MCAZ Medicines Control Authority of Zimbabwe

POLICY TITLE: MCAZ RELIANCE POLICY			
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1.0 INTRODUCTION

1.1 What is Reliance?

The World Health Organisation defines reliance as the act whereby the regulatory authority, in one jurisdiction may take into account and give significant weight to – i.e. totally or partially rely upon – evaluations performed by another regulatory authority or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others.

1.2 Why Reliance?

Many new medicines being developed to benefit patients, e.g. 7000 in 2015 (PhRMA 2015). Regardless of maturity level or whether located in a developing or developed country, no National Regulatory Authority (NRA) has sufficient resources to perform timely, cost-efficient, assessment and issue a regulatory decision on all products without relying, in part or in full, on the evaluations performed by other NRAs.

All stakeholders impacted by regulatory systems have the potential of benefiting from Regulatory Reliance. Reliance ensures timely access to safe, effective and good quality medicines for healthcare providers and patients. Efficient

utilization of National Regulatory Authority resources by avoiding duplication of work and providing opportunities to strengthen the regulatory system, while maintaining sovereignty over decision-making. It helps pharmaceutical manufacturers to streamline management of regulatory submissions and global supply systems as well as ensure predictable, timely approvals.

1.3 Zimbabwe Context

The Medicines Control Authority of Zimbabwe (MCAZ) is the statutory body responsible for protecting public and animal health by ensuring that all medicines, devices, allied substances, and other health commodities are safe, effective, and of good quality. This is achieved through registration of medicines; licensing of persons and premises that handle medicines; review, approval, and monitoring of clinical trials that involve the use of medicines; and quality testing and safety monitoring of all health commodities granted market authorisation.

In 2021 MCAZ had a staff complement of less than 150 staff members, including support staff. Only 100 officers were responsible for planning, managing, controlling and execution of regulatory functions. This number is inadequate to conduct a full evaluation of the over 250 new applications received per annum; evaluation of applications for re-registration of previously registered products, conducting full Good Manufacturing Practices (GMP) inspections for new applications and re-inspection every 2-3 years for facilities producing approved products; conducting review and approval of new clinical trials; testing samples for registration and post-marketing quality surveillance. In addition, MCAZ does not have adequate and full technical expertise to evaluate specialised aspects of novel products.

The above limitations threaten the Authority's ability to ensure timely access to safe, effective, and quality-assured medicines to the Zimbabwean public and healthcare delivery systems. The same limitations also affect the sister regulatory agencies in the Sothern African Development Conference (SADAC) region.

It is against this background that MCAZ must use reliance, collaborative approaches, and recognition to leverage its limited human, technical and material resources.

2.0 MCAZ RELIANCE

MCAZ has been applying the principles of reliance over the years, though these were not documented. There is also a need to adopt broader reliance to respond to the growing volume of and complexity of work and the increasing demand for faster turnaround times by patients, the health care system, the state and applicants. The reliance framework allows MCAZ to rely on other NRAs as well as allows other NRAs to rely on MCAZ.

3.0 Registration Reliance

3.1 When MCAZ is conducting evaluation and registration of medicines it considers:

3.1.1 Registration in the country of origin as a basic minimum
3.1.2 World Health Organisation Prequalification (WHO-PQ) for medicines.
3.1.3 WHO Prequalification for vaccines.
3.1.4 WHO Prequalification for devices and Diagnostics (once the regulations are approved)
3.1.5 WHO Emergency Use Listing of medicines or devices in the face of public health emergencies
3.1.6 Zazibona Collaborative Registration Procedure
3.1.7 Agreements/MoUs signed with other regulators who are willing to share information with MCAZ with the manufacturers' consent. Currently MCAZ has functional agreements with Egyptian Drugs Authority (EDA) and South African Health Products Authority (SAHPRA). In addition, MCAZ is working on further agreements with the Islamic Republic of Iran Food and Drugs Authority (IFDA).
3.1.8 Approval by Stringent Regulatory Authorities (European Medicines Agency (EMA), United States Food and Drug Authority (USFDA), Medical Health Products Regulatory Authority (MHPRA), Japan Pharmaceutical and Medical Devices Authority (PMDA), Health Canada, Swissmedic, Australia Therapeutic Goods Administration (TGA))
3.1.9 European Union (EU) Article 58 Scientific Opinion evaluation reports for medicines developed in Europe for use outside EU

