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South African
Health Products
Regulatory Authority

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5.08 RELIANCE GUIDELINE

This guideline is intended to provide recommendations to applicants wishing to submit new registration applications, as well as variations for reliance review-based evaluation. It represents the Authority's current thinking on the safety, efficacy and quality of medicines. It is not intended as an exclusive approach. SAHPRA reserves the right to request any additional information to establish the safety, efficacy and quality of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The Authority is committed to ensure that all registered medicines will be of the required safety, efficacy and quality. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

UPDATE HISTORY

Clinical and Quality & Bioequivalence First publication released for implementation: Version 1.0	July 2019
Date of implementation of this guideline (consolidation of already published information pertaining to SAHPRA Reliance approaches): Version 2.0	October 2021
Inclusion of references to forms and removal of reference to list of GMP Recognised Regulators, as this information is already included in 4.01 SA Guide to Good Manufacturing Practice: Version 3.0	March 2022

LIST OF ABBREVIATIONS AND TERMINOLOGY

The table below summarises the key abbreviations and terminology used in this document, including the reconciliation of related terminology used by SAHPRA and EMA.

Abbreviation / terminology	Explanation
API	Active Pharmaceutical Ingredient
CHMP	Committee for Medicinal Products for Human Use
CPQ	Confirmation of WHO API Prequalification
CTD	Common Technical Document
EA	Extension Application
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GRP	Good Regulatory Practice
ME&R	Medicines Evaluation and Research
MAH	Market Authorisation Holder: Equivalent to HCR: Holder of the Certificate of Registration
MHLW	Ministry of Health, Labour and Welfare (Japan)
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
NCE	New Chemical Entity
Package Leaflet	Equivalent to PIL: Patient Information Leaflet
P&A	Pharmaceutical and Analytical
PBRER	Periodic Benefit-Risk Evaluation Report
PIC/S	Pharmaceutical Inspection Cooperation Scheme
PQ	Pre-qualification
PSUR	Periodic Safety Update Report
SAHPRA	South African Health Products Regulatory Authority
SCoRE	Summary of Critical Regulatory Elements
SmPC	Summary of Product Characteristics: Equivalent to PI: Professional Information
RRA	Recognised Regulatory Authority – a term used to refer to the list of regulatory authorities with which SAHPRA aligns itself
TGA	Therapeutic Goods Administration (Australia)

US FDA	United States of America Food and Drug Administration
WHO	World Health Organisation

Table of Contents

1. INTRODUCTION TO RELIANCE-BASED EVALUATION

1.1 Purpose

This guideline is intended to provide information and guidance to applicants/HCRs on the prescribed requirements and process to be followed, in cases where a new registration or variation application is submitted to SAHPRA with the applicant/HCR requesting a reliance-based evaluation.

1.2 Legislative provisions

The Medicines and Related Substances Act (101/1965), as amended, details under section 2B(2)(a)(2)(b) that:

(2)(a) The Authority may -
liaise with any other regulatory authority or institution and may, without limiting the generality of this power, require the necessary information from, exchange information with and receive information from any such authority or institution in respect of –

(i) matters of common interest; or
(ii) a specification investigation; and

(2)(b) enter into agreements to co-operate with any regulatory authority in order to achieve the objects of this Act.

Regulation 16 to this Act, furthermore, states that:

(8) In the case where a medicine in respect of which an application for registration is made, is or was registered with any regulatory body outside the Republic, the following information in respect of such medicines shall accompany the application:
(a) a copy of the certificate of registration;
(b) professional information relating to the medicine;
(c) conditions of such registration; and
(d) any other information as may be required by the Authority.

1.3 RELIANCE-BASED EVALUATION PATHWAYS

The World Health Organisation defines reliance as “[t]he 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.” Wherever possible, SAHPRA will leverage these pathways, relying on the evaluation efforts of Recognised Regulatory Authorities (RRAs) in order to reduce evaluation times.

