) and NCEs should be approved and readily available

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on any market. This will reduce the cost of the medicine, unlike the situation in which the unregistered NCE is imported for the patient under section 75, a provision in the Medicines and Allied Substances Control Act, which waives the requirement for registration of unregistered medicines imported on a doctor's prescription and named patient basis. NCEs or innovative products are normally only launched onto the African market after a number of years of approval and use in well-resourced markets (Rago et.al, 2008) making them low-risk products with established efficacy and safety, which have undergone a rigorous review by a mature agency. The results of this study show that the MCAZ uses risk stratification for all NCEs by conducting an abridged review. This process once proved effective, as the median approval time for NCEs was for the first three years the lowest of all the product types registered in Zimbabwe, ranging from 239 to 306 calendar days (8-10 months) over the study period and did not result in any increase in the incidence reports of post-marketing adverse events at the time. The review times for NCEs for the first three years of the study period were comparable to the time taken by mature agencies and much lower than the 3-6 years reported for review of new active substances in other countries in the region who conduct a full review (Keyter, 2020). This however, changed in the last two years in which there is now a very small difference between the time taken for abridged review and full review implying that the abridged review is not being implemented effectively. The results of this study show that all products are placed in the same queue for review regardless of the type of review to be conducted which may also be contributing to the long timelines for abridged review in recent years. This is different from some countries in the region where applications for NASs are placed in a different queue from applications for generic medicines (Keyter, 2020). There has been a decrease in the number of NCEs registered in Zimbabwe from 2017 to 2021 which could be due to various reasons, such as economic factors beyond the regulator's control. However, the MCAZ can encourage submission or registration of NCEs by having a separate queue for these products since the numbers are very low compared with generics, and the type of review conducted is different. It is also likely that the NCEs will be addressing an unmet medical need. This will be a process improvement that will reduce approval time and improve access to new and innovative life-saving medicines by patients in Zimbabwe.

Biologicals and biosimilars

The LMICs in the African region suffer the highest burden of infectious diseases such as HIV/AIDS and tuberculosis (Corbett, 2003; WHO, 2019f) which has resulted in most of the countries developing policies to promote the prescription and use of generic medicines (Kaplan, 2012) to ensure access to treatment by as many patients as possible

at affordable prices. In addition, in recent years, there has been a rise in the prevalence of non-communicable diseases such as cancer in LMICs (Bos 2006; Miranda 2008) and the cost of biologicals used for treatment of diseases such as cancer is prohibitive, leading to a rise in the use of biosimilar medicines. Review of applications for registration of biologicals and biosimilars requires different competencies to those required for small molecules. There is also a component of benefit-risk assessment to be considered for biosimilars that is not critical for small-molecule generic medicines.

From this study, we found that most biosimilars received in Zimbabwe require a full review as they are not approved by any of the reference authorities. The median approval time for biosimilars and biologicals of 844 calendar days (28 months) in 2017 was the highest for all product types during the study period. This was because in 2017, the agency had only just established a dedicated unit for biological products with three reviewers and there was limited knowledge and experience to review these products. However, the greatest reduction in median approval time over the study period was observed for biologicals and biosimilars from 844 calendar days in 2017 to 267 days in 2018 owing to the reviewers gaining more knowledge and expertise in the area as well as the use of an abridged review for biologicals and biosimilars approved by a recognized reference authority. However, in 2021 the median approval time for biologicals/biosimilars increased to 675 days and this could be attributed to the loss of critical staff. A study should be conducted to determine why more manufacturers/ applicants of biosimilars approved by reference authorities are not seeking market authorization for their products in the LMICs. Such products would drastically reduce the cost of treatment for patients who often have to pay out of pocket for treatment and therefore justifies shorter registration times for such products.

Local products

Markets eroded by sub-standard and falsified medicines due to weak regulation, inadequate technology, outdated equipment and facilities, inadequate research and development and lack of appropriately skilled personnel were cited as some of the challenges faced by the pharmaceutical manufacturers in Africa in the Pharmaceutical Manufacturing Plan for Africa (PMPA) business plan developed by a partnership of the African Union Commission (AUC) and the United Nations Industrial Development Organization (AUDA NEPAD, 2020). The figures presented in this study on the number of generics registered from local and foreign companies, show that local manufacturers contributed 5%, 2%, 7%, 12% and 5% respectively of the generic products registered from 2017–2021. Recognizing the role that local manufacturers can play in reducing the cost of medicines and contributing to public

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health, the MCAZ has adopted a policy to prioritize the review of locally manufactured medicines. This has resulted in a reduction in the median approval time (inclusive of the applicants' time) of local generics from 611 calendar days (20 months) in 2017 to 346 days (11.5 months) in 2018, 287 calendar days (9.5 months) in 2019, 335 days (11.2 months) in 2020 and 249 (8.3 months) in 2021. The MCAZ also plays a capacity-building role through the collaboration on the GMP roadmap for manufacturers and trainings offered to industry through its RCORE. It is envisaged that as the challenges identified in the PMPA business plan are addressed, the product portfolio of local manufacturers as well as their presence on the market will increase. The median approval time can be further reduced by limiting the number of review cycles and applicants adhering to the deadlines to respond to questions.

Electronic tracking system

The MCAZ has implemented an electronic tracking system that should enable easier tracking and reporting of the *clock stop, clock start* but this is yet to be fully optimised. This will help both applicants/sponsors and the agency to see their contribution to the overall approval time. At present, the authority's target timelines are set and measured inclusive of the applicant's time. The shortcoming of this approach is that the authority includes company time when measuring its performance and yet this is not within its control. An element of good review practices yet to be implemented by the MCAZ is to enable applicants to track the progress of their applications. The authority should consider further improving the electronic tracking system to allow applicants to submit applications online and track their progress.

The MCAZ implements the three types of review models in line with international standards. The milestones in the review process are formally recorded and targets have been set for each milestone. Performance against set targets is monitored. All except four indicators for good review practices are either formally or informally implemented. Although good decision-making practices are implemented, there is need to have a formal decision-making framework in place.

CHAPTER 03

BENCHMARKING THE MCAZ REGULATORY REVIEW PROCESS AGAINST THE ACSS COUNTRIES

SUMMARY

- Benchmarking regulatory systems of low- and middle-income countries with mature systems of comparable size provides an opportunity to identify gaps, enhance review quality, and reduce registration timelines, thereby improving patients' access to medicines.
- The aim of this study was to compare the medicines registration process of the Medicines Control Authority of Zimbabwe (MCAZ) with the regulatory processes in Australia, Canada, Singapore, and Switzerland.
- A questionnaire was completed by a senior member of the divisions responsible for issuing marketing authorizations in the five regulatory authorities.
- The MCAZ had far fewer resources than the regulatory authorities in the comparator countries, but employed three review models, in line with international best practice.
- The MCAZ registration process was similar to the comparator countries in the key milestones identified and monitored, but differed in the target timelines for these milestones.
- The MCAZ was at one time able to achieve timelines comparable to the mature agencies through efficient use of resources such as the implementation of reliance and international best practices including the setting and monitoring of targets for key milestones in the review process. However, there was a need to go back to the drawing board as the timelines had increased in recent years as a result of the impact of the Covid-19 pandemic
- The MCAZ was comparable to the comparator authorities in implementing the majority of good review practices, although it significantly lagged behind in transparency and communication.
- This study identified opportunities for improvement such as the use of online submission systems, removal of the requirement for a CPP and building capacity in the assessment of new active substances. If these were implemented, it would enable the MCAZ to effectively execute its role as the SADC MRH project's implementing agency as well as achieving its vision to be a leading regulatory authority on the African continent.

RECOMMENDATIONS

This comparative study identified MCAZ's strengths and highlighted the opportunities for improvement, which if implemented, would strengthen the regulatory review process. MCAZ may wish to consider the following recommendations:

- Expediting the process of expanding its scope of control to regulate all medical devices, in vitro diagnostics, and blood and blood products.
- Removing the requirement for a Certificate of Pharmaceutical Product, since the authority currently conducts a full review (type 3 A) and allow applicants the option of providing a marketing authorization license instead.
- Building capacity to enable the independent assessment of products, particularly innovative medicines, not approved elsewhere.
- Using online submission tools or increasing the number of administrative officers to reduce validation time. The TGA observed that online submissions resulted in significant improvements in efficiency for South-East Asian authorities (J. Skerritt, personal communication, March 11, 2021).
- Setting targets for the primary and second round of assessments and measuring performance against these targets in order to effectively monitor where time is spent in the review process.
- Taking applications and assessment reports to the Committee only after assessors have reviewed the applicant responses to formal questions and seeking clarifications from the applicant during the review process.
- Defining and communicating the target for the overall approval time excluding the sponsor / applicant time to effectively monitor the agency approval time.
- Applying strategies to shorten the queue time including implementing parallel instead of sequential reviews as well as increasing the number of competent assessors.
- Improving transparency and communication with stakeholders to fulfil a goal of the Zimbabwe Vision 2030 to have responsive institutions.
- Developing and formally implementing a documented framework for quality decision-making practices.

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INTRODUCTION

The United Nations Sustainable Development Goal (SDG 3) "to ensure healthy lives and promote well-being for all at all ages" (United Nations, 2021) is supported by the regulation of medicines, which ensures that medicines and medical products, made available to the public, are quality- assured, safe and effective (Guzman et.al, 2020; Khadem et.al, 2020). One of the targets for SDG 3 is universal health coverage by 2030. This can be defined as access to essential health services, including prevention, treatment, rehabilitation and palliative care for all people, regardless of financial standing (Evans et.al, 2013; WHO, 2021) and medicine regulatory authorities are a pivotal component of the healthcare system (Lumpkin et.al, 2012).

Currently, many low- and middle-income countries (LMICs) have regulatory systems that need strengthening (Khadem et.al, 2020; Ndomondo-Sigonda et.al, 2017), and this results in backlogs of applications for marketing authorization. These challenges affect the timely access to quality assured medicines and healthcare delivery. Effective regulation of medicines reduces the costs incurred by patients and the healthcare delivery system due to undesirable outcomes such as adverse reactions caused by the use of unsafe medicines, and treatment failure or the development of resistance due to the use of unregistered medicines that may have sub-therapeutic levels of active ingredients (Rägo et.al, 2008). Moreover, the cost of medicines also decreases with the increase in registered alternatives of the same molecule (Dunne et.al, 2013; Kaplan et.al, 2012). Therefore, the need for improvement and the strengthening of regulatory systems in LMICs cannot be overstated. The World Health Organization (WHO), supported by the World Health Assembly resolution 67.20, has been working to strengthen regulatory systems for medical products in these countries using the Global Benchmarking Tool (GBT) (WHO 2021b). The GBT evaluates the maturity level of a regulatory system, with a level 1 designation signifying that 'some elements of a regulatory system exist' and level 4, 'a regulatory system operating with an advanced level of performance and continuous improvement is established' (WHO 2014). The outcome of the GBT assessment is the designation of a maturity level, from 1 to 4, by WHO and the development of an Institutional Development Plan, which summarizes gaps as well as the activities and resources required to strengthen the regulatory system (WHO 2019d). A separate process for designation of WHO-listed authority status is under consideration. A number of African countries have already been assessed using the WHO GBT, and Egypt, Ghana, Nigeria and Tanzania have attained maturity level 3, which represents a stable, well-functioning and integrated regulatory system' (Khadem et.al, 2020; WHO, 2019e; WHO, 2021c, WHO 2022). The MCAZ underwent a formal benchmarking assessment from August 2021.

The MCAZ is now in the process of developing corrective and preventive actions (CAPA) to address the findings identified in the Institutional Development Plan (IDP).

Regulatory landscape in Zimbabwe

Zimbabwe is a country in the Southern African region bordered by Botswana, Mozambique, Namibia, South Africa, and Zambia (IMF, 2017), with a population of just under 15 million in 2020. The gross domestic product (GDP) for Zimbabwe in 2020 was USD 18 billion (World Bank, 2021), however, the government has declared a goal for Zimbabwe to become a "prosperous and empowered upper middle-income economy by 2030" coining the phrase "Vision 2030" (Republic of Zimbabwe, 2018). Accordingly, various measures are being implemented to achieve this including the objective of responsive public institutions (Republic of Zimbabwe, 2018). The Medicines Control Authority of Zimbabwe (MCAZ) is an autonomous agency under the Ministry of Health and Child Care and successor to the Drugs Control Council established by an Act of Parliament, the Drugs and Allied Substances Act of 1969 (MCAZ, 2020; Sithole et.al, 2021c). The MCAZ is responsible for regulating medicinal products for human and veterinary use as well as medical devices (Sithole et.al, 2021c) and there are plans to expand its scope of control to an extended range of medical devices and blood and blood products. The scope of activities carried out by the MCAZ are the issuing of marketing authorizations/product licenses, post-marketing surveillance, laboratory analysis of samples, clinical trial authorization, regulation of advertising, site inspections/visits, import and export control, and licensing of premises and persons responsible for the manufacture, supply, distribution, storage, and sale of medicines (Sithole et.al, 2021c)

Over the years, the MCAZ has been involved in various activities with the aim to improve capacity, for example, participation in the WHO prequalification of medicines and global benchmarking programmes as well as the Southern African Developing Community (SADC) regional work-sharing initiative, ZaZiBoNa, which MCAZ coordinates as the SADC medicines registration harmonization (MRH) project's implementing agency. As a result of this investment, the MCAZ has been recognized by the African Union Development Agency New Partnership for Africa Development (AUDA NEPAD) as a regional center of regulatory excellence (Ndomondo-Sigonda et.al, 2018; Sithole et.al, 2021c) and was identified in the Zimbabwe National Development Strategy for 2021 - 2025 as being pivotal in the improvement of the pharmaceutical value chain. The same strategy specified that registration timelines must be reduced to facilitate access to medicines by the Zimbabwean people (Republic of Zimbabwe, 2021). Sithole and colleagues (2021) recommended a comparison of the registration

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process of Zimbabwe with other countries in the Southern African Developing Community (SADC) region as well as higher income countries of comparable size with mature regulatory authorities, for the purpose of continuous improvement and benchmarking (Sithole et.al, 2021c). The aim of this chapter therefore was to review the registration process of Zimbabwe in comparison with Australia, Canada, Singapore, and Switzerland to identify areas of strength of the MCAZ as well as opportunities for improvement including implementing best practices with the goal to ultimately reduce registration timelines and improve patients' access to life-saving medicines.

STUDY OBJECTIVES

The objectives of this study were to identify the strengths and opportunities for improvement by comparing the Medicines Control Authority of Zimbabwe with the regulatory authorities of Australia, Canada, Singapore and Switzerland by examining the following;

- Registration process including key milestones
- Target timelines
- Review models employed
- Data requirements and extent of scientific assessment
- Number of NASs approved from 2019 – 2021
- Review times for NASs approved from 2019 – 2021
- Quality measures employed

METHODS
Study participants

The regulatory authorities included in this study were the Therapeutic Goods Administration (TGA) of Australia; Health Canada, Health Sciences Authority (HSA) of Singapore, and Swissmedic of Switzerland. These authorities were selected because of their size and the type of review models employed. In addition, it was imperative to include mature, WHO-recognized agencies that would contribute to the goals of this comparison, allowing the MCAZ to learn from best practices. The strength of the group of countries selected for this comparison is their similarity to the MCAZ in their participation in collaborative regulatory initiatives.

Data collection

Data for the comparator authorities was originally collected in 2014 and subsequently updated for 2020 and 2021, including metrics data for all the comparator agencies (CIRS, 2020, CIRS 2021) except HSA, which was updated from public domain, whilst data

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for Zimbabwe was collected in 2019 (Sithole et.al, 2021c) and subsequently updated for 2020 and 2021. A questionnaire that standardizes the review process, allowing key milestones, activities and practices of the five regulatory authorities to be identified (McAuslane et.al, 2009) was completed by a senior member of the division responsible for issuing marketing authorizations and validated by the head of the agency.

The 5-part questionnaire comprises the following:

- *Part 1: Organization of the agency*; that is, the organization, structure, and resources of the agency.
- *Part 2: Types of review model;* that is, the review models employed for scientific assessment, the level of data required, and the extent of assessment of the data as well as reliance on other authorities if applicable.
- *Part 3: Key milestones in the review process*; that is, the process of assessment starting from receipt of the dossier, validation/screening, the number of cycles of scientific assessments including the questions to the sponsor/applicant, expert registration committee meetings to the final decision on approval or refusal of a product for registration. A standardized process map, developed based on the experience of studying established and emerging regulatory authorities, was embedded in the questionnaire. Data for new active substances (NASs), approved by the study participants in 2019 – 2021 was extracted from the literature as well as the information provided by the agency.
- *Part 4: Good review practices (GRevP)*; that is, the activities adopted to improve the consistency, transparency, timeliness, and competency, building quality in the review process.
- *Part 5: Quality decision-making processes*; that is, the practices implemented to ensure quality decision making during the process of registration.

Models of regulatory review

There are three models that can be used by national authorities for the regulatory review of products (McAuslane et.al, 2009) and these are:

Verification review (type 1): the agency relies on assessments and approval by two or more reference regulatory authorities and employs a verification process to ensure that the product under review conforms to the previously authorized product specifications. A reference regulatory authority is defined as a mature and established authority whose reviews or decisions are relied on by another regulatory authority.

Abridged review (type 2): the agency conducts an abridged review (reduced in scope and length, while retaining essential elements) of a medicine approved by at least one reference authority, taking into consideration local cultural and environmental factors.

Full review (type 3A): the agency performs a full review of quality, safety, and efficacy of the product, but requires prior approval by another authority and/or type 3B which involves independent assessment of the same but does not require prior approval of the product by an authority.

In recent years, regulatory authorities have successfully implemented a work-sharing model of review in the form of joint reviews or coordinated assessments. For Zimbabwe, this is achieved through participation in the ZaZiBoNa initiative (Sithole et.al, 2020) and for Australia, Canada, Singapore and Switzerland, through the ACCESS consortium (McAuslane et.al, 2017). The other members of the ZaZiBoNa initiative are Angola, Botswana, Comoros Islands, Democratic Republic of Congo, Eswatini, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, United Republic of Tanzania and Zambia. In January 2021, the United Kingdom also became a member of the ACCESS consortium.

RESULTS

For the purpose of clarity, the results will be presented in five parts: Part I – organization of the regulatory authorities; Part II – review models; Part III – key milestones in the review process; Part IV – good review practices; and Part V – quality decision-making practices.

Part I - Organization of the regulatory authorities

The five authorities have similar scopes and mandates to regulate medicinal products and medical devices although for the MCAZ the scope for medical devices is currently limited to gloves and condoms. In addition, TGA, Health Canada and Swissmedic also regulate in vitro diagnostics while only TGA and Health Canada regulate blood and blood products. Cell and tissue products, food, complementary medicines and/or natural health products were outside the scope of this study. The MCAZ has 143 employees in total, translating to a staff to population ratio of 9 per million. This figure is very low when compared with the other four countries: TGA 31, Health Canada (Health Products and Food Branch) 60, HSA 102 and Swissmedic 45. In general, the fees charged for both proprietary and non -proprietary products are much lower for MCAZ compared with the fees charged by the four authorities in the high-income countries.

The MCAZ receives no funding from the government. In comparison, the TGA review of medicines and medical devices is fully cost recovered with no government funding, while for Health Canada, HSA and Swissmedic government contribution to funding is 67%, 80% and 18%, respectively.

Part II - Review models

The major difference in the review models between Zimbabwe and the other four countries is that the MCAZ requires a certificate of pharmaceutical product (CPP) – confirming that the medicine has been approved in the country of origin before it can be registered. The MCAZ conducts a full review (type 3A) only for generics and biosimilars not approved by a reference authority but approved in the country of origin while the other agencies conduct a full review for all products. All of the studied agencies, with the exception of Health Canada, conduct abridged reviews while only the MCAZ and HSA conduct verification reviews (Table 3.1). The MCAZ currently uses verification review only for WHO-prequalified products while HSA conducts verification reviews for products approved by two reference authorities. All five agencies have a formal priority review procedure for medicines used in conditions for which no other treatment exists or for medicines improving existing therapies.

Part III - Key milestones in the review process

The MCAZ has defined key milestones and target timelines in the regulatory review process. The simple map (Figure 3.1) (Sithole et.al, 2021c) illustrates the full review process for a product that is approved after one cycle with no questions raised after assessment.

Steps taken in the event that a registration application is refused, are not depicted in the process map. The review process and milestones recorded are similar for TGA,

Table 3.1. Models of assessment employed by the five agencies

Review model	Zimbabwe	Australia	Canada	Singapore	Switzerland
Verification review (type 1)	✓	✗	✗	✓	✗
Abridged review (type 2)	✓ `	✓	✗ [a]	✓	✓
Full review (type 3A)	✓	✓	✓	✓	✓
Full review (type 3B)	✗	✓	✓	✓	✓

[a] A forward regulatory plan 2020 – 2022 has been developed with an initiative title of 'regulations amending the food and drug regulations - use of foreign decisions pathway' which will enable abridged review of products approved by a trusted authority.

Figure 3.1. Regulatory review process map for Zimbabwe showing target times in calendar days
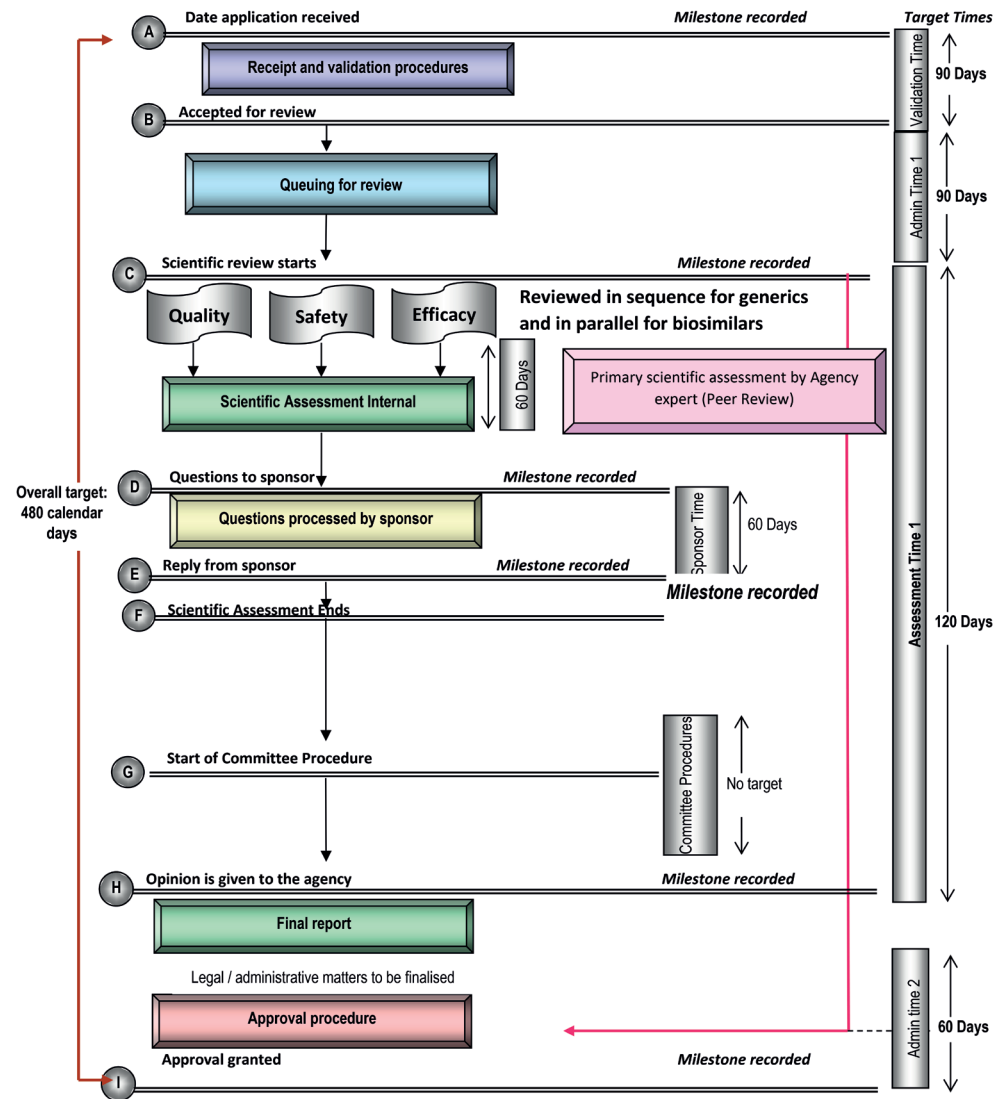
[The map represents the review and authorization of a product that goes to approval after one review cycle – the additional two cycles would add another 120 calendar days resulting to 480 as target review time]

HSA and Swissmedic; however, the targets for each milestone are different. For Health Canada, the milestones are similar; however, the clock is only stopped for a notice of deficiency but not for clarification requests, which are sent during review. In addition, the agency does not have a target or formal milestone for queuing in the review process. All five agencies have defined target times for the key milestones in their review processes (Table 3. 2).

Pre-submission procedure

The MCAZ has no pre-submission procedure for applicants who are planning to submit applications for registration. However, the HSA requires a notice of intent to submit an application for type 3 review. The TGA, Health Canada and Swissmedic provide applicants an opportunity to meet with agency staff to discuss upcoming submissions. This allows the agency to plan resources, become familiar with the application and discuss any issues with the applicant prior to submission.

Validation

All five agencies perform this administrative step in the review process to screen applications for completeness within specified timelines (Table 3.2). The legal status of the applicant as well as format, fees and good manufacturing process (GMP) status are some of the issues checked at this stage. The MCAZ has the longest target time for validation at 90 days, followed by Health Canada at 55 days, then HSA and Swissmedic at 30 days while TGA has the shortest target time of 15 – 21 days.

Queuing

The queue time is the time taken between acceptance of a submission for evaluation and the start of the scientific assessment. Queuing is indicative of a backlog and lengthens the overall approval time of products. The MCAZ has a target queue time of 90 days while the HSA queue time is 90 -180 calendar days. Health Canada does not have a queue time milestone but reviews do not necessarily start following acceptance. The TGA and Swissmedic reported that they do not have a backlog therefore there is no queuing of applications.

Scientific assessment and data requirements

All five agencies require the full modules 1 to 5 of the Common Technical Document format; that is, chemistry, manufacturing and control (CMC), non-clinical and clinical data as well as summaries, regardless of the review model used. An extensive assessment of all the sections is conducted under the full review model. The review of the quality,

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Table 3. 2. Comparison of target times in the full review process for the five agencies (calendar days)

Target	Zimbabwe	Australia	Canada	Singapore	Switzerland
Validation (including screening)	90	15 – 21	55	30	30
Scientific assessment	60 / cycle	180	300	N/A	300
Applicant response time	60	30 - 60	15 per clarifax 90 for NOD[a]	14 – 60	90
Expert Committee(s)	No target	75 – 105[b]	N/A	N/A	N/A
Authorisation procedure	60	30	N/A	N/A	30 - 90
Overall Approval time	480 (incl. applicant time)	330 (incl. applicant time)[c]	355 (excl. applicant time)	360 – (excl. applicant time)	330 (excl. applicant time)

N/A = Not available
[a] clarifax = request for clarification; NOD = notice of deficiency.
[b] Includes consideration of the applicant's pre-Advisory Committee on Medicines response as well as writing up of the Committee's advice.
[c] From acceptance for evaluation through to the registration decision. The legislated TGA commitment for the same milestone is 255 working days (357 calendar days); however, this is not used for planning or for target times.

safety and efficacy data is carried out in parallel by four of the agencies, whereas MCAZ reviews these sections sequentially for all products excluding biosimilars (Sithole et.al, 2021c). The pricing of medicines is not regulated in Zimbabwe. Pricing negotiations are separate from the technical review in the comparator agencies; however, in Australia and Canada, there is an option for health technology assessments to be conducted in parallel with the regulatory review.

For Health Canada, 90% of NASs are issued with a decision after the first review cycle, whereas assessments are completed in one or two cycles for TGA and Swissmedic 4and three to four cycles for MCAZ. The TGA, Health Canada and Swissmedic set targets for both the primary scientific assessment and the second round of assessment and in addition share the assessment reports with the applicant. Similarly, the MCAZ also sets targets for both the primary and second round of assessments although the MCAZ does not share assessment report with applicants. The MCAZ however, does not share assessment reports with applicants. The TGA, Health Canada, Swissmedic and HSA make use of internal and external experts to perform reviews while the MCAZ currently uses internal experts for reviews and external experts only for the Committee procedure. The MCAZ has provision for use of external experts for reviews however, none were employed at the time of the study.

Questions to applicant

Applicants are given the opportunity to respond to questions arising during the assessment in all the five agencies. The MCAZ collects all the questions into a single batch and sends these to the applicant at the end of each review cycle (stop-clock) and only after presentation to the external expert Committee. The HSA and Swissmedic send the questions to the sponsor/ applicant at the end of a review cycle but before presentation to the Committee. Health Canada sends questions to applicants during review known as clarification requests. This is done independently by the safety, efficacy and quality review streams. However, the review is paused and a notice of deficiency (NOD) sent to the applicant if the observed deficiencies prevent continuation of the review. Applicants are allowed only one NOD per application. This is similar to TGA, whose assessors can contact the applicant directly to seek clarification during the review process. The TGA usually presents the report to the committee when it is at an advanced stage, although there is scope to obtain committee or subcommittee advice at an earlier stage, whereas there is no formal procedure for committee involvement at Health Canada. The time given to the applicant by the five agencies ranges from 14 – 90 days (Table 3.2).

Expert committee

All five agencies engage expert or advisory committees at different points in the regulatory review process. The MCAZ is the only agency mandated to follow the committee's decision. The other four agencies use the committee in an advisory capacity to provide expert opinions and additionally the committee for Swissmedic may also conduct assessments or reviews.

Authorization

Labelling issues must be addressed before a product is authorized in all five agencies. At the MCAZ, responsibility for the marketing authorization decision lies with the Registration Committee. The Director General makes the decision on registration for Health Canada and HSA, whereas for TGA, the responsibility is delegated to a senior medical officer, and at Swissmedic the decision is made by the case team with the involvement of the Head of Division/Sector. In all five agencies, compliance with GMP is audited during the review process and the outcome informs product authorization. The target time for the overall approval for a full review for the MCAZ is 480 days, inclusive of the applicant's time and this is comparable to the target times for the comparator countries: TGA, 330 days including the applicant time; Health Canada, 355 days excluding applicant time to respond to an NOD and any other approved pauses, ranging from 5 to 90 days; HSA, 378 calendar days excluding the queue and applicant time; and Swissmedic, 330 days excluding the applicant time (Table 3.2). The target times are comparable because the 480 days for MCAZ includes the applicant's time. If the applicant's time (target 60 days per assessment cycle for 2 cycles) was to be excluded, this would come down to 360 calendar days.

Metrics of approved products and review times

The number of NASs approved in 2019 - 2021 was documented (Figure 3.2). In 2019, Health Canada had the highest number of NASs approved at 35, followed by Swissmedic at 28, TGA at 25, MCAZ at 19 and HSA at 17. In 2020, Swissmedic had the highest number of NASs approved at 36, followed by Health Canada at 33, TGA at 27, HSA at 13 and MCAZ at 4. In 2021, Swissmedic had the highest number of NASs approved at 37, followed by TGA at 35, Health Canada at 34 and MCAZ at 15. Data for HSA for 2021 was not available. The median approval time (from submission to completion of scientific assessment) for NASs in 2019 - 2021 for the five agencies was evaluated (Figure 3.3) and in 2019, MCAZ had the shortest approval time of 272 calendar days followed by Swissmedic at 312, Health Canada at 342, TGA at 346 and HSA at 414 calendar days. In 2020, Health Canada had the shortest approval time of 306 calendar days followed

Figure 3.2. Comparison of the number of new active substances (NAS) approved by the five agencies in 2019 - 2021
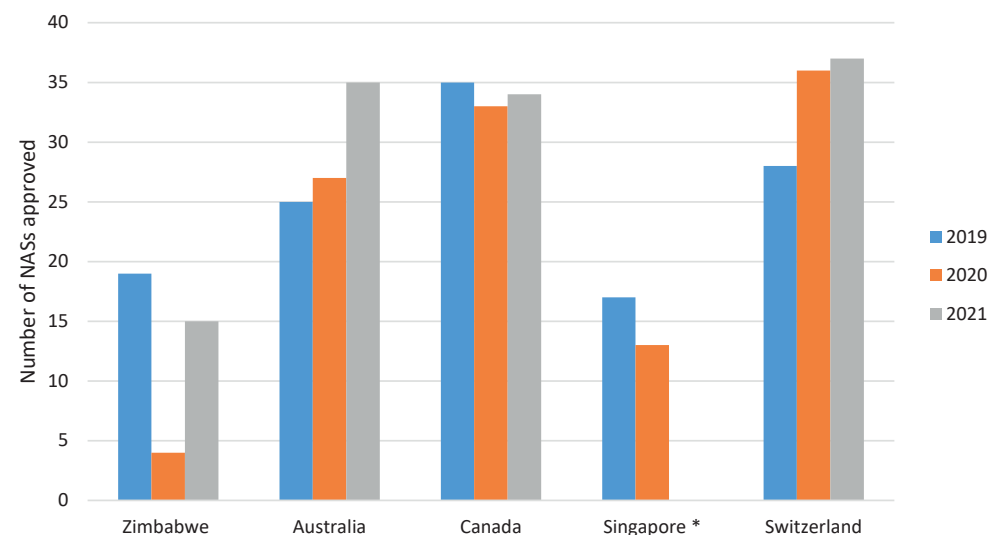
*Figures for 2019 and 2020 were obtained from industry data. Data for 2021 was not available

by TGA at 315. These approval times were also shorter than the previous year's times. However, Swissmedic, HSA and MCAZ's review times increased to 470, 456 and 486 days respectively in 2020. In 2021, Health Canada had the shortest approval time of 301 days, followed by TGA at 350 days, Swissmedic at 392 days and MCAZ at 478 days. It should be noted however that the MCAZ and HSA conduct an abridged review of NASs, as these would have already been approved by a reference agency. The times presented for Australia, Canada and Switzerland are for a full review.