3.2 Due to the success of the African Medicines Regulatory Harmonization Initiative (AMRH) in the SADC Region, MCAZ is exploring the following reliance mechanisms:

3.2.1 Reliance on approvals issued by other SADC National Medicine Regulatory Authority's that participate in ZAZIBONA programme Botswana Medicines Regulatory Authority-BOMRA, Zambia Medicines Regulatory Authority-ZAMRA, Tanzania Medicines & Medical Devices Authority-TMDA, Namibia Medicines Regulatory Council-NMRC etc)

Reliance on approvals issued by eleven African ReCoREs outside SADC such as Ghana Food and Drug Authority-GFDA, Nigeria National Agency for Food and Drug Administration and Control - NAFDAC, Burkina Faso Direction General de la Pharmacie du Medicament et des Laboratoires where full evaluation reports are provided.

3.3 In order for the MCAZ Evaluations and Registration Division to consider a product for reliance it needs the following information, in order of increasing importance:

3.3.1 A registration certificate from the country of origin
3.3.2 A registration certificate from Stringent Regulatory Authority (SRA).

3.3.3 A public assessment report from the NRA in country of origin.
3.3.4 A public assessment report, including scientific discussion and SmPC from the NRA in the country of origin.
3.3.5 A public assessment report including, scientific discussion and SmPC from an SRA.
3.3.6 A public assessment report from WHO.
3.3.7 Full assessment report and SmPC from a ZAZIBONA country.
3.3.8 Full assessment report and SmPC from a maturity level 3 NRA in Africa or abroad.
3.3.9 A full WHO Prequalification assessment report release via WHO Collaborative Registration Process agreements between applicant, WHO and MCAZ.
3.3.10 Full assessment report from the country of origin given with the consent of the applicant and the NRA.
3.3.11 Full assessment report from the NRA in an SRA where the product is registered, with consent of the applicant, NRA and MCAZ,
3.3.12 Quality information summary (QIS) summarising the current approved properties of a product by the reference regulatory authority.
3.3.13 Full assessment report from WHO Prequalification with the consent of applicant, WHO and MCAZ.

3.4 Enablers that support MCAZ Reliance on other Reference NRAs

3.4.1 Willingness and consent of the applicant whose product has already been approved by a reference body e.g. WHO PQ, SRA, other ML3 NRAs, to have their product expeditiously considered through reliance route.
3.4.2 The applicant submitting a replica dossier, in terms of technical information, to MCAZ that was submitted to and approved by the reference NRA, whether in country of origin or an SRA i.e. sameness of the product submitted by the applicant with that approved by the reference regulatory authority should be demonstrated.
3.4.3 Three-way confidentiality and non-disclosure agreements between applicant, reference NRA and MCAZ.
3.4.4 The reference NRA providing the full unredacted evaluation report of the product to MCAZ after written consent of the applicant.
3.4.5 MCAZ legal undertaking to maintain confidentiality of the evaluation report and information shared by the reference NRA, with the consent of the applicant, and use it only for the purposes of expedited approval of the product.
3.4.6 MCAZ committing to expedite approval of the product from 16-24 months to 3 months when a replica dossier from the applicant and the full evaluation report from the reference NRA were provided.
3.4.7 Participation or observer status for MCAZ when the reference body or agency is assessing or deliberating of approval of the product e.g. EU-Medicines for all (EU-M4all) products are being discussed by EU experts.