Reliance-based evaluation pathways for medicines applications for new registrations and variations in South Africa will follow one of three evaluation / review pathways:

a) Abridged review

b) Verified review

c) Recognition

Note that pathways (a), (b) and (c) replace the prior Abbreviated Medicines Review Process (AMRP). The application of and use-cases for reliance-based evaluation pathways differ between the Clinical and PEM units (see Section 2.2 below).

2. GENERAL DESCRIPTIONS OF THE RELIANCE-BASED EVALUATION PATHWAYS

a) Abridged review: A streamlined review based primarily on unredacted assessment reports from RRAs, replacing the need to evaluate all of the data (and summaries thereof) submitted in support of an application.

b) Verified review: A streamlined review based primarily on verifying, instead of evaluating, information submitted in the application against information which has already been approved by SAHPRA or an RRA. Note that unredacted reports are required for PEM verified reviews as a fall-back option for evaluators

c) Recognition: A streamlined registration / approval process based on directly recognising the outcome of a review from an RRA with which SAHPRA shares a recognition agreement.

Note: SAHPRA is currently in the process of negotiating recognition agreements with RRAs. Once such an agreement is in place, SAHPRA will publish a framework for the practical implementation thereof. The guiding principle is that applications approved by RRAs with which SAHPRA shares a recognition agreement may not need to be evaluated separately by SAHPRA. Please note that this is not to be confused with collaborative / work-sharing procedures, e.g. Zazibona.

The abridged and verified review processes do NOT involve an abbreviated application – all data and information required for a full review should be submitted, i.e. the full CTD module structure, as well as the SCoRE document. Evaluators may still need to review data in the dossier as required (even when presented with unredacted reports).

Any and all decisions regarding approval and final registration will be made by SAHPRA, in consideration of multiple factors including an RRA registration.

2.1 SAHPRA'S RECOGNISED REGULATORY AUTHORITIES

To qualify for a reliance evaluation pathway, an application must have been approved by one or more of the RRAs with which SAHPRA aligns itself.

SAHPRA's current RRAs include:

- European Medicines Agency Centralised Procedure (EMA CP)

- European Medicines Agency Decentralised Procedure (EMA DCP) (no restrictions on which member state acts as the reference member state)
- Health Canada
- Medicines and Health Products Regulatory Agency (MHRA), UK
- Ministry of Health, Labour and Welfare (MHLW), Japan
- Swiss Agency for Therapeutic Products (Swissmedic)
- Therapeutic Goods Administration (TGA), Australia
- US Food and Drug Administration (US FDA)

Two additional procedures can be used for reliance / collaborative review, which are not strictly regulatory authorities:

- World Health Organisation Prequalification (WHO PQ)
- Zazibona collaborative procedure

2.2 INDEPENDENT APPLICATION OF RELIANCE FOR CLINICAL AND PEM

A given application often differs in complexity for Clinical versus PEM evaluation. For example, a typical application for a generic / multisource medicine requires a relatively straightforward verification of PIs for Clinical, yet PEM faces the added complexity of bioequivalence. As a result, SAHPRA's reliance pathways are applied independently for PEM and Clinical. This has the following two key implications:

- Evaluation pathways may differ for PEM and Clinical evaluation (e.g., Clinical may follow a verification procedure, while PEM follows a full review, based on the nature of the application and the quality of reliance documents submitted)
- The RRAs referenced in an application may differ for PEM and Clinical evaluation (e.g., Clinical may refer to the SAHPRA-approved local innovator PI and latest EMA SmPC as part of a verified review, while the PEM evaluation makes reference to information approved by the TGA).

This approach widens the use of reliance, by not limiting an application to the same pathway / reference RRA for PEM and Clinical evaluation.

2.3 TECHNICAL SCREENING OF APPLICATIONS

Applicants are to provide SAHPRA with the intended evaluation pathways for PEM and Clinical evaluation, along with a brief motivation. The intended evaluation pathways should be indicated on the new registration / variation validation template in the relevant sections. Providing the intended pathways prevents unnecessary screening for reliance documentation in instances where a full review is intended by the applicant.