Part IV - Good review practices

Good review practices (GrevPs) can be defined as measures or practices implemented with the goal to ensure quality, transparency and consistency as well as continuous improvement in the regulatory review process. These were evaluated for the five agencies and compared for quality measures, transparency and communication, continuous improvement initiatives and training and education.

Quality measures

The study evaluated a number of quality measures (Table 3.3). The MCAZ, Health Canada and Swissmedic have a dedicated quality department and implement all

Figure 3.3. Comparison of median approval time for NASs approved in 2019 - 2021 by the five agencies
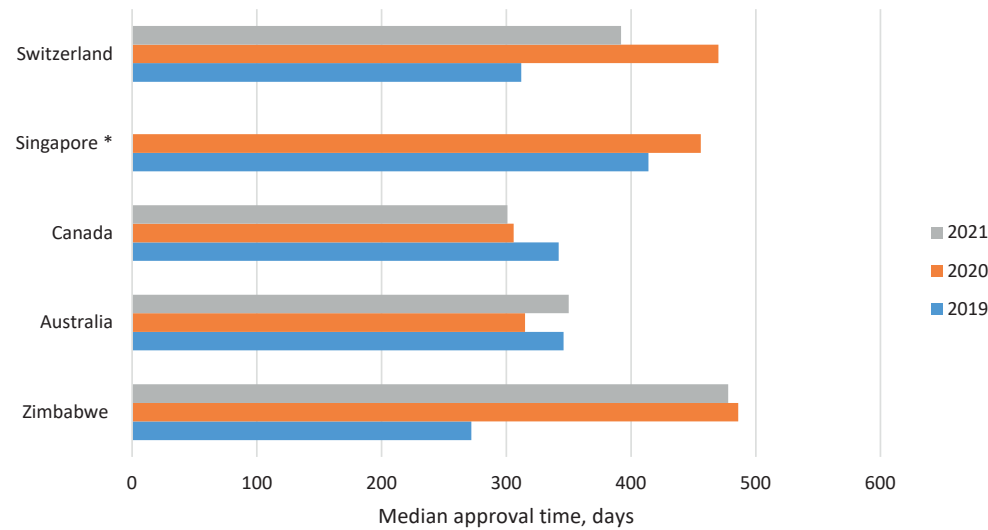
* Figures for 2019 and 2020 were obtained from industry data. Data for 2021 was not available.

eight of the quality measures. In addition, Health Canada has established a quality management system and a dedicated office for the Biologic and Radiopharmaceutical Drugs Directorate and is in the process of establishing one for the Therapeutic Products Directorate, incorporating all quality measures. The TGA implement seven of the eight measures and the HSA implement six quality measures. Health Canada and Swissmedic have formally implemented GRevPs, while the other three authorities have informally implemented GRevPs. All five agencies participate in shared and joint reviews. The MCAZ is a member of the medicines' registration harmonization initiative, ZaZiBoNa (MCAZ, 2020), and the four comparator agencies are members of the ACCESS Consortium (TGA, 2021) and both initiatives have worked extremely successfully.

Transparency and communication with industry stakeholders

A well-established and mature regulatory authority is expected to practice transparency and communication with stakeholders. This is also one of the indicators evaluated by the WHO Global Benchmarking Tool, which seeks to determine the maturity level of a regulatory system (Khadem et.al, 2020). This comparative study evaluated the performance of the five regulatory authorities using nine transparency

Table 3.3. Comparison of the quality measures implemented by the five agencies

Quality Measure	Zimbabwe (8/8)	Australia (7/8)	Canada (8/8)	Singapore (6/8)	Switzerland (8/8)
Good review practice system	✓ (informally)	✓ (informally)	✓ (formally)	✓ (informally)	✓ (formally)
Internal quality policy	✓	✓	✓	✗	✓
Standard operating procedures for guidance of assessors	✓	✓	✓	✓	✓
Assessment templates	✓	✓	✓	✓	✓
Peer review	✓	✓	✓	✓	✓
Dedicated quality department	✓	✗	✓	✗	✓
Scientific Committee	✓	✓	✓	✓	✓
Shared and joint reviews	✓	✓	✓	✓	✓

Informally – System is in place but not documented.

and communication parameters (Table 3.4). Of the five agencies, MCAZ implements the lowest number of parameters. Currently, post-approval feedback on submitted applications, contact details of technical staff, the summary basis of approval and advisory committee dates are not shared with the stakeholders. The HSA do not share the advisory committee dates with applicants and in addition, HSA does not publish the summary basis of approval or provide feedback to the applicant on submitted dossiers. The TGA implements all of the nine transparency and communication parameters as does Swissmedic and Health Canada while the HSA implements six and the MCAZ five of the nine measures (Table 3.4).

Continuous improvement initiatives

A comparison was made of the continuous improvement initiatives that have been implemented by the five regulatory authorities. The MCAZ and Swissmedic implement all five initiatives, the TGA, HSA and Health Canada implement four of the five initiatives (Table 3.5).

Training and education

All five regulatory authorities implement all eight of the measures for training and education namely induction training, on-the-job training, attendance at internal and external courses, international workshops and secondments to other regulatory authorities, sponsoring of post-graduate degrees, in-house courses as well as external speakers being invited to the authority.

Part V - Quality decision-making practices

The 10 Quality Decision Making Practices (QDMPs) were recorded as part of the development of the Quality of Decision-Making Scheme (QoDoS) instrument, which has been implemented in a number of medicines development scenarios (Bujar et.al, 2017; Bujar et.al, 2019). Generally, all five authorities either partially or fully implement the majority of the ten QDMPs that were evaluated in the study (Table 3.6). However, the MCAZ does not have a documented framework in place on QDMPs.

DISCUSSION

The results from this study show that the human and financial resources available to national regulatory authorities (NRAs) in LMICs are much lower compared with those in higher income countries. However, the funding models of the regulators in the higher income countries do differ significantly – ranging from majority government funding through to full industry funding of regulatory activities. A challenge that exists for

Table 3.4. Comparison of the transparency and communication parameters with regulated parties in the five agencies

Parameter	Zimbabwe (5/9)	Australia (9/9)	Canada (9/9)	Singapore (6/9)	Switzerland (9/9)
Post-approval feedback to applicant on submitted dossiers	✗	✓	✓	✗	✓
Details of technical staff to contact	✗	✓	✓	✓	✓
Pre-submission scientific advice to industry	✓[b]	✓	✓	✓	✓
Official guidelines to assist industry	✓	✓	✓	✓	✓
Industry can track progress of applications	✓	✓	✓	✓	✓
Publication of summary of grounds on which approval was granted	✗	✓	✓	✗	✓
Approval times	✓	✓	✓	✓	✓
Advisory committee meeting dates	✗	✓	✓	✗	✓
Approval of products	✓	✓	✓	✓	✓

[b] Provided to local manufacturers upon request

Table 3.5. Comparison of continuous improvement initiatives in the five agencies

Measure	Zimbabwe (5/5)	Australia (4/5)	Canada (4/5)	Singapore (4/5)	Switzerland (5/5)
External quality Audits	✓	✗	✓	✗	✓
Internal quality Audits	✓	✓	✓	✓	✓
Internal tracking Systems	✓	✓	✓	✓	✓
Reviews of assessors' feedback	✓	✓	✗	✓	✓
Reviews of stakeholders' feedback	✓	✓	✓	✓	✓

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Table 3.6. Comparison of implementation of quality decision making practices

Measure	Zimbabwe (9/10)	Australia (8/10)	Canada (8/10)	Singapore (9/10)	Switzerland (10/10)
1. Have a systematic, structured approach	✓	✓	✓	✓	✓
2. Assign clear roles and responsibilities	✓	✓	✓	✓	✓
3. Assign values and relative importance to decision criteria	✗	✗	✗	✗	partially
4. Evaluate both internal and external influences/biases	partially	✓	✗	✓	✓
5. Examine alternative solutions	✓	✓	✓	✓	✓
6. Consider uncertainty	✓	✓	✓	✓	✓
7. Re-evaluate as new information becomes available	✓	✓	✓	✓	✓
8. Perform impact analysis of the decision	partially	✗	✓	✓	✓
9. Ensure transparency and provide a record trail	✓	✓	✓	✓	✓
10. Effectively communicate the basis of the decision	✓	✓	✓	✓	✓

a country such as Zimbabwe, whose NRA relies 100% on fees, is the high cost of entry to the market for applicants due to the registration fees being high relative to the country's GDP and the population's ability to pay for the medicines (Morgan et.al, 2017; World Bank, 2021). This means that it may not be possible for the MCAZ to increase registration fees in order to improve available resources for regulatory reviews, therefore the use of reliance may be a more appropriate strategy. The need for reliance and the efficient use of limited resources by LMICs has been documented in the literature (Ahonkhai et.al, 2016; CIRS, 2018; Luigetti et.al, 2016; Sithole et.al, 2020), with the argument that it allows NRAs to focus their limited resources on products not approved elsewhere (Sithole et.al, 2021c). Reliance also provides the NRAs the opportunity to build capacity without hindering access to medicines by their populations. Participation in harmonization initiatives such as ZaZiBoNa (Sithole et.al, 2020) by countries with low GDPs and small populations may also provide manufacturers the potential incentive of a larger market. It has been pointed out that it is no longer adequate for the regulator to just passively wait to assess submissions received from industry. The regulator must now be proactive in providing pathways that facilitate and encourage the timely registration of medicines to promote public health (CIRS, 2018; Lumpkin et.al, 2012) and information on these pathways should be documented and publicly available.

The requirement for a CPP is not necessary where a full review is conducted (Rodier et.al, 2020). The findings of this study show that of the regulatory authorities studied, only the MCAZ requires the CPP as a pre-requisite for registration and does not accept products that are not approved in the country of origin. This is consistent with findings from studies in the literature that showed that regulatory authorities in the emerging economies still require CPPs (Rodier et.al, 2020). Manufacturers have indicated that the time taken to obtain a CPP can delay the submission of applications for registration and subsequent supply of life-saving medicines to countries enforcing that requirement. Therefore, the requirement for a CPP should be removed where a full review is conducted (Ahonkhai et.al, 2016) and an alternative such as the marketing authorization license used if evidence of approval is required. Furthermore, there is a need for regulatory authorities in LMICs to build adequate capacity to independently assess NASs (new chemical entities and biologicals) even though at present, most companies only file applications for registration in developing economies several years after approval and use in well-resourced markets (Ahonkhai et.al, 2016; Rägo et.al, 2008). In the near future, we could see products developed for diseases endemic to Africa submitted directly to the African countries and therefore

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the capacity to conduct independent reviews needs to be developed (Gwaza, 2016; Sithole et.al, 2020).

The key milestones recorded in the review process, data requirements and the extent of scientific assessment were similar for the five agencies with the only difference being the practice by TGA and Health Canada of requesting clarifications formally during the scientific assessment in addition to the formal questions sent to the applicant at the end of a review cycle. This is a practice that could potentially reduce the number of review cycles and questions eventually sent out during the clock stop. Generally, the MCAZ target times were longer for validation and queue time but comparable for questions to the applicant and overall approval time. The MCAZ ability to have a comparable review process and timelines with less resources than the other authorities is a positive attribute although the MCAZ's review times for 2020 and 2021 increased as a result of the impact of the Covid-19 pandemic. There is an opportunity for the MCAZ to learn from the authorities in this study to adopt practices that could potentially further reduce approval times. Another step in the review process implemented by TGA, Heath Canada and HSA that could benefit MCAZ is to provide applicants, especially the local manufacturing industry, more opportunity for pre-submission meetings. The MCAZ was found to be the only NRA in the study relying on an expert committee to make the decision on the marketing authorization of products, whereas for the other authorities, this decision was made by the Head of the Agency, Head of Section or agency staff, with the expert committee used in an advisory capacity. The MCAZ could consider adopting a similar position, as preparation for the frequent committee meetings adds to the registration time. However, this would require a legislative amendment, as all statutory decisions are made by the Authority (Board).

Another strength of the MCAZ is the implementation of GRevPs such as ensuring quality in the review process, use of standard operating procedures, guidelines and templates, continuous improvement initiatives such as quality audits and internal tracking systems, and training and education of assessors. However, there is room for improvement on transparency and communication with stakeholders. There is also scope to improve decision-making practices by the MCAZ through the development of a formal framework. Although the issues of pricing and availability of medicines are outside the scope of this paper, Zimbabwe could learn from the high-income countries such as those that took part in this study, and establish a health technology assessment (HTA) agency to better tackle the issues of accessibility and affordability of health services including medicines. This will facilitate the prioritisation of health

interventions and the formulation of evidence based health policies leading to better outcomes for patients. The WHO has also recommended that member states build capacity in health intervention and technology assessment to support universal health coverage (WHO, 2021d). The absence of formal HTA agencies, lack of capacity and shortage of resources are some of the reasons cited as contributing to the lack of health technology assessments in LMIC (Attieh et.al, 2012; Nemzoff e.al, 2021)

Several studies have been conducted for South Africa, Turkey, Jordan and Saudi Arabia in comparison with other mature agencies (Al Haqaishet.al, 2017; Ceyhan et.al, 2018; Hashan et.al, 2016; Keyter et.al, 2019). Like Zimbabwe, these countries had strengths in their review processes that were comparable to those of the mature agencies. The challenges identified and the recommendations made although different, provided the opportunity for these countries to strengthen their regulatory review processes.

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CHAPTER 04

COMPARISON OF THE REGULATORY REVIEW PROCESS OF THE SADC WORK SHARING INITIATIVE MEMBER COUNTRIES

SUMMARY

- National medicines regulatory agencies are faced with challenges including limited resources and technical capacity, resulting in countries collaborating and sharing resources to improve the efficiency of the review process and facilitate access to quality-assured medicines by their populations.

- One such collaboration is the Southern African Development Community (SADC) medicines registration collaborative initiative, ZaZiBoNa. Countries participate in the initiative by contributing to the regulatory reviews and good manufacturing practices inspections.

- The aim of this study was to review and compare the registration processes of regulatory authorities of Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe and to identify strategies for better alignment.

- An established and validated questionnaire (Optimising Efficiencies in Regulatory Agencies) was completed by each of the respective agencies.

- The six countries varied in population and in the size of their respective regulatory agency as well as the resources allocated to regulatory reviews.

- The review processes of the six agencies were similar; however, differences were noted in the milestones recorded; for example, two of the countries did not record the start of the scientific assessment.

- Decisions for marketing authorisation were made by an expert committee in four of the countries and by the head of the agency and the Minister of Health in two countries. The frequency of meeting of the expert committees also varied from monthly to quarterly.

- All six agencies implemented the majority of good review practices; however, the need for improvement in the areas of transparency and communication and quality decision making was a common finding for all six countries.

- Participation in the ZaZiBoNa initiative has improved the way in which the six agencies perform regulatory reviews in their countries, highlighting the realisation of one of the key objectives of the initiative, which was building the expert capacity of member countries.

- Other agencies in the SADC region and beyond can use the approach described in this study to identify best practices, which in turn, could improve their regulatory performance.

RECOMMENDATIONS

As a result of this study several recommendations could be considered by these agencies.

- **Performance measurement**: In order to benchmark the regulatory review process and monitor performance, agencies should consider measuring and documenting the key milestones and publishing the relevant timelines.

- **Improvement initiatives:** Agencies could consider re-examining their processes to evaluate where they can be improved, and to learn from agencies with comparable workloads who are achieving shorter timelines.

- **Sharing assessment reports:** Agencies participating in the ZaZiBoNa initiative should consider entering into a memorandum of understanding to share unredacted assessment reports for products that are not submitted to the initiative, which constitute the majority of the agencies' workload.

- **Increased transparency and communication**: Agencies would benefit from implementing additional measures of transparency and communication in line with international best practices such as sharing of assessment reports with applicants and publishing approval times, as well as advisory committee dates and a summary basis of approval.

- **Improved performance**: Agencies should consider using the results of this study to propose the provision of adequate resources to improve timelines and patients' access to medicines.

- **Quality decisions**: There is a need in some agencies for training and capacity building in quality decision making.

- **ZaZiBoNa operating model**: The participating countries could consider reviewing the existing operational model for improved efficiency.

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INTRODUCTION

The Southern African Development Community (SADC) is made up of 16 countries; Angola, Botswana, Comoros Islands, Democratic Republic of Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Swaziland, United Republic of Tanzania, Zambia, and Zimbabwe (SADC, 2021a). Although the countries have differing capacities to regulate medicines (Dube-Mwedzi et.al, 2020), they share the common challenge of inadequate capacity to review applications for medicines, resulting in backlogs and delayed access to medicines by patients. This led to the formation of a collaborative medicines registration initiative called ZaZiBoNa by four countries, Zambia, Zimbabwe, Botswana and Namibia with technical support from the World Health Organization (WHO) Prequalification team and the Southern African Regional Programme on Access to Medicines and Diagnostics (SARPAM) in 2013 (Sithole et.al, 2020). The initiative was formally endorsed by the SADC Ministers of Health in 2015, and member states who signed the memorandum of agreement to participate in the initiative were assigned active or non-active status, depending on their capacity to conduct assessments and good manufacturing practices (GMP) inspections. The remaining countries, Mauritius and Lesotho, participate as observers (Sithole et.al, 2020).

Operational aspects of ZaZiBoNa

ZaZiBoNa is a SADC work-sharing initiative, in which regulatory authorities conduct joint or shared reviews of applications for registration of medicines submitted to participating countries with the applicant's consent (Sithole et.al, 2020). One of the successes of the ZaZiBoNa initiative is that since its inception in 2013, more than 300 products have been reviewed and the median time to a recommendation was shorter than that achieved by individual participating countries using the national procedure (Masekela, 2020). However, because the ZaZiBoNa initiative is not a legally constituted regulatory authority, it relies significantly on the participating countries to achieve a number of key milestones in the review process, particularly those of an administrative nature (Sithole et.al, 2020). As a result, one of the challenges that has been identified with this initiative is the fact that differences in country review processes result in questions to applicants for the same product being sent at different times by the agencies, affecting registration timelines and negating the benefit of simultaneous access to various markets. Sithole and colleagues recommended that the regulatory review processes in the individual participating countries be reviewed and the outcomes compared (Sithole et.al, 2020, Sithole et.al 2021c). The aim of this study therefore was to review and compare the registration processes of regulatory authorities of Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe

to develop recommendations for better alignment, while presenting an opportunity for the countries to learn from each other and enhance their regulatory review and patients' access to life-saving medicines. This chapter, details the findings, focusing on the review processes and good review practices. The next chapter will address review models and metrics of the process.

METHODS

Study participants

Nine countries with active member status in the ZaZiBoNa initiative were invited to participate in the study following a face-to-face presentation. Active member status is defined as 'the capacity to conduct assessments and GMP inspections'. One of the countries (Botswana) could not complete the questionnaire because their agency had only recently been established and the participation by two countries (the Democratic Republic of Congo and Malawi) was unlikely because of disruptions caused by the Covid-19 pandemic. Therefore, the six regulatory agencies included in this study were the National Directorate of Pharmacy in the Mozambique Ministry of Health; Namibia Medicines Regulatory Council (NMRC) in the Namibia Ministry of Health and Social Services; the South African Health Products Regulatory Authority (SAHPRA); the Tanzania Medicines and Medical Devices Authority (TMDA); the Zambian Medicines Regulatory Authority (ZAMRA); and the Medicines Control Authority of Zimbabwe (MCAZ).

Data collection

Each of the six agencies completed an established and validated questionnaire (Optimising the Efficiencies of Regulatory Agencies) (McAuslane et.al, 2009) in 2020, which described the organisational structure, the regulatory review system for market authorisation for new active substances (NASs) and generics as well as their overall review times from the date of application to the date of approval, good review practices (GrevP) and quality decision-making practices. The questionnaire allowed for the collection of data in a standardised format, enabling comparison and analyses of information collected from the six agencies.

The questionnaire consists of five parts: *Part 1*, documents the structure, organisation and resources of the agency; *Part 2*, identifies different types of review model (s) used for the scientific assessment of medicines; *Part 3*, documents information on the key milestone dates and the process using a standardised process map; *Part 4*, records how quality is built into the regulatory process (GrevP) and *Part 5*, explores the quality of the decision-making practices of the agency.

RESULTS

For the purpose of clarity, the results of this chapter will be presented in four parts: Part I – organisation of the regulatory authorities; Part II – key milestones in the review process; Part III – good review practices; and Part IV – quality decision-making practices.

Part I - Organisation of the regulatory authorities

The six countries, Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe, vary in population and size of their respective regulatory agency (Table 5.1). South Africa (58.8 million) and Tanzania (58.6) have the largest populations, while Namibia has the smallest (2.6). Four countries, South Africa, Tanzania, Zambia and Zimbabwe have autonomous agencies independent of the Ministry responsible for Health. All six agencies have the common mandate to regulate medicinal products, medical devices and in vitro diagnostics for human and veterinary use, except for Mozambique, which does not regulate products for veterinary use. In addition, the South African agency also has the mandate to control the development and use of radiation procedures.

The ratio of total staff per million residents varied across the six countries, with Namibia having the highest ratio of 10, followed by Zimbabwe at 8.8, Zambia at 6.9, South Africa at 2.9, Mozambique at 2.8 and Tanzania at 1.8. The professional background of the agency reviewers was primarily pharmacy for all six agencies and only South Africa and Tanzania had physicians as part of their review teams. Tanzania had the highest proportion of reviewers to total agency staff (44%), followed by South Africa (34%), Zambia (16%), Namibia (15%), Zimbabwe (13%) and Mozambique (6%). The agencies in South Africa, Tanzania and Zambia made use of external experts in the review of applications for registration, employing at the time of the study, 32, 36 and 8 external reviewers, respectively, while the other countries used only internal experts. Zimbabwe, however, had a provision for use of external experts even though none were employed at the time of the study.

If, hypothetically, all new applications received in a year were reviewed in that same year, then the workload; that is, the number of dossiers to be reviewed per year per internal reviewer for 2019 was the highest for Mozambique (42), followed by Namibia (37), Zambia (31), Tanzania (19) and Zimbabwe (11).The workload for South Africa could not be calculated as the agency was unable to provide data for products in 2019 due to mitigating circumstances related to the unfit status of the organisation's premises. However, all six agencies reported that they had a backlog of pending applications, therefore not all applications were reviewed in the year that they were received.

The analysis also did not take into account the type of review to be conducted, the competence of reviewers or other work such as post-approval variations. It should be noted that in some of the countries due to low numbers of staff, the same reviewer was responsible for reviewing the quality, pre-clinical and clinical sections of the dossier. The countries with greater numbers of reviewers had one reviewer focusing on quality and different reviewers for non-clinical and clinical.

Source of funding

The Namibian agency was funded entirely by its government, in Mozambique the greater proportion of agency funding was from its government and a small percentage from other sources, in South Africa, 70% of agency funding was provided by its government and 30% from fees, in Tanzania, 12% of agency funding was by its government, 76% from fees and 12% from other sources, in Zambia, 95% of agency funding came from fees and 5% from other sources and the Zimbabwe agency was funded entirely from fees. There is a significant range of fees applied for the registration of the products, depending on their category such as new chemical entities, biologicals or generics. It is worth noting that none of the agencies charged fees for scientific advice given to applicants.

Namibia charged the lowest fees (333 USD) for new chemical entities, while South Africa charged the highest (3,558 USD) (Table 4.2). For biologicals, Namibia charged the lowest fees (333 USD) while Tanzania charged the highest (3,500 USD). For generics, Namibia charged the lowest fees (333 USD), while Zimbabwe charged the highest (2,500 USD). The agencies funded largely or entirely by government charged the lowest fees, whilst those relying on fees charged higher amounts with the exception of South Africa which received 70% of its budget from the Government, but charged fees comparable to Tanzania, Zambia and Zimbabwe agencies, which are funded largely through fees.

Part II – Key milestones in the review process

A standardised process map for the review and approval of medicines is shown in Figure 4.1. This is a simplified representation of the key milestones that are typically recorded and monitored in the review of applications in a mature regulatory system. The process map represents the review and authorisation of a product that goes to approval after one review cycle; however, in practice it usually takes more than one cycle for a medicine to be approved, some agencies limit the number of review cycles and opportunities given to applicants to respond to questions.

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Table 4.1. Comparison of the country population, size of agencies and workload in 2019

Country	Mozambique	Namibia	South Africa	Tanzania	Zambia	Zimbabwe
Population (millions)	29.5	2.6	58.8	58.6	17.4	16.2
Agency staff	83	26	170	103	120	143
Staff per million residents	2.8	10	2.9	1.8	6.9	8.8
Number of internal reviewers	5	4	57	45	19	18
Reviewers in agency staff	6%	15%	34%	44%	16%	13%
Total applications received	208	146	N/A*	873	585	203
Number of applications per reviewer	42	37	N/A*	19	31	11

* SAHPRA was unable to provide data for 2019 due to mitigating circumstances related to the unfit status of the organisation's premises.

Table 4.2. Comparison of fees charged and source of funding in 2019

Country	Mozambique	Namibia	South Africa	Tanzania	Zambia	Zimbabwe
Source of funding*	Majority % government, remainder % other sources	100% government	70% government 30% Fees	12% government; 76% fees; 12% other	95% fees 5% other	100% fees
Fees for review of a new chemical entity (USD)	360	333	3,558	2,000	2,800	3,000
Fees for review of biologicals (USD)	360	333	2,833	3,500	2,800	3,000
Fees for review of generics (USD)	350	333	1,781	2,000	2,000	2,500

* Actual percentages vary year to year.

Receipt and validation procedures

All six agencies validated applications received for completeness in line with the applicable guidelines and statutory fees and all six agencies recorded these two milestones. At this stage, the pathway for review was determined; that is, either verification, abridged or full review. Applications that passed validation were placed in a queue awaiting scientific assessment. Incomplete applications were removed from the queue and communication was made to the applicant to provide the missing information.

Queue time

The queue time is the time between the completion of validation/acceptance for review of an application and the start of the scientific assessment. This milestone was recorded by all six agencies.

Primary scientific assessment

The start of the primary scientific assessment was recorded by four of the six agencies, namely Mozambique, South Africa, Tanzania and Zimbabwe.
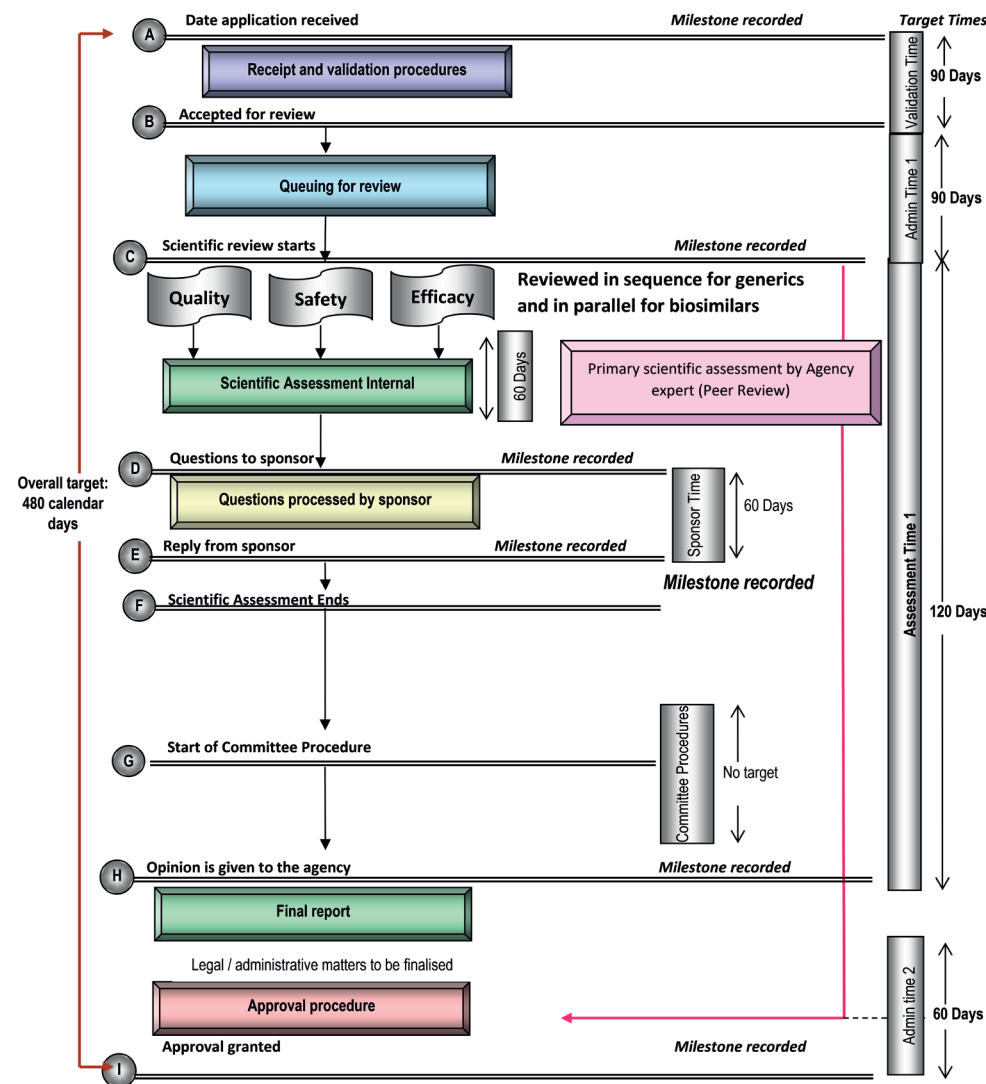
Questions to applicants

All six agencies collected questions into a single batch after each cycle of scientific assessment and sent these to the applicant. This time is also referred to as "clock stop" or company time, when the assessment is paused and the applicant given an opportunity to respond to queries.

Review by expert committees

Five agencies made use of a panel of external experts known as the expert committee during the review process with the agency staff serving as the secretariat, with the exception of Mozambique. The expert committee was involved after questions had been sent to applicants in some agencies and in the other agencies, questions were only sent to applicants after the committee procedure. The external committees are referred to by different names in each of the agencies; however, their function is similar. Namibia, South Africa, Zambia and Zimbabwe were mandated to follow the Expert Committee's opinion on a product and the Committee had the responsibility for the marketing authorisation decision. For Tanzania, the Committee made a recommendation, although the final decision was made by the Director General. The decision for marketing authorisation in Mozambique was made by the Minister of Health.

Figure 4.1. Standardised review process map for the six regulatory agencies

[The map represents the review and authorization of a product that goes to approval after one review cycle – It should be noted that in some countries milestone G (committee procedure) may come before milestone D (questions to the applicant)]

Authorisation procedure

Once an opinion or decision had been made on an application for marketing authorisation, there was an administrative step to finalise reports and update the labelling before the issuance of the marketing authorisation. This step was performed in all six countries.

Part III – Good review practices

For the purpose of clarity, GRevPs are presented under four categories: quality measures; transparency and communications; continuous improvement initiatives; and training and education.

Quality measures

The quality measures evaluated in this comparative study are listed in Table 4.3. Tanzania, Zambia and Zimbabwe implemented all eight quality measures while the remaining three countries (South Africa, Namibia and Mozambique) implemented six of the eight quality measures. Apart from Mozambique, five agencies made use of expert scientific committees as well as implementing a good review practice system (formally or informally). All of the six agencies had standard operating procedures and assessment templates in place. The assessment reports were prepared in English by five agencies; whereas Mozambique prepared their reports in Portuguese, their official language. An internal quality policy was implemented by all agencies apart from Namibia. Four agencies had dedicated quality departments, apart from Namibia and South Africa, although South Africa has now appointed a quality manager with a view to establishing a dedicated quality department. All six agencies conducted a peer review of assessment reports.

Transparency and communication

Transparency in the review process improves stakeholders (applicants as well as other stakeholders such as local agents (which may be different from applicants), wholesalers, customers who are potential applicants, ministry of health or the patients.)' confidence in the system. It also assists the pharmaceutical industry in preparing submissions and planning product launch dates. Transparency saves a regulatory agency time and effort as the industry would be able to access information and requirements independently.