3.5 Enablers for other foreign NRAs to rely on MCAZ as the Reference NRA

3.5.1 Willingness of the applicant who has registered a medicine with MCAZ to have the same product expeditiously considered by another NRA using reliance procedure.
3.5.2 Three-way confidentiality and non-disclosure agreements between applicant, MCAZ as the reference NRA and referring NRA.
3.5.3 Applicant submission of a replica dossier to the referring NRA as submitted to MCAZ.
3.5.4 Applicant authorising MCAZ to share the full unredacted evaluation with the referring / rely NRA
3.5.5 The referring NRA making a legal undertaking to MCAZ that it will only utilise the shared full evaluation report for the purpose of expeditious assessment of the product.
3.5.6 The referring NRA committing to expedited evaluation and make a regulatory decision in the shortest time possible e.g. 3 months
3.5.7 MCAZ publishing of list of approved products, Summary of Product Characteristics truncated public assessment reports so that Zimbabwe patients can access product information and foreign NRAs with or without memorandum of understandings (MoUs) with MCAZ can still access the product information
3.5.8 Memorandum agreement between MCAZ and referring SADC NRAs to share full evaluation reports for applications from consenting applicants.
3.5.9 Joint Virtual Committee Registration Committee meetings between MCAZ and the referring NRA to approve products of common interest, when necessary and feasible.
3.5.10 Wide dissemination and consent of pharmaceutical industry to utilise the opportunity for submission of applications through the expedited reliance route.

4.0 GMP Inspection Reliance

4.1 When MCAZ is determining suitability of a manufacturing facility that will produce a product that is seeking marketing authorisation in Zimbabwe, it considers the following in order of increasing importance:

4.1.1 GMP certification issued by the NRA in the country of manufacture
4.1.2 GMP certification issued by an SRA NRA (EMA, USFDA, PMDA, HCanada, TGA, Swissmedic), Pharmaceutical Inspection Co-operation Scheme-PIC/S and other WHO-listed maturity level 3 NRAs
4.1.3 Facilities inspected by WHO Prequalification Programme for medicines and vaccines

4.2 The information needed for MCAZ to rely on inspections conducted by other NRAs, in order of increasing importance, is as follows,:

4.2.1 GMP certificate from NRA in country of manufacture for non-SRA, non-PICs country
4.2.2 GMP certificate issued by SRA-, PICs- NRA
4.2.3 GMP certificate issued by a ZAZIBONA country or WHO Listed NRAs ML 3 in Africa or Abroad
4.2.4 WHO Public Inspection Report for manufacturing facility

4.2.5 Full inspection report from NRA in country of manufacture
4.2.6 Full GMP inspection report by SRA-, PICs-associated NRA, WHO listed NRA ML 3 NRA.
4.2.7 Full WHO Prequalification GMP Inspection Report

4.3 Enablers for MCAZ to rely on GMP inspections conducted by reference NRAs/ bodies

4.3.1 Willingness of applicant to have the GMP compliance of their manufacturing facility considered through reliance route
4.3.2 The manufacturers submitting the exact Site Master Files (SMF) and confirmation that the exact facilities (physical address, block number) and manufacturing lines approved by the reference NRA, whether in country of origin or SRA, are the same for MCAZ
4.3.3 Three-way confidentiality and non-disclosure agreements between manufacturer reference NRA and MCAZ
4.3.4 MCAZ committing to expedite the reliance based inspection relative to the longer process for physical inspection that entails: pre-visit planning, travel, engagement, inspection and debriefing, return travel, report writing and final decision
4.3.5 Participation or observer status for MCAZ inspectors alongside the Reference NRA when inspections of sites that produce products to supplied to Zimbabwe e.g. reference NRAs inspecting facilities that produce Article 58 products, PEPFAR tentatively approved products or WHO PQ products.

4.4 Enablers for other NRAs to rely on MCAZ GMP inspections

4.4.1 Willingness of the applicant and manufacturer to have their MCAZ-approved facility be considered by another NRA using reliance procedure
4.4.2 Three-way confidentiality and non-disclosure
4.4.3 Submission of the SMF for the exact sites, block numbers, manufacturing lines to the referring NMRA as submitted to and approved by MCAZ
4.4.4 MCAZ publishing a list of approved GMP compliant facilities and MCAZ public inspection reports
4.4.5 Memorandum of agreement between MCAZ and referring SADC NRAs on sharing full GMP reports for inspections of consenting applicants.
4.4.6 Joint physical or virtual GMP inspection of manufacturing facilities, and joint Virtual Committee meetings between MCAZ as the reference agency and the referring NRA to approve manufacturing facilities of common interest, when necessary
4.4.7 Wide dissemination and consent of pharmaceutical industry to utilise the opportunity for GMP approvals through the expedited reliance route

5.0 Laboratory Testing Reliance

5.1 When MCAZ is assessing the quality of medicines through quality control testing in its laboratories it considers the following:

5.1.1 The analytical method, test specifications and CoA of a Quality Management System accredited or certified laboratory.

