MCAZ Medicines Control Authority of Zimbabwe

MCAZ/EVR/GL-04

RELIANCE GUIDELINES FOR REGULATION OF MEDICINES

EFFECTIVE DATE: 10/2022

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Authorised for use by: Director-General	 Signature	28/09/2022 Date

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ABBREVIATIONS

API:	Active Pharmaceutical Ingredient
CTD:	Common Technical Document
EMA:	European Medicines Agency
FPP:	Finished Pharmaceutical Product
GMP:	Good Manufacturing Practice
NRA:	National Regulatory Authority
ICH:	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals
INN:	International Non-proprietary Name
PD:	Product Dossier
PI:	Package Insert
RRA:	Reference Regulatory Authority
SmPC:	Summary of Product Characteristics
TGA:	Therapeutic Goods Administration (Australia)
The Authority:	Relevant regulatory authority, in this case MCAZ
USFDA:	United States Food and Drug Administration
NCE:	New Chemical Entity
MAH:	Marketing Authorization Holder
RMP:	Risk Management Plan

1.0 APPLICATION

This document covers reliance activities in the field of regulatory oversight of medicines, addressing all regulatory functions spanning the full life cycle of medicine. In addition, this document is intended for use in assessments of pre-marketing and post-marketing changes/variations of medicines.

2.0 PURPOSE

The objective of this document is to promote a more effective and efficient approach to regulation as part of a "smart regulation" approach, thereby promoting access to quality-assured medicinal products.

2.0 BACKGROUND / INTRODUCTION

The Medicines Control Authority of Zimbabwe (MCAZ) supports the implementation of reliance on other regulators' work as a general principle in order to make the best use of available resources and expertise. This principle enables leveraging the output of others whenever possible while placing a greater focus at the national level on value-added regulatory activities that cannot be undertaken by other authorities, such as in-country vigilance activities and oversight of local manufacturing and distribution.

Reliance approaches facilitate timely access to safe, effective and quality-assured medicinal products. They can help in regulatory preparedness and response, particularly during public health emergencies.

4.0 DEFINITIONS

4.1 **Abridged regulatory pathways**. Abridged regulatory pathways are regulatory procedures facilitated by the use of reliance, whereby the regulatory decision is solely or widely based on the application of reliance. Normally this would also involve some degree of work by the relying NRA (see "risk-based approach"). The expectation is that the use of reliance in these pathways would save resources and shorten the timelines compared to the standard pathways, while ensuring that the standards for regulatory oversight are maintained.

4.2 **Assessment**. For the purpose of this document, the term "assessment" covers the outcome of any evaluation conducted for a regulatory function (e.g. evaluation of an initial authorization for a medicine or any subsequent post-authorization changes, etc.).

4.3 **Reliance versus Recognition**. Reliance may take many forms and reflect varying degrees of application in recognizing or taking account of the assessments, decisions or any other authoritative information available from other authorities and institutions. Recognition may be seen as a special and more complete form of reliance whereby one regulatory authority relies on the decisions of another regulatory authority, system or institution, obviating the need for additional regulatory assessment in reaching its own decision. Recognition usually requires formal and enabling legal provisions.

4.4 **Risk-based approach**. MCAZ uses its own strategy regarding the appropriate risk-based approach to reliance that considers factors, such as the type and source of products evaluated, the level of resources and expertise available in the MCAZ, the public health needs and priorities of the country, and opportunities for reliance. Using marketing authorisation and post-marketing authorisation changes/variations as an example, MCAZ uses two levels of reliance involving an increasing degree of additional assessment by the relying NRA:

4.5 **Verification of applicability of the assessment outcomes** of another authority for regulatory decision-making in the national context, for example, in terms of legal and regulatory settings, benefit-risk assessment, unmet medical needs, risk management plans and any quality-related specificities such as climatic zones for product stability.

4.6 **Abridged assessment** of the quality, safety and efficacy/performance data taking into account information in the assessment reports of the reference regulatory authority.

4.7 **Joint assessment** and work-sharing between two or more regulatory authorities from regional regulatory networks. MCAZ is part of the SADC harmonization initiative 'ZAZIBONA'. Confirmation of sameness of the product to ensure that the medicine is the same as the one that had been assessed by the reference regulatory authority.

