South African Health Products
Regulatory Authority
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2 November 2023

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.

DOCUMENT HISTORY

Final Version	Reason for Amendment	Effective Date
1	First publication released for implementation	31 July 2019
2	Consolidation of already published information pertaining to SAHPRA Reliance approaches	31 October 2021
3	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	31 March 2022
4	- Transfer of content to the latest SAHPRA Guideline template - Old document number 5.08 Reliance Guideline changed to SAHPGL-BAU-01 in alignment with the latest SAHPRA document coding structure - Updated to reflect new requirements for reliance submissions	02 November 2023

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GLOSSARY

Abbreviation/ Term	Meaning
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
EMA CP	EMA Centralized Procedure
EMA DP	EMA Decentralized Procedure
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRP	Good Regulatory Practice
MAH	Market Authorization Holder: Equivalent to HCR: Holder of the Certificate of Registration
HCR	Holder of 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
PMDA	Pharmaceutical and Medical Devices Agency
PI	Professional information
PIL	Patient Information Leaflet
P&A	Pharmaceutical and Analytical
PBRER	Periodic Benefit-Risk Evaluation Report
PIC/S	Pharmaceutical Inspection Cooperation Scheme
PQ	Pre-qualification
PAR	Public assessment reports
PSUR	Periodic Safety Update Report
Q and BE	Quality and Bioequivalence
SAHPRA	South African Health Products Regulatory Authority
SCoRE	Summary of Critical Regulatory Elements
SmPC	Summary of Product Characteristics: Equivalent to PI
SRA	Stringent regulatory authority
SwissMedic	Swiss Agency for Therapeutic Products
Sameness	Sameness refers to two products having identical essential characteristics. It is an important aspect of reliance that ensures that the same product that was assessed by the reference regulatory authority is the same one being applied for to the relying authority. The essential characteristics that are required to be the same or sufficiently similar include, but are not limited to: manufacturing sites and/or suppliers of the API, FPP and excipients (/IPIs); manufacturing processes and control of both the API, FPP and excipients; pharmaceutical form, strength, use, qualitative and quantitative composition. Additionally, the results of supporting studies of safety, efficacy and quality, indications and conditions of use should be the same.

Recognition	A streamlined registration / approval process based on directly recognizing the outcome of a review from an RRA with which SAHPRA shares a recognition agreement.
RMA	Risk Management Plan
RRA	Recognized Regulatory Authority – a term used to refer to the list of regulatory authorities with which SAHPRA aligns itself
TGA	Therapeutic Goods Administration (Australia)
UK	United Kingdom
US FDA	United States of America Food and Drug Administration
WHO	World Health Organization
WHO-(WLA)	WHO listed Authorities (WLA)
Zazibona	Zazibona is a collaborative medicines registration initiative in Southern Africa focusing on dossier assessments and good manufacturing practice (cGMP) inspections.

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INTRODUCTION

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 LEGAL PROVISION

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 Quality and bioequivalence units (see Section 2.2 below). For clones and replicas refer to communication to industry.

2. GENERAL DESCRIPTIONS OF THE RELIANCE-BASED EVALUATION PATHWAYS

a) Abridged review: A streamlined review based primarily on full 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 full assessment reports are required for Quality and bioequivalence 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.

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, /Pharmaceutical and Medical Devices Agency (PMDA (Japan)
- Swiss Agency for Therapeutic Products (SwissMedic)
- Therapeutic Goods Administration (TGA (Australia)
- US Food and Drug Administration (US FDA)
- WHO listed Authorities (WLA)

- RRA's with which SAHPRA has MOU's with

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

- World Health Organisation collaborative registration process:
  - Prequalification
  - SRA approved
- Zazibona collaborative procedure
- European Medicines Agency
- Mutual Recognition procedure and National Procedures within the EMA
- SwissMedic Marketing Authorisation for Global Health Products (MAGHP) procedure
- PIC-s Member States

SAHPRA's recognized regulatory authorities for registration of veterinary medicines include:

- EMA
- US FDA
- JMAFF
- APVMA
- UKVMD
- HC
- New Zealand
- Swiss Medic

2.2 INDEPENDENT APPLICATION OF RELIANCE FOR QUALITY & BIOEQUIVALENCE (QUALITY AND BIOEQUIVALENCE) AND CLINICAL

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

- Evaluation pathways may differ for Quality and bioequivalence and Clinical evaluation (e.g., Clinical may follow a verification procedure, while Quality and bioequivalence 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 Quality and bioequivalence 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 Quality and bioequivalence 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 Quality and bioequivalence, and Clinical evaluation.