5.1.2 The analytical methods, test specifications and CoA of a non-QMS accredited or certified national control laboratory (NCL)

5.1.3 The analytical methods, test specifications and CoA of a QMS accredited, WHO Prequalified or certified (ML3) national control laboratory (NCLs) in SADC, other AU RECs, SRAs

5.1.4 The analytical methods, test specifications and CoA of a QMS accredited or certified WHO reference laboratory

5.1.5 Utilizing and or subcontracting testing services to any ISO 17025 accredited or WHO prequalified laboratory within its network NRAs laboratories for analysis of medical products.

5.1.6 Use of laboratory testing related decisions made by NRA laboratory in the country of origin, other NRAs laboratories, ISO 17025, WHO prequalified laboratories or competent regional and international bodies.

5.1.7 Use laboratory testing related reports produced by NRA laboratory in the country of origin, other NRAs laboratories, ISO 17025, WHO prequalified laboratories or competent regional and international bodies.

5.1.8 Use of information (published or not published) from other national regulatory agencies (NRAs), competent laboratories (ISO 17025 and WHO Prequalified) or regional and international bodies in the field of quality control of medicines.

5.2 Chemical Reference Reliance on Primary Standards from Manufacturers

5.2.1 MCAZ does not prepare its own chemical reference standards but purchases them from suppliers of chemical reference standards. Therefore, it relies on the Certificate of Analysis (CoA) and Validity checks as provided by the manufacturers.

5.3 Enablers to MCAZ using Reliance for Laboratory testing

5.3.1 Willingness of other NRA laboratories to utilise ISO 17025 or WHO Prequalification as the common technical basis for expedited determination of product conformity via reliance route.

5.3.2 Willingness of other NRA laboratories to have their ISO 17025 or WHO Prequalification audit or inspection reports shared with MCAZ laboratory for use through reliance route.

5.3.3 Willingness of other NRA laboratories to share out-of-specification (OOS) results and reports with MCAZ laboratory for use through reliance route.

5.3.4 Willingness of other NRA laboratories to share their annual laboratory reports with MCAZ laboratory for use through reliance route.

5.3.5 Three-way confidentiality and non-disclosure agreements between manufacturer, other NRA laboratory and MCAZ laboratory.

5.3.6 Willingness of other NRA laboratories to share the third party technical agreements, subject to prior consent by the third party, when the reference NCL has also relied on a third NCL.

5.3.7 The reference NCL allow MCAZ analysts to participation in joint quality control testing projects, where possible and necessary.

5.3.8 Willingness to participate in staff exchange programmes where MCAZ and collaborating NRAs/NCLs exchange analysts as part of work and knowledge sharing programmes.

5.3.9 The reference laboratory on which MCAZ relies agrees to issue test results and/or providing statements of conformity, opinions and interpretations of laboratory results based on scientific data, regulatory requirements and specifications for the purposes of reliance.

5.4 Enablers for other NRAs /NCLs to rely on MCAZ Laboratory as the reference laboratory for testing

5.4.1 Willingness of other NRAs and manufacturers to rely on MCAZ laboratory testing to expedite product registration or market access.

5.4.2 Willingness by MCAZ laboratory to share its finished product analytical results with the referring NRA/NCL.

5.4.3 Willingness by MCAZ laboratory to have their ISO 17025 or WHO Prequalification audit or inspection reports shared with other NRAs laboratories for reliance use.

5.4.4 Willingness by MCAZ laboratory to share OOS results and reports with other NRA laboratories for reliance use.

5.4.5 Willingness by MCAZ laboratory to share their annual laboratory reports with other NRA laboratories for reliance use

5.4.6 Three-way confidentiality and non-disclosure agreements between other referring NRA laboratory and MCAZ laboratory.