Decisions related to an application's final evaluation pathway and the extent of reliance on a RRA's evaluation are fully at SAHPRA's discretion and will depend on the availability and quality of reliance documentation submitted. SAHPRA 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.

2.4 UNREDACTED ASSESSMENT REPORTS AND THE LETTER OF ACCESS

Where indicated as a requirement for an abridged or verified review, applicants are to provide SAHPRA with full, unredacted assessment reports from an RRA (submitted in Module 1.10).

The following requirements apply:

- Unredacted assessment / evaluation reports should at least include safety, efficacy and quality report(s) prepared by the RRA upon which the registration / approval decision was based.

- Where unredacted assessment / evaluation reports from the RRA are in a language which is not English, translated versions need to be provided.

- In instances where applicants do not have access to relevant unredacted assessment reports, SAHPRA requires a signed Letter of Access, appended to the Letter of Application in Module 1 (see Appendix 1 for template), included in the application. This allows SAHPRA to request unredacted reports from the associated RRA(s). However, SAHPRA does not guarantee that these reports will be obtained. For a given RRA, only one letter should be signed covering both ME&R and Clinical access to the unredacted reports. The Letter of Access must also be signed by the MAH in the associated RRA country or by the principal from whom the dossier is purchased. Note that SAHPRA prefers receiving unredacted reports directly from the applicant and has introduced the Letter of Access only for instances where this is not possible. If the reports are not obtained, the application in question will most likely default to a full review, extending evaluation time.

3. PRINCIPLES OF RELIANCE-BASED EVALUATION - CLINICAL

For PI/PIL content, SAHPRA will be using reliance wherever applicable. As per the documentation requirements in section 4, this typically involves the submission of the latest approved (and attainable) PI/PIL from a regulatory authority with which SAHPRA aligns itself (Recognised Regulatory Authority – RRA). SAHPRA considers PI/PILs previously approved by the EMA (either Centralised Procedure or Decentralised Procedure) as a default reference for reliance pathways. Alternatively, applicants can provide an approved PI/PIL from any other RRA.

Note that an application for an API that has not yet been registered by SAHPRA will be considered as a New Chemical Entity (NCE) in South Africa, regardless of whether the molecule has already been registered by other regulatory authorities.

3.1 ABRIDGED REVIEW

The abridged review is based primarily on the overviews of pre-clinical and clinical data in CTD Modules 2.4 and 2.5. All supporting documents as stipulated in Section 4 of this guideline should be included in the submission in order to qualify for an abridged review.

All NCE and biological applications, generic applications with clinical data, Type II variations and EAs that have prior approval from an 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:

3.1.1 Monocomponent medicines

- For registration of an NCE already approved by an RRA
- For registration of an NCE based on well-established use (relying on literature), where the medicine has already been registered on the same basis by an RRA
- For a monocomponent multisource medicine / generic registered by an RRA, and where clinical data generated with the generic has been supplied in support of the application
- Biological medicine registered by an RRA
- Biosimilar medicine where the reference biological medicine has already been registered by SAHPRA

3.1.2 Multicomponent medicines

- For a multicomponent fixed dose combination of two or more chemical entities, where the combination is not registered by SAHPRA, but registered by a RRA

3.1.3 Type II variations

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

3.1.4 EAs

For all EAs which have not yet been approved by SAHPRA for a given molecule, but have been approved by an RRA

3.2 VERIFIED REVIEW

The verified review is initiated to limit the evaluation time of generic applications for APIs already registered by SAHPRA. The verified review is effectively a comparison of an applicant's proposed PI against an up-to date reference PI (from a Clinical safety perspective). The primary reference is the latest approved PI of the associated local innovator product. The latest-approved foreign innovator PI may be supplied as an additional/alternative reference only where the local innovator is materially outdated or no longer marketed (see 2.16 Guideline on Professional Information for Human Use for which sections require complete localisation to the SA innovator product).

All Type IB variations, and generic applications (without clinical data) for APIs already registered by SAHPRA will be considered for a verified review. In addition, EAs which have already been approved by SAHPRA will be considered for a verified review.