All six agencies assigned high priority to transparency with stakeholders. Nine best practices in transparency and communication with stakeholders were evaluated and used for this comparison (Table 4.4). All agencies had official guidelines and lists of approved products, which were made available to the industry through their websites. Five of the agencies did not provide post-approval feedback to applicants on quality of submitted dossiers or publish advisory committee meeting dates apart from South Africa. Four of the agencies did not provide applicants with details of technical staff to contact during review of their application apart from Mozambique and South Africa. Four agencies did not provide pre-submission scientific advice to the pharmaceutical

Table 4.3. Comparison of the quality measures implemented by the six regulatory authorities

Quality measure	Regulatory authority					
	Mozambique (6/8)	Namibia (6/8)	South Africa (6/8)	Tanzania (8/8)	Zambia (8/8)	Zimbabwe (8/8)
Good review practice system	✗	✓[a]	✓	✓[a]	✓	✓[a]
Internal quality policy	✓	✗	✓	✓	✓	✓
Standard operating procedures for guidance of assessors	✓	✓	✓	✓	✓	✓
Assessment templates	✓	✓	✓	✓	✓	✓
Peer review (internal)	✓	✓	✗	✓	✓	✓
Dedicated quality department	✓	✗	✗[b]	✓	✓	✓
Scientific Committee	✗	✓	✓	✓	✓	✓
Shared and joint reviews	✓	✓	✓	✓	✓	✓

[a] Implemented but not formally documented.
[b] A Quality Manager has now been appointed with a view to establishing a dedicated department.

companies except for South Africa, which implemented this informally and Zimbabwe, which provided this only for the local industry.

All six agencies allowed the industry to track progress of their applications (Table 4.4) via email and telephone contact; however, only Mozambique and Tanzania allowed applicants electronic access to the status of their applications under review. None of the agencies shared the full assessment report with applicants or published a summary basis of approval; however, Tanzania more recently has put in place a procedure for publishing public assessment reports and these were to be available in 2021. All six agencies shared a list of questions after assessment and reasons for refusal with the applicant. Only Tanzania published approval times on their website, whereas South Africa and Zimbabwe published these in their annual performance plan and annual reports, respectively.

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Table 4.4. Comparison of the transparency and communication parameters in the six agencies

Quality measure	Regulatory authority					
	Mozambique (4/9)	Namibia (3/9)	South Africa (8/9)	Tanzania (4/9)	Zambia (4/9)	Zimbabwe (5/9)
Post-approval feedback to applicant on quality of submitted dossiers	✗	✗	✓	✗	✗	✗
Details of technical staff to contact	✓	✗	✓	✗	✗	✗
Pre-submission scientific advice to industry	✗	✗	✓ ᵃ	✓	✓	✓ ᶜ
Official guidelines to assist industry	✓	✓	✓	✓	✓	✓
Industry can track progress of applications	✓	✓	✓ ᵃ, ᵇ	✓	✓	✓
Publication of summary of grounds on which approval was granted	✗	✗	✗	✗	✗	✗
Approval times	✗	✗	✓	✗	✗	✓
Advisory committee meeting dates	✗	✗	✓	✗	✗	✗
Approval of products	✓	✓	✓	✓	✓	✓

ᵃ Implemented informally; ᵇ Only for backlog project; ᶜ Only for local industry.

Continuous improvement initiatives

The continuous improvement initiatives included both internal and external quality audits, an internal tracking system, as well as reviews of assessors' and stakeholders' feedback. South Africa, Tanzania and Zimbabwe implemented all of the five initiatives, while Zambia and Mozambique implemented four out of the five initiatives. Namibia implemented only two out the five initiatives (Table 4.5). Five agencies, apart from Namibia, conducted internal quality audits. Five agencies had internal tracking systems, except for Namibia. The assessors' feedback was reviewed by all six agencies; however, only Namibia, South Africa, Tanzania, Zambia and Zimbabwe reviewed stakeholders' feedback.

Training and education

The measures evaluated under training and education contribute to the development of personnel and the efficiency of the regulatory review process. These measures are induction training, on-the-job training, in-house and external courses, international workshops, placements and secondments in other regulatory authorities, postgraduate degrees and collaboration with other agencies. All six of the regulatory authorities in this comparative study implemented all of the measures for training and education. However, four agencies had formal training programmes for assessors except for Mozambique and Namibia.

Part IV - Quality decision-making practices

The decision-making process should be routinely measured to ensure consistency and quality of decisions made in the review and approval of medicines. Three of the agencies had a framework in place that forms the basis of the decision to approve or reject applications for new medicines, namely South Africa, Tanzania and Zambia. South Africa and Tanzania fully incorporated all of the ten quality decision-making practices (QDMPs) developed by Donelan and colleagues as an aid to decision making (Donelan et.al, 2016) into their frameworks and these were fully adhered to in practice. Zambia incorporated six of the ten practices into their framework and fully adhered to four. Zimbabwe did not have a documented decision-making framework, but used a decision tree approach, fully adhering to seven out of the ten decision-making practices and partially adhering to three. Mozambique and Namibia did not have a documented quality decision-making framework. Interestingly, all six agencies stated that the decision-making process could be improved, while the two agencies without frameworks indicated their intention is to develop them by 2022.

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Table 4.5. Comparison of continuous improvement initiatives in the six regulatory authorities

Quality measure	Regulatory authority					
	Mozambique (4/5)	Namibia (2/5)	South Africa (5/5)	Tanzania (5/5)	Zambia (4/5)	Zimbabwe (5/5)
External quality Audits	✓	✗	✓	✓	✗	✓
Internal quality Audits	✓	✗	✓	✓	✓	✓
Internal tracking Systems	✓	✗	✓ᵃ	✓	✓	✓
Reviews of assessors' feedback	✓	✓	✓ᵃ	✓	✓	✓
Reviews of stakeholders' feedback	✗	✓	✓	✓	✓	✓

[a] Implemented informally with no documented system.

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DISCUSSION

The aim of this study was to evaluate the regulatory review processes of six countries in the SADC region that are active members of the ZaZiBoNa collaborative medicines registration initiative and compare the outcomes in order to identify best practices. A common finding among the six regulatory authorities was that participation in the ZaZiBoNa initiative has improved the way in which they perform regulatory reviews in their countries, and this highlights how one of the key objectives of the initiative, which is to build expert capacity of member countries, is being realised. In addition to identifying the differences and similarities in the processes in countries currently participating in the ZaZiBoNa initiative as active members, the results of this study will enable the regulatory authorities, the majority of which are in low-to-middle-income countries (LMICs), to benchmark processes, resources and capacity, something which in the past was difficult due to lack of information in the public domain (Gwaza, 2016).

For industry, the results of this study provide an opportunity to better understand the regulatory review processes in the six agencies as well as the relevant challenges when planning future submissions. The commitment to continuous improvement, transparency and the desire to engage with industry shown by all the agencies, reflects a new way of doing business that should encourage further investment in terms of medicines development and regulatory submissions made to these countries and the SADC region as a whole.

Mature agencies such as Australia's Therapeutic Goods Administration and Health Canada's Health Products and Food Branch have a staff per million residents' ratio in 2021 of 31 and 60 respectively (Sithole et.al, 2021d). In contrast, all six agencies in this study had a staff per million residents' ratio less than 10, confirming resource limitations faced by agencies in LMICs. In addition, a finding of this study was that there is a difference in human resources available to conduct reviews in the six agencies within the SADC region. Of note, countries with higher workloads had no targets for the scientific assessment or overall approval process, which points to overwhelmed resources. A workforce should be adequate in skill and numbers for greater operational efficiency. In addition, retention of skills after investing in staff training is of paramount importance for agencies to deliver their mandate in a timely manner.

The results of this study can be used as a baseline going forward and presents an opportunity for agencies to re-examine their processes to determine areas of improvement, particularly where another agency with a comparable workload is able to achieve shorter registration times. Routine recording of the milestones studied

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here will enable the monitoring and measurement of key performance indicators such as timelines for validation, queue time, scientific assessment and the overall approval, will enable the rapid identification of areas requiring improvement and a proposal of gap-closing measures such as re-engineering of processes or the injection of additional resources by the agencies.

While most of the agencies in the study indicated that resources could be optimised by placing reliance on mature agencies, there is opportunity to further reduce timelines through reliance on other agencies in the SADC region, as is already being done by Namibia.

Although the ZaZiBoNa collaborative medicines registration process was not directly evaluated in this study, it was possible to see the reason for the difference in time to registration among the participating countries after a recommendation for approval by ZaZiBoNa. The initiative relies on countries with differing capacities, resources and administrative processes. There is a need for a review of the current model used for the ZaZiBoNa initiative in the next strategic period to minimise the dependence on the country process and increase operational efficiency.

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CHAPTER 05

REVIEW MODELS AND APPROVAL TIMELINES OF THE SADC WORK SHARING INITIATIVE MEMBER COMPANIES

SUMMARY

- Regulatory reliance, harmonisation and work sharing have grown over the last few years, resulting in greater sharing of work and information among regulators, enabling the efficient use of limited resources and preventing duplication of work.
- Various initiatives on the African continent include ZaZiBoNa, the Southern African Development Community (SADC) collaborative medicines registration initiative.
- ZaZiBoNa has resulted in significant savings in time and resources; however, identified challenges include a lack of clear information regarding the participating countries registration processes and requirements as well as lengthy registration times.
- The aim of this study, therefore, was to compare the data requirements and review models employed in the assessment of applications for registration, the target timelines for key milestones and the metrics of applications received and approved in 2019 and 2020 by Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe.
- An established and validated questionnaire (Optimising the Efficiencies of Regulatory Agencies) was completed by each of the respective agencies.
- The majority of applications received and approved by all six agencies in 2019 and 2020 were generics. The mean approval times for generics varied across the countries, with ranges of 218–890 calendar days in 2019 and 158–696 calendar days in 2020.
- All three types of scientific assessment review models were used by the six agencies and data requirements and the extent of scientific assessment were similar for five countries, while SAHPRA conducted full reviews for new active substances.
- A large variation was observed in the targets set by the six agencies for the different milestones as well as overall approval times.
- The study identified the strengths of the countries as well as opportunities for improvement and alignment. Implementation of the recommendations made in this study will enhance the countries' individual systems, enabling them to efficiently support the ZaZiBoNa initiative.

RECOMMENDATIONS

As a result of this study, the following recommendations should be considered by the six agencies taking part in this study and others in the region.

- **ZaZiBoNa as a reference agency:** All agencies participating in the ZaZiBoNa collaborative medicines registration initiative should consider formally recognising ZaZiBoNa as a reference agency under the verification and abridged review models.
- **Timelines and targets**: In order to benchmark the regulatory review process, agencies should consider documenting the key milestones and publishing the relevant timelines. Ideally, targets should be established for all the key milestones in order to support the monitoring and measuring of performance.
- **Publication of data:** Agencies should consider publishing the review models that they use for assessment, including the procedure criteria, recognised reference authorities and timelines. Agencies that do not have procedural guidelines and assessment templates should consider developing these.
- **Capacity building**: Agencies should consider building capacity to enable a full review of new chemical entities that are received and not approved by a reference agency.
- **Performance measurement**: Countries that currently set targets inclusive of the applicant's time should also have targets for agency time only to facilitate performance measurement.

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INTRODUCTION

The regulation of medicines contributes to public health by ensuring the timely access to medicines that have been reviewed and found to be safe, effective and of good quality. Medicines regulations have evolved from the publishing of minimum standards for compliance to the development of legislation controlling the development, manufacture, distribution, sale and use of medicines (Rägo et.al, 2008). One function, performed by regulatory authorities worldwide to fulfil their mandate, is the process of reviewing applications for registration or market authorisation submitted by companies interested in marketing their products in a particular country or jurisdiction. This process can be long in some countries, hindering access to life-saving medicines by patients and this has led to regulatory agencies relying on the reviews and decisions of other regulators (Luigetti et.al, 2016).

Reliance

It is now acknowledged that no one regulator can do everything for themselves due to the increasing workload and complexity of products (WHO, 2021e) and this is especially true for maturing agencies in low- -to-middle-income countries (LMICs) who often do not have adequate resources or the capacity to perform full regulatory functions. Reliance on work carried out by other agencies drastically reduces the time to market for medicines, resulting in improved patient access (Liberti, 2017; Luthuli et.al, 2018). The World Health Organization (WHO) has now published its guidance on good reliance practices (WHO, 2021e) and recommends the use of reliance to effectively and efficiently perform regulatory functions in a timely and cost-effective manner.

Registering medicines in LMICs: Challenges

Applicants submitting applications for registration of medicines to LMICs have often cited the challenges of lack of clear information on the registration process and timelines, inefficiencies in the registration process, lack of harmonisation of requirements for countries in one region and long registration timelines (Dansie et.al, 2019; Narsai et.al, 2012). On the other hand, applicants also contribute to the delay in the approval process by taking too long to respond to queries raised by the regulators (Ahonkhai et.al, 2016). There is therefore a need for an evaluation of the regulatory review processes and registration timelines of agencies in LMICs to address the challenges identified and fill the knowledge gap. In chapter five, we evaluated and compared the regulatory review processes of the regulatory authorities of Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe, who are

active members of the ZaZiBoNa initiative and proposed recommendations for better alignment. The aim of this chapter, was to compare the data requirements and review models employed in the assessment of applications for registration, the target timelines for key milestones and the metrics of applications received and approved in 2019 and 2020 by the six countries.

METHODS

Study participants

Nine countries with active member status in the ZaZiBoNa initiative were invited to participate in this study following a face-to-face presentation. Active member status is defined as the capacity to conduct assessments and GMP inspections. One of the countries (Botswana) could not complete the questionnaire because their agency had only recently been established and the participation by the two countries (the Democratic Republic of Congo and Malawi) was unlikely because of disruptions caused by the Covid-19 pandemic. Therefore, the six regulatory agencies included in this study were the National Directorate of Pharmacy in the Mozambique Ministry of Health; Namibia Medicines Regulatory Council (NMRC) in the Namibia Ministry of Health and Social Services; the South African Health Products Regulatory Authority (SAHPRA); the Tanzania Medicines and Medical Devices Authority (TMDA); the Zambian Medicines Regulatory Authority (ZAMRA); and the Medicines Control Authority of Zimbabwe (MCAZ).

Data collection

Each of the six agencies completed an established and validated questionnaire (McAuslane et.al, 2009) in 2020, which described the organisational structure, the regulatory review system for market authorisation of new active substances (NASs) and generics as well as the overall target and review times from the date of application to the date of approval, good review practices (GRevPs) and good decision-making practices. The questionnaire allowed for the collection of data in a standardised format, enabling comparison and analyses of information collected from the six agencies.

The questionnaire consists of five parts: *Part 1*, documents the structure, organisation and resources of the agency; *Part 2*, identifies different types of review model(s) used for the scientific assessment of medicines; *Part 3*, documents information on the key milestone dates and the process using a standardised process map; *Part 4*, records how overall quality is built into the regulatory process (GrevPs) and *Part 5*, explores the quality of the decision-making practices of the agency.

Models of regulatory review

There are three models for the scientific regulatory review of a product that can be used by regulatory authorities (McAuslane et.al, 2009):

- **The verification review (type 1),** which requires prior approval of a product by two or more reference or competent regulatory authorities, allowing the agency relying on such assessments to employ a verification process to validate a product and ensure that it conforms to the previously authorised product specifications. This should also conform with the prescribing information such as the use, dosage and precautions.
- **The abridged review (type 2),** which involves an abridged evaluation of a medicine, taking into consideration local factors and the environment as well as a benefit-risk assessment in relation to its use in the local ethnic population including medical practice and pattern of disease. This further requires registration by at least one reference or competent regulatory authority.
- **The full review, type 3A,** which involves the agency carrying out a full review, including supporting scientific data, of quality, safety and efficacy, but requires that the product be previously reviewed by an agency and issued a Certificate of Pharmaceutical Product (CPP) **or type 3B**, which involves an independent assessment of a product's quality, preclinical and clinical safety and efficacy, which has not previously been evaluated by any other agency.

RESULTS

For the purpose of clarity, the results will be presented in three parts: Part I – metrics of applications received and registered; Part II – review models, extent of scientific assessment and data requirements; and Part III – targets of key milestones in the review process.

Part I – Metrics on NASs, generics and WHO-prequalified generics
Applications received and approved

The majority of applications received and approved by all six agencies in 2019 and 2020 were for generics. In 2019 Mozambique and Zambia did not receive any applications for new active substances (NASs), while Tanzania only received 1, with Namibia, South Africa and Zimbabwe receiving 14, 11 and 8 respectively (Table 5.1). Tanzania received the highest number of generic applications (858) and Namibia received the lowest (132). Interestingly, even though Zambia and Zimbabwe are comparable in population size and fees payable, Zambia received close to three times the number of generic applications compared with Zimbabwe and this might be attributed to differences

Figure 5.1. Comparison of number of generics approved from 2019 – 2020
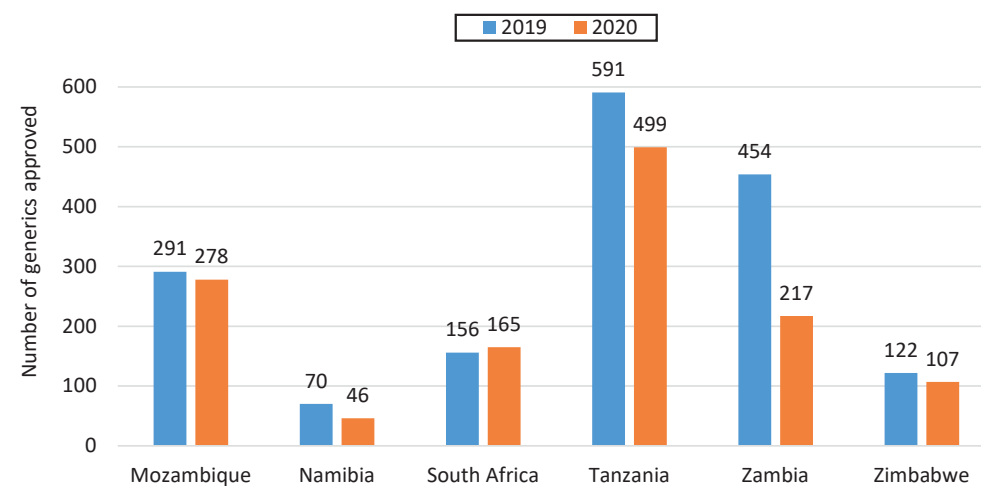
in their economies and perceived return on investment by applicants (Figure 5.1). The year 2020 saw a decline in applications for NASs received by the agencies, with the exception of South Africa, which saw an increase. Tanzania, Zambia and Zimbabwe saw a decrease in generics in 2020, while Mozambique, Namibia and South Africa saw an increase (Table 5.1). Namibia and Tanzania saw a decrease in WHO-prequalified generics in 2020 while Mozambique, Zambia and Zimbabwe saw an increase.

Mean approval times

For NASs, South Africa had the longest average approval time of all the agencies (Table 5.2) as they are the only country that conducts a full review of NASs. Namibia had an approval time of 170 days while Zimbabwe had an approval time of 219 days and these were assessed using abridged review (Table 5.2). Mozambique, Tanzania and Zambia did not approve any NASs in the two years. For generics, Tanzania had the shortest approval time even though they received the highest number of applications. Tanzania's approval times for generics were comparable to Zambia's times. The longest approval time for generics was observed for Namibia in 2019 however the time was significantly reduced in 2020. South Africa and Zimbabwe's approval times for generics were comparable (Figure 5.2). South Africa is implementing reliance in their backlog programme resulting in much shorter review times than those reported for business as usual.

Table 5.1. Comparison of metrics on NASs, generics and WHO prequalified generics (2019 – 2020)

Country	Mozambique		Namibia		South Africa		Tanzania		Zambia		Zimbabwe	
Year	2019	2020	2019	2020	2019ᵃ	2020ᵇ	2019	2020	2019	2020	2019	2020
NASs												
Received	0	0	14	0	11	57	1	0	0	0	8	4
Approved	0	0	14	0	43	97	1	0	9	1	4	0
Generics												
Received	198	339	132	227	29	331	858	631	574	206	195	179
Approved	291	278	70	46	156	165	591	499	454	217	122	107
WHO-prequalified generics												
Received	10	15	8	4	0	N/A	14	7	11	28	5	9
Approved	8	9	8	1	0	0	14	7	11	28	7	7

NASs = new active substances; WHO = World Health Organization. N/A=Not available.
ᵃ Data is for August to December due to closure of the agency for part of the year.
ᵇ Data for business as usual only. Excludes backlog

Table 5.2. Comparison of mean approval times of NASs, generics and WHO prequalified generics 2019 – 2020 (calendar days)

Country	Mozambique		Namibia		South Africa		Tanzania		Zambia		Zimbabwe	
Year	2019	2020	2019	2020	2019ᵃ	2020ᵇ	2019	2020	2019	2020	2019	2020
NASs	0	0	170	0	490	585	0	0	0	0	219	0
Generics	310	398	890	158	589	683	218	202	240	214	611	696
WHO PQ generics	100	118	120	131	0	298	78	83	45	53	150	137

ᵃ Data is for August to December due to closure of the agency for part of the year
ᵇ Data for business as usual only. Excludes backlog

Figure 5.2. Comparison of mean approval times for generics from 2019 – 2020
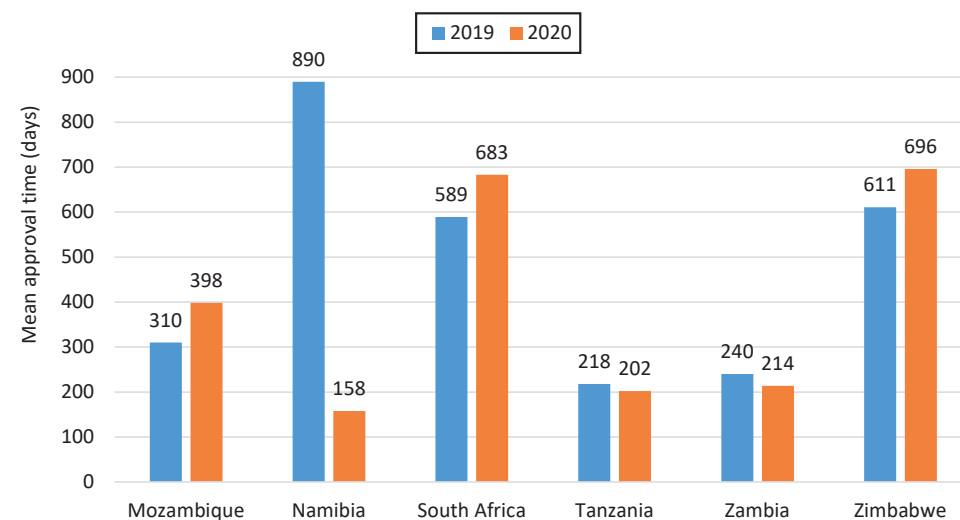
Part II - Review models used for scientific assessment

In general, all three types of review models are used for scientific assessment by the six agencies (Table 5.3).

Verification review (type 1)

Five agencies apart from Tanzania conducted verification reviews with the requirement for the product to have been approved by at least one reference agency, while South Africa required approval by two reference agencies. Unredacted reports were required to facilitate a verification review. However, because of a lack of agreements with other WHO-listed regulatory authorities, Mozambique and Zimbabwe only recognised WHO prequalification (WHO PQ) and the ZaZiBoNa collaborative procedure as reference agencies for this pathway.

In addition to products approved by WHO Prequalification and ZaZiBoNa, Namibia, South Africa and Zambia conducted verification reviews of products approved by WHO-listed regulatory authorities; however, only South Africa and Zambia had agreements to access the unredacted reports from these reference agencies. Namibia also recognised South Africa and Zimbabwe as reference agencies. The reference agencies common to all countries were the WHO PQ, European Medicines Agency (EMA), Medicines and Healthcare Products Regulatory Authority (MHRA), United States Food Drug Administration (USFDA), Australia's Therapeutic Goods Administration (TGA), Health Canada, Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and

other mature agencies (WHO listed authorities) in Europe. Mozambique, South Africa, Zambia and Zimbabwe had a target time of 90 calendar days for verification review, while the target was 270 calendar days for Namibia.

Abridged review (type 2)

Five agencies, except Zambia, conducted an abridged review for products approved by at least one reference agency. For this type of review, redacted or public assessment reports were used and differences in medical culture/practice, ethnic factors, national disease pattern and unmet medical needs were taken into account during benefit-risk assessment. These considerations were also made during a verification review. For Zambia, an abridged review was conducted for established products that were considered to be of low risk. South Africa had a target time of 90 calendar days, Tanzania 126 calendar days, Mozambique, Namibia and Zimbabwe 270 calendar days and Zambia 351 calendar days.

Full review (type 3)

All six agencies conducted a full review (type 3) of quality, safety and efficacy for all major applications that were not eligible for verification or abridged review (Table 6.4).

For Mozambique and Namibia, this comprised an extensive assessment of the chemistry, manufacturing and control (CMC) data for all product types as well as the bioequivalence for generics as all new chemical entities received had already been approved by a reference agency. For South Africa, Tanzania and Zambia, this involved a full review of the CMC for all product types, bioequivalence for generics, and non-clinical and clinical data for new chemical entities, biologicals and biosimilars inclusive of those that had not been approved anywhere else. For Zimbabwe, this involved an extensive assessment of the CMC for all product types, bioequivalence for generics and the non-clinical and clinical data for biosimilars only as all new chemical entities received had already been approved by a reference agency (Table 5.4). In five agencies the quality, safety and efficacy sections were reviewed sequentially whereas South Africa conducted all reviews in parallel. Zimbabwe reviewed the majority of applications sequentially, although biosimilars were reviewed in parallel. Namibia had no target time for the overall approval of a full review. The target for Mozambique was 365 days excluding applicant's time and this is comparable to the target times for the comparator countries: South Africa 350 days excluding the applicant time; Tanzania 252 days excluding applicant time; Zambia 351 days inclusive of the applicant time; and Zimbabwe 480 days inclusive of the applicant time (Table 5.3). These targets are further broken down into individual milestones in Table 5.6)

Table 5.4. Extent of scientific assessment for full review

	Mozambique	Namibia	South Africa	Tanzania	Zambia	Zimbabwe
Chemistry, manufacturing and control (CMC) data extensive assessment	✓	✓	✓	✓	✓	✓
Non-clinical data extensive assessment	✗	✗	✓	✓	✓	✓[a]
Clinical data extensive assessment	✗	✗	✓	✓	✓	✓[a]
Bioequivalence data extensive assessment	✗	✓	✓	✓	✓	✓
Additional information obtained (where appropriate)	✓	✓	✓	✓	✓	✓
Other agencies internal review reports	✓	✓	✓	✓	✓	✓
Medical and scientific literature	✓	✓	✓	✓	✓	✓

[a] For biosimilar products not approved by a reference agency only

Fast-track/priority review

The target for priority review was 90 calendar days for Namibia, 113 calendar days for Zambia, 126 calendar days for Tanzania, 180 calendar days for Zimbabwe, 250 calendar days for South Africa and >180 calendar days for Mozambique (Table 5.3). All six agencies had a fast-track review pathway in which applications were charged a higher fee to be reviewed in a shorter time and a justification for this may be an unmet medical need.

Data requirements

For five of the agencies in this study apart from Namibia, the CPP should be provided either at the time of the application or before the product is authorised depending on the type of review (Table 5.5). In the absence of unredacted reports from reference agencies, the CPP or evidence of authorisation in the country of origin is used to confirm similarity and approval status of the product when an abridged review is carried out. Evidence of compliance with GMP for both the active pharmaceutical ingredient and finished pharmaceutical product manufacturer, product samples, copies of the labelling and a full dossier (modules 1– 5) were required for all review types by Mozambique, Namibia, South Africa and Zimbabwe. Tanzania required full data for modules 1–5 for a full review and full data for module 3 as well as summaries of modules 4 and 5 for an abridged review. Zambia required full data for modules 1–5 for a full review and only summaries of modules 3, 4 and 5 for verification and abridged reviews. A detailed assessment of the data was carried out and the relevant assessment reports prepared. Benefit-risk assessments were performed during verification and abridged review, taking-into-account differences in medical culture/practice, ethnic factors, national disease patterns and unmet medical needs. All six agencies participated in the WHO collaborative registration procedure through which access to reports for prequalified products is given. As members of the ZaZiBoNa collaborative procedure, all six agencies had access to reports assessed by this initiative. South Africa and Zambia accessed internal assessment reports from their reference agencies. All six agencies made use of publicly available reports such as European Public Assessment Reports (EPARs) during the review process. The primary scientific assessment in all six agencies was conducted by internal staff, although South Africa and Tanzania also made use of external reviewers.

Part III – Targets for key milestones in the review process

The review process and key milestones for the six agencies were reported in chapter 4. The targets for the key milestones are discussed in this chapter. Targets should be set for each milestone and the overall process in line with good review practices. Figure 5.3

Table 5.5. Summary comparison of key features of the regulatory systems for medicines

Marketing authorisations	Mozambique	Namibia	South Africa	Tanzania	Zambia	Zimbabwe
Certificate of a Pharmaceutical Product (CPP): CPP is required with the application or before authorisation is issued	✓	✗	✓	✓[a]	✓	✓
Common technical document (CTD): CTD format is mandatory for applications	✓	✓	✓	✓	✓	✓
Medical staff: More than 25% within the agency review staff are physicians	✗	✗	✗	✗	✗	✗
Review times: The agency sets targets for the time it spends on the scientific assessment of NASs and generic applications	✓	✗	✓	✓	✓	✓
Approval times: The agency has a target for the overall time for the review and approval of an application	✓	✗	✓	✓	✓	✓
Questions to sponsors are batched at fixed points in the review procedure	✓	✓	✓	✓	✓	✓
Company response time: Recording procedures allow the company response time to be measured and differentiated in the overall processing time	✓	✓	✗	✓	✓	✓
Priority reviews: The agency recognises medical urgency as a criterion for accelerating the review and approval process for qualifying products	✓	✓	✓	✓	✓	✓
Sequential processing: Different sections of technical data reviewed sequentially rather than in parallel	✓	✗	✗	✓	✓	✓[b]

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Table 5.5. (continued)

Marketing authorisations	Mozambique	Namibia	South Africa	Tanzania	Zambia	Zimbabwe
Price negotiation: Discussion of pricing is separate from the technical review and does not delay the approval of products	✓	✓	✓	✓	✓	✓
Sample analysis: The focus is on checking quality in the marketplace and requirements for analytical work do not delay the marketing authorisation	✓	✓	✓			

ᵃ For abridged review (type 2) only. ᵇ Biosimilars reviewed in parallel.

is a standardised process map for the review and approval of medicines representing the key milestones monitored in a mature regulatory review system.

Receipt and validation

The target for this milestone was 15 calendar days for Mozambique, 18 calendar days for South Africa, 20 calendar days for Tanzania and Zambia, 42 calendar days for Namibia and 90 calendar days for Zimbabwe (Table 5.6).

Queue time

Queue time is the time between the completion of validation/acceptance for review of an application and the start of the scientific assessment. Namibia had the longest target queue time of over 365 calendar days followed by the Mozambique at 180-365 calendar days, Zambia at 180 calendar days, Zimbabwe at 90 calendar days and Tanzania had the shortest target time of 60 calendar days. South Africa reported no target for the queue time (Table 5.6).

Primary scientific assessment

Tanzania had a target of 14 calendar days for the scientific assessment (including peer review) while Zimbabwe had a target of 60 calendar days for the same period.

[The map represents the review and authorization of a product that goes to approval after one review cycle – It should be noted that in some countries milestone G (committee procedure) may come before milestone D (questions to the applicant)]

Primary Scientific Assessment (continued)

Tanzania was able to achieve the timeline through the use of retreats away from the office that allowed reviewers to focus on the review of applications for registration without any distractions. In addition, the application was split between a quality reviewer and a bioequivalence reviewer. Mozambique and South Africa did not report targets for the scientific assessment even though the milestone was recorded. Namibia and Zambia did not have a target for primary scientific assessment and neither did they record the start of this milestone.