5.4.7 Willingness of MCAZ laboratory to share its third party technical agreements with other laboratories that rely on MCAZ testing results, subject to prior consent of the third party NRA/NCL.

5.4.8 Willingness of MCAZ to allow referring Laboratories to participation in joint- or witnessing, quality control testing, where possible.

5.4.9 MCAZ laboratory allowing staff from referring NRAs to come for attachment and secondment, physical and virtual training and information-sharing under the MCAZ Quality Testing ReCoRE activities.

5.4.10 MCAZ providing statements of conformity, opinions and interpretations of laboratory results based on scientific data, regulatory requirements and specifications for use by referring NRA/NCL.

6.0 Clinical Trials Reliance

6.1 The MCAZ employs the reliance model approach for clinical trial design and/or investigational products. The MCAZ implements the reliance model especially for where

6.1.1 the safety and efficacy of the investigational product have already been confirmed through WHO prequalification

6.1.2 the investigational product has been approved in SRAs, WHO listed countries and any other countries considered to be publicly accessible Clinical Trials registries

6.1.3 the clinical trial design and/or investigational product has been evaluated and found satisfactory at a joint review meeting facilitated by the World Health Organization such as AVAREF.

6.2 The approach facilitates conducting regulatory reviews and evaluations in a timely manner and at the same time, accelerate the evaluation process without compromising the quality, safety and efficacy of investigational products, as well as the design of clinical trials. The Authority will however maintain its own regulatory responsibilities for decision-making.

6.3 In order for the MCAZ to use the reliance approach for the clinical trials it needs proof of approval of the clinical trial design and/or investigational product by the reference NRA Please note that reliance approach will not be applicable to localised requirements, such as ethical approvals, informed consent forms, pharmacy plan, participants insurance etc.

6.4 Enablers that support MCAZ Clinical Trials Reliance on other NRAs

6.4.1 Willingness of applicant/sponsor to have their clinical trial application considered through expedited reliance route.

6.4.2 Submission of the exact clinical trial design and/or investigational product information to MCAZ as submitted in the reference NRA .

6.4.3 Three-way confidentiality and non-disclosure agreements between applicant, reference NRA and MCAZ.

6.4.4 MCAZ committing to expedite Clinical Trial approval within much shorter time that normal timelines.

6.5 Enablers for other NRAs to rely on MCAZ Clinical Trial assessments

6.5.1 Willingness of the applicant/sponsor to have their MCAZ-approved clinical trial report to be considered by another NRA using reliance procedure.

6.5.2 Three-way confidentiality and non-disclosure agreements between applicant/sponsor, MCAZ and referring NRA.

6.5.3 Submission of the exact clinical trial design and/or investigational product information to the referring NMRA as submitted to MCAZ

6.5.4 Memorandum agreement between MCAZ and referring NRAs to share full evaluation reports for applications from consenting applicants/sponsors.

6.5.5 Joint Virtual Committee meetings (eg AVAREF Joint review meetings to approve clinical trials of common interest, when necessary.

6.5.6 Joint Virtual Committee meetings where MCAZ invites interested referring NRAs to virtually witness PVCT meeting deliberations on approval of clinical trials ~~CT~~ of interest, when necessary and feasible.

7.0 Vigilance Reliance

7.1 The MCAZ continually ensures the safety of marketed products through its established Pharmacovigilance system. To ensure that safety issues are promptly identified and the necessary interventions implemented, the MCAZ considers vigilance related decisions, reports or information from other countries, regional or international bodies such as WHO in making decisions on the safety and effectiveness of medical products. The regulatory decisions by the MCAZ – leveraging safety decisions from well–resourced or reference NRAs - are geared towards ensuring appropriate and safe use of registered medical products. The MCAZ considers vigilance reports and decisions from the following:

7.1.1 WHO Global pharmacovigilance newsletters, and databases.

7.1.2 WHO listed countries.

7.1.3 Any other countries or bodies with functional and reliable pharmacovigilance systems.

8.0 REFERENCES

8.1 Health Advances analysis; Adis R&D Insight Database. March 2015, compiled by PhRMA

8.2 WHO's Good Regulatory Practices, 2016

8.3 NEPAD/ AUDA Regional Centres of Regulatory Excellence https://*www.nepad.org/publication/regional-centres-of-regulatory-excellence-rcores*

8.4 EMA, Medicines for use outside the European Union [Accessed April 2024] https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/medicines-use-outside-european-union.