A verified review is indicated specifically for the following types of applications:

3.2.1 Monocomponent medicines

- For duplicates/clones of medicines registered by SAHPRA
- For a multisource medicine/generic with identical therapeutic indications, formulation/dosage form and strength for APIs previously approved by SAHPRA

3.2.2 Multicomponent medicines

- For a multicomponent fixed dose combination of two or more chemical entities, where the combination is already registered by SAHPRA

3.2.3 Type IB variations

- For all Type IB variations reviewed by SAHPRA

3.2.4 EAs

- For all EAs which have already been approved by SAHPRA for a given molecule
- For all EAs related to new pharmaceutical forms which follow the same route of administration as that which has already been approved by SAHPRA (e.g., EA for a capsule, where SAHPRA has already approved use of a tablet)[1]

[1]Regardless of whether SAHPRA or a RRA has previously approved the EA for a given molecule (i.e. the EA for a capsule may not have been approved by SAHPRA or a RRA, but the application qualifies for verification as SAHPRA has previously approved the same [oral] route of administration).

4. DOCUMENT/DATA REQUIREMENTS FOR NEW REGISTRATION - CLINICAL

4.1 ABRIDGED REVIEW REQUIREMENTS

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

4.1.1 Full review requirements:

i. Applicant cover letter (M1.0)
ii. Proposed PI and PIL (M1.3)
iii. Administrative and Clinical technical screening checklists (M1.8)
iv. Completed SCoRE document (M3.2.R.8 – MS Word version should also be included in the 'working documents' folder)
v. Registration status and dates of approval with other regulatory authorities (M1.10) [Applicants are requested to highlight SAHPRA's RRAs on this list] vi. Risk Management Plan (RMP) (M1.13)
vii. Latest Periodic Safety Update Report (PSUR) / Periodic Benefit-Risk Evaluation Report (PBRER) if already registered by an RRA, if applicable – (M5)

Preclinical data (proof of concept, in vitro/in vivo data, animal data)

viii. Overview of preclinical data (M2.4)
ix. Synopsis of preclinical findings of relevance to humans (M2.6)
x. Preclinical data expert report from the applicant (M2.4)
xi. Full preclinical data (M4)

Clinical data

xii. Overview of clinical data (incl. safety, efficacy, pharmacology and benefit/risk analysis) (M2.5)
xiii. Clinical expert reports on safety and efficacy from the applicant (M2.5)
xiv. Synopsis of each clinical study included in the application (M2.7)
xv. Full clinical study data with formulation as applied for (FAAF) (M5)
xvi. Studies demonstrating pharmacology including mechanism of action and pharmaco- toxicology (M5)
xvii. Studies demonstrating pharmacodynamic properties (M5)
xviii. Studies demonstrating pharmacokinetic properties, including PK/PD relationship, and where relevant, pharmacokinetic properties in special populations (e.g. hepatic, renal, gender, race, elderly, children, other age groups) and pharmacodynamic/ pharmacokinetic interactions with other medicines relevant to the indication and target population (M5)

4.1.2 Unredacted rapporteur assessment reports from RRAs, if available (M1.10)

4.1.3 Letter of access granting SAHPRA permission to receive unredacted reports from RRAs (attached to Letter of Application – M1.0) [Not required in instances where the applicant supplies the unredacted reports of RRAs to SAHPRA directly]

4.1.4 The relevant reference PI approved by an RRA (M1.10.3)

4.1.5 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) (M1.8)

4.1.6 Correspondence between the Applicant and other reference RRAs, concerning queries relating to safety, efficacy, risk/benefit and RMP issues (if not included in the unredacted assessment report). Detailed explanation/reasons if registration/approval was refused by a Regulator with which SAHPRA aligns itself (M1.10)

4.2 VERIFIED REVIEW REQUIREMENTS

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

4.2.1 Full review requirements (i – v) (refer 4.1.1 above)

4.2.2 Full review requirement (vi) if/when applicable for specified molecules and indications (refer 4.1.1 above)

4.2.3 The relevant primary reference innovator PI approved by SAHPRA (M1.3)

4.2.4 The relevant secondary reference PI approved by an RRA, if applicable in instances where the local innovator PI is materially outdated (M1.3)

5. PRINCIPLES OF RELIANCE-BASED EVALUATION - QUALITY & BIOEQUIVALENCE

Reliance-based evaluation will be based on the following principles:

- Reliance is applicable for both new registration and variation applications (Type IB and Type II).