2.3 TECHNICAL SCREENING OF APPLICATIONS

Applicants are to provide SAHPRA with the intended evaluation pathways for Quality and bioequivalence 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 ASSESSMENT REPORTS

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

The following requirements apply:

- Full 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 (refer to table 2 for list of documents required for Q-BE).

- Where full assessment / evaluation reports from the RRA are in languages other than English, translated versions need to be provided in line with regulation 16 (4).

Note: SAHPRA requires for assessment reports to be sent directly from the applicant. If the reports are not obtained, the application in question will most likely default to a full review, extending evaluation time.

For applications where USFDA is the RRA, a letter of confirmation from the USFDA marketing authorisation holder (proprietary owner) confirming that they are the legal holder of the proprietary information and that they wish to share information of this product with SAHPRA should be provided.

For applications with RRAs listed in section 2.1, with the exception of WHO collaborative procedures, EMA CP and US FDA based applications, SAHPRA will not source the RRA assessment reports, and the letter of access will not be applicable. Applicants are required to source the full reports from the marketing authorisation holder. Where the MAH wishes to submit the reports directly to SAHPRA, the reports can be sent to the following dedicated email address: reliancereports@sahpra.org.za.

Note: SAHPRA retains the right to request additional information from applicants with regards to the application. If no full assessment reports are received from the RRA within 3 months of request, the application will be reviewed using full review.

All marketing authorization holders that wish to submit assessment reports directly to SAHPRA should use the dedicated email address: reliancereports@sahpra.org.za. The application number must be specified when sending the reports.

QUALITY VARIATIONS

For products registered through reliance only:

Type IA

- For Type IA & IAin variations submitted to and implementable in the RRA, the applicant must provide proof of submission to RRA and if available the acknowledgement or approval communication. The list of variations must be clearly reflected on the covering letter submitted to the RRA and these must concur with covering letter submitted to SAHPRA. Any rejection/query letter with regard to these Type IA variations must be provided. These Type IA variations submitted to the RRA must be classified as Type IA and may be grouped as a single variation to SAHPRA.

Type IB

- Type IB variations approved by the RRA may be classified as a Type IA variation provided the applicant is able to provide approval/acknowledgement communication and assessment reports from the RRA at the time of submission to SAHPRA. These variations may be grouped as a single Type IA variation. The list of variations must be clearly reflected on the covering letter submitted to the RRA and these must concur with the covering letter submitted to SAHPRA. Any rejection/query letter with regard to these Type IB variations must be provided.

- If full assessment reports are not available, the change will remain a Type IB variation and must be submitted under applicable code as per EMA variations guideline.

Type II

- Type II variations approved by the RRA may be classified as Type IB variations provided the applicant is able to provide approval/acknowledgement communication and assessment reports from the RRA at the time of submission to SAHPRA. Each change must be classified as a separate Type IB variation.

- If full assessment reports are not available, the change will remain a Type II variation and may only be implemented once approval letter is issued by SAHPRA.

For classification and conditions & required documents refer to variation addendum.

Please note that for changes which affects both Inspectorate and Quality Units, the above classifications are not applicable.

All supporting documents and amended sections of dossier must be submitted to SAHPRA regardless of evaluation pathway.