4.8 **Reference Regulatory Authority:** means a national or regional authority or an institution such as World Health Organization prequalification (WHO PQ) whose regulatory decisions and/or regulatory work products are relied upon by another regulatory authority to inform its own regulatory decisions.

4.9 **Mutual recognition:** The approval of medicines is based on a single assessment system, so that an assessment report from any agency in the network can be used as a basis for reliance by other regulators.

4.10 Unilateral recognition: NRA unilaterally recognizes marketing authorizations from certain reference regulatory authorities.

5.0 GUIDELINES

5.1 QUALITY, SAFETY AND EFFICACY REVIEW PATHWAYS

An application for approval of registration of medicine or variations of medicine will follow one of the following review types, namely:

5.1.1 Full Review

5.1.2 Abridged Review (new applications for registration, variations/notifications)

5.1.3 Verification Review

5.1.4 Mutual Recognition

5.1.5 Joint assessment and work-sharing ('ZAZIBONA' SADC harmonization initiative)

5.1.6 Unilateral recognition

Review types (5.1.2), (5.1.3), (5.1.4) and (5.1.6) represent reliance pathways, which MCAZ shall be implementing to reduce evaluation times. To qualify for a reliance pathway, an application must receive prior approval from a Reference Regulatory Authority (RRA). Reliance pathways are applied independently for quality, safety and efficacy sections based on the quality of documents submitted. Zimbabwe is also exploring mutual recognition as a reliance pathway.

Reference Regulatory Authorities for registration of medicines include countries on the WHO List of Stringent Regulatory Authorities List which are Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom, United States of America, Norway.

In order for an application to be considered for the reliance evaluation, additional documentation must be submitted with the application.

The final evaluation pathway decision for an application is at the discretion of MCAZ, and will depend on the type of molecule, indications, availability and quality of reliance documentation submitted. MCAZ will share screening queries with applicants regarding insufficient reliance documentation to ensure that as many applications as possible qualify for abridged and verified reviews. Where applicable, applications will default to a full review in the absence of a suitable reliance pathway. Whilst the medicine is under review, applicants shall inform MCAZ of any prohibition and restriction imposed by the RRAs of any country in which the medicine is marketed and of any other information which might influence the evaluation of the benefits and risks of the medicine concerned.

5.2 FULL REVIEW

A full review involves a thorough review of all aspects of the dossier, particularly the quality, safety and efficacy sections of the data submitted under CTD modules 1, 2, 3, 4

and 5 or the biologicals guidelines. All New Chemical Entity (NCE), biological medicine applications, generic applications with clinical data, major variations and extension applications (EAs) that lack adequate reliance documentation or prior approval from a RRA will be considered for a full review. A full review is indicated specifically for the following types of applications:

5.2.1 Medicines with single APIs

i. For a medicine with single APIs NCE (new chemical entity) not registered by specified RRA.

ii. For a medicine with single APIs not registered with a RRA, and where quality and clinical data generated with the generic has been supplied in support of the application.

iii. Biological medicine not registered with a RRA.

5.2.2 Fixed Dose Combinations of Medicines

For a fixed dose combination of two or more chemical entities, where the combination is not registered with MCAZ or with a RRA.

5.2.3 Major variations

For major variations where the amendment applied for has not been approved by a RRA.

5.2.4 Line Extensions

For all Line Extensions which have not yet been approved by MCAZ or by a RRA for a given molecule.

5.3 ABRIDGED REVIEW

The abridged review is initiated to limit the evaluation time of medicines that are registered with RRAs. It is primarily based on the overviews of quality, safety and efficacy data in CTD and or biologicals guidelines.

All supporting documents as stipulated in Section 5.4.2 of this guideline should be included in the submission in order to qualify for an abridged review. The abridged review process does not involve an abbreviated application–the full CTD module structure and or the requirements specified in the biologicals guidelines should be submitted by the applicant. Assessors may still wish to review quality, safety and efficacy data in modules 3, 4 and 5 as required.

Applicants need to draft and sign a letter of access, allowing MCAZ to request un-redacted reports from the associated RRA(s). Only one letter should be signed covering both quality and clinical access to the un-redacted reports. The letter of access must also be signed by the Marketing Authorization Holder (MAH) in the associated RRA country or by the principal from whom the dossier is purchased. This is a minimum requirement in order for an application to be considered for an abridged review (see section 5 and 6 of this guideline). However, there is one exception to this requirement: the letter of access does NOT need to be provided if the applicant supplies MCAZ with the un-redacted reports directly. MCAZ prefers receiving un-redacted reports directly from the applicant, and has introduced the letter of access for instances where this is not possible.