Questions to applicants

This time is also referred to as "clock stop" or company time, when the assessment is paused and the applicant given an opportunity to respond to queries. The target for questions to applicants (clock stop) after each review cycle was 42 calendar days for

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Table 5.6. Comparison of targets for key milestones in the full (type 3) review process (calendar days)

Target	Mozambique	Namibia	South Africa	Tanzania	Zambia	Zimbabwe
Receipt and validation (A – B)	15	42	18	20	20	90
Queuing (B – C)	180-365	> 365	No target	60	180	90
Primary scientific Assessment (C – D)	No target	No target	No target	14	No target	60
Questions to applicant (Clock stop) (D – E)	60	90	42	180	120	60
Review by Expert Committee (G – H)	N/A	No target	No target	1	1 - 3	1
Approval procedure (Admin)	> 180	< 30	14	< 30	< 30	60
Overall approval time (A – I)	365 (excl. applicant time)	No target	350 for generics (excl. applicant time)	252 (excl. applicant time)	351 (incl. applicant time)	480 (incl. applicant time)

N/A - No expert Committee

Figure 5.3. Standardised review process map for the six regulatory agencies
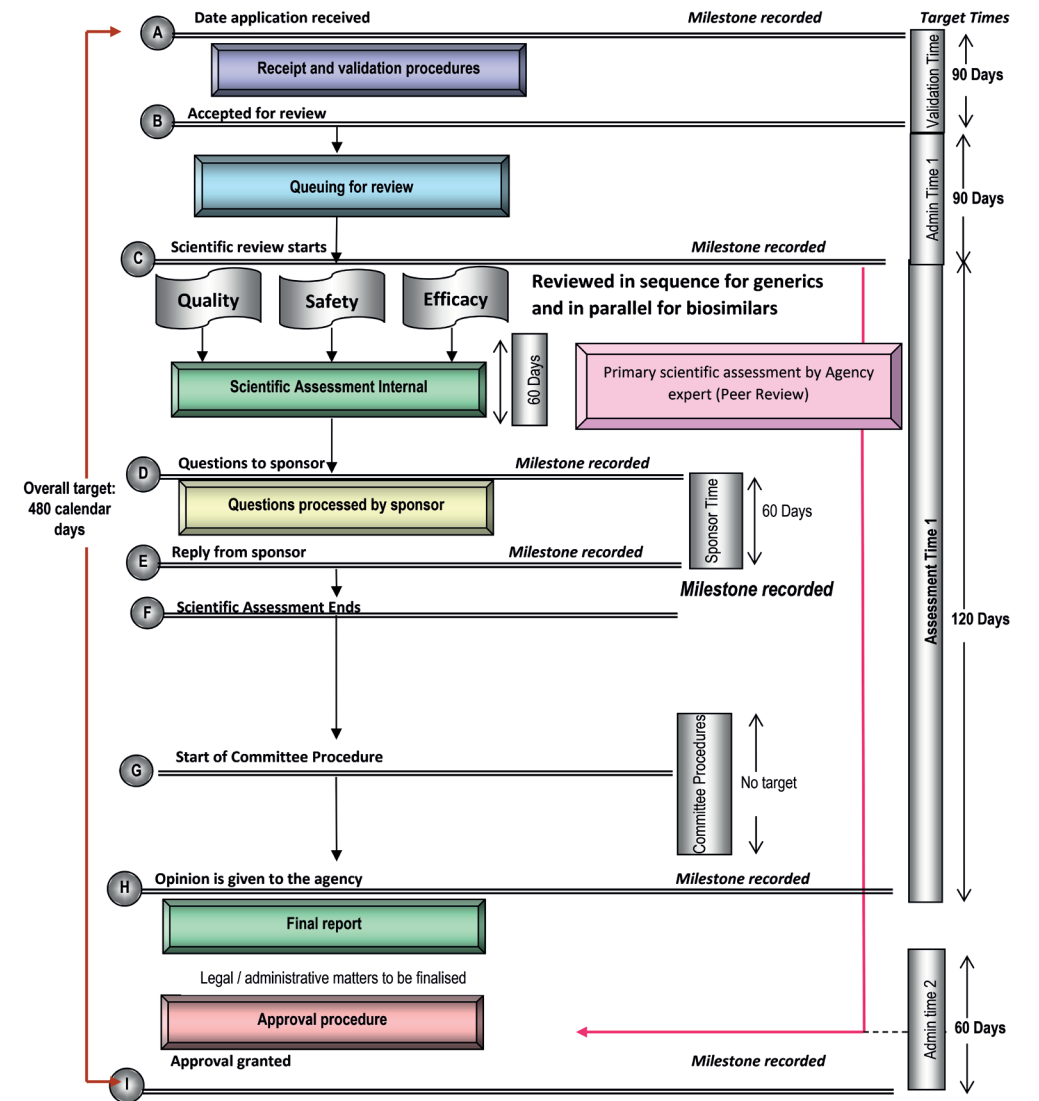
South Africa, 60 calendar days for Mozambique and Zimbabwe, 90 calendar days for Namibia, 120 calendar days for Zambia and 180 calendar days for Tanzania.

Review by Expert Committee

In four of the countries, the expert committee made decisions on the registration or refusal of products. This was carried out after the first and peer review of applications for registration by internal reviewers and circulation of reports to members of

the expert committee some days or weeks in advance of the meeting. In one of the countries, the expert committee was used in an advisory capacity. The value of the expert committee was that it consisted of external members with wide and varying expertise who provided an independent review of the products in addition to the review conducted by internal reviewers before making the decision on the registration of products. Namibia and South Africa had no target time for their committee (council) procedures while for Tanzania and Zimbabwe the target was 1 day and for Zambia 1 – 3 days (Table 5.6). The expert committees for Namibia, Tanzania and Zambia met once a quarter, while the committees for South Africa and Zimbabwe met once every month.

Authorisation procedure

The target for this step was 14 calendar days for South Africa, and less than 30 calendar days for Namibia, Tanzania and Zambia. The applicant was not informed of a positive opinion before authorisation for these agencies. The target for the authorisation procedure was 60 calendar days for Zimbabwe and this was because the applicant was first informed of a positive opinion and given an opportunity to respond before authorisation. The authorisation procedure took more than 180 calendar days for Mozambique and the applicant was not informed of a positive opinion before authorisation.

DISCUSSION

The aim of this study was to compare the review models, target timelines and metrics of the six countries in the SADC region that are active members of the ZaZiBoNa collaborative medicines registration initiative. In terms of numbers of applications received, the countries with larger populations and those with the lowest fees receive the highest number of applications. This study also confirmed the findings reported by previous studies (Rägo et.al, 2008; Gwaza, 2016), mainly that the number of new active substances launched in LMIC is very low compared with high income countries, demonstrated by some countries having received no applications for registration of NASs in the study period. Policies promoting generic prescribing that are implemented by these countries (Kaplan et.al, 2012) as well as the lack of affordability by the population may also be contributing to the high number of applications for generics received compared to NASs. The resultant effect is the lack of development of capacity to assess new active substances / new chemical entities in these countries. Thus, a deliberate effort to build capacity has to be made. Generally, the number of products approved declined in 2020 for the majority of the countries and this could be due to disruptions to work streams, because of the Covid 19 pandemic.

The six countries studied are implementing reliance by using the verification and abridged review models for the assessment of applications for registration. This should result in improved access to life-saving medicines for patients. A great opportunity identified from this study of review models is for countries in the region to begin to rely on each other's decisions for products assessed using the national procedure. The findings of this study will aid countries in better understanding the review processes of the other countries facilitating trust, reliance and in the future, mutual recognition of regulatory decisions. The targets set by the countries for the different review models vary, however this presents another opportunity for countries to standardise and argue for resources available to other countries in the region.

Five of the six countries required the WHO certificate of pharmaceutical product (CPP) at some stage in the review process confirming findings in the literature that this is still a requirement for emerging economies (Rodier et.al, 2020). Countries should review the need for the CPP where there is capacity to conduct a full review as this can affect the registration and supply of medicines by applicants. Key milestones reported by the six countries are similar and in line with international best practice. The countries that set targets inclusive of the applicant's time should also have targets for agency time only to facilitate measurement and comparison of performance. Protracted timelines are undesirable as they affect applicants' ability to plan or launch new medicines onto the market. In addition to guidelines, the availability of information in the public domain on models of review employed, review processes, timelines for review and approval of medicines, expert committee meeting dates and status of pending products will improve the support for existing applicants and attract new applications, resulting in a growth in the number of products approved on the market.

CHAPTER 06

**EFFECTIVENESS AND EFFICIENCY OF
THE ZAZIBONA INITIATIVE:
REGULATORY AUTHORITY PERSPECTIVE**

SUMMARY

- ZaZiBoNa, the work-sharing initiative in the Southern African Development Community (SADC) that has been in operation for 8 years, has successfully assessed over 300 dossiers / applications, with an overall median time to recommendation of 12 months.
- All 16 SADC countries participate in the initiative as either active or non-active members. While the successes of ZaZiBoNa are evident, some challenges still exist.
- The aim of this study was to solicit the views of the participating authorities on the effectiveness and efficiency of the current operating model of the ZaZiBoNa initiative.
- Data were collected in 2021 using the Process, Effectiveness and Efficiency Rating (PEER) questionnaire developed by the authors, for the nine active agencies namely Botswana, Democratic Republic of Congo, Malawi, Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe.
- ZaZiBoNa serves as a platform for work sharing, information exchange, capacity building and harmonisation of registration requirements.
- One of the benefits to regulators had been the improvement in the capacity to conduct assessments. Manufacturers benefited from compiling one package (modules 2 -5) for the initial submission as well as a single response package to the consolidated list of questions, which saved time and resources. Respondents were of the view that patients had benefited as ZaZiBoNa had contributed to an improved availability and accessibility to quality-assured medicines.
- Some of the challenges identified were the inadequacy of resources and differences in time to the implementation of ZaZiBoNa recommendations by the individual countries.
- The establishment of a regional unit hosted in one of the member countries to enable centralised submission and coordination was identified as the best strategy to improve the effectiveness and efficiency of the initiative in the interim, with the long-term goal being the establishment of a regional medicines authority.
- The study identified the strengths of the ZaZiBoNa initiative as well as the opportunities for improvement. The recommendations made would further strengthen this initiative.

RECOMMENDATIONS

Key recommendation to improve the effectiveness and efficiency of the ZaZiBoNa work-sharing initiative include:

- **Measuring and monitoring regulatory timelines**: The ZaZiBoNa initiative has measured and published the review timelines for the 333 dossiers / applications reviewed to date. This needs to be improved to include the monitoring, measuring and publication of the time to finalisation of ZaZiBoNa dossiers / applications in the individual participating countries.
- **Capacity building and training of assessors**: The ZaZiBoNa initiative has successfully facilitated and enabled the training of assessors in the 16 SADC countries. Going forward, the training and capacity-building activities should be separated from assessment activities, which will enable countries to second only competent assessors and inspectors, improving the effectiveness and efficiency of the initiative.
- **Information for applicants**: Requirements, guidelines, timelines and the process for submission of dossiers / applications to ZaZiBoNa should be made available on all participating country websites, including the contact details of the focal person.
- **Transparency of process and decision making**: Since 2017, the ZaZiBoNa initiative has prepared scientific summaries for approved medicinal products. These should be made available on the ZaZiBoNa and country websites.
- **Establishment of a regional medicines authority**: In the short-term, a regional unit hosted in one of the member countries to centrally receive ZaZiBoNa applications and coordinate communication with applicants should be piloted with the goal to establish a SADC regional medicines authority in the near future.
- **African Medicines Agency**: Although this was not the focus of this study, there is need for engagement of the SADC member states to encourage them to sign and ratify the African Medicines Agency (AMA) treaty, as this is the future of medicines regulation in Africa.

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INTRODUCTION

In October 2013, the inaugural meeting of the ZaZiBoNa collaborative medicines registration initiative was held in Windhoek, Namibia (Sithole et.al, 2020). Named using the first two letters of the four founding countries in the Southern African Development Community (SADC), namely Zambia, Zimbabwe, Botswana and Namibia (WHO, 2019a). ZaZiBoNa was a vision of the Heads of Agencies of those countries, with the support of the World Health Organization (WHO) prequalification team and the Southern African Regional Programme on Access to Medicines and Diagnostics (SARPAM) (Sithole et. al, 2020). The main objectives of the ZaZiBoNa initiative were 'a reduced workload, reduction in timelines to registration, the development of mutual trust and confidence in regulatory collaboration and to provide a platform for training and collaboration in other regulatory fields' (Sithole et. al, 2020).

Prior to the launch of this initiative, the national medicines regulatory authorities in SADC operated in isolation, despite facing similar challenges such as large registration backlogs that resulted in long registration times, hindering access to critical medicines by their populations (Gosling, 2007). Poor retention of human resources, and inadequate capacity to assess certain types of medicinal products were also common challenges faced by the countries, making a collaborative approach involving sharing of resources and expertise not only desirable but absolutely imperative. The four countries signed memoranda of understanding agreeing to participate in the initiative and agreed that this would be a requirement for other SADC countries wishing to join the initiative (Sithole et. al, 2020). Today, all 16 SADC countries participate in the ZaZiBoNa initiative, either as active members or non-active members depending on their capacity to conduct dossier assessments and good manufacturing practice (GMP) inspections (Sithole et. al, 2020; Sithole et.al, 2021a). ZaZiBoNa was absorbed into the SADC medicines registration harmonisation project in 2015 which, together with other regional economic communities in Africa, is overseen by the African Medicines Regulatory Harmonisation Initiative (AMRH) (Ndomondo-Sigonda, 2018).

In the current model of the ZaZiBoNa initiative, applicants simultaneously submit applications for registration and pay fees to each of the countries in which they wish to market their medicinal products (Sithole et.al, 2020; Masekela, 2020; MCAZ, 2022c). The assessment of dossiers / applications is carried out using a rapporteur and co-rapporteur before consideration of the report by a group of assessors from all the active member countries. In the absence of a regional legal framework, ZaZiBoNa does not have centralised submissions or approvals/registrations (Sithole et.al, 2020). Therefore, once the evaluation is concluded, an assessment report

with a recommendation and a consolidated list of questions is produced (Sithole et.al, 2020) and communication of the list of questions to the applicants as well as the final decision on the registration / marketing authorisation of medicinal products is left to the individual participating countries (Sithole et.al, 2020; Masekela, 2020). The process map is illustrated in Figure 6.1 (Sithole et.al, 2020). The Heads of Agencies serve as a governing body and countries participate in the initiative through multilateral agreements.

A key success of ZaZiBoNa has been its ability to continue operating with limited resources, with participating countries also contributing financially to the initiative since its inception (Sithole et.al, 2020).

Another important achievement is the shorter timelines for the 333 dossiers / applications that have been assessed to date (December 2021) compared with the timelines achieved by some of the participating countries using their national procedures (Masekela, 2020). For example, ZaZiBoNa has an overall median time to recommendation of 12 months (Masekela, 2021), whereas some of the participating countries had approval times of over 650 calendar days in 2020 (Sithole, 2022b). The gap in regulatory capacity among participating countries has also been reduced through the training of assessors and inspectors, bringing further harmonisation in the way assessments and GMP inspections are conducted in the SADC region.

Figure 6.1. ZaZiBoNa process map
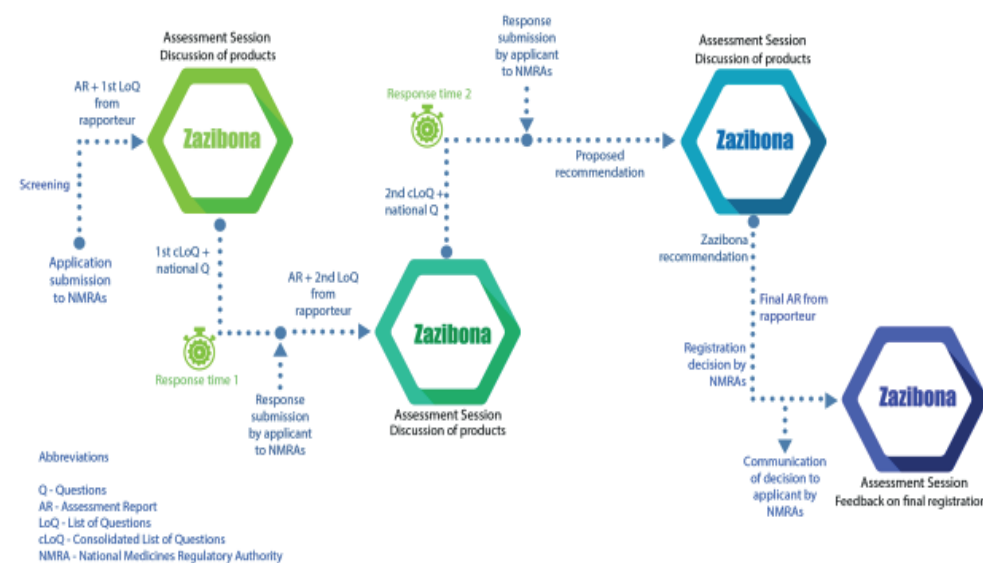
Despite these successes, some challenges have been identified through feedback from applicants such as differences in time to implement ZaZiBoNa recommendations by the participating countries (Sithole et.al, 2020, Sithole et.al, 2021a). This is not surprising, as the participating countries have some differences in their registration processes; for example, frequency of expert Committee meetings (Sithole et.al, 2021a, Sithole et.al, 2021b), which may affect the implementation of the ZaZiBoNa recommendations.

Sithole and colleagues therefore recommended a review of the ZaZiBoNa operating model to identify opportunities for improved efficiency (Sithole et.al, 2021a). The aim of this study was to solicit the views of the authorities on the effectiveness and efficiency of the current operating model of the ZaZiBoNa initiative. To our knowledge, no similar study has been conducted or published in the literature.

STUDY OBJECTIVES

The objectives of this study were to
1. Obtain the views of the individual medicines' regulatory authorities of the
2. ZaZiBoNa work-sharing initiative
3. Identify the challenges experienced by individual authorities since the inception of the ZaZiBoNa initiative
4. Determine the strengths and weaknesses of the initiative
5. Identify the ways of improving the performance of the initiative
6. Envisage the strategy for moving forward

METHODS
Study participants

All nine active members of the ZaZiBoNa initiative participated in the study translating to a response rate of 100%. These are, Botswana, Democratic Republic of Congo, Malawi, Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe.

Active member status is determined by "the capacity to conduct assessments and GMP inspections" (Sithole et.al, 2020).

Development of the PEER questionnaire

The Process, Effectiveness and Efficiency Rating (PEER) questionnaire (Figure 6.2) was developed by the authors. The questionnaire comprised five sections under the headings; demographics, benefits of the ZaZiBoNa initiative, challenges of

the ZaZiBoNa initiative, improving the performance (effectiveness and efficiency) of the work-sharing programme and envisaging the strategy for moving forward.

Pilot Study

To examine the applicability and practicality of the PEER questionnaire, it was piloted with two member authorities in July 2021 prior to undertaking the main study. As a result of the pilot study, a comment box was added at the end of the questionnaire to allow respondents to make additional comments that they felt were not previously addressed in the questionnaire. Subsequently, an additional 7-item questionnaire was completed by all participants to establish the content validity and relevance of the PEER questionnaire using the following questions;

1. Did you find the questions clear and straightforward to respond to?

Yes ☐ No ☐

2. Did you find the response options relevant to the heading of each section (A to E)?

Yes ☐ No ☐

3. Did you find the questions relevant to the aims and objectives of the study?

Yes ☐ No ☐

4. Did you find the questions relevant to your authority and ZAZIBONA work sharing initiative?

Yes ☐ No ☐

5. Did you find any relevant questions missing?

Yes ☐ No ☐

If yes, please state which questions were missing in the space after this list of questions.

6. Did you find any questions that should be excluded?

Yes ☐ No ☐

If yes, please state the questions that should be excluded in the space after this list of questions.

7. Did you find the questionnaire useful to reflect on both your agency experience as well that of ZAZIBONA?

Yes ☐ No ☐

All respondents were of the view that the content of the final PEER questionnaire was adequate and therefore did not propose any further changes.

Data collection

Data were collected in August 2021 using the PEER questionnaire developed by the authors. The questionnaire was completed by the focal person in each country and approved by the head of the authority. Semi-structured interviews were carried out in September 2021 with each of the member authorities following completion of the PEER questionnaire.

RESULTS

For the purpose of clarity, the results are presented in five parts: Part I – Demographics and authority resources; Part II – Benefits of the ZaZiBoNa initiative; Part III – Challenges of the ZaZiBoNa initiative; Part IV – Improving the performance of the work-sharing programme; and Part V – Envisaging the strategy for moving forward.

Part I - Demographics and authority resources

The study respondents' age ranged from 31 – 49 years, with a range of regulatory experience from 4 – 16 years. Five of the respondents were female and 4 were male. Authority resources, including the number of authority assessors assigned to ZaZiBoNa reviews are listed in Table 6.1.

Part II – Benefits of the ZaZiBoNa initiative
Benefits of the ZaZiBoNA initiative

Information sharing among regulators (9/9), building of capacity for assessments (9/9) and harmonisation of registration requirements across the region (8/9) were identified as the top 3 benefits of the ZaZiBoNa initiative by the countries. However, less than a third of the countries believed that assessment through ZaZiBoNa resulted in shorter timelines for approval of medicines (2/9) or that the operating model was clear (2/9) (Figure 6.3).

Strengths of the ZaZiBoNa process at country level

The availability of information on the submission process and timelines for ZaZiBoNa dossiers / applications on the country website was selected as the top strength by most of the countries (6/9). The availability of a separate register and tracking, priority review and regular committee meetings, which enabled the timely recommendation of dossiers / applications were also identified as strengths by the majority of countries

Figure 6.2. The Process, Effectiveness and Efficiency Rating (PEER) questionnaire

Figure 6.2. (continued)

with **any third party or made public**. External reports or presentations of the data will include only blinded results together with appropriate analytical interpretations.

The questionnaire is divided into five short sections and will take 20 minutes to complete. Thank you for taking time to complete it. We value your input

A. DEMOGRAPHICS

1. Please state the name of your country ____

2. Please provide your responses to the following questions by writing your answer in the space provided or ticking the relevant box.

   a. Age: ____ years

   b. Sex: ☐ Male ☐ Female

   c. Number of years of regulatory experience: ____ years

3. What is the total number of staff in your agency? ____

4. What is the number of reviewers of marketing authorization applications? ____

5. How many reviewers participate in the ZAZIBONA assessments? ____

6. Does your agency have a separate record of applications received for assessment under ZAZIBONA? ☐ Yes ☐ No

B. VIEWS ON THE BENEFITS OF THE ZAZIBONA INITIATIVE
Select your answers by ticking the relevant box(es)

1. In your view, what are 3 (or more) benefits of the ZAZIBONA initiative to date?

   ☐ Leadership commitment/Governance structure
   ☐ Clear Operating Model
   ☐ Shorter timelines for approval
   ☐ Information sharing among regulators
   ☐ Building of capacity for assessments
   ☐ Sustainable resource base because of self-funding by countries
   ☐ Harmonisation of registration requirements across the region

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☐ Other (Please specify) ____

2. What would you say are 3 (or more) strengths of your process for ZAZIBONA products at country level that other countries could learn from?

   ☐ Separate register and tracking of ZAZIBONA products
   ☐ Priority review of ZAZIBONA products
   ☐ Information on the submission process and timelines for ZAZIBONA products are available on your country website
   ☐ Products approved under ZAZIBONA are available on your country   website
   ☐ Regular Committee meetings enabling timely finalisation of products after ZAZIBONA recommendation
   ☐ Other (Please specify) ____

3. How has the ZAZIBONA initiative benefited member countries (regulators)?

   ☐ Training to improve the performance of the assessors
   ☐ Provides the platform for interaction and information exchange with other regulators
   ☐ Shared workload resulting in shorter timelines for approval than in individual countries
   ☐ Enables application of high standards of assessment regardless of size of country or maturity of regulatory agency
   ☐ Improved quality of dossiers submitted
   ☐ Other (Please specify) ____

4. How has the ZAZIBONA initiative benefited manufacturers (applicants)?

   ☐ Reduced burden as they compile one dossier (modules 2 -5) for submission to multiple countries
   ☐ Savings on time and resources as they receive same list of questions from multiple countries enabling compilation of a single response package
   ☐ Shorter timelines for approval compared to that for the individual countries
   ☐ Access to various markets at the same time
   ☐ Other (Please specify) ____

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Figure 6.2. (continued)

5. How has the ZAZIBONA initiative benefited patients in your country or in the SADC region?

   ☐ Quicker access to quality assured medicines
   ☐ Reduced prices of medicines
   ☐ Increased availability of medicines
   ☐ Other (Please specify) ____

C. VIEWS ON CHALLENGES OF THE ZAZIBONA INITIATIVE
Select your answers by ticking the relevant box(es)

1. In your view, what are 3 (or more) challenges of the ZAZIBONA initiative?

   ☐ Lack of detailed information on the process for applicants
   ☐ Low or decreasing number of applications for assessment
   ☐ Unequal workload among member countries
   ☐ Dependence on the countries' process for communication with applicants and expert Committees
   ☐ Lack of centralised submission and tracking
   ☐ Lack of jurisdiction power
   ☐ Other (please specify) ____

2. In your view, what are 3 (or more) challenges that you face at country level in assessing/finalising ZAZIBONA products?

   ☐ Inadequate human resources
   ☐ Poor record keeping and tracking of ZAZIBONA products
   ☐ Lack of priority review for ZAZIBONA products
   ☐ ZAZIBONA work not recognized as part of agency work to be done during working hours
   ☐ Unpredictable schedule of Committee meetings
   ☐ Lack of buy-in from expert Committee(s)
   ☐ Failure by manufacturers to follow the requirement to submit the exact same dossier to all countries of interest
   ☐ Failure by manufacturers to adhere to deadlines for response to questions
   ☐ Other (Please specify) ____

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3. What are the challenges faced by manufacturers submitting applications to the ZAZIBONA initiative?

   ☐ Differences in time to implementation of ZAZIBONA recommendations by member countries.
   ☐ Lack of clarity about the process for submission and follow up in each country
   ☐ Lack of information on country websites and the ZAZIBONA website about the process, milestones, timelines, pending and approved products
   ☐ ZAZIBONA process is more stringent than some country processes
   ☐ Differing labeling requirements in participating countries
   ☐ Other (Please specify) ____

D. IMPROVING THE PERFORMANCE (EFFECTIVENESS AND EFFICIENCY) OF THE WORK SHARING PROGRAMME
Select your answers by ticking the relevant box(es)

Effectiveness can be defined as 'doing the right thing' often measured by the value derived by customers/stakeholders from an organisation's processes or services while *Efficiency* can be defined as 'doing things right' which saves the organization time and resources.

1. What are 3 or more ways to improve the effectiveness of the ZAZIBONA initiative in your view?

   ☐ Decision-making transparency e.g. publishing Public Assessment Reports
   ☐ Make publicly available any information that might help applicants in managing their submissions - templates of documents, lists of Q&A, timelines and milestones, disclosure of internal SOPs, etc.
   ☐ Consistency in application of guidelines and decisions
   ☐ Use of risk-based approaches e.g. reliance pathways
   ☐ Engagement and interaction with stakeholders
   ☐ Publishing of pending products
   ☐ Publishing of approved products
   ☐ Minimise the need for country specific documents
   ☐ Other (Please specify) ____

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Figure 6.2. (continued)

2. What are 3 or more ways to improve the efficiency of the ZAZIBONA initiative in your view?

☐ Specific and clear requirements made easily available to applicants

☐ Compliance with target timelines by measuring and monitoring each milestone in the review process

☐ Use of robust IT systems

☐ Transparency on metrics and statistics e.g. % completed within timeline

☐ Improved central tracking of ZAZIBONA products

☐ Improved resources e.g. number of assessors

☐ Centralised system for submission of applications and communication with applicants

☐ Other (please specify) _____

E: ENVISAGING THE STRATEGY FOR MOVING FORWARD

1. Rate the following proposals to improve the current ZAZIBONA operating model from 1 – 3, number 1 representing what you think would be **most effective** in improving efficiency and number 3 the **least effective**. *Enter the appropriate number in the space provided before each proposal.*

☐ To continue with the current operating model unchanged.

☐ To continue with the current operating model but provide full information on the process including timelines and milestones as well as approved products on every participating country's website and on the ZAZIBONA website.

☐ The establishment of a regional administrative body to centrally receive and track ZAZIBONA applications which would be responsible for allocating the applicable fees to countries, tracking of applications and communication with applicants.

2. In your view, would the establishment of a SADC regional medicines agency, if legally possible, be the best strategy for improved performance going forward?

☐ Yes ☐ No

Please explain why? _____

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3. In conclusion, what other strategies not previously highlighted can you think of that would strengthen the ZAZIBONA initiative going forward?

_____
_____
_____

Please feel free to use the comment box below to elaborate on any of your answers or to highlight questions and answers that you believe should have been included in this questionnaire.

Name of person completing the questionnaire: _____

Title (position): _____

Date: _____

Thank you for your time and help

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Table 6.1. Authority resources

	Botswana	D.R Congo	Malawi	Mozambique	Namibia	South Africa	Tanzania	Zambia	Zimbabwe
Number of staff	93	300	53	87	17	237#	290#	120	135
Number of internal assessors	9	75	8	9	8	33	59	18	20
Number of assessors involved in ZaZiBoNa	9	4	4	5	6	12	20	14	20

Permanent

Figure 6.3. Benefits of the ZaZiBoNa initiative according to regulatory authority respondents

Figure 6.4. Strengths of the ZaZiBoNa process at country level according to regulatory authority respondents
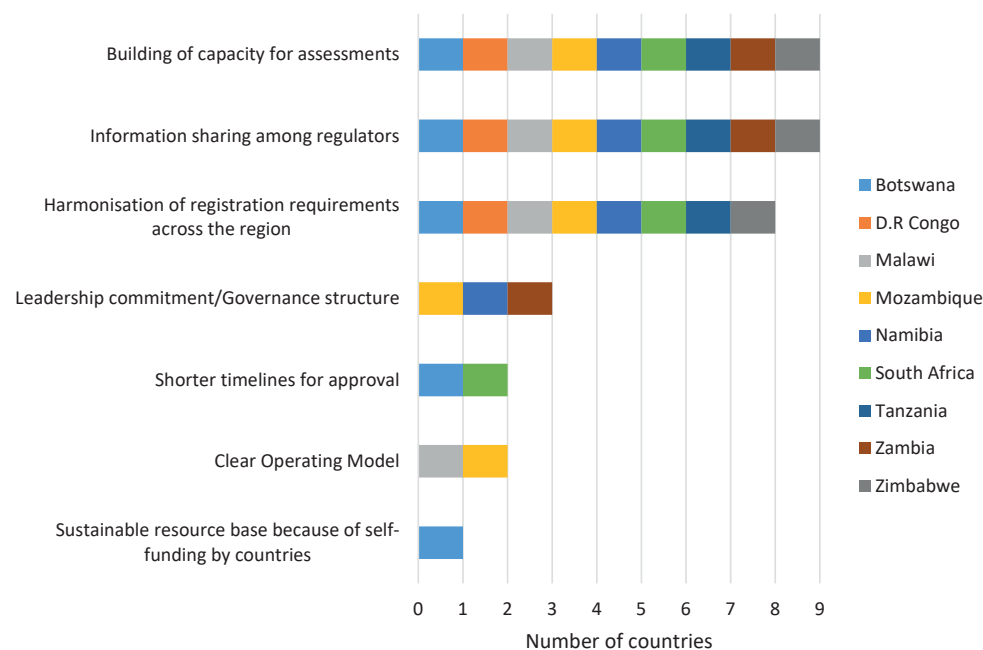
(5/9). However, less than one third of the countries (2/9) published a list of medicinal products approved under ZaZiBoNa on their website, which could be regarded as a weakness of the initiative (Figure 6.4).
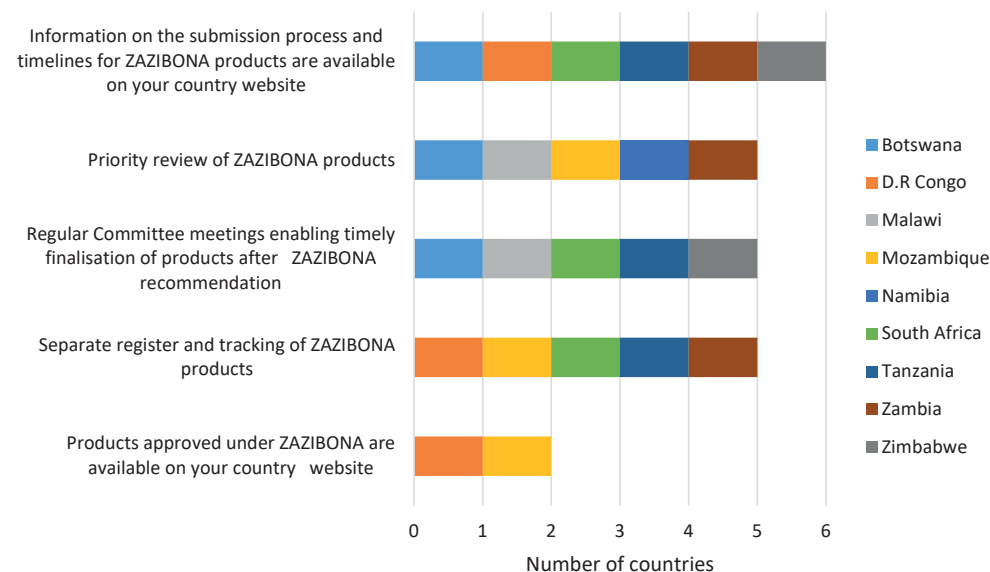
Benefits of the ZaZiBoNa initiative to member countries (regulators)

The majority of the countries agreed that the ZaZiBoNa initiative provided them with benefits that included training, which has improved the performance of the assessors (9/9), a platform for interaction and information exchange with other regulators (9/9), an improvement in the quality of dossiers submitted (8/9) and the ability to apply high standards of assessment regardless of the size of the country or maturity of regulatory authority (7/9). However, less than one third of the countries (2/9) believed that the sharing of the workload through ZaZiBoNa resulted in shorter timelines for approval than in the individual countries, confirming the observation that this is a weakness of the initiative (Figure 6.5).