- The application submitted for registration by SAHPRA should be the same as the most updated product on record at the RRA, i.e. all **approved** variations for the RRA's registered product should be incorporated in the application submitted for registration by SAHPRA. Pending variations with the RRA should **not** be included in the application submitted to SAHPRA in order for the application to qualify for reliance.

5.1 ABRIDGED REVIEW REQUIREMENTS

An abridged review is a reliance-based review comprising:

- Validation by SAHPRA to ensure that the product application submitted for registration by SAHPRA is the same as the product registered by the specified RRA

- Evaluation of Module 1: Regional administrative information (as required)

- Evaluation of specific aspects of the dossier, depending on the type of application submitted

An abridged review is applicable to the following types of applications:

i. For a new registration application for a generic medicine already registered by an RRA ii.

For a new registration for a WHO PQ product:

- Applicants are required to follow SAHPRA's process for the WHO Collaborative Registration Procedure

iii. Backlog-specific: For a new registration application for a generic or NCE medicine that has received prior P&A Committee approval, where any information relevant to P&A Committee approval has been updated since approval

iv. For a Type II variation where the variation applied for has already been approved by an RRA

5.2 VERIFIED REVIEW REQUIREMENTS

A verified review is a reliance-based review comprising:

- Validation by SAHPRA to ensure that the product application submitted for registration by SAHPRA is the same as the product registered by the specified RRA
- Evaluation of Module 1: Regional administrative information (as required) A verified

review is applicable to the following types of applications:

i. For a new registration application for an NCE medicine already registered by an RRA
ii. Backlog-specific: For a new registration application for a generic or NCE medicine that has received prior P&A Committee approval, where Module 1, 2 or 3 has not been updated since approval (i.e. the information relevant to the prior P&A Committee approval has not changed)
iii. For a Type IB variation where the variation applied for has already been approved by an RRA

6. DOCUMENT/DATA REQUIREMENTS FOR NEW REGISTRATION – QUALITY & BIO-EQUIVALENCE

To qualify for a reliance-based review, an applicant needs to submit additional documentation to the documentation required for a full review.

Table 1: Documentation required for reliance-based evaluation

Document required	Applicable types of applications
• Completed abridged review template	5.1 i, ii
• Completed verified review template	5.2 i
• Full, unredacted assessment / evaluation reports from the RRA where the product is registered, or • If the applicant cannot obtain full, unredacted assessment / evaluation reports from the RRA where the product is registered, the Letter of Access (Appendix 1) must be completed, and • Details of the outcomes of the application in all jurisdictions where it has been submitted, and • Foreign registration certificate(s), and • SmPC, a copy of the patient information leaflet (PIL) and label of the product that has been registered by the RRA, and • <u>If available</u>: initial scientific assessments, regulatory correspondence with the sponsor / applicant, follow-up assessments, and any other documentation from the RRA related to the final registration decision, and • <u>If available and where applicable</u>: risk management plans and on-site inspection reports (or equivalent), for example GCP / GRP. Does not include the data package filed with the RRA	5.1 i, iv 5.2 i, iii
• Letter of approval from the RRA	5.1 iv 5.2 iii
• Declaration: Sameness (Appendix 2)	5.1 i, ii 5.2 i
• Declaration: Previous P&A Committee approval (Appendix 3)	5.1 iii 5.2 ii

Additional documentation requirements for the various types of applications may be stipulated in other sections of this guideline or other guidelines. Additional documentation requirements for WHO PQ products are detailed in SAHPRA's process for the WHO Collaborative Registration Procedure.

Additional documentation requirements for reliance-based review of variations applications are detailed in SAHPRA's Variations Addendum for Orthodox Medicines.