All NCE and biological applications, generic applications, major variations and line extensions that have prior approval from a RRA will be considered for an abridged review. In addition, all applications for biosimilar medicines will be considered for an abridged review. An abridged review is indicated specifically for the following types of applications:

5.3.1 Medicines with single APIs

i. For registration of a NCE already approved by a RRA
ii. For registration of a NCE based on well-established use (relying on literature), where the medicine has already been registered on the same basis by a RRA.
iii. For medicines with single APIs / generic registered with a RRA.
iv. Biological medicine registered with a RRA.

5.3.2 Fixed Dose Combinations of medicines

For fixed dose combination of two or more chemical entities, where the combination is not registered with MCAZ, but registered with a RRA.

5.3.3 Major variations

For major variations where the amendment applied for has already been approved by a RRA (e.g. additional/amended therapeutic indications, posology and method of administration).

5.3.4 Line Extensions

For all line extensions which have not yet been approved by MCAZ for a given molecule, but have been approved by a RRA.

5.4 New-registration document/data requirements for the various evaluation pathways.

5.4.1 Full Review Requirements

i. Applicant cover letter
ii. Proposed Package Inserts and Product Labels
iii. Administrative and Clinical technical screening checklists
iv. Registration status and dates of approval with other regulatory authorities [Applicants are requested to highlight MCAZ's RRAs on this list]
v. Risk Management Plan (RMP).
vi. Latest Periodic Safety Update Report (PSUR) / Periodic Benefit-Risk Evaluation Report (PBRER) if already registered with an RRA, if applicable - Preclinical data (proof of concept, in vitro/in vivo data, animal data).
vii. Full dossier in line with the CTD Guidelines on submission of documentation for registration of medicines in Zimbabwe or Guidelines on submission of documentation for registration of biologicals in Zimbabwe.
viii. Product sample.

5.4.2 Abridged Review Requirements

Some requirements may not be applicable to a certain application type for abridged review

i. Full review requirements

ii. Un-redacted rapporteur assessment reports from RRAs, if available. These should also include reports of post approval changes made after registration of a medicine.
iii. Letter of access granting MCAZ permission to receive un-redacted reports from RRAs (attached to cover letter) [Not required in instances where the applicant supplies the un-redacted reports of RRAs to MCAZ directly]
iv. The relevant reference PI approved by a RRA
v. Declaration that the information in the application is materially the same as the information submitted to the regulatory authority (name the RRA) which approved the medicine (include approval date)
vi. Correspondence between the applicant and other reference RRAs, concerning queries relating to safety, efficacy, risk/benefit and Risk Management Plan (RMP) issues (if not included in the un-redacted assessment report). Detailed explanation/reasons if registration/approval was refused by a Regulator with which MCAZ aligns itself.

5.4.3 Verified Review Requirements

Some requirements may not be applicable to a certain application type for verified review

i. Full review requirements.
ii. The relevant, primary reference innovator PI approved by MCAZ
iii. The relevant secondary reference PI approved by a RRA, if applicable in instances where the local innovator PI is materially outdated.

6.0 KEY RELEVANT DOCUMENTS

6.1 MCAZ Reliance Policy Rev 0_July 2021

6.2 Good reliance practices in the regulation of medical products: high level principles and considerations. WHO TRS 1033 Annex 10

7.0 HISTORY

DOCUMENT HISTORY		
Revision Number	Date Approved	Reviewed to Incorporate WHO GBT Findings
0	December 2021	**Abbreviations** **Changed from** RRA Recognised Regulatory Authority **Changed to** RRA Reference Regulatory Authority (and all other instances) **Section 4.8**

		Changed from **4.8 Specified RRA:** means those RRA mentioned in the WHO List of Stringent Regulatory Authorities (SRAs) **Changed to** **4.8 Reference Regulatory Authority:** means a national or regional authority or an institution such as World Health Organization prequalification (WHO PQ) whose regulatory decisions and/or regulatory work products are relied upon by another regulatory authority to inform its own regulatory decisions