Benefits of the ZaZiBoNa initiative to applicants

The benefits to applicants selected by countries included the reduction of the burden of compiling several dossiers for different countries, as only one dossier (modules 2 -5)

is required for submission to multiple countries through ZaZiBoNa (8/9) and savings in time and resources as the same list of questions is received from multiple countries enabling compilation of a single response package (9/9) with potential simultaneous access to various markets (9/9). However, only one third of the respondents (3/9) believed that applicants were receiving the promised benefit of shorter timelines for approval compared with timelines achieved for the individual countries (Figure 6.6).

Benefits of the ZaZiBoNa initiative to patients

Increased availability and access to quality-assured medicines (7/9) were identified as the benefits of the ZaZiBoNa initiative for patients by the majority of the countries, although access was not regarded as always being faster than through individual countries (6/9). However, less than one third of the countries (2/9) were of the view that the initiative resulted in reduced prices of medicines (Figure 6.7)

Part III - Challenges of the ZaZiBoNa initiative
Challenges of the ZaZiBoNa initiative

The top two challenges of the ZaZiBoNa initiative that were selected were the lack of centralised submission and tracking (8/9) and dependence on the member country processes for communication with applicants and expert committees (7/9). An unequal workload among member countries (5/9), lack of jurisdictional power (5/9),

Figure 6.5. Benefits of the ZaZiBoNa initiative to member countries (regulators) according to regulatory authority respondents
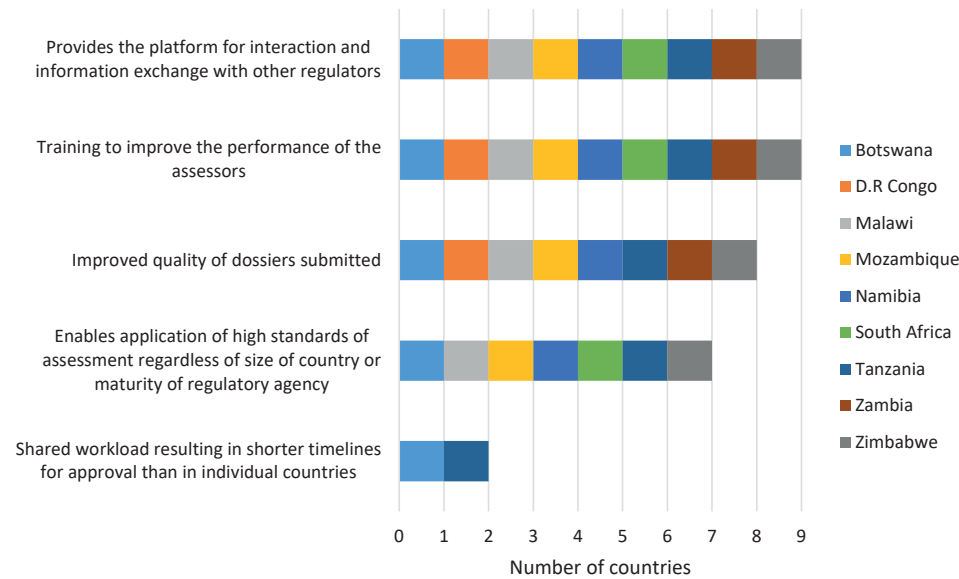

Figure 6.6. Benefits of the ZaZiBoNa initiative to applicants according to regulatory authority respondents

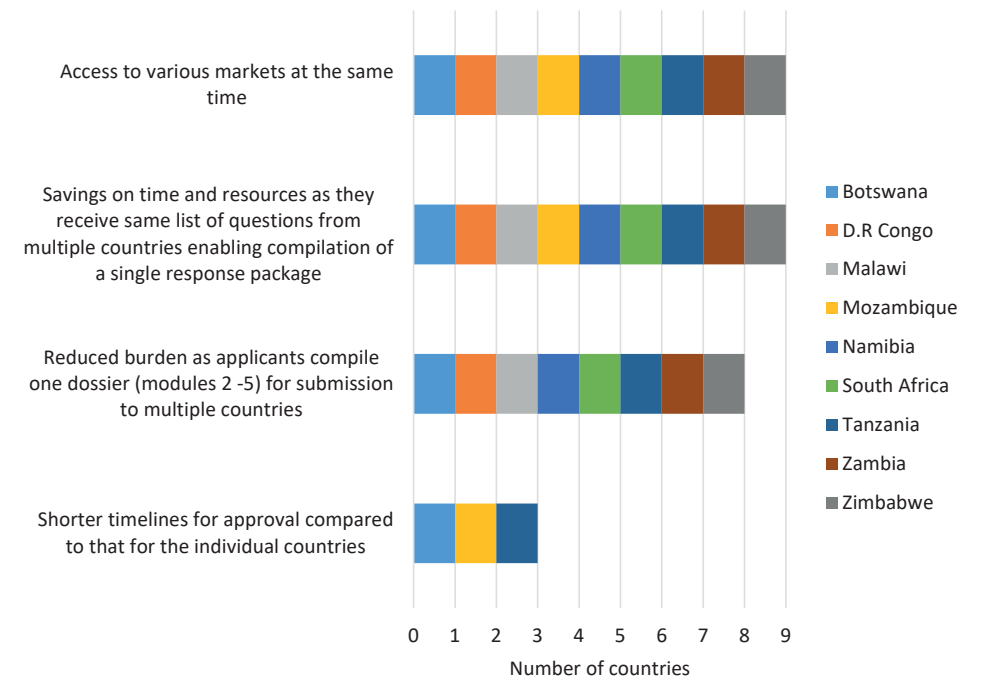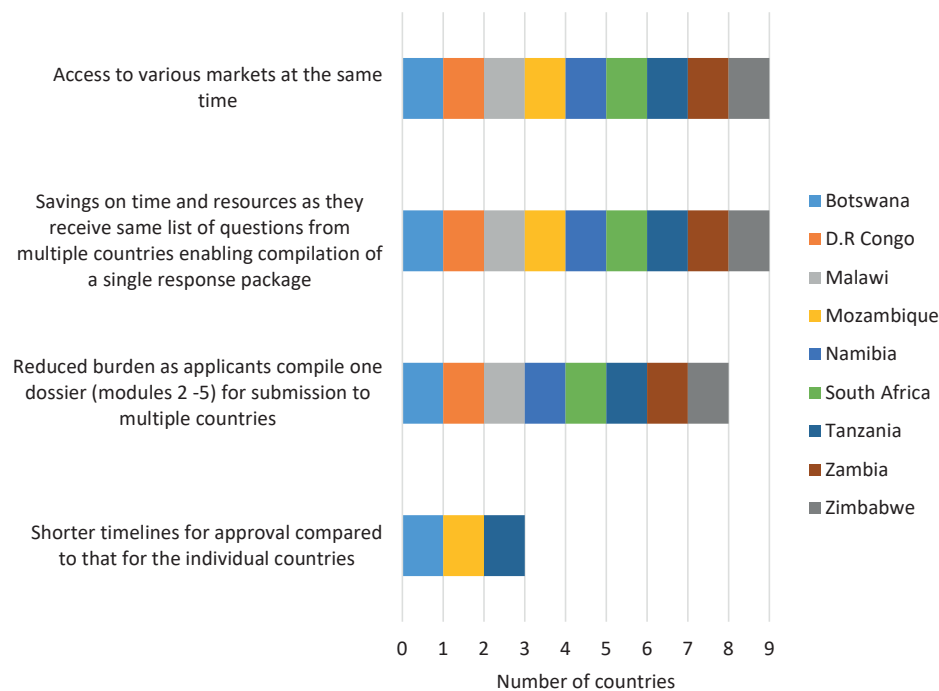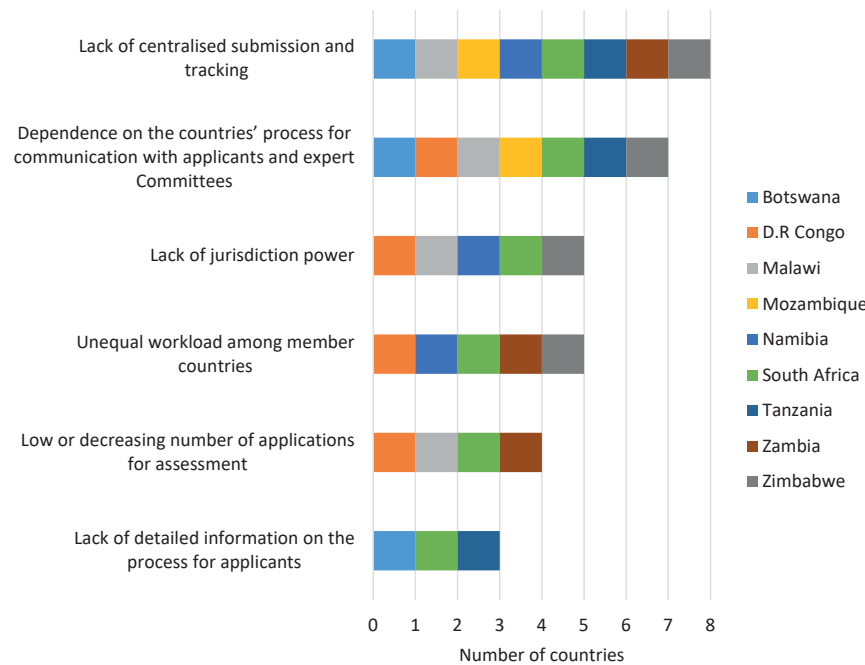**Figure 6.7. Benefits of the ZaZiBoNa initiative to patients according to regulatory authority respondents**

a low or decreasing number of applications (4/9) and lack of detailed information on the process for applicants (3/9) were also identified as challenges by the countries (Figure 6.8).

Challenges at a country level in assessing ZaZiBoNa dossiers / applications

Inadequate human resources (8/9) and the failure by applicants to adhere to deadlines in response to questions (7/9) were cited as the greatest challenges at a country level. Additionally, the majority of the countries (5/9) were of the view that failure by manufacturers to follow the requirement to submit the exact same dossier to all countries of interest was an issue. The other challenges identified were poor record keeping and tracking (3/9), unpredictable scheduling of expert committee meetings (2/9), lack of buy-in from expert committees (1/9) and a failure by authorities to designate ZaZiBoNa assessments as part of the authority's workload (1/9) (Figure 6.9)

Figure 6.8. Challenges of the ZaZiBoNa initiative according to regulatory authority respondents

Figure 6.9. Challenges at a country level in assessing ZaZiBoNa products according to regulatory authority respondents

Challenges for applicants submitting applications to the ZaZiBoNa initiative

The majority of the countries agreed that differing labelling requirements in participating countries (8/9) and lack of information on individual country and ZaZiBoNa websites about the process, milestones, timelines as well as pending and approved medicinal products (7/9) were the greatest challenges faced by applicants with this initiative. Additionally, most of the countries were of the view that the ZaZiBoNa process is more stringent than some country processes (6/9), presenting a challenge for applicants. Other issues identified were lack of clarity about the process for submission and follow-up in each country (4/9) and differences in time to the implementation of ZaZiBoNa recommendations by member countries (3/9) (Figure 6.10).

Part IV - Improving performance (effectiveness and efficiency)
Ways to improve the effectiveness of the ZaZiBoNa initiative

Some of the ways identified by the countries to improve the effectiveness of the initiative included decision-making transparency; for example, publishing public assessment reports (7/9), listing approved medicinal products (6/9), minimising the need for country-specific documents (5/9), engagement and interaction with
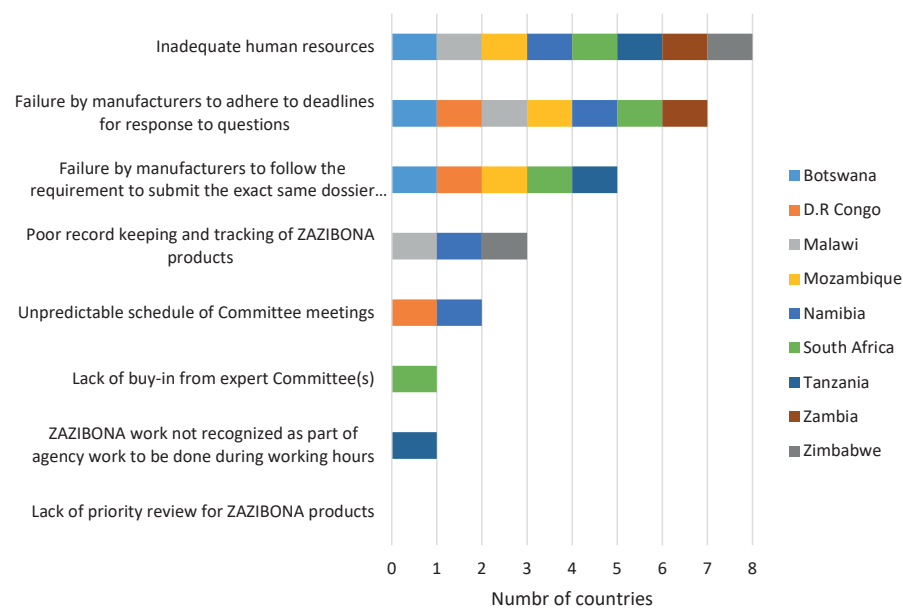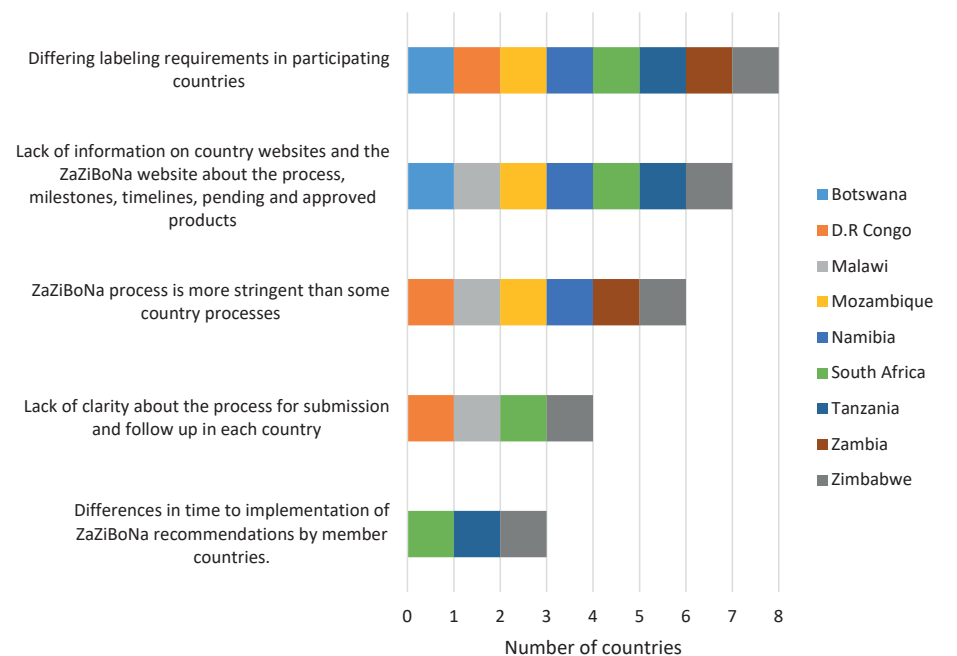
Figure 6.10. Challenges for applicants submitting applications to the ZaZiBoNa initiative according to regulatory authority respondents

stakeholders (5/9), use of risk-based approaches e.g reliance pathways (5/9), consistency in application of guidelines and decisions (5/9), making information that might help applicants in managing their submissions publicly available (5/9) and publishing lists of pending dossiers / applications (3/9) (Figure 6.11).

Ways to improve the efficiency of the ZaZiBoNa initiative

Improved central tracking of ZaZiBoNa dossiers / applications (8/9), a centralised system for submission of applications and communication with applicants (7/9), use of robust information technology systems (6/9), compliance with target timelines by measuring and monitoring each milestone in the review process (6/9), specific and clear requirements made easily available to applicants (6/9), improved resources; for example, number of assessors (5/9) and transparency on metrics and statistics; for example, percentage completed within the timeline (2/9) were selected as ways to improve the efficiency of the initiative (Figure 6.12).

Figure 6.11. Ways to improve the effectiveness of the ZaZiBoNa initiative according to regulatory authority respondents
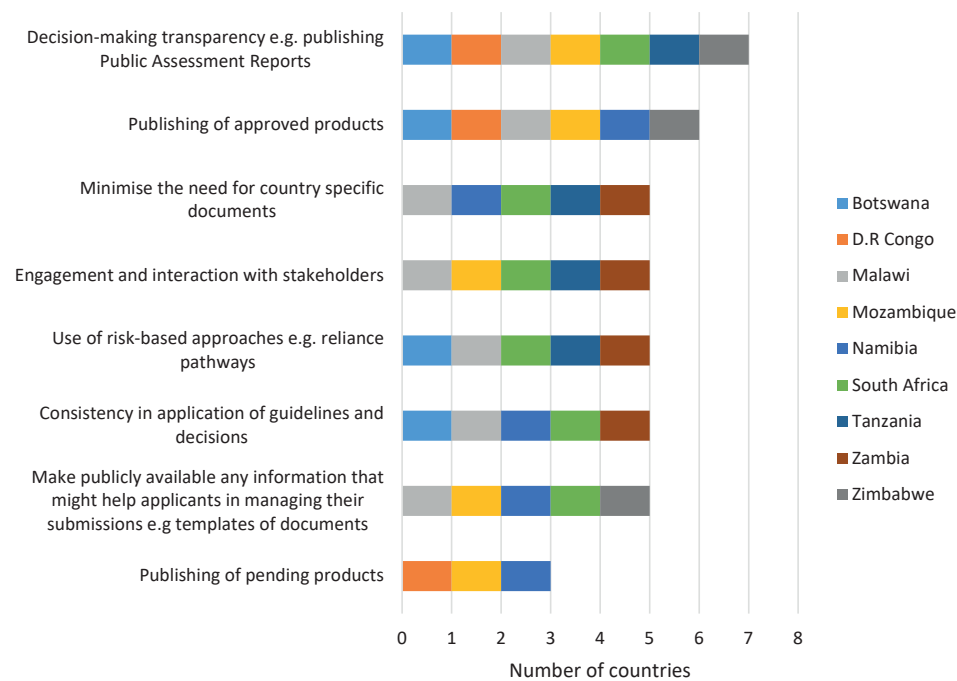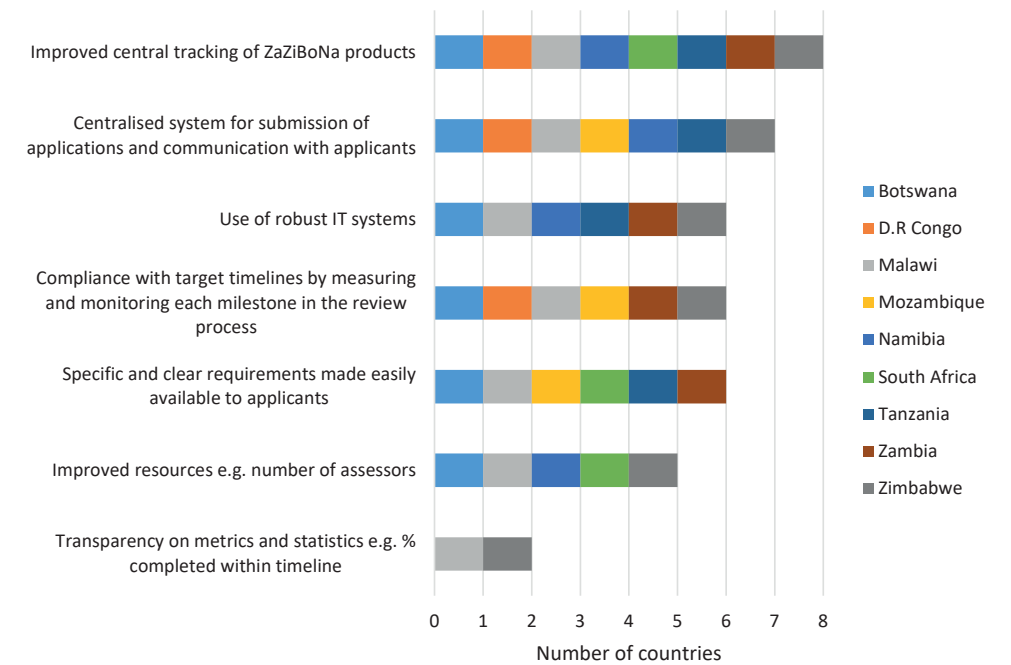

Figure 6.12. Ways to improve the efficiency of the ZaZiBoNa initiative according to regulatory authority respondents

Part V - Strategies for moving forward

The establishment of a regional unit hosted in one of the member states, to centrally receive and track ZaZiBoNa applications and be responsible for allocating work, apportioning the applicable fees to countries, tracking applications and communicating with applicants was selected by the majority of countries (8/9) as the best strategy moving forward in the interim. The majority of countries (7/9) were also of the view that to continue with the current operating model was the least effective strategy. All countries expressed the opinion that the establishment of a SADC regional medicines authority would be the best strategy, if it were legally possible, to address the challenges and areas requiring improvement in this initiative.

DISCUSSION

The results of this study show that the ZaZiBoNa initiative has achieved the majority of its objectives, which included facilitating greater information sharing and harmonisation of registration requirements. The capacity of countries to conduct assessments and inspections has markedly improved as a result of their participation in this initiative (Sithole et.al, 2021a; Sithole et.al, 2021b). Reliance is being implemented within

the initiative, as countries can quickly approve dossiers/applications that they had not previously reviewed but whose reports can be accessed through ZaZiBoNa. One of the key objectives of the ZaZiBoNa initiative was to reduce timelines for the approval of medicines, with a target median time of nine months inclusive of the applicant's time and the study results underscored the expected benefit to applicants of reduced timelines. However, the majority of countries did not believe that shorter timelines were being achieved and this may be problematic in the future, as it can negatively affect applicants' interest and motivation to use this process. The additional challenges faced by applicants and acknowledged by the countries need to be addressed in order to make the initiative more attractive.

Clear communication of timelines for each milestone with applicants as well as the requirements for dossiers/applications to be reviewed will increase the applicants' confidence in the process. At present, not all the participating countries have full information about ZaZiBoNa on their websites, including contact details of the focal person for follow-up. This is information that would be useful for applicants who may be planning submissions to ZaZiBoNa and is in place with other successful global work-sharing initiatives (Swissmedic, 2021; TGA, 2021). Some of the shortcomings at a country level can be attributed to inadequate resources, which may also impact the quality of the assessments. A weakness of this initiative that was identified from the study was the use of inexperienced assessors as experienced assessors were unavailable in some of the countries to carry out the ZaZiBoNa work. The initiative should have standard operating procedures in place to ensure that only competent assessors and inspectors are seconded by the respective countries to participate in the initiative, an approach modelled on the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA, 2021).

It has been established that ZaZiBoNa uses an operating model similar to other global work-sharing initiatives (Swissmedic, 2021; Makvana, 2014; Jawahar, 2015); however, a number of challenges have been identified. This could be due to the significantly reduced resources; for example, the number of assessors, available to ZaZiBoNa countries when compared with countries in the other initiatives. Most of the active member countries in ZaZiBoNa are faced with the challenge of limited resources and a high number of applications (Sithole et.al, 2021a; Sithole et.al, 2021b, Sithole et.al, 2021c; Keyter, 2018; Keyter, 2020) for the national procedure, which negatively impacts the work-sharing initiative. The use of a regional unit to coordinate assessments would also assist in addressing the identified challenges, particularly in a resource-constrained setting. In the long term, the establishment of a SADC regional medicines

authority would be preferable and would address the challenge of the lack of jurisdictional power identified in this study.

CHAPTER 07

EFFECTIVENESS AND EFFICIENCY OF THE ZAZIBONA INITIATIVE: PHARMACEUTICAL INDUSTRY PERSPECTIVE

SUMMARY

- The common technical document (CTD) format harmonised the requirements for the registration of medicines, which had traditionally differed from country to country, making it possible for countries to collaborate and conduct joint reviews of applications.
- One such collaborative medicines registration initiative is the Southern African Development Community ZaZiBoNa, established in 2013.
- A recent study was carried out with the nine active member regulatory authorities of the ZaZiBoNa to determine their views on its operational effectiveness and efficiency.
- Having obtained the authorities' views, the aim of this study was to evaluate the effectiveness and efficiency of the current operating model of the ZaZiBoNa initiative including the challenges it faces as well as identifying opportunities for improvement from the applicants' perspective.
- Data were collected in 2021 using the Process, Effectiveness and Efficiency rating questionnaire (PEER-IND) developed by the authors for 19 pharmaceutical companies.
- The pharmaceutical industry was of the view that the ZaZiBoNa initiative has achieved shorter timelines for approval of medicines, resulting in increased availability of quality-assured medicines for patients in the SADC region.
- Harmonisation of registration requirements and joint reviews have reduced the workload for both the pharmaceutical industry and the regulatory authorities.
- Some of the challenges identified were the lack of a centralised submission and tracking system, and the lack of information for applicants on the process for submission of ZaZiBoNa dossiers / applications in the individual countries, including contact details of the focal person.
- The establishment of a regional unit hosted in one of the member countries to centrally receive and track ZaZiBoNa dossiers / applications was identified as the best strategy for moving forward in the interim with the long-term goal being the establishment of a regional medicine's authority.
- There was consensus between the pharmaceutical industry and the regulatory authorities as to the way forward to improve the effectiveness and efficiency of the ZaZiBoNa initiative. Implementation of the recommendations identified in this study will lead to enhanced regulatory performance.

RECOMMENDATIONS

Key recommendations to improve the effectiveness and efficiency of ZaZiBoNa work-sharing initiative include:

- **Information for applicants** - Full information on the ZaZiBoNa process including contact details of the focal person, timelines and milestones as well as approved medicinal products should be published on the website of every participating authority as well as ZaZiBoNA.
- **Submission procedures** -The initiative should introduce expression of interest forms, which will be completed by applicants prior to submission of dossiers. Communication of acceptance for assessment under the ZaZiBoNa initiative or otherwise should be made within a defined period from the date of submission.
- **Information management systems** - The initiative should use automated systems to enable the online submission and tracking of applications through all the stages of review including information on the meetings at which dossiers / applications are discussed. Applicants should also be able to track their dossiers / applications using the same system.
- **Product life-cycle management** - The initiative should establish a process for the review of post approval changes. Variation requirements should be harmonised so that one application can cater for all markets.
- **Reliance** – The WHO-facilitated SRA procedure for ZaZiBoNa has yielded significant results for some applicants and should be promoted and used for more medicinal products.
- **Centralised submission, tracking and communication system** – As an interim measure, a regional unit hosted in one of the member countries should be piloted to centrally receive, track and coordinate ZaZiBoNa dossier submissions. This will address the various challenges faced by the industry with the current operating model such as differences in the time to implementation of the ZaZiBoNa recommendations for assessments and GMP inspections as well as the lack of a specified person/office to escalate matters in cases in which applicants have challenges with participating countries.
- **Regional medicines authority** – In the long term, a binding memorandum of understanding should be developed mandating the establishment of a regional medicines' authority. This would be similar to the model employed for the SQAM programme in the Southern African Development Community. This would ideally make it possible for a SADC-approved medicinal product to be marketed

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in all the SADC countries. In the meantime, countries should make a deliberate effort to collectively review their legislation, guidelines, and processes in order to truly harmonise the registration and labelling requirements for medicinal products in the SADC region.

INTRODUCTION

Medicines and other medical products undergo a rigorous review to ensure compliance with quality, safety, efficacy and local requirements before they are registered in most countries (Rägo et.al, 2008; Molzon, 2007). Other factors such as compliance of the manufacturing site(s) with current good manufacturing practices (cGMP) and compliance of product samples with specifications are considered before a medical product is registered by a national medicines regulatory authority (Rägo et.al, 2008). Traditionally, requirements for registration differed from country to country, which meant that applicants had to compile a new data set each time they wanted to submit their dossiers / applications for registration (Molzon, 2007). This presented many challenges in an industry often characterised by multinational operations. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) common technical document (CTD) format, which was finalised in the early 2000s, addressed this challenge by harmonising the technical requirements for new drug applications (Molzon, 2007). The CTD format is made up of 5 modules. Module 1 is region specific; for example, application forms and labels; and it has been acknowledged from the onset that the module 1 is required and will be different from country to country, while modules 2 – 5 are the same across all regions, module 2 is for overviews and summaries with module 3 for quality, module 4 for non-clinical study reports and module 5 for clinical study reports (Figure 8.1) (Molzon, 2007; Jordan, 2014; ICH, 2022). The development of the CTD format is a powerful example of the benefits that can result from collaboration between regulators and the pharmaceutical industry.

Figure 7.1. The Common Technical Document triangle
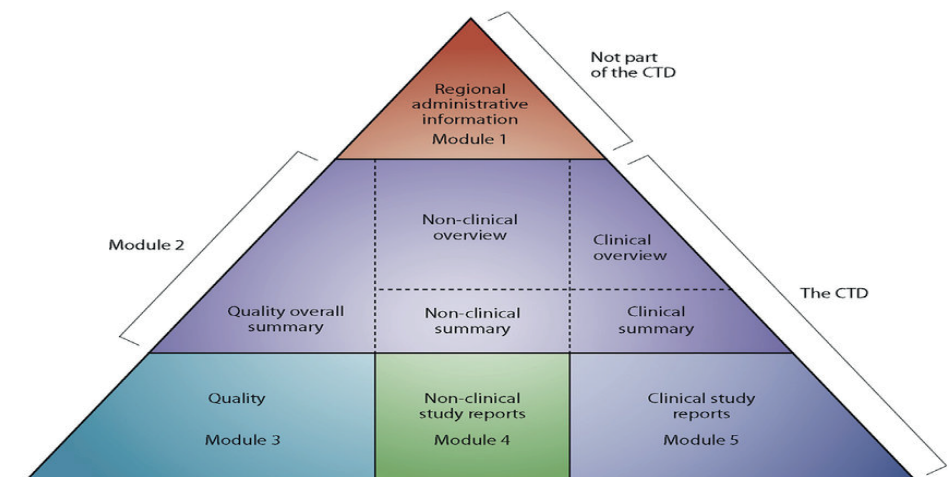
Regulatory harmonisation in Africa

The CTD format is now used by other countries that are not ICH members (Badjatya, 2013). The World Health Organization (WHO) prequalification "Guidelines for submission of documentation for a multisource (generic) finished product and preparation of product dossiers in common technical document format" (WHO, 2011) have been adapted or adopted for use by many low- and middle-income countries in the last decade. The CTD format has facilitated harmonisation of medicines registration requirements, work sharing and joint reviews on the African continent (Sithole et.al; 2020; Mashingia et.al, 2020) as is the case in other emerging markets (Badjatya, 2013; Achin et.al, 2013). Established in 2009, the African Medicines Regulatory Harmonisation Initiative (AMRH) is the driving force behind harmonisation of medicines regulation in Africa (Ndomondo-Sigonda et.al, 2018). The AMRH works through the five regional economic blocks recognised by the African Union, for example, Southern African Development Community (SADC), East African Community (EAC) and the Economic Community of West African States (ECOWAS) (Ndomondo-Sigonda et.al, 2017).

ZaZiBoNa collaborative medicine registration initiative

ZaZiBoNa is a collaborative medicines registration initiative in the SADC region established in 2013 and formally endorsed by the SADC Health Ministers in 2014 (Sithole et.al, 2020). All 16 SADC countries, Angola, Botswana, Comoros Islands, Democratic Republic of Congo, Eswatini, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, United Republic of Tanzania, Zambia, and Zimbabwe (SADC, 2021a), participate in the initiative as either active or non-active members (Sithole et.al, 2020). As at December 2021, 333 dossiers / applications had been assessed under the ZaZiBoNa initiative with a median time to recommendation of 12 months (Masekela, 2021), which is much shorter than the timelines reported by some of the participating countries for their national procedures (Sithole et.al, 2021b). Although some feedback on the performance of the initiative has been sought from manufactures through stakeholder meetings in the past, there has not been a comprehensive and structured evaluation of the work-sharing programme for its future direction. Therefore, a study was carried out with the nine active members (regulatory authorities) of the ZaZiBoNa work-sharing initiative to determine their views on its operational effectiveness and efficiency in chapter 7 (Sithole et.al, 2022a). The aim of this study was to evaluate the effectiveness and efficiency of the current operating model of the ZaZiBoNa initiative including the challenges it faces as well as identifying opportunities for improvement from the perspective of applicants.

STUDY OBJECTIVES

The objectives of this study were to
1. Obtain the views of the applicants of the ZaZiBoNa initiative about the performance of the programme to date
2. Identify the challenges experienced by individual applicants since the inception of the ZaZiBoNa initiative
3. Determine the strengths and weaknesses of the initiative
4. Identify the ways for improving the performance of the work-sharing programme
5. Envisage the strategy for moving forward

METHODS

Study participants

Twenty-three applicants who had submitted registration/marketing authorisation applications for both generic and innovator products to the ZaZiBoNa initiative during the period 2017-2021 were identified and invited to participate in the study. Nineteen out of the twenty-three applicants responded with completed questionnaires, translating to a response rate of 83%. Applicants who submitted applications for registration of generic medicines manufactured outside of the SADC region will be referred to as *Generics (Foreign)* in this report. Applicants who submitted applications for registration of generic medicines manufactured within the SADC region will be referred to as *Generics (Local)*. Applicants who submitted applications for registration of innovator medicines will be referred to as *Innovator*. There were no locally manufactured innovator medicines submitted to ZaZiBoNa in the period under review (2017-2021).