7. GOOD MANUFACTURING PRACTICE (GMP) INSPECTIONS

Good Manufacturing Practice (GMP) describes a set of principles and procedures that, when followed, ensure that medicines and related substances are of high quality, safety and efficacy. SAHPRA is a participating authority of the Pharmaceutical Inspection Cooperation Scheme (jointly known as PIC/S). PIC/S aims to develop international standards between countries and pharmaceutical inspection authorities, to provide harmonised and constructive co-operation in the field of GMP. PIC/S affiliation is subject to initial and periodic assessment of the participating authority to ensure that it has equivalent legislation, regulatory and enforcement procedures and inspection capacity. Besides employing a reliance approach to PIC/S affiliated authorities, SAHPRA Inspectorate also applies reliance to WHO and ZAZIBONA inspections.

7.1 PRINCIPLES OF GOOD MANUFACTURING PRACTICE RELIANCE

GMP agreements with competent international regulatory authorities support information sharing and other desirable objectives for international regulatory collaboration. These agreements do not permit automatic acceptance of the decisions of the other party, but may be used to enhance regulatory oversight and significantly reduce regulatory burden without diminution of compliance.

Manufacturers of medicines supplied in the South African market must demonstrate compliance with the relevant code of GMP. This is usually, but not always, done through an on-site inspection and with acceptable documentary GMP evidence.

GMP approval guidance for sites involved in the manufacture of products can be found below. Please note that adherence to these requirements does not guarantee a site will be deemed GMP compliant by SAHPRA.

SAHPRA reserves the right to request additional documentation, schedule an inspection or reject any sites regardless of adherence to the below requirements • The site has been approved by a recognised regulator AND

- The site was approved by the recognised regulator within the previous 3 years AND
- The dosage form of the product within the application is within the same dosage form grouping as the dosage form approved by the recognised regulator AND
- The product type applied for is the same as the product type approved by the recognised regulator AND
- The activities applied for by the applicant are the same activities that have been approved by the recognised regulator

See the latest GMP guideline for the recognized regulators, dosages, product types and activity groupings

8. CLINICAL TRIAL APLLICATION

Clinical Trial data is crucial in supporting the safety and efficacy of the product intended for registration. During the review process the Authority consider information regarding the review status of the clinical trial with other Regulatory Authorities, as requested in the application form. As most of the clinical trials

are multi-center trials, the Authority will further take into consideration proper monitoring of trial and local conditions or prevalence of disease within the context of SA.

9 PHARMARCOVIGILANCE

The vigilance is important for ensuring that health products available on the South African markets are safe, effective and of acceptable quality and performance throughout the life cycle of the product. In order to ensure that the Authority fulfills its mandate of monitoring the benefit-risk profile of the health products, the Authority will take into account the safety information communicated or actions taken by other Recognised Regulatory Authorities. The Authority takes into account and gives significant weight to assessments performed by Recognised Regulatory Authorities in reaching its own regulatory decision. Furthermore, SAHPRA is an independent Authority and therefore is responsible and accountable for the decisions taken, even when it relies on the decisions and information from other Regulatory Authorities.

REFERENCES

LETTER OF ACCESS: APPENDIX TO 2.01 GENERAL INFORMATION GUIDELINE

SAMENESS DECLARATION FOR RELIANCE-BASED EVALUATION MODELS: APPENDIX 2 TO 2.02 QUALITY AND BIOEQUIVALENCE GUIDELINE

DECLARATION FOR PREVIOUS P&A COMMITTEE APPROVAL: APPENDIX 3 TO 2.02 QUALITY AND BIOEQUIVALENCE GUIDELINE

Amendment History

Version	Date	Reason for amendment
1.0	July 2019	New
2.0	October 2021	Consolidation of already published information pertaining to SAHPRA Reliance Approaches
3.0	March 2022	Inclusion of references to forms and removal of reference to list of GMP Recognised Regulators, as this information is already included in 4.01 SA Guide to Good Manufacturing Practice.