8.5 TRS 1033 - Annex 10: Good reliance practices in the regulation of medical products: high level principles and considerations, 2021

9.0 ATTACHMENTS

N/A

10.0 HISTORY

DOCUMENT HISTORY		
Revision Number	Date Approved	Reason for Change
0	May 2021	Aligning the Reliance Policy to the requirements of World Health Organisation Global Bench marking Tool (WHO GBT) Avoid reliance on the manufacturer's QC's results **Removed 5.1.1** The analytical method, test specifications and certificate of analysis (CoAs) of the product by non-QMS accredited or certified manufacturers laboratory **Added** **5.2 Chemical Reference Reliance on Primary Standards from Manufacturers** 5.2.1 MCAZ does not prepare its own reference standards but outsources from suppliers of Primary and Secondary standards. Therefore relies on the Certificate of Analysis (CoA) and Validity checks as provided by the manufacturers.
1	February 2022	System Improvement and to number the policy according to document control procedure requirements Details of changes **Header** Reference number changed from PM01/2021 to QPM 09

		Section 1.3 Added ….. evaluation of applications for re-registration of previously registered products,……. **Section 3.1.7** Added 3.1.7 Agreements/MoUs signed with other regulators who are willing to share information with MCAZ with the manufacturers' consent. Currently MCAZ has functional agreements with Egyptian Drugs Authority (EDA) and South African Health Products Authority (SAHPRA). In addition, MCAZ is working on further agreements with the Islamic Republic of Iran Food and Drugs Authority (IFDA). **Section 3.2.1** **Deleted** SAHPRA as Reliance on approvals issued by other SADC National Medicine Regulatory Authority's that participate in ZAZIBONA programme. **Section 3.3.12** Added section Quality information summary (QIS) summarising the current approved properties of a product by the reference regulatory authority. **Section 3.4.2** changed from The applicant submitting a replica dossier, in terms of technical information, to MCAZ was submitted to and approved by the reference NRA, whether in country of origin or an SRA. **Section 3.4.2** changed to The applicant submitting a replica dossier, in terms of technical information, to MCAZ that was submitted to and approved by the reference NRA, whether in country of origin or an SRA i.e sameness of the product submitted by the applicant with that approved by the reference regulatory authority should be demonstrated. **Section 3.4.7** Changed from ……e.g Products are being discussed by EU experts Changed to …..e.g EU-Medicines for all (EU-M4all) products are being discussed by EU experts

		Section 5.2.1 Changed from MCAZ does not prepare its own reference standards but outsources from suppliers of Primary and Secondary standards. Therefore, relies on the Certificate of Analysis (CoA) and Validity checks as provided by the manufacturers. **Section 5.2.1** changed to MCAZ does not prepare its own chemical reference standards but purchases them from suppliers of chemical reference standards. Therefore, it relies on the Certificate of Analysis (CoA) and Validity checks as provided by the manufacturers. **Added References** 8.4 EMA, Medicines for use outside the European Union [Accessed April 2024] https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/medicines-use-outside-european-union 8.5 TRS 1033 - Annex 10: Good reliance practices in the regulation of medical products: high level principles and considerations, 2021.

ACRONYMS

AVAREF	African vaccines Regulatory Forum
BOMRA	Botswana Medicines Regulatory Authority
EU	European Union
ML 3	Maturity Level 3
NAFDAC	National Agency for Food and Drug Administration and Control
NCL	National Control Laboratory
NMRC	Namibia Medicines Regulatory Council
NRA	National Regulatory Authority
PEPFAR	The President's Emergency Plan for AIDS Relief
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PMDA	Pharmaceutical and Medical Devices Agency
SAHPRA	South African Health Products Regulatory Authority
ZAMRA	Zambia medicines Regulatory Authority