Development of the PEER-IND questionnaire

The Process, Effectiveness and Efficiency Rating questionnaire for industry (PEER-IND) (Figure 7.2) was developed by the authors. The questionnaire comprised five sections under the headings; demographics, benefits of the ZaZiBoNa initiative, challenges of the ZaZiBoNa initiative, improving the performance (effectiveness and efficiency) of the work-sharing programme and envisaging the strategy for moving forward.

Pilot Study

To examine the applicability and practicality of the PEER-IND questionnaire, it was piloted with five applicants in August 2021 prior to undertaking the main study and an additional question rating the individual countries was included in the questionnaire based on the feedback from the participants. Subsequently, an additional 7-item

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questionnaire was completed by all participants to establish the content validity and relevance of the PEER-IND questionnaire using the following questions;

1. Did you find the questions clear and straightforward to respond to?

Yes ☐ No ☐

2. Did you find the response options relevant to the heading of each section (A to E)?

Yes ☐ No ☐

3. Did you find the questions relevant to the aims and objectives of the study?

Yes ☐ No ☐

4. Did you find the questions relevant to your authority and ZAZIBONA work sharing initiative?

Yes ☐ No ☐

5. Did you find any relevant questions missing?

Yes ☐ No ☐

If yes, please state which questions were missing in the space after this list of questions.

6. Did you find any questions that should be excluded?

Yes ☐ No ☐

If yes, please state the questions that should be excluded in the space after this list of questions.

7. Did you find the questionnaire useful to reflect on both your agency experience as well that of ZAZIBONA?

Yes ☐ No ☐

All respondents were of the view that the content of the final PEER-IND questionnaire was adequate and therefore did not propose any further changes.

Data collection

Data were collected in September 2021 using the PEER-IND questionnaire. The questionnaire was completed by a representative responsible for ZaZiBoNa submissions in each company.

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Figure 7.2. The Process, Effectiveness and Efficiency Rating questionnaire for industry (PEER-IND)

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ZAZIBONA COLLABORATIVE MEDICINES REGISTRATION INITIATIVE

PROCESS EFFECTIVENESS & EFFICIENCY RATING (PEER-IND)

Pic taken from https://www.referenceforbusiness.com/management/Or-Ex/Effectiveness-and-Efficiency.html

PEER-IND QUESTIONNAIRE

August, 2021

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INTRODUCTION

The ZAZIBONA collaborative medicines registration initiative was established in 2013 and formally endorsed by the SADC health ministers in 2014. Since its inception, there has not been a formal and structured evaluation of this work sharing programme and for its future direction, although some feedback has been sought from manufactures through stakeholder meetings.

A recent study has been carried out among the nine active members of the ZaZiBoNa work sharing initiative using a similar questionnaire to the one being sent to the applicants, so that the benefit is gained from both key stakeholders.

In recent years, there has been a drive within regulatory agencies to re-engineer their processes for improved efficiency and effectiveness and this often begins with a baseline evaluation of the current process to identify strengths and weaknesses. *Effectiveness* can be defined as 'doing the right thing' often measured by the value derived by customers/stakeholders from an organisation's processes or services while *Efficiency* can be defined as 'doing things right' which saves the organization time and resources.

Study Participants
The PEER Questionnaire is being sent to applicants who have submitted marketing authorisation applications for assessment under the ZaZIBoNa initiative.

AIM

The aim of this study is to evaluate the effectiveness and efficiency of the current operating model of the ZAZIBONA initiative including the challenges it faces as well as identifying opportunities for improvement.

STUDY OBJECTIVES

1. Obtaining the views of the applicants of the ZaZiBoNa initiative about the performance of the programme to date.
2. Identifying the challenges experienced by individual applicants throughout the life cycle of the ZaZiBoNa initiative.
3. Determining the strengths and weaknesses of the initiative
4. Identifying the ways of improving the performance of the work sharing programme.
5. Envisaging the strategy for moving forward

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Figure 7.2. (continued)

Thank you for agreeing to participate in this survey. **Your responses will be treated in strictest confidence and no identifiers of companies or respondents will be shared with any third party or made public.** External reports or presentations of the data will include only blinded results together with appropriate analytical interpretations.

The questionnaire is divided into five short sections and will take 20 minutes to complete. Thank you for taking time to complete it. We value your input!

A. DEMOGRAPHICS

1. Please state the name of your company ___

2. Please provide your responses to the following questions by writing your answer in the space provided or ticking the relevant box.
   a. Age: ___ years
   b. Sex: □ Male □ Female
   c. Number of years of regulatory affairs experience: ___ years

3. State the SADC countries in which your company markets products

□ Angola	□ Botswana
□ Comoros	□ Democratic Republic of Congo
□ Eswatini	□ Lesotho
□ Madagascar	□ Malawi
□ Mauritius	□ Mozambique
□ Namibia	□ Seychelles
□ South Africa	□ Tanzania
□ Zambia	□ Zimbabwe

4. Do you have a separate record of applications submitted for assessment under ZAZIBONA to facilitate tracking and adherence to deadlines? □ Yes □ No

B. VIEWS ON THE BENEFITS OF THE ZAZIBONA INITIATIVE
Select your answers by ticking the relevant box(es)

1. In your view, what are 3 (or more) benefits of the ZAZIBONA initiative to date?

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□ Leadership commitment/Governance structure
□ Clear Operating Model
□ Shorter timelines for approval
□ Information sharing among regulators
□ Building of capacity for assessments
□ Sustainable resource base because of self-funding by countries
□ 'Harmonisation of registration requirements across the region
□ Other (Please specify) ___

2. How has the ZAZIBONA initiative benefited you as applicants?

□ Reduced burden as applicants compile one dossier (modules 2 -5) for submission to multiple countries
□ Savings on time and resources as applicants receive the same list of questions from multiple countries enabling compilation of a single response package
□ Shorter timelines for approval compared to that for the individual countries
□ Access to various markets at the same time
□ Other (Please specify) ___

3. How has the ZAZIBONA initiative benefited patients in the individual countries or in the SADC region?

□ Quicker access to quality assured medicines
□ Reduced prices of medicines
□ Increased availability of medicines
□ Other (Please specify) ___

C. VIEWS ON CHALLENGES OF THE ZAZIBONA INITIATIVE
Select your answers by ticking the relevant box(es)

1. In your view, what are 3 (or more) challenges of the ZAZIBONA initiative?

□ Lack of detailed information on the process for applicants
□ Differences in regulatory performance of the countries
□ Dependence on the countries' process for communication with applicants

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Figure 7.2. (continued)

□ Lack of centralised submission and tracking
□ Lack of ability to mandate central registration
□ Other (please specify) ___

2. What are the challenges faced by applicants submitting applications to the ZAZIBONA initiative?

□ Differences in time to implementation of ZAZIBONA recommendations by member countries.
□ Lack of clarity about the process for submission and follow up in each country
□ Lack of information on country websites and the ZAZIBONA website about the process, milestones, timelines for pending and approved products
□ ZAZIBONA process is more stringent than individual country processes for reviews and GMP audits
□ Differing labeling requirements in participating countries
□ Failure by countries to adhere to promised timelines
□ Risk of losing access to all member states once a product is rejected by ZAZIBONA (i,e can no longer pursue registration in individual countries)
□ Low motivation and appeal to use the ZAZIBONA route as there are few success stories available or publicized
□ Low motivation to use the ZAZIBONA route as other review routes are now being used by individual countries e.g reliance on SRA approvals or other SADC countries are faster
□ Other (Please specify) ___

3. In your view, what do you believe are the challenges faced by agencies in reviewing the ZAZIBONA applications? ___

D. IMPROVING THE PERFORMANCE (EFFECTIVENESS AND EFFICIENCY OF THE WORK SHARING PROGRAMME
Select your answers by ticking the relevant box(es)

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Effectiveness can be defined as 'doing the right thing' often measured by the value derived by customers/stakeholders from an organisation's processes or services while *Efficiency* can be defined as 'doing things right' which saves the organization time and resources.

1. What are 3 or more ways to improve the effectiveness of the ZAZIBONA initiative in your view?

□ Decision-making transparency e.g., publishing Public Assessment Reports
□ Make publicly available any information that might help applicants in managing their submissions - templates of documents, lists of Q&A, timelines and milestones, disclosure of internal SOPs, etc.
□ Consistency in application of guidelines and decisions
□ Use of risk-based approaches e.g., reliance pathways
□ Engagement and interaction with stakeholders
□ Publishing of pending products
□ Publishing of approved products
□ Minimising the need for country specific documents
□ Other (Please specify) ___

2. What are 3 or more ways to improve the efficiency of the ZAZIBONA initiative in your view?

□ Specific and clear requirements made easily available to applicants
□ Compliance with target timelines by measuring and monitoring each milestone in the review process
□ Use of robust IT systems
□ Transparency on metrics and statistics e.g., % completed within a timeline
□ Improved central tracking of ZAZIBONA products
□ Improved resources e.g., number of assessors
□ Centralised system for submission of applications and communication with applicants
□ Other (please specify) ___

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Figure 7.2. (continued)

3. Evaluate the performance of individual countries that you have submitted applications to for review under ZAZIBONA *Please complete only for the countries that you have submitted ZAZIBONA applications to and have experience with*

Measure	Botswana		D.R Congo		Malawi		Mozambique		Namibia		South Africa		Tanzania		Zambia		Zimbabwe	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
The contact person is known	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
The process for submission of applications is clear	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
The process and timelines for ZAZIBONA products are available on the website	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Communication of queries is carried out timeously (NMT 30 days after a session)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Registration after a ZAZIBONA recommendation is carried out timeously (i.e in NMT 3 months from the date of the recommendation)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

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Figure 7.2. (continued)

E: ENVISAGING THE STRATEGY FOR MOVING FORWARD

1. Rate the following proposals to improve the current ZAZIBONA operating model from 1 – 3, number 1 representing what you think would be **most effective** in improving efficiency and number 3 the **least effective**. *Enter the appropriate number in the space provided before each proposal.*

☐   To continue with the current operating model unchanged.

☐   To continue with the current operating model, but provide full information on the process including timelines and milestones as well as approved products on every participating country's website and on the ZAZIBONA website.

☐   The establishment of a regional administrative body to centrally receive and track ZAZIBONA applications which would be responsible for allocating work, apportioning the applicable fees to countries, tracking of applications and communication with applicants.

2. In your view, would the establishment of a SADC regional medicines agency, if legally possible, be the best strategy for improved performance going forward?
☐ Yes   ☐ No

Please explain why? _____

_____

3. In conclusion, what other strategies not previously highlighted can you think of that would strengthen the ZAZIBONA initiative going forward?

_____

_____

_____

Please feel free to use the comment box below to elaborate on any of your answers or to highlight questions and answers that you believe should have been included in this questionnaire.

Name of person completing the questionnaire: _____

    Title (position): _____

    Date: _____

Thank you for your time and help

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RESULTS

For the purpose of clarity, the results are presented in five parts: Part I – Demographics; Part II - Benefits of the ZaZiBoNa initiative; Part III – Challenges of the ZaZiBoNa initiative; Part IV – Improving the performance of the work-sharing programme; and Part V – Envisaging the strategy for moving forward.

Part I - Demographics

The study respondents' age ranged from 33 – 59 years, with a range of regulatory experience from 5–30 years. Eleven of the respondents were female and eight were male. Study participants were classified according to their product portfolio and location of their manufacturing site. Fifteen (79%) were foreign generic pharmaceutical companies, one (5%) was a local manufacturer of generics and three (16%) were innovator pharmaceutical companies. Of the 333 dossiers / applications assessed as at 31 December 2021, 94% were generics submitted by foreign companies, 5% were new active substances submitted by innovator companies and 1% were generics submitted by the local company.

Part II - Benefits of the ZaZiBoNa initiative
Benefits of the ZaZiBoNA initiative

Information sharing among regulators (16/19), harmonisation of registration requirements across the region (15/19) and shorter timelines for approval (14/19) were identified as the top three benefits of the ZaZiBoNa initiative by the majority of the applicants. However, of note is that less than one third of the applicants believed that the operating model was clear (5/19) or that self-funding by countries created a sustainable resource base for the initiative (3/19) (Figure 7.3).

Benefits of the ZaZiBoNa initiative to applicants

The majority of applicants (16/19) viewed the savings of time and resources as a benefit of the initiative, as they received the same list of questions from multiple countries, enabling compilation of a single response package (Figure 7.4). In addition to this, a large number of applicants (14/19) believed that the burden of compiling several dossiers for different countries was reduced as under ZaZiBoNa they only compiled one dossier (modules 2 -5) for submission to multiple countries. Access to various markets at the same time (13/19) and shorter timelines for approval compared with that of the individual countries (11/19) were also identified as benefits to applicants, although some applicants were of the view that ZaZiBoNa timelines of approximately 12 months were comparable to the national timelines for some countries who had improved their timelines in the last 2 – 3 years.

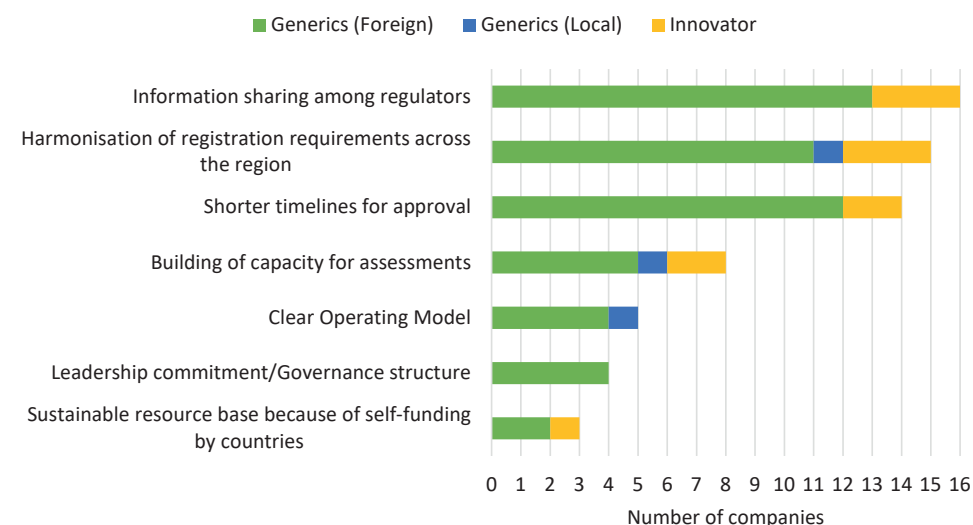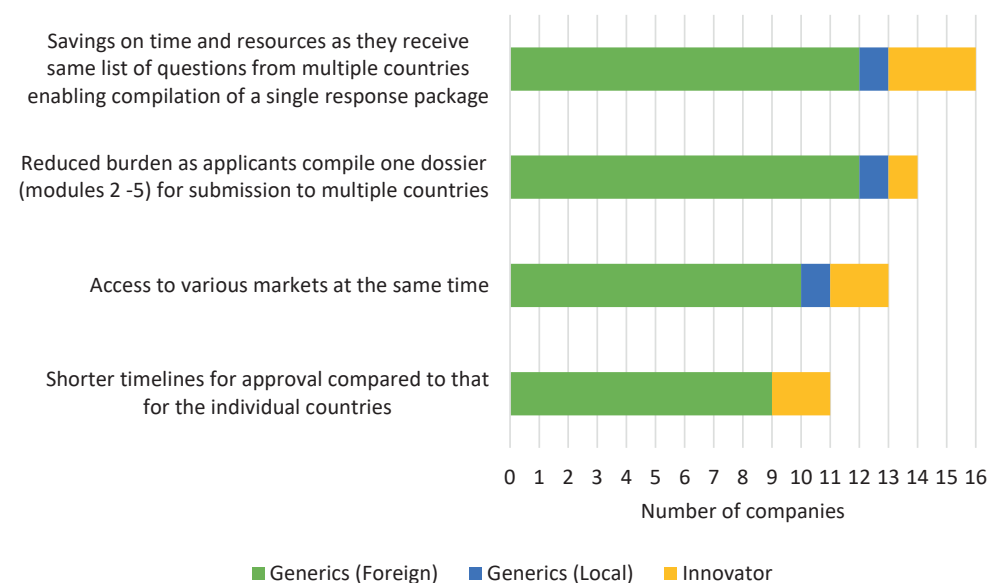**Figure 7.3. Benefits of the ZaZiBoNa initiative according to pharmaceutical industry respondents**

Figure 7.4. Benefits of the ZaZiBoNa initiative to applicants according to pharmaceutical industry respondents

Benefits of the ZaZiBoNa initiative to patients

Increased availability of medicines (15/19) and quicker access to quality-assured medicines (14/19) were identified as the benefits of the ZaZiBoNa initiative to

patients by the majority of applicants. This was attributed by some applicants to improved commercial viability in otherwise under-resourced territories, resulting from the acceptance/supply of a harmonised medicinal product across the region. However, only 2 out of the 19 applicants believed that the initiative resulted in reduced prices for medicines (Figure 7.5).

Part III - Challenges of the ZaZiBoNa initiative
Overall challenges of the ZaZiBoNa initiative

The major challenges of the ZaZiBoNa initiative were identified as the lack of centralised submission and tracking (18/19), differences in regulatory performance of the countries (13/19), lack of ability to mandate a central registration (12/19) and dependence on the countries' processes for communication with applicants (12/19) (Figure 7.6). Additional challenges highlighted were the failure by some countries to adhere to the 90 working days set for registration after the ZaZiBoNa recommendation, difficulty following up on dossiers / applications in some countries as there was no clear ZaZiBoNa contact person and the lack of an overall central person in ZaZiBoNa to submit complaints when individual countries were uncooperative.

Challenges for applicants submitting applications to the ZaZiBoNa initiative

The top two challenges faced by applicants, indicated by the respondents, were lack of information on the country and ZaZiBoNa websites about the process, milestones, timelines and pending and approved mediinal products (15/19) and the differences in time to the implementation of ZaZiBoNa recommendations by member countries (14/19). Additional challenges identified by a majority of the applicants were differing labelling requirements in participating countries (11/19), lack of clarity about the process for submission and follow-up in each country (10/19) and low motivation to use the ZaZiBoNa route as other review routes now used by individual countries such as reliance on stringent regulatory authority (SRA) approvals or approvals by other SADC countries were faster (10/19) (Figure 7.7). The lack of alignment resulting in some of the ZaZiBoNa member countries being more stringent than others was perceived to put smaller companies at a disadvantage compared with larger established companies. Applicants also expressed frustration at having to duplicate efforts in completing WHO forms, which are currently used for ZaZiBoNa as well as national forms; for example, WHO versus national Quality Information Summary and Quality Overall Summary.

Figure 7.5. Benefits of the ZaZiBoNa initiative to patients according to pharmaceutical industry respondents
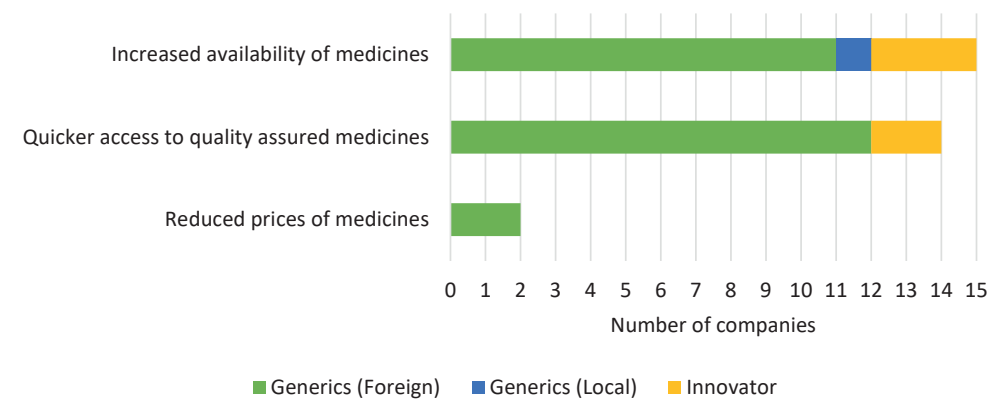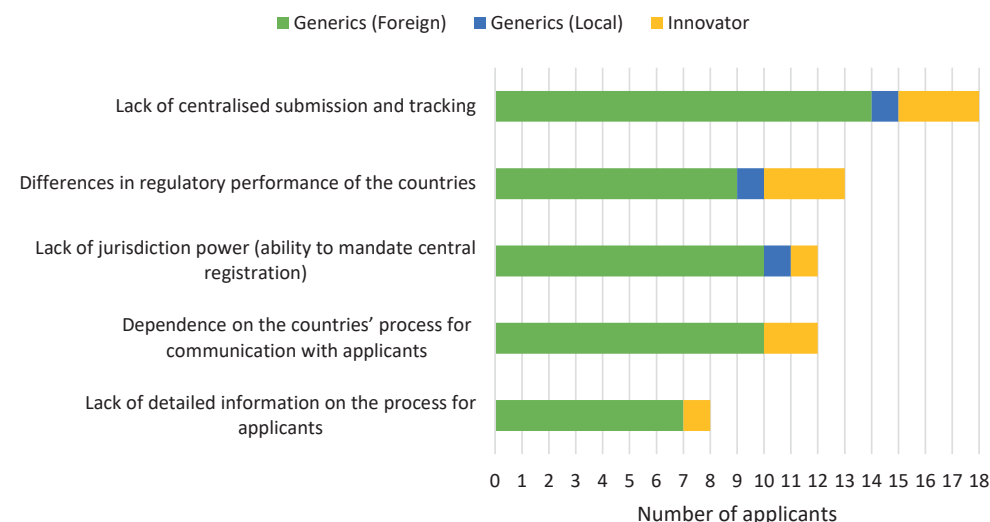

Figure 7.6. Overall challenges of the ZaZiBoNa initiative according to pharmaceutical industry respondents
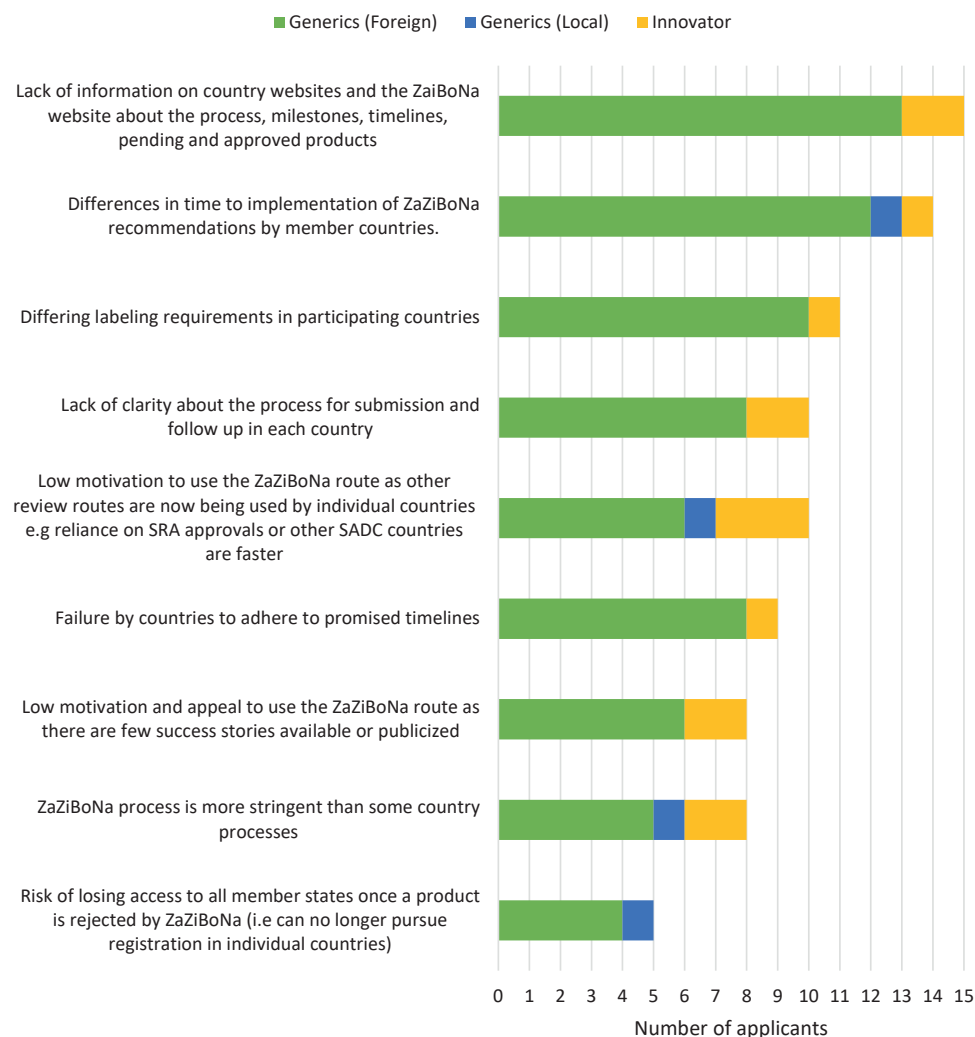
Industry's views of the challenges faced by regulators

Industry identified some challenges faced by regulators:

- submission of dossiers and query responses at different times in the member countries, making it difficult to initiate harmonised assessment;
- different internal processes in each of the authorities leading to dissimilar times for adoption of recommendations and processing of query letters and registration certificates;

Figure 7.7. Challenges for applicants submitting to the ZaZiBoNa initiative according to pharmaceutical industry respondents

- limited number of assessors with adequate skills) available for the ZaZiBoNa process; and
- lengthy assessments and queries due to the combined process and lack of a dedicated team to review the ZaZiBoNa applications.

Part IV - Improving performance (effectiveness and efficiency)
Improving the effectiveness of the ZaZiBoNa initiative

The following approaches, namely minimising the need for country-specific documents (16/19), making publicly available any information that might help applicants in managing their submissions such as document templates, lists of Q&As, timelines and milestones, disclosure of internal standard operating procedures (13/19), use of risk-based approaches such as reliance pathways and engagement (13/19) and interaction with stakeholders (13/19) were selected as the top ways to improve effectiveness of the initiative by the industry. Applicants proposed that having clear communication as to whether a dossier / application has been accepted into the ZaZiBoNa process, the availability of contact details of the focal person in each respective country to enable follow-up of pending dossiers / applications and centralising submission were additional measures that would improve the effectiveness of the initiative (Figure 7.8).

Improving the efficiency of the ZaZiBoNa initiative

Applicants selected improved central tracking of ZaZiBoNa dossiers / applications (17/19) and a centralised system for the submission of applications and communication with applicants (17/9) as the top ways to improve the efficiency of the initiative for applicants. Also identified as contributing to improved efficiency were specific and clear requirements made easily available to applicants (15/19) and compliance with target timelines by measuring and monitoring each milestone in the review process (13/19) (Figure 7.9).

Part V - Strategies for moving forward
The majority of applicants (15/19) were of the view that the establishment of a regional unit hosted in one of the member countries to centrally receive and track ZaZiBoNa applications was the best strategy for moving forward in the interim. The unit would be responsible for allocating work, apportioning the applicable fees to countries, tracking of applications and communication with applicants. The majority of applicants (12/19) were also of the view that to continue with the current operating model was the least effective strategy.

- inadequate infrastructure and information technology (IT) system and resources;
- unavailability of reliance-related documentation from Stringent Regulatory Authorities (SRA's) for WHO facilitated SRA reviews;
- difficulty in sharing additional information provided by applicants during submission of responses to respective authorities;
- facilitating various views during the review of a single application by all participating countries;
- limited capacity for the review of bio-therapeutics by some authorities;

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Figure 7.8. Improving the effectiveness of the ZaZiBoNa initiative according to pharmaceutical industry respondents
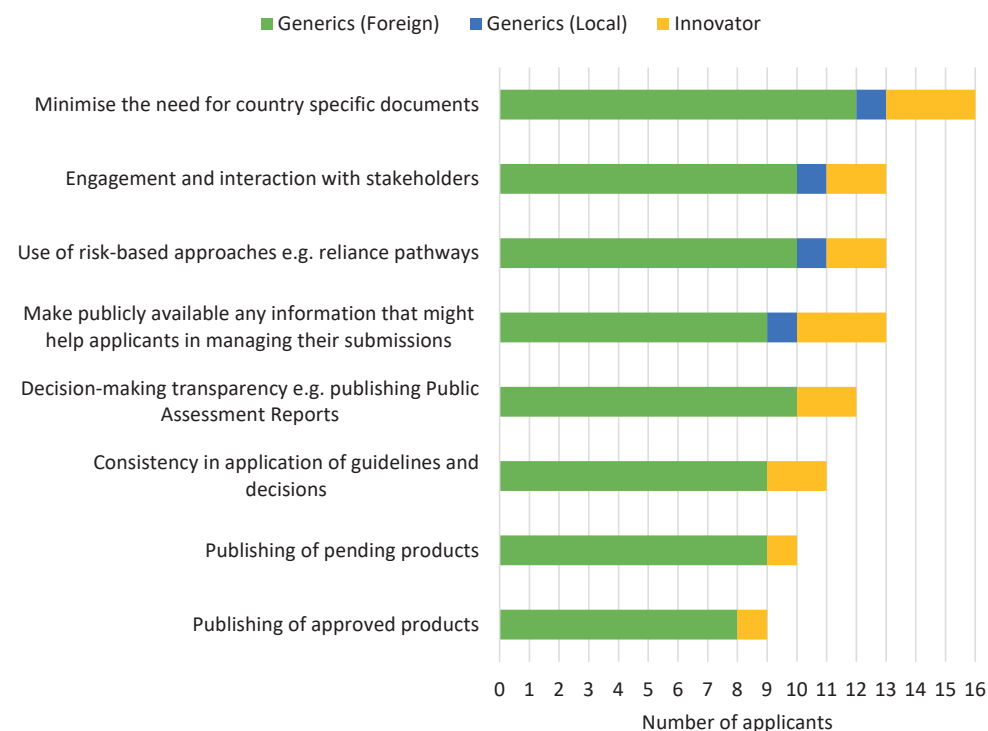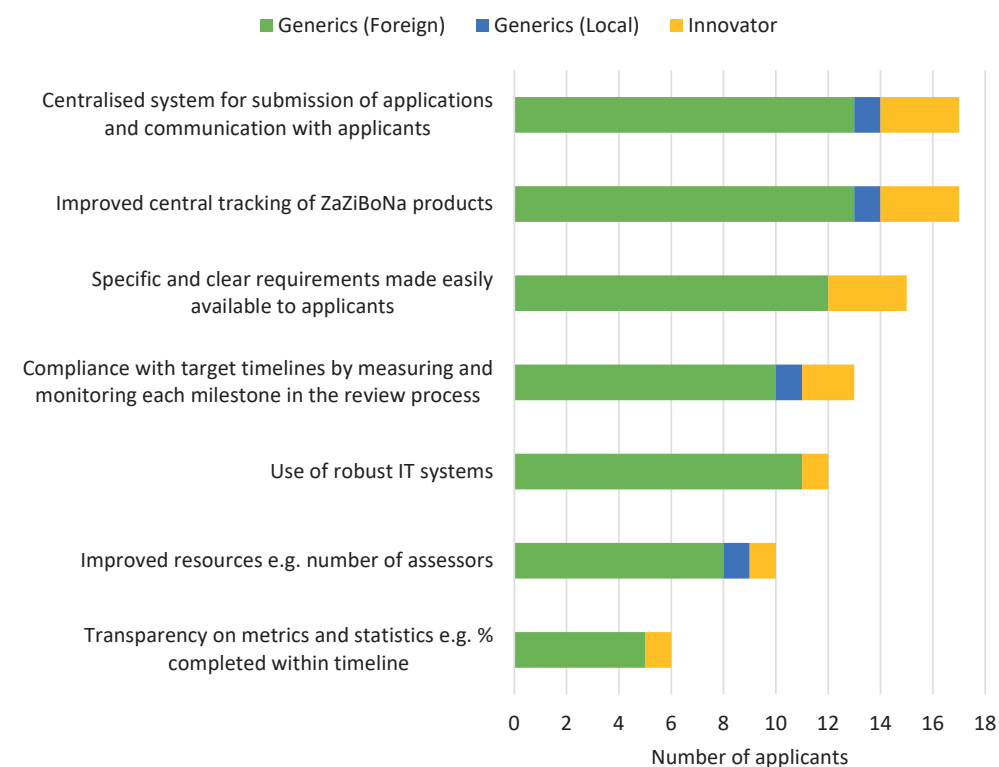

Figure 7.9. Improving the efficiency of the ZaZiBoNa initiative according to pharmaceutical industry respondents

Fifteen out of 19 applicants were of the view that if it were legally possible, the establishment of a SADC regional medicines authority would be the best strategy to address the challenges and areas requiring improvement in the initiative. However, it was acknowledged by some of the applicants that immense legal and administrative hurdles exist in the SADC setting; for example, lack of harmonisation in the regional dossier sections, as well as differences in country-specific registration requirements, which will need to be addressed if a regional authority is to be established. An example of this is the requirement of the South African Health Products Regulatory Authority (SAHPRA) that comparative dissolution studies should be conducted between an SRA oral formulation versus the local test medicinal product to demonstrate equivalence in three different dissolution media is unique to SAHPRA and different to all other ZaZiBoNa members. A few of the applicants (3/19) were not in support of the establishment of a SADC regional medicines authority, as some of these felt that it would increase the operating costs of the entire evaluation process, which would affect them in the end.

DISCUSSION

The results of this study show that applicants perceive that there has been a high degree of success and benefit from the ZaZiBoNa initiative for applicants, patients and regulators. A similar study (chapter 6) was conducted with regulators (Sithole et.al, 2022a) and the responses compared. Regulators and industry commonly agreed that information sharing among regulators and harmonisation of registration requirements across the region were the main benefits of the ZaZiBoNa initiative. There was agreement too that as a result, the initiative has saved the industry time and resources spent compiling submissions and responses to queries. Both regulators and the pharmaceutical industry were of the view that the initiative has resulted in greater access to quality-assured medicines by patients, although there was a difference in opinion regarding the time that this is taking. A number of applicants were of the view that ZaZiBoNa resulted in shorter timelines, while only a minority of regulators believed that this was achieved (Sithole et.al, 2022a). Further investigation is required to understand why the initiative is not resulting in reduced prices of medicines for

patients, since both regulators and industry acknowledge that time, resources and the effort required to get medicines approved has been reduced.

While the successes and benefits of the ZaZiBoNa initiative have been examined in this study, it is apparent that there is now a need to review the operating model in order to address the challenges that have been identified to make it more effective and efficient. Views of the regulators (Sithole et.al, 2022a) and industry were compared and there was agreement on the challenges such as lack of information for applicants on country websites, failure by applicants to meet deadlines for submission of responses, inadequate resources, an unclear operating model and differing performance by participating regulatory authorities.

Interestingly, only a minority of the regulators and industry were of the view that self-funding by countries created a sustainable resource base for this initiative; therefore, there is still a need for partner support or other sources of funding at present. This is supported by studies in the literature highlighting the inadequacy of resources currently available to authorities in low- to middle-income countries (Keyter et.al, 2018; Keyter et.al, 2020; Sithole et.al, 2020, Sithole et.al, 2021a, Sithole et.al, 2021c). Challenges highlighted by the industry but not identified in the regulators study (Sithole et.al, 2022a) are the difficulties faced by applicants when they need to follow up on pending dossiers / applications or seek arbitration in situations in which individual authorities were uncooperative. The challenges identified in this study are not unique to this initiative, as they have been identified for other regions such as the East African Community, with applicants indicating that the goal of harmonisation, which was to ensure quicker access to quality-assured medicines was not always being met (Dansie et.al, 2019). Addressing the challenges identified in this study presents a unique opportunity for ZaZiBoNa to re-engineer its operating model, thus ensuring that the initiative remains competitive when compared with the other routes available for registration of medicines.

The removal of country-specific requirements was identified in both this and the regulators study (Sithole et.al, 2022a) as one of the best ways to improve effectiveness and efficiency. Authorities in the SADC region now require submission of the dossier in CTD format; however, there are some country-specific requirements identified in this study such as bioequivalence, labelling and local Quality Information Summary and Quality Overall Summary that still impede harmonisation efforts and this is consistent with findings from other studies in the literature (Narsai et.al, 2012; Sithole et.al, 2020). There is now a need for countries to make a deliberate effort

to collectively review their legislation in order to include provisions that facilitate the harmonisation of the registration and labelling requirements for medicinal products in the SADC region.

Although the ZaZiBoNa initiative has been in operation for eight years, the process for submission in some countries remains unclear to applicants (Sithole et.al, 2020,). This, in addition to a number of other challenges idenfied in this study such as failure by some countries to register medicines and issue GMP certificates within the set timelines after a ZaZiBoNa recommendation, can be attributed to the participating authorities having differing capacities (Sithole et.al, 2021a; Sithole et.al, 2021b). Centralised submission and tracking were therefore proposed by both regulators and industry as ways to improve the effectiveness and efficiency of this initiative. This can be achieved through the development of a regional unit hosted in one of the member countries to coordinate submissions. A proposal made by industry, but not identified by regulators, was the need to implement a system that would allow applicants to submit an "expression of interest" to have their dossiers / applications assessed under ZaZiBoNa. This would enable the regulators to adequately plan and allocate resources as well as ensure that applicants are informed from the outset as to whether their dossiers / applications have been accepted for review under ZaZiBoNa. At present, some applicants only become aware that their dossier / application will be reviewed under ZaZiBoNa months after submission. Although some of the participating countries have information on the ZaZiBoNa process on their websites and the contact details of the focal person are known, this is not the case in all the countries and this detracts from the initiative's effectiveness and efficiency.

Way forward

In the long term, the establishment of a regional medicines authority was proposed as a strategy for moving forward. This is not unique to SADC and has also been proposed for other harmonisation initiatives (Dansie et.al, 2019; EMA, 2017; Arik et.al, 2020). To do this, a binding memorandum of understanding should be developed mandating the establishment of the regional medicines authority. A similar model has been implemented in the Standardisation, Quality Assurance, Accreditation and Metrology (SQAM) Programme in the Southern African Development Community (SADC, 2021b). This would ideally make it possible for a SADC-approved medicinal product to be marketed in all the SADC countries. Issues such as the need to strengthen pharmacovigilance systems and to have an agreement on the use of labelling that is in the three official SADC languages, English, Portuguese and French, should be considered before implementation as these are important for patient

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safety. In addition, the concern of increased costs to applicants that was raised by a few of the applicants who were not in support of this proposal should also be taken into consideration.

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CHAPTER 08

A PROPOSED REGULATORY REVIEW MODEL FOR THE ZAZIBONA INITIATIVE: FUTURE STRATEGY

SUMMARY

- The ZaZiBoNa initiative is a collaborative medicines registration initiative which was established in 2013 and has been in operation for over 8 years.
- This initiative has a membership of 16 SADC countries, however only 9 of these actively participate in the assessment of applications for registration and GMP inspections due to capacity.
- A number of studies have been conducted in this research programme to evaluate the regulatory review system in ZaZiBoNa beginning with a literature review of the initiative. The regulatory review processes of active member countries were also evaluated and compared. Lastly, the views of both the regulatory authorities and pharmaceutical industry on the effectiveness and efficiency of this initiative were obtained. Several findings have been made from these studies including the successes and opportunities for improvement.
- The aim of this chapter was to analyse the findings from the studies conducted in this research programme and propose measures to address these gaps leading to an improved model of the ZaZiBoNa initiative.
- Data were collected between 2019 and 2022 using the literature review method and the questionnaire technique (OpeRA, PEER, PEER – IND).
- Robust individual member country processes contribute to a more effective and efficient ZaZiBoNa; therefore, the gaps in the regulatory review processes of the participating countries have been identified and solutions proposed to strengthen these processes.
- Recommendations for the improvement of the current model of the ZaZiBoNa initiative have been made to address the challenges identified with the initiative particularly those around a lack of central tracking and coordination. The implementation of these recommendations will result in an immediate improvement to the effectiveness and efficiency of the initiative whilst a longer term solution is considered.
- Lastly, a new model, namely a centralised procedure has been proposed as well as the legal framework that would enable this and the additional considerations that need to be made by the decision makers in the member countries in order to implement this new model.

INTRODUCTION

The ZaZiBoNa collaborative medicines registration initiative was established in 2013 by four countries, Zambia, Zimbabwe, Botswana and Namibia with the support from WHO prequalification and the Southern African Regional Programme on Access to Medicines and Diagnostics (SARPAM) (Sithole et.al, 2020). This work sharing initiative was intended to address a number of challenges that were being faced by the member countries, for example, large backlogs of pending products and long registration times (Sithole et.al, 2020). The heads of the founding agencies also wished to establish a platform for capacity building, information sharing and harmonization of regulatory requirements (Gwaza, 2016), and therefore entered into a collaboration by signing a memorandum of understanding. Today, this initiative has grown to include all of the 16 SADC countries (9 active members, 5 non-active members and 2 observers) and to a great extent, the goals and objectives of the initiative have been met (Sithole et.al, 2021c).

Evaluation of the Regulatory Review Process of the ZaZiBoNa initiative

In order to evaluate the regulatory review process of the ZaZiBoNa initiative, Sithole et.al, (2020) conducted a review of the literature. The aim was to review the history of the ZaZiBoNa initiative as well as reflect on what has been realised in its eight years of operation and what still needed to be achieved. Although the statistics of the work carried out by this initiative were available in the literature there had not been a critical review of the process in recent years including an analysis of factors contributing to the success of the initiative and conversely those negatively affecting performance. Therefore, the statistics, meeting records, terms of reference and various unpublished documents contributing to the initiative were reviewed. The literature that was publicly available on this initiative was also included in this review. The results of this study documented the history and inception of the initiative, its legal position and organisational structure, participating countries, scope of products, operating model, statistics of work carried out from 2013 – 2021 as well as the challenges. The key recommendations for improvement of this initiative were subsequently developed.

A key recommendation that was made after the review of the ZaZiBoNa initiative was the need to evaluate the regulatory review processes of the individual participating countries that contributed to the reviews and GMP inspections (Sithole et.al, 2020) to further understand why some of the challenges identified with ZaZiBoNa existed. For the first time, the regulatory review processes of six of the active member countries participating in and contributing to ZaZiBoNa assessments were evaluated and compared in this research programme (Sithole et.al, 2021b; Sithole et.al, 2021c).

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The study participants were Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe. The results of these studies provided an overview and comparison of the organisation of the agencies, the fees charged for different types of products, sources of funding, requirements for marketing authorisation applications, types of review models, the extent of scientific assessment, key milestones in the review process and target timelines, the numbers of NASs and generics received and approved (2019 and 2020), the mean approval times for NASs and generics (2019 and 2020) and the implementation of good review practices. In addition, the results of these studies indicated that there were some key differences in the countries' processes that needed alignment for example, the frequency of the meetings of the expert committees and the target timelines set for key milestones were different. The recommendations made as a result of this study highlighted the need for the strengthening of the individual participating countries' regulatory review processes for them to effectively support the ZaZiBoNa initiative.

A key recommendation from the studies comparing the review processes of the active member countries was the need for a review of the ZaZiBoNa operating model to identify opportunities for improved efficiency (Sithole et.al, 2021b). Although some feedback on the performance of the initiative had been sought from manufactures through stakeholder meetings previously and an analysis of the initiative conducted in its third year of operation (Gwaza, 2016), there had not been a comprehensive and structured evaluation of the work sharing programme for its future direction in recent years. Therefore, for the first time, the views of both the regulatory agencies and the pharmaceutical industry on the effectiveness and efficiency of the initiative were obtained and compared (Sithole et.al 2022a; Sithole et.al, 2022b). All nine active member countries participated in the study as well as 19 out of the 23 pharmaceutical companies that submitted applications to ZaZiBoNa from 2017 – 2021. The aim of the studies was to evaluate the effectiveness and efficiency of the current operating model of the ZaZiBoNa initiative including the challenges it faces as well as identifying opportunities for improvement from the perspective of both regulatory agencies as well as the pharmaceutical industry. The results of the studies documented the successes and challenges of the ZaZiBoNa initiative as well as measures that might improve its effectiveness and efficiency. The benefits and challenges to regulators, applicants and patients were also identified. Overall the evaluation of the regulatory review process of the ZaZiBoNa initiative identified the successes and challenges resulting in the development of a number of recommendations for improvement.

Successes of ZaZiBoNa

The initiative has assessed over 330 products in its 8 years of operation, the highest number of products assessed by any regional harmonization initiative on the African continent (Masekela, 2021, Mashingia et.al, 2020). The median time to ZaZiBoNa recommendation of 13 months or less inclusive of the applicant's time has been achieved for all the years except in 2018 (Figure 8.1) and this is lower than the registration times achieved by some of the individual participating countries (Sithole et.al, 2021c). Regulatory authorities have reported that participating in the initiative has increased their capacity to conduct assessments and good manufacturing practice inspections in addition to providing a platform for the sharing of information with other regulators (Sithole et.al, 2022a). Applicants have benefited from compiling one package (modules 2 -5) for the initial submission as well as a single response package to the consolidated list of questions which saves time and resources (Sithole et.al, 2022a; Sithole et.al 2022b). The ZaZiBoNa initiative has achieved shorter timelines for the approval of medicines resulting in increased availability of quality-assured medicines for patients in the SADC region (Sithole et.al, 2022a; Sithole et.al 2022b). The harmonisation of registration requirements and joint reviews have reduced the workload for both the pharmaceutical industry as well as the regulatory agencies.

Challenges of ZaZiBoNa worksharing initiative

A number of challenges were identified with the initiative such as the failure by countries to implement ZaZiBoNa recommendations to register products in a timely manner and simultaneously (Mahlangu, 2018; Sithole et.al, 2020). Another challenge for the initiative was the lack of tracking, monitoring and evaluation of the time taken by participating countries to finalise products after a ZaZiBoNa recommendation (Sithole et.al, 2020). In addition, the initiative's tracking system was not able to separate the agency time from the company time. The majority of products assessed by the ZaZiBoNa initiative have been generics and as a result the initiative had developed assessment templates for the review of generics in line with WHO prequalification standards. A gap that existed however, was the lack of standardised review templates addressing benefit-risk assessment for new active substances and biosimilars (Sithole et.al, 2020).

The lack of a centralized submission system and the tracking for applications as well as a lack of clarity and information about the process in some of the participating countries were also cited as challenges by both applicants and regulators (Sithole et.al, 2020; Sithole et.al, 2022a; Sithole et.al, 2022b). Other challenges identified were the unclear operating model, differing labelling requirements, a lack of expertise in some

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Figure 8.1. Trend in median time to recommendation (2014-2021)
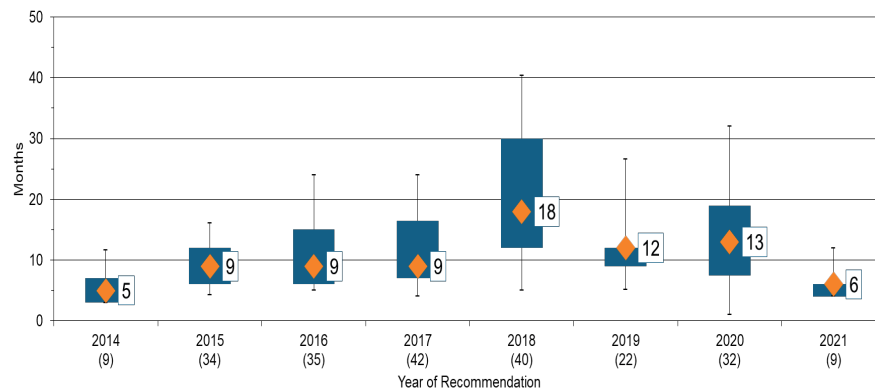
Data are shown for applications that were given a recommendation (positive or negative) between 2014 and 2021 (inclusive)
(n) = number of products given a recommendation.
◆ = Median. Box: 25th and 75th percentiles. Whiskers: 5th and 95th percentiles.

countries to assess certain types of products, inadequate human resources, unequal workload among participating countries and the inability of the initiative to mandate central registration (Sithole et.al, 2022a; Sithole et.al, 2022b). These challenges have led to some inefficiencies over the years and it is therefore now necessary to develop an improved model drawing from the lessons learned in implementing the current operating model piloted in 2013. The aim of this chapter was to develop an improved model for the ZaZiBoNa initiative.

METHODOLOGY

Five studies were conducted between 2019 and 2022 and the opportunities for improvement identified in each study were analysed. A number of measures were then proposed to close the identified gaps culminating in the development of an improved model for the ZaZiBoNa initiative.

Study 1: A literature review of statistics, meeting records, terms of reference and various unpublished documents belonging to the initiative were reviewed as well as publicly available literature on the initiative (Chapter 1).

Study 2: A questionnaire technique was used. A senior member of the division responsible for issuing marketing authorisations completed an established and validated questionnaire (McAuslane et.al, 2009), which standardised the review process, allowing key milestones, activities and practices of the six regulatory

authorities. The completed OpERA (Optimising Efficiencies in Regulatory Agencies) questionnaires were validated by the heads of the respective agencies and the study participants were Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe (Chapters 4 and 5).

Study 3: A questionnaire technique was used. Data were collected using the Process, Effectiveness and Efficiency rating questionnaire (PEER) developed by the authors (Sithole et.al, 2022a). The questionnaire was completed by the ZaZiBoNa focal person in each country and approved by the head of the agency. Semi-structured interviews were carried out with each of the member agencies following completion of the questionnaire. The active members of the ZaZiBoNa initiative, namely Botswana, Democratic Republic of Congo, Malawi, Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe participated in the study. Active member status is determined by 'the capacity to conduct assessments and GMP inspections' (Chapter 6).

Study 4: A questionnaire technique was used. Applicants who had submitted registration / marketing authorization applications for assessment under the ZaZiBoNa initiative during the period 2017-2021 were recruited into the study. Data were collected using the Process, Effectiveness and Efficiency rating questionnaire (PEER-IND) developed by the authors (Sithole et.al, 2022b). The questionnaire was completed by a representative responsible for ZaZiBoNa submissions in each company (Chapter 7).

RESULTS AND DISCUSSION

For the purpose of clarity the results will be presented in three parts: Part I – improvements to the active member countries in ZaZiBoNa; Part II – proposed improvement to the current operating model of ZaZiBoNa; and Part III – proposed new improved model for ZaZiBoNa initiative.

Part I - Improvements to the Active Member Countries in ZaZiBoNa

The implementation of the recommendations and measures detailed below to close the gaps identified, will strengthen the regulatory review processes of the individual participating countries. This will ensure the success and efficiency of the national procedures as well as the ZaZiBoNa initiative. A model regulatory review process (Figure 9.2) can be used as a reference by the individual active member agencies to improve their current processes. This includes the implementation of the Universal Methodology for Benefit Risk Assessment (UMBRA) in the review process, the establishment of quality decision-making practices by utilizing the QoDoS questionnaire and publishing the resulting regulatory decisions

Information on ZaZiBoNa

Some of the active member countries did not have any information on the ZaZiBoNa initiative on their websites which contributed to the challenges faced by applicants in understanding the processes to be followed when submitting ZaZiBoNa applications to the various countries. This lack of clear, detailed information may result in reluctance by the pharmaceutical industry to use this initiative as was highlighted in other harmonisation initiatives (Dansie et.al, 2019). It should be a requirement that all NRAs in the regions should have uniform and up to date information about the ZAZIBONA initiative as a pathway/procedure for approval of medicines on their websites. Details of the contact persons at a country level should also be included.

Harmonisation of requirements

Currently, the participating countries have differing labelling requirements as well as requirements for the selection of the test product to be used when conducting dissolution studies in support of an application for registration. Countries should make a deliberate effort to collectively review their legislation, guidelines and processes in order to harmonise the registration and labelling requirements for products in the SADC region.

Review Models and Reliance

Although all the active member countries stated that they implemented the three review models, verification, abridged and full review, this information was not available on some of the countries' websites. In addition, some of the countries did not formally include ZaZiBoNa as a recognized reference agency under the verification and abridged review models. Agencies should publish the review models that are used for assessment, including the procedure criteria, recognized reference authorities and timelines. Agencies without procedural guidelines and assessment templates should develop these. It should also be mandatory for all agencies participating in the ZaZiBoNa collaborative medicines registration initiative to formally recognize ZaZiBoNa as a reference agency under the verification and abridged review models. Reliance is currently only being applied for products coming from beyond Africa's borders. The agencies are encouraged to enter into a memorandum of understanding with other SADC countries to share unredacted assessment reports for products that are not submitted to the ZaZiBoNa initiative, as these constitute the majority of the agencies' workload.

Figure 8.2. Proposed regulatory review process map for an NRA
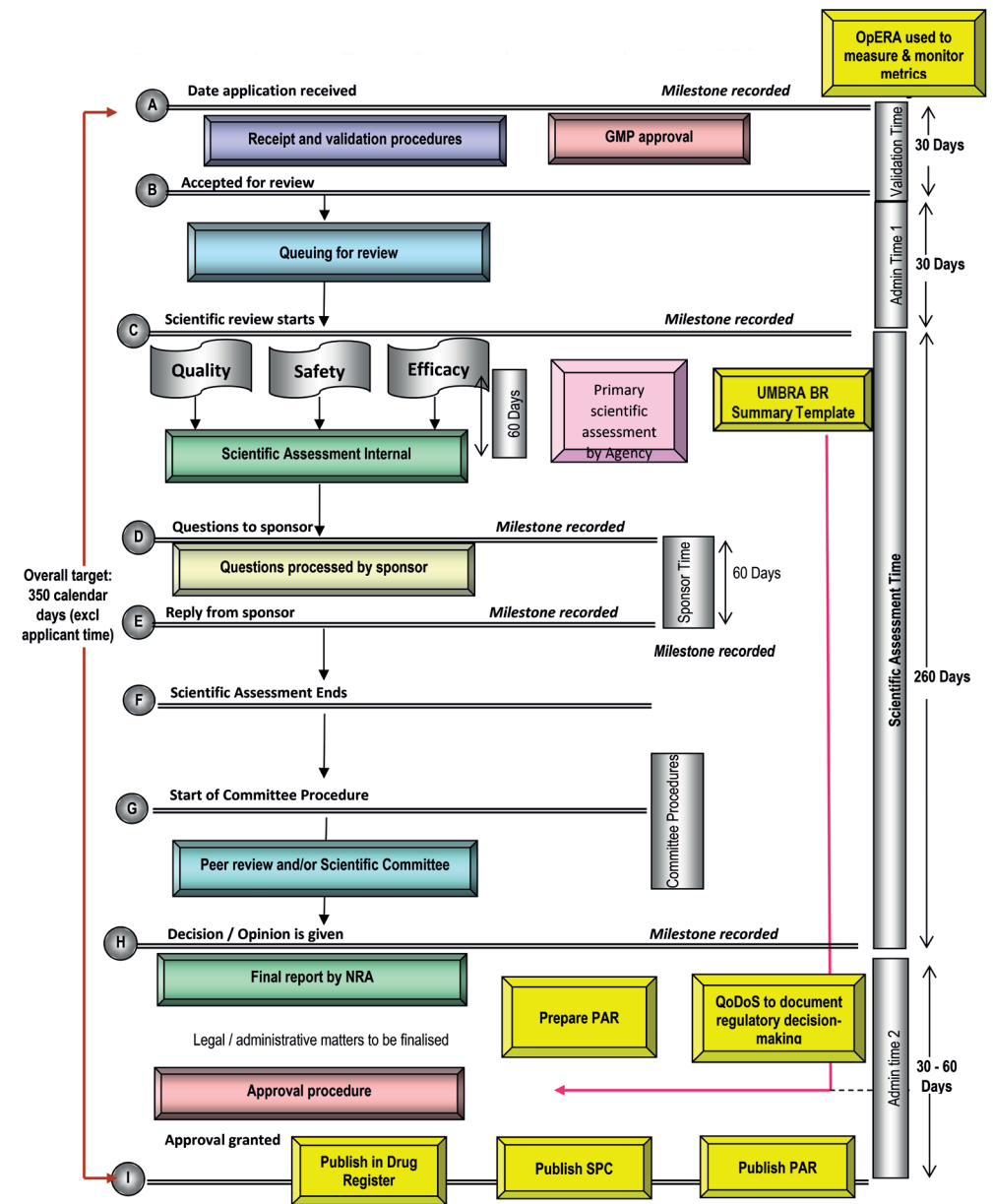
Monitoring and Measuring

All active member countries set targets for many of the key milestones in the regulatory review process and record these, however, some countries were found to not have targets for some important milestones such as the start of the scientific assessment

or the overall approval time. In addition, some countries were not able to separate the agency time from the applicant time as tracking was carried out manually. Countries should set targets for all key milestones and adopt the use of information management systems (IMS) or electronic tracking systems such as the Optimising Efficiencies in Regulatory Agencies (OpERA) online tool in order to effectively monitor their performance. The IMS should also be able to facilitate the online submission of applications and allow the industry to track the progress of their applications.

Transparency and Communication

Generally, the area of transparency and communication was the weakest of all the measures assessed even though the agencies stated that this was a high priority. Most of the agencies did not share assessment reports with applicants or publish a summary basis of approval / public assessment report. The approval times and expert committee dates were also not shared with stakeholders in most of the countries. Agencies would benefit from implementing measures of transparency and communication in line with international best practices such as the sharing of assessment reports with applicants and publishing approval times, advisory committee dates and a summary basis of approval. The publishing of public assessment reports would not only aid other countries wishing to rely on the regulatory decisions of the active member countries, but would also give confidence to clinicians when deciding on the most suitable therapies for their patients.

Review of NASs

Only one out of the active member countries studied (South Africa) conducted a full review of new active substances and this was done using external reviewers. The rationale for this could be that the NASs received by the other countries would have already been approved elsewhere therefore reliance is used instead of conducting a full review. This however, results in limited capacity to review these products which could prove catastrophic in emergency situations which require the urgent review of NASs, for example, the Covid 19 pandemic. All agencies in the SADC region should work on building internal capacity to review new active substances that are received but not approved by a reference agency. To do this, the agencies should develop a structured, formalised and quantitative approach to benefit-risk assessment, including the assignment of relative importance to benefit and risk considerations and develop standardized templates for assessment of the NASs using tools available such as the Universal Framework for the Benefit-Risk Assessment of medicines (UMBRA) template.

Good Decision Making Practices

The 10 Quality Decision Making Practices (QDMPs) were articulated as part of the development of the Quality of Decision-Making Scheme (QoDoS) instrument, which has been implemented in a number of medicines development scenarios (Bujar et.al 2017; Bujar et.al 2019). Generally all the active member agencies either partially or fully implement the quality decision making practices, however, training and capacity building is required in this area for full implementation and development of formal frameworks.
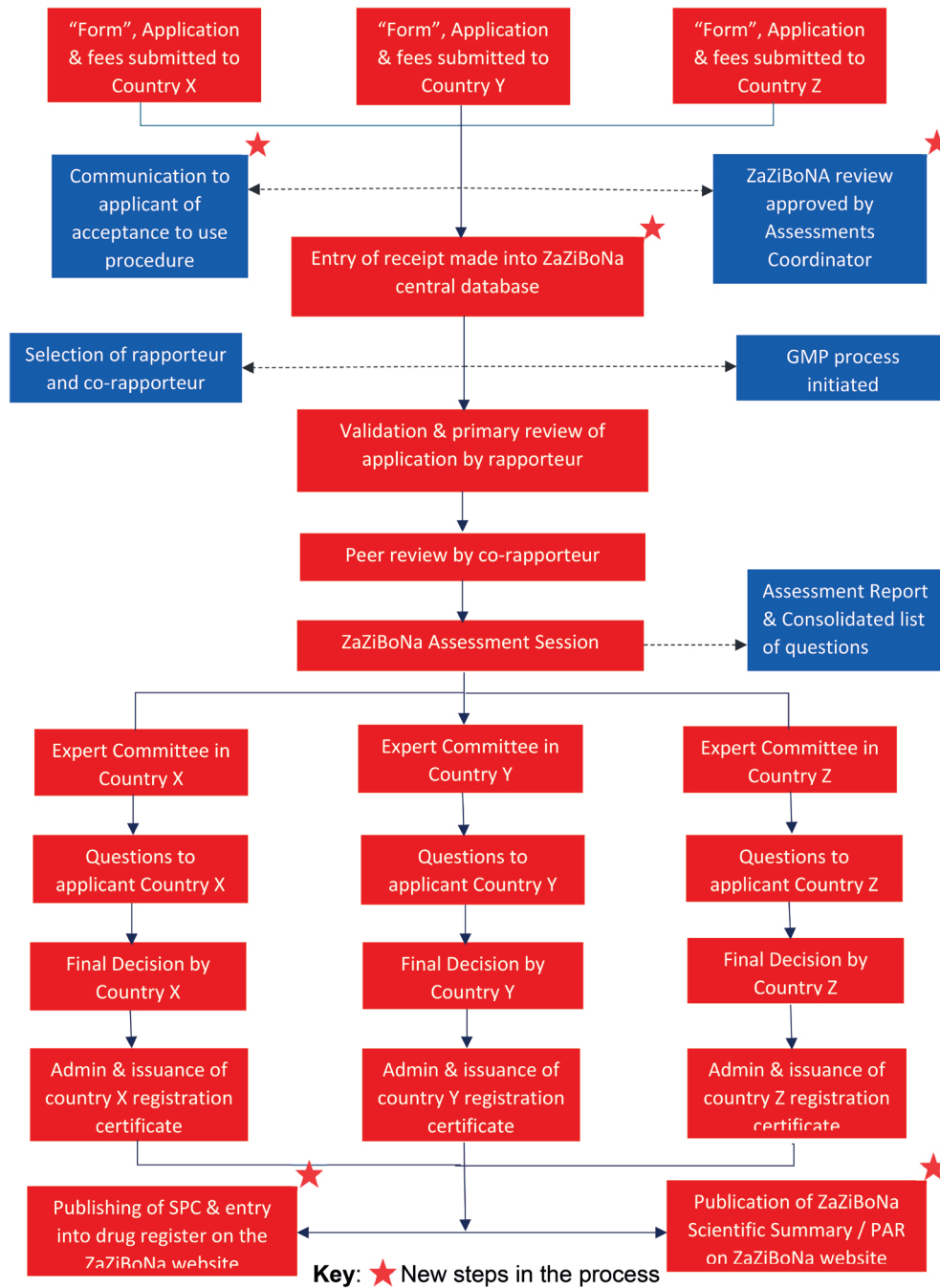
Part II – Proposed Improvements to the Current Operating Model of ZaZiBoNa

While the goal is to ultimately move to a new improved model, it is acknowledged that this process will require a considerable amount of resources, time, planning, and consultation before its full implementation. In the meantime, since the initiative is already in operation, the measures proposed in this section can immediately be implemented to address findings from this study and improve the current model of the ZaZiBoNa initiative in addition to the improvements already proposed for the individual active member countries (Figure 8.3).

The regulatory review process of medicines approved through the ZaZiBoNa route is depicted in Figure 8.3 including new steps proposed for an improvement to the process. The map is a simplified representation of the main steps in the review of applications for registration of a single product submitted to three ZaZiBoNa countries, X, Y and Z, and reviewed using the collaborative process. The exact same dossier is submitted to each of the three countries simultaneously and the applicable registration fees paid. In order to improve the existing process and address the challenges highlighted earlier in this chapter, it is proposed that at this stage, applicants be required to complete and submit a form requesting to use the ZaZiBoNa procedure together with their application. The request should then be forwarded to the assessments coordinator for approval before the products are entered into the ZaZiBoNa central database essentially starting the 'clock' for tracking purposes. Concurrently, communication should be made to the applicant informing them that their request to use the ZaZiBoNa route has been approved. The rapporteur, once selected, is responsible for validating and assessing the application before it is peer reviewed by the co-rapporteur and discussed at a ZaZiBoNa assessment session.

The output of the assessment session is a consolidated assessment report, list of questions and a recommendation for approval which are considered by the expert

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Figure 8.3. Proposed improvements to the current model of the ZaZiBoNa initiative

"Form", Application & fees submitted to Country X	"Form", Application & fees submitted to Country Y	"Form", Application & fees submitted to Country Z

Communication to applicant of acceptance to use procedure

ZaZiBoNA review approved by Assessments Coordinator

Entry of receipt made into ZaZiBoNa central database

Selection of rapporteur and co-rapporteur

GMP process initiated

Validation & primary review of application by rapporteur

Peer review by co-rapporteur

ZaZiBoNa Assessment Session

Assessment Report & Consolidated list of questions

Expert Committee in Country X

Expert Committee in Country Y

Expert Committee in Country Z

Questions to applicant Country X

Questions to applicant Country Y

Questions to applicant Country Z

Final Decision by Country X

Final Decision by Country Y

Final Decision by Country Z

Admin & issuance of country X registration certificate

Admin & issuance of country Y registration certificate

Admin & issuance of country Z registration certificate

Publishing of SPC & entry into drug register on the ZaZiBoNa website

Publication of ZaZiBoNa Scientific Summary / PAR on ZaZiBoNa website

Key: ★ New steps in the process

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committees in each of the three countries. The product is subsequently registered in the three countries after consideration of any country specific issues. An additional new step proposed to improve the current process in line with good review practices and to address the challenges that have been highlighted earlier in this chapter, is the publication of the approved product, summary of product characteristics and the public assessment report (PAR) / scientific summary on the ZaZiBoNa website. The process map represents the review and authorization of a product that goes to approval after one review cycle. In reality, it could take more than one review cycle before the review of a product is finalised.

Receiving procedure of applications

Applicants submitting dossiers for review under ZaZiBoNa may indicate in their application that they wish for their product to be assessed under ZaZiBoNa, however this has not been the standard practice in all the countries. In addition, acknowledgement of acceptance for review under ZaZiBoNa was not normally communicated at submission resulting in applicants not knowing if their request for review under ZaZiBoNa had been accepted or not. In other instances, applicants were only informed months after submission that their application would be assessed under ZaZiBoNa as consent was sought from them to use this initiative. To address these challenges, the initiative should improve the central database/register of applications such that it is proactively updated as applications are submitted for registration to the different participating countries. This will make it possible for the initiative to monitor products from the date of receipt to the date of approval. Currently applications are only entered into the database when the scientific assessment begins at ZaZiBoNa. Furthermore, the initiative should develop a "form" which would be used by applicants to express their interest to use ZaZiBoNa for the review of the product. This "form" would be submitted together with the dossier. Communication of acceptance for assessment under the ZaZiBoNa initiative or otherwise should be made to the applicant by the receiving countries within a stipulated time period from the date of submission. The products should then undergo screening and assessment procedures in line with the set target timelines.

Handling of ZaZiBoNa applications in the countries

ZaZiBoNa applications were given a priority review in some of the countries, however, this was not an explicitly defined position in some of the countries resulting in applications spending time in queues for all products waiting for screening and/ or scientific assessment as well as spending a long-time awaiting finalization in the countries. A comparison of the review processes of the active member countries

(Sithole et.al, 2021b) demonstrated that the frequency of expert committee meetings ranged from monthly to quarterly which subsequently affected the time to finalization of ZaZiBoNa products. In addition, the targets set for key milestones in the review process were different in each of the countries. To address these challenges, ZaZiBoNa should require that countries create a separate queue for ZaZiBoNa applications to be prioritized as the need arises. This initiative should also establish harmonized target timelines for all key milestones in the review process from receipt to finalisation which would be applicable to ZaZiBoNa products and require that these are adopted and adhered to by the participating countries.

Monitoring and evaluation

The timelines monitored and reported by this initiative include the time that the assessment report is discussed at the ZaZiBoNa assessment session up to the time that the product is given a recommendation. The ZaZiBoNa initiative measured and published the review timelines for the 333 dossiers/applications reviewed (December 2021), however, this excluded the steps in the review process performed before the first assessment session in which the product was discussed and the steps after the scientific assessment ended i.e when a ZaZiBoNa recommendation was given. As a result, the time taken for the finalisation of ZaZiBoNa dossiers/applications in the individual participating countries was not monitored or published. The time that the product spent in the respective country agency before being assessed under ZaZiBoNa was also not documented. There is a need to monitor target timelines for all the key milestones in the review process of ZaZiBoNa products from receipt to approval and this can be carried out using the improved central database proposed. This will enable an improved and efficient central coordination and tracking of timelines as well as reporting. The use of automated systems for tracking and information management would increase the efficiency and transparency as applicants would be able to check the status of their dossiers/applications (Figure 8.3).

Product life-cycle management

The ZaZiBoNa initiative only handles new registration applications while variations and renewals are not considered. This initiative should establish a process for the review of post approval changes/variations and renewals which should be harmonised so that one application can cater for all markets.

Capacity building and training of assessors

The ZaZiBoNa initiative successfully facilitated and enabled the training of assessors in the 16 SADC countries. However, the assessment sessions were being used as

Figure 8.4. Proposed ZaZiBoNa/SADC centralised procedure

a training opportunity for inexperienced assessors, which then affected productivity. Going forward, training and capacity-building activities should be separated from the assessment activities, which would enable countries to consider secondment only for competent assessors and inspectors, improving the effectiveness and efficiency of the initiative. A model similar to the one used by the Medicines Control Authority of Zimbabwe's Regional Centre of Regulatory Excellence (RCORE) could be used for the training of assessors in the SADC region.

Transparency of process and decision making

Since 2017, the ZaZiBoNa initiative has prepared scientific summaries for approved medicinal products, although these have not been publicly available. It is proposed that the scientific summaries should be made available on the ZaZiBoNa website (Figure 8.3).

Part III - Proposed New Improved Model for the ZaZiBoNa Initiative

A major challenge identified in this study was the lack of centralised submission and tracking which resulted in the initiative being ineffective and inefficient. As a result timelines were not always met and the benefit to applicants of simultaneous access to multiple markets was not always realised. Previously, it has not been possible for applicants to submit applications for registration directly to ZaZiBoNa as it was not legally mandated to receive and approve applications for registration on behalf of SADC. It is therefore proposed that a legal framework, that can be used by SADC countries, should be established to address this challenge (Figure 8.4).

The proposed new improved model for regulatory review in ZaZiBoNa is depicted in Figure 8.4. This centralised procedure would be a further improvement to the amended process proposed in figure 8.3. Applicants wishing to market medicinal products in the SADC region would, after a pre-application procedure, be able to submit a single application and fees to the regional medicines agency. Upon completion of the receipt and validation procedures, the application would then be reviewed by the rapporteur and co-rapporteur before consideration by the "ZaZiBoNa Assessors Committee". The applicant would then receive a single set of questions from the agency before a final decision on the registration is made by the responsible body/Committee mandated by SADC to carry out this function. Once all the administrative issues have been concluded, a registration certificate, valid in all 16 SADC countries, would then be issued and the approved product, SPC and PAR published on the ZaZiBoNa website. The process map represents the review and authorization of a product that goes to

approval after one review cycle. In reality, it could take more than one review cycle before the review of a product is finalised.

Legal Framework

The need for a binding legal framework has been highlighted in the literature as a way of ensuring success and efficiency of harmonisation initiatives (Giaquinto et.al, 2020). The primary sources of law in SADC are the treaty, protocols and memorandum of understanding (Zongwe, 2021) and these MoUs have been used in the past to mandate the establishment of regional frameworks or institutions in the SADC region for example, the MoU on Standardisaton, Quality Assurance, Accreditation and Metrology (SQAM) programme (SADC, 2022).

A SADC level Memorandum of Understanding can therefore be used to develop a framework for the cooperation on the regulation of medicines in the region. This would include the establishment of a regional medicines agency to facilitate a centralised procedure for the registration of medicines. The financing, organizational structure, scope of products and detailed review process for approval (Table 8.1) have not been discussed in depth as this will be dependent on a number of variables which would require extensive consultation with the decision makers in all 16 SADC countries as well as other stakeholders.

The ZaZiBoNa process in the current model borrows certain elements from both the decentralised procedure (i.e simultaneous submissions and registrations) and the centralised procedure (use of a rapporteur and co-rapporteur for assessment before consideration by an expert group) (Sithole et.al, 2020). In addition to the proposal to create a fully centralised regional model/process (Figure 8.4), the MoU on registration of medicines may also include non-centralised procedures that would be implemented at a national level such as the decentralised, mutual recognition and work-sharing procedures which have successfully been implemented in the EU and by initiatives such as the ACCESS consortium (EMA, 2022; Swissmedic, 2021).

Considerations to be made for implementation of the centralised model

The results of this research programme show that the ZaZiBoNa initiative is currently funded by partners as well as the participating countries (Sithole et.al, 2020). The review of the participating countries, which are rated as low and middle income countries, showed that their human and financial resources are currently inadequate for their national work as well as work carried out for the ZaZiBoNa initiative which has resulted in some of the challenges identified with this initiative. There is therefore

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a need for the issue of financial and human resources (both numbers and expertise) to be addressed in the development and implementation of a centralised process for registration of medicines in the SADC region. Consideration, also needs to be made on how the proposed centralised process will integrate into the processes of the African Medicines Agency once these are fully established. A regional administrative unit hosted in one of the member countries, responsible for tracking and coordinating ZaZiBoNa applications and equipped with a robust information management system can be piloted in the interim, while the legal framework necessary for the establishment of the regional medicines agency is under development.

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CHAPTER 09

CONCLUDING REMARKS

INTRODUCTION

Countries on the African continent have varying capacities to regulate medical products although all 54 countries, except one, have a regulatory authority or department within the ministry of health responsible for the regulation of medicines (Ndomondo-Sigonda et.al, 2017). These challenges in capacity have led to protracted timelines delaying access to quality assured medicines as well as the problem of substandard and falsified medicines (Roth et.al, 2018). This is further complicated by the high burden of disease in sub-Saharan Africa (de-Graft Aikins et.al, 2010). Regulatory harmonisation and collaboration through the pooling of expertise and resources of the regulatory authorities on the African continent have been explored to mitigate these challenges (Ndomondo-Sigonda et.al, 2017).

The African Medicines Registration Harmonisation Initiative (AMRH) was established in 2009 and one of its goals was to facilitate the harmonisation of the fragmented regulatory systems on the continent (Ndomondo-Sigonda et.al, 2017). The AMRH oversees medicines registration harmonisation (MRH) projects implemented through the five regional economic blocks recognised by the African Union include the East African Community (EAC), Southern African Development Community (SADC), Economic Community of West African States (ECOWAS), Economic Community of Central African States (ECCAS) and Intergovernmental Authority on Development (IGAD) (Ndomondo-Sigonda et.al, 2018; Ndomondo-Sigonda et.al, 2021). These regional harmonisation initiatives are at different stages of implementation (Ndomondo-Sigonda et.al, 2018).

Studies have been conducted in the past to review the performance of some of the regional initiatives such as the EAC (Dansie et.al, 2019, Giaquinto et.al, 2020, Mashingia et.al, 2020; Ndomondo-Sigonda et.al, 2021), and the SADC's ZaZiBoNa (Gwaza, 2016) however, there had not been a formal evaluation of the ZaZiBoNa review process and operating model in recent years. Therefore, this research sought to evaluate the regulatory review system in ZaZiBoNa with a view to enhance the review process and patients' access to medicines.

This was achieved by conducting six studies beginning with a review of literature on the SADC collaborative medicines registration initiative (ZaZiBoNa) to gain understanding of the history, governance structure, operating model and current performance (Study 1: Chapter 1). This was followed by an evaluation of the regulatory review process of the Medicines Control Authority of Zimbabwe (MCAZ) as the implementing agency of the SADC MRH project (Study 2: Chapter 2). The MCAZ is responsible for coordinating the SADC MRH project including ZaZiBoNa assessments and inspections therefore the opportunities for improvement identified will further strengthen the coordination of this initiative in its current model. This evaluation was followed by a comparison of the registration processes of Zimbabwe (the SADC MRH implementing agency) with Australia, Canada, Singapore, Switzerland to benchmark best practices which can also be implemented by the other countries in the region (Study 3: Chapter 3). Regulatory reviews under ZaZiBoNa are conducted by the active member countries through the use of a rapporteur and co-rapporteur therefore a comparison of the good review practices, review models and target timelines of six countries (Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe) that are active members of ZaZiBoNa was conducted, to identify opportunities for strengthening and alignment (Study 4: Chapters 4 and 5). The research programme was concluded with an evaluation of the effectiveness and efficiency of the ZaZiBoNa initiative by the regulatory authorities (Study 5: Chapter 6) and the pharmaceutical industry (Study 6: Chapter 7). The data collected from each study were analysed and reviewed individually to facilitate a thorough evaluation of the regulatory review process of ZaZiBoNa and the participating countries contributing to the initiative.

RESEARCH OUTCOMES AND CONTRIBUTIONS

A previous study of the ZaZiBoNa described the operating model, success factors and forecasted potential challenges with sustainability over time (Gwaza, 2016). This study was done at a time when the initiative had been in operation for just over 2 years and had a membership of just the 4 founding members (Gwaza, 2016). Since then, the initiative has grown to nine active member countries and has been in operation for over eight years. The number of products considered has increased and more applicants have had the opportunity to use the procedure. This programme of research represents the first formal evaluation of the ZaZiBoNa initiative's regulatory review process and operating model.

This research commenced with a literature review of the ZaZiBoNa initiative in chapter 1. The results of this study confirmed the successes achieved to date and enabled the challenges and opportunities for improvement to be identified. The concerns were the differences in the time to registration in the participating countries after a ZaZiBoNa recommendation, lack of a centralised submission procedure, inadequate tracking systems, lack of capacity and review templates for the assessment of new chemical entities, biological and biosimilars. Another outcome of this research is that updated information on the ZaZiBoNa initiative's current operating model and review process is now published and readily accessible in the public domain. This

transparency will aid applicants that are interested in using the initiative as a pathway for the registration of their medicines in the various SADC countries. Having the full information in the literature is also beneficial for existing work sharing initiatives as well as new ones in the process of being established as they can use ZaZiBoNa as a benchmark and learn from the successes and challenges encountered to date.

The evaluation of the Medicines Control Authority of Zimbabwe's regulatory review process which was the focus of chapter 2 included a review of its organisational structure and the registration process for all types of products as well as an assessment of the level of implementation of Good Regulatory Practices (GRPs) and Good Review Practices (GRevPs) by the MCAZ. The results of this study documented the regulatory approval time for generics, NCEs, biologicals and biosimilars in Zimbabwe and the associated milestones within the review process. This study provided an overview of the median approval timelines achieved by the MCAZ during 2017 - 2021 and highlighted that the MCAZ was initially able to reduce its timelines from 2017 – 2019 however the timelines started to increase again and in its current capacity, the MCAZ was not able to achieve the target timelines set for the regulatory review. This can be attributed to various factors such as the Covid-19 pandemic which was at its peak in 2020 forcing organisations to adopt a 'work from home' model due to travel restrictions resulting in loss of time and productivity in the beginning as adjustments were made. Other factors contributing to increased timelines were the loss of critical staff, withdrawal of measures previously implemented to reduce timelines such as retreats and the strain on resources during the expedited review of Covid-19 vaccines. Recommendations were made to close the gaps which will enable the MCAZ as the SADC MRH implementing agency, to effectively execute its role of coordinating ZaZiBoNa assessments and inspections in the current operating model.

The MCAZ's registration process was compared with the processes of the national regulatory authorities in Australia, Canada, Singapore and Switzerland in chapter 3. The results of this study showed that the MCAZ had far fewer resources than the regulatory authorities in the comparator countries, but was at one time able to achieve timelines comparable to the mature agencies through efficient use of resources such as the implementation of reliance and the international best practices of setting and monitoring of targets for key milestones in the review process. The results also showed that although MCAZ was comparable to the comparator authorities in implementing the majority of good review practices, it significantly lagged behind in transparency and communication. This confirms the lack of transparency in LMIC that has been cited in the literature (Ahonkhai et.al, 2016). Recommendations made as

a result of this study highlighted the need for implementation of an online submission system, removal of requirements for the CPP, implementing parallel reviews, increasing the number of competent assessors and improving transparency to match the standard used in the mature regulatory systems. Another outcome of this research programme is that the results of the comparison of the MCAZ with mature regulatory agencies of comparable size and the benchmarking of best practices which have been published provide a blueprint to be followed by countries in the SADC region and other low and middle income countries to achieve timelines comparable to that of the mature agencies.

It has not been possible in the past for low-and-middle income countries to benchmark themselves against countries with similar resources and capacity because of a lack of information in the public domain (Gwaza, 2016). However, this research has for the first time compared regulatory review processes, review models and target timelines of six countries in the SADC region in chapters 4 and 5, closing that gap in information. The evaluation covered the organisational structure and the registration process for all types of products as well as an assessment of the level of implementation of Good Regulatory Practices (GRPs) and Good Review Practices (GRevPs) by the six countries. This documented target times for generics and NASs and the associated milestones within the review process providing the median approval timelines achieved by the six countries during 2019 – 2020. This showed that review processes of the six agencies were similar; however, differences were noted in the milestones that were monitored and recorded. A key finding was that the frequency of the expert committee meetings in the active member countries ranged from monthly to quarterly providing insight into the differences in the time taken to implement a ZaZiBoNa recommendation by the member countries. All six agencies implemented the majority of good review practices; however, the need for improvement in the areas of transparency and communication and good-quality decision making was a common finding. In addition, as a result, information on the regulatory review processes of these countries as well as the similarities and differences have been published and are now available for applicants to consult as they plan their registration application submissions. This has the potential to reduce the registration timelines for life-saving medicines in these individual countries as the applicants are able to submit complete applications reducing the number of assessment cycles required before a product is approved. As far as ZaZiBoNa is concerned, the comparison of the resources and processes of the six countries who are active members of this initiative made it possible for differences in the regulatory review processes that hinder the performance of the work sharing

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initiative to be identified and for strategies for alignment to be proposed for further strengthening of the initiative.

A study of the pharmaceutical industry and regulatory authorities' perceptions of the EAC MRH by Dansie et al (2019) reported a low response rate of 33% from the regulatory authorities. However, a 100% response rate was achieved by the regulatory authorities in our study evaluating the effectiveness and efficiency of the ZaZiBoNa initiative (see chapter 6). This included the successes and challenges, ways to improve the effectiveness and efficiency as well as the way forward. This showed that ZaZiBoNa served as a platform for work sharing, information exchange, capacity building and harmonisation of registration requirements. As a result, regulators had benefited from a reduced workload, applicants reduced effort and cost in compiling submissions and patients benefited from improved availability of quality assured medicines. Some of the challenges were the inadequacy of resources and differences in time to the implementation of the ZaZiBoNa recommendation in the member countries. The delays in obtaining national registration after a joint review recommendation was also identified in the EAC MRH initiative (Dansie et.al, 2019; Mashingia et.al, 2021).

Following this study, the views of the pharmaceutical industry were explored in chapter 7. This showed that the pharmaceutical industry believed that the ZaZiBoNa initiative had achieved shorter timelines for approval of medicines resulting in increased availability of quality-assured medicines for patients in the SADC region. In addition, that harmonisation of registration requirements and joint reviews have reduced the workload for both the pharmaceutical industry and the regulatory authorities. However, a lack of a centralised submission and tracking system, and information for applicants on the process for submission of ZaZiBoNa dossiers / applications in the individual countries, including contact details of the focal person were not available. Both the regulatory authorities and the pharmaceutical industry agreed that the way forward was to establish a regional administrative unit hosted in one of the member states to improve coordination and tracking of ZaZiBoNa products in the interim with a goal of having a regional medicines agency in the long term. This is similar to other regional initiatives on the African continent that have proposed the establishment of a regional agency as the way forward (Arik et.al, 2021)

STUDY LIMITATIONS

The scope of the research was limited to the review process, milestones and timelines. Therefore, the inputs and outputs of the process were not evaluated, for example,

the quality of the actual assessments conducted and whether they include a benefit-risk assessment using an standardised templates and reports as well as standard operating procedures. In addition, although quality decision-making practices were adhered to intuitively by ZaZiBoNa, the SADC MRH implementing agency MCAZ and the other active member regulatory authorities; the implementation of these practices was not measured using a structured systematic approach.

The performance metrics data collected and analysed in chapter 3 was limited to the information that was documented and made available by the Zimbabwean NRA, that is, the date of receipt of the dossier and the date of approval of the product (time to registration). It was therefore not possible to calculate how much of this time was spent validating the application or the time taken for the actual review (agency time) or the applicant response time for each review cycle (company time). In addition, the analysis of the performance metrics was limited to registered products while products that were refused registration were not included.

Certain data used in chapter 3 for the HSA was obtained from the public domain and the metrics data from an industry survey. In addition, the metrics (number of approved products and median approval times) analysed in this study were limited to new active substances while generic medicines, biosimilars and complementary medicines were not included.

Chapters 4 and 5 described the results following the distribution of a questionnaire to the nine active member agencies of ZaZiBoNa to gather information pertaining to the regulatory review process, review practices, review models and timelines. Responses to the questionnaire were received from only six out of the nine NRAs as three agencies indicated they did not have resources.

The scope of the studies in chapters 6 and 7 was limited to the ZaZiBoNa initiative's process and operating model therefore quantitative data such as the actual metrics of the time taken to register the medicinal products in the individual countries after a ZaZiBoNa recommendation were not determined. The status of commercialisation and pricing of the medicinal products in the individual countries were also not evaluated.

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FUTURE WORK
Assessments

This research evaluated the overall regulatory review processes of the ZaZiBoNa initiative and participating countries. It would be of benefit in future for an evaluation to be conducted of the quality of the actual assessments performed for the initiative by the active member agencies, whether these include a benefit-risk assessment as well as a review of the assessment templates and reports standard operating procedures.

Regional Harmonisation Initiatives

It would be valuable to study other regional harmonisation initiatives such as EAC and ECOWAS following the model used in this research to identify opportunities for improvement.

Regulatory review processes of African countries

The use of the questionnaire applied in Study 2 (Chapter 2), Study 3 (Chapter 3) and Study 4 (Chapters 4 and 5) should be replicated by other African countries to evaluate and strengthen their regulatory review processes. This will also help the agencies to implement the good review practice of transparency as the results of these evaluations could then be shared with their stakeholders.

Reliance

The regulatory agencies that participated in these studies indicated that they implement a reliance stratagy. It would be useful to determine the criteria and current practices regarding reliance by the NRAs in the SADC region in order to gain a better understanding of how these are implemented and for this information to be made publicly available.

Quality Decision-Making Practices

Although most of the regulatory agencies that participated in study 4 (Chapters 4 and 5) indicated that they implement quality decision – making practices, it would be helpful to conduct a structured systematic evaluation to identify strengths and opportunities for improvement in this area.

Performance of ZaZiBoNa

The scope of studies 5 and 6 (Chapters 6 and 7) were limited to the review process. In future, it would be helpful to obtain quantitative data to support the views of the respondents which would include actual metrics of the time taken to register a medicinal products in the individual countries after a ZaZiBoNa recommendation. The status of commercialisation and pricing of the medicinal products in the individual countries as well as the factors influencing this could be the subject of a future study.

CONCLUSION

This programme of research has presented the history of how the ZaZiBoNa collaborative medicines registration initiative was established, the goals and objectives at inception and the current governance structure, operating model and performance. For the first time the regulatory review processes of the implementing agency and the other active member agencies of ZaZiBoNa, all LMIC, were studied using validated methods and techniques. This included evaluation of data requirements, the extent of scientific assessment, milestones and timelines, models of regulatory review, implementation of good review practices, quality measures and quality decision-making practices and strategies for alignment. Recommendations to further strengthen the country processes were also made which will support the countries in fulfilling their mandates. The study comparing the registration process for the SADC MRH project implementing agency MCAZ, an agency in a low-income country to WHO recognised mature authorities in high income countries was a first and resulted in the formulation of recommendations that will not only strengthen the MCAZ in its role as coordinator of ZaZiBoNa in the current operating model but also make it possible for other agencies in LMIC to benchmark best practices. This programme of research has been the first to assess and compare the views of the regulatory authorities and the pharmaceutical industry on the successes, challenges, effectiveness and efficiency of the current operating model of the ZaZiBoNa initiative. As a result, recommendations for an improved model for the ZaZiBoNa initiative have been proposed. It is hoped that the proposed improved model for regulatory review process will be implemented and enhance patients' access to quality-assured, life-saving medicine in the SADC region. It is also believed that the other harmonisation initiatives in Africa and beyond stand to benefit from the findings and recommendations made in this research programme.

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APPENDIX &

ABOUT THE AUTHORS
Dr Tariro Sithole
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Dr Sithole has over 13 year's experience in the regulation of medical products specialising in the assessment of marketing authorization applications and the regulatory review process. She currently is the project coordinator for the European and Developing Countries Clinical Trials Partnership (EDCTP) funded project titled, 'Competence based fellowships for African reviewers'. In this role, she has been responsible over the last 4 years for supporting 8 fellows from 5 different countries and facilitating the training of over 340 regulatory affairs professionals working in regulatory authorities and the pharmaceutical industry in the Southern African region

Dr Sithole received her Bachelor of Pharmacy (Honours) degree from the University of Zimbabwe. She was awarded a Master of Science in Pharmaceutics and a Doctor of Philosophy (Pharmacy) from the University of Hertfordshire, United Kingdom. She was also a pre-doctoral fellow in the AIDS International Training and Research Programme at the University at Buffalo, New York and her area of research was in the formulation and characterisation of poly lactic glycolic acid (PLGA) and magnetite nanoparticles containing the anti-tubercular drug rifampicin.

Dr Sithole began her career as a regulatory officer in the Evaluations and Registration division of the Medicines Control Authority of Zimbabwe and after a few years was promoted to senior regulatory officer. Her core responsibility was the assessment of the marketing authorisation applications. She was later promoted to chief regulatory officer (Human medicines), a managerial position which she held for 7 years. In this role, Dr Sithole was the lead assessor for medicines, supervising and training assessors in the division as well as ensuring that the regulatory review process was in line with international standards. She led her division's adoption of the ISO 9001 quality management system and subsequent certification. In that time, Dr Sithole also served as a temporary advisor to the WHO prequalification of medicines programme for 3 years and as an expert on technical working groups of the Southern African Development Community (SADC) set up to develop regional guidelines for registration and select centres of excellence for various regulatory functions. She has been actively involved in the SADC regional collaborative medicines registration initiative, ZaZiBoNa, since its inception in 2013. Dr Sithole also serves as a temporary advisor to the WHO regulatory systems strengthening programme, assessing national regulatory authorities using the Global Benchmarking Tool. Dr Sithole has published several studies in peer reviewed journals and presented at both national and international conferences.
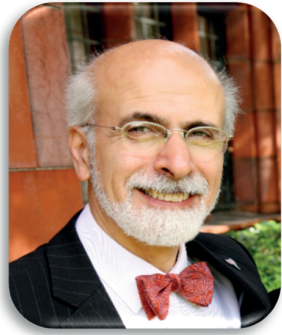
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Sam Salek is Professor of Pharmacoepidemiology in the School of Life and Medical Sciences, University of Hertfordshire, UK where he leads the Public Health & Patient Safety research group. He is also the Director of the Institute of Medicine Development, Cardiff, UK, a visiting Professor at the State of Hessen, Germany and Vice-President of the PharmaTrain Federation. Professor Salek is the co-founder and the past chair of the Patient Engagement Special Interest Group of the International Society of Quality of Research, co-chairs the European Hematology Association Scientific Working Group for Quality of Life and Symptoms and chairs the EHA SWG 'Gaucher's Disease Task Force'.

Professor Salek completed his undergraduate degree at the University of Oklahoma in 1978. He later moved to Cardiff where he studied for his PhD, 1985–1989. Since completing his PhD, Professor Salek has held a number of academic posts on both sides of the Atlantic. His major research interests include: pharmaceutical regulatory science to improve patient access to new medicines; benefit-risk assessment of medicines; development, evaluation and application of instruments to assess patient-reported outcomes and health-related quality of life (HRQoL); and pharmacoeconomics/ health economics. Over the past four decades he has received a number of government and industry research grants for projects in the areas of pharmaceutical regulatory science covering jurisdictions such as Middle East, Far East, Africa, India, South and North America.

Professor Salek has developed a few undergraduate, postgraduate diploma and MSc programmes over the past 35 years which they continue to be successful. Of noteworthy: he developed and modernised the 2-year part-time Postgraduate Course in Pharmaceutical Medicine (Dip Pharm Med) and was the Course Director of the same for 30 years; he is the founder of the MSc in International Pharmaeconomic & Health Economics in 2007 and was the Programme Director of the same until 2015; he is the founder of the Integrated Master of Regulatory Science (an undergraduate programme) which received approval from the University of Hertfordshire Validation Board in April 2017 and commenced in September 2018.

Professor Salek is a fellow of the Royal College of Physicians, the Royal Pharmaceutical Society of Great Britain, European Society of Clinical Pharmacy, Global Fellow of the IFAPP in Medicines Development and member of the Cardiff Medical Society. He is a member of five Editorial boards and has published 19 books and over 650 journal articles and abstracts. He has developed and validated 11 general and disease-specific patient-reported HRQoL measures, a quality decision making tool (QoDoS), a quality outpatient discharge information checklist, whilst also collaborating with the pharmaceutical industry to design HRQoL protocols for clinical trials. Increasingly, Professor Salek is shifting his emphasis towards the practical applications of HRQoL measures in clinical decision-making and policy, quality decision-making and patient engagement in research as partners/collaborators.

Professor Stuart Walker
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Professor Stuart Walker is an Independent Consultant in Pharmaceutical Medicine and Founder of both CMR International & the Centre for Innovation in Regulatory Science. For thirty-five years he held the position of Professor of Pharmaceutical Medicine, School of Pharmacy & Pharmaceutical Sciences, Cardiff University, Wales, but now is Professor of Regulatory Science, University of Hertfordshire, Hatfield, UK. He is also a Fellow of the School of Pharmacy, London University, Academic Regulatory Expert, Center of Regulatory Excellence, Singapore and Honorary Professor, University of Witwatersrand, South Africa.

Professor Walker spent ten years at London University, which included lectureships in biochemical pharmacology at St Mary's Hospital Medical School and Clinical Pharmacology at the Cardiothoracic Institute. This was followed by eight years with Glaxo Group Research in the UK where he had international responsibility for several major clinical research programmes.

Current research interests include studies to improve productivity, efficiency and decision-making in global drug development and the regulatory review process. In addition he has been involved in Good Review Practices in the Regulatory Environment in the Developing Markets of the Asia-Pacific Region, Latin America, Africa & the Middle East, including the Benefit Risk Assessment & Quality Decision making Practices as well as public policy issues that relate to these research activities.

During his research career, Professor Walker has supervised thirty PhD programmes, co-authored over 350 research papers and co-edited twenty-eight books in the fields of toxicology, drug discovery, clinical development, regulatory policies, the Benefit/Risk Assessment of Medicines and more recently Quality Decision Making Practices

Professor Walker has been a member of a number of academic, professional and industrial committees as well as the editorial boards of several scientific journals. He was given the "Drug Information Association" Outstanding Service Award in 2001 and received a Lifetime Achievement Award from Informa in the same year & the TOPRA lifetime achievement award in 2011. He is frequently involved in the organisation of national and international meetings on key issues that concern the pharmaceutical industry and the Regulatory Review and has lectured extensively throughout Europe, the United States, Japan and the Asia-Pacific Region, Latin America as well as Africa & the Middle East.

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ZAZIBONA Terms of Reference of the SADC Collaborative Medicines Registration Process (unpublished).

LIST OF ABBREVIATIONS

ACCESS	Australia, Canada, Singapore, Switzerland and United Kingdom
ACSS	Australia, Canada, Singapore, Switzerland
AMA	African Medicines Agency
AMRH	African Medicines Regulatory Harmonisation Initiative
ATC	Anatomic Therapeutic Chemical Classification
AU	African Union
AUC	African Union Commission
AUDA NEPAD	African Union Development Agency New Partnership for Africa Development
BRAIN	Benefit-Risk Assessment in New and Old Drugs
CAPA	Corrective and Preventive Actions
CHMP	Committee for Medicinal Products for Human Use
CIRS	Centre for Innovation in Regulatory Science
CMC	Chemistry, Manufacturing and Control
COBRA	Consortium on Benefit Risk Assessment
CPP	Certificate of Pharmaceutical Product
CRO	Clinical Research Organisation
CRP	Collaborative Registration Procedure
CTD	Common Technical Document
DFID	United Kingdom Department of International Development
EAC	East African Community
ECCAS	Economic Community of Central African States
ECDA	Ethics Committees with Delegated Authority
ECOWAS	Economic Community of West African States
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GBT	Global Benchmarking Tool
GDP	Gross Domestic Product
GMP	Good Manufacturing Practice
GrevP	Good Review Practices
GRP	Good Regulatory Practices
HIV/AIDS	Human immunodeficiency virus / Acquired immune deficiency syndrome
HSA	Health Sciences Authority
HTA	Health Technology Assessment

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDP	Institutional Development Plan
IGAD	Intergovernmental Authority on Development
IMF	The International Monetary Fund
IMS	Information Management Systems
ISO	International Organisation for Standardisation
IT	Information Technology
LMIC	Low- and Middle-Income Countries
LMS	Life and Medical Sciences
MCAZ	Medicines Control Authority of Zimbabwe
MHRA	Medicines and Healthcare Products Regulatory Authority
MRH	Medicines Registration Harmonization
NAS	New Active Substances
NCE	New Chemical Entities
NMRC	Namibia Medicines Regulatory Council
NOD	Notice of Deficiency
NRA	National Regulatory Agency
PrOACT-URL	Decision making guide with eight steps: Problems, Objectives, Alternatives, Consequences, Trade-oofs, Uncertainty, Risk attitudes, and Linked decisions
OpERA	Optimising Efficiencies in Regulatory Agencies
PAR	Public Assessment Report
PEER	Process, Effectiveness and Efficiency Rating
PEER-IND	Process, Effectiveness and Efficiency Rating for Industry
PhRMA BRAT	Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team
PMPA	Pharmaceutical Manufacturing Plan for Africa
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
QDMP	Quality Decision Making Practices
QMS	Quality Management Systems
RCORE	Regional Centre of Regulatory Excellence
REC	Regional Economic Community
SADC	Southern African Development Community
SADCAS	Southern African Development Community Accreditation Services
SAHPRA	South African Health Products Regulatory Authority

SARPAM	Southern African Regional Programme on Access to Medicines and Diagnostics
SAZ	Standards Asssociation of Zimbabwe
SDG	Sustainable Development Goal
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SQAM	Standardisation, Quality Assurance, Accreditation and Metrology
SRA	Stringent Regulatory Authority
TGA	Therapeutic Goods Administration
TMDA	Tanzania Medicines and Medical Devices Authority
UK	United Kingdom
UMBRA	Universal Methodology for Benefit Risk Assessment
UN	United Nations
USA	United States of America
USD	United States Dollar
USFDA	United States Food and Drugs Administration
WHO	World Health Organization
WHO PQ	WHO Prequalified
WHO PQT	WHO prequalification team
ZAMRA	Zambian Medicines Regulatory Authority

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