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 (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 an 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, safety amendments 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 an 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 an 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 QOS & QIS 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 Rapporteur assessment reports from RRAs, if available (M1.10)
4.1.3 The relevant reference PI approved by an RRA (M1.10.3)
4.1.4 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)
4.1.5 Correspondence between the Applicant and other reference RRAs, concerning queries relating to safety, efficacy, risk/benefit and RMP issues (if not included in the 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.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. 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

Document required	Applicable types of applications
• Full, assessment / evaluation reports from the RRA where the product is registered. • 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 • If available: 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 • If available and where applicable: 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	5.1 i, ii 5.2 i

Table 2: Documents that comprise a complete assessment for each RRA.

The table below lists the documents that comprise a complete assessment for each RRA. The full set of documents must be submitted in your reliance report-based application.

RRA	Required documentation
Therapeutic Goods Administration, Australia	• Comprehensive details of all studies submitted and assessed • All assessment report(s) • Questions from the regulator to the Market Authorisation Holder (and answers) • Summaries of meetings with TGA (including presubmission advice, where relevant) • Approval letter • Post marketing reviews Note: All relevant Milestone dates specified in the submission evaluation plan.

European Medicines Agency (EMA)	• Comprehensive details of all studies submitted and assessed • Centralised procedure assessment reports (where applicable): – Day 80 Quality, Non-Clinical, Clinical, and Overview Assessment Reports – Day 120 List of Questions (and answers) – Day 150 Quality, Non-Clinical, Clinical, and Overview Assessment Reports – Day 180 Joint Assessment Report – Day 180 List of Outstanding Issues – Final Assessment Report • Decentralised procedure assessment reports (where applicable): – All assessment reports – Questions from the regulator to the Market Authorisation Holder (and responses) • Summaries of meetings with the EMA and/or assessors (including presubmission advice, where relevant) • Committee for Medicinal Products for Human Use (CHMP) Summary of Opinion • Any other questions from the regulator to the Market Authorisation Holder • Letter of undertaking • European Commission decision • Risk Management Plan review(s) • Post marketing review(s) (e.g. Periodic Safety Update Reports)
Pharmaceutical and Medical Devices Agency (PMDA), Japan	• Comprehensive details of all studies submitted and assessed • Discussion documents, questions from PMDA and answers provided, and Finalised Minutes from Scientific Consultation Meetings (if applicable) • Outcome of Orphan designation, priority or SAKIGAKE determination (if relevant)

	• Copies of questions and answers exchanged between Sponsor and PMDA • Un-redacted English Translated Review Report consisting of: – Review Report 1 – Review Report 2 – Review Result • Report on the Deliberation Results • Approval Letter • Post-marketing review(s) (e.g. Re-examination Review Report, Periodic Safety Reports)
Health Canada	• Comprehensive details of all studies submitted and assessed • Screening: Screening Report • Clinical Review: Pharmaceutical Safety and Efficacy Assessment Report (PSEAR) • Quality: Quality Evaluation Summary (QES) and Manager's Memo • Bioequivalence: Comprehensive Summary – Bioequivalence (CS-BE) and Manager's Memo • Biostatistics: Biostatistics Consult Report (if applicable) • Risk Management Plan: Risk Management Plan Assessment Report (if applicable) • Questions from the regulator to the Market Authorisation Holder (and responses) • Summaries of meetings with Health Canada (including presubmission advice, where relevant) • Final Manager's Memo, and Executive Summary
Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom	• Comprehensive details of all studies submitted and assessed • All assessment reports as part of the iterative process • Questions from the regulator to the Market Authorisation Holder (and responses) • Committee for Medicinal Products for Human Use

	(CHMP) Summary of Opinion • Summaries of other meetings with the MHRA (including presubmission advice, where relevant) • Approval letter • Post marketing review(s) (e.g. Periodic Safety Update Reports)
Swiss Medic, Switzerland	• Comprehensive details of all studies submitted and assessed • All assessment report(s) • Questions from the regulator to the Market Authorisation Holder (and answers) • Summaries of meetings with SwissMedic (including presubmission advice, where relevant) • Approval letter • Post marketing reviews
United States Food and Drug Administration (US FDA)	• Comprehensive details of all studies submitted and assessed • Medical review(s) • Chemistry review(s) • Pharmacology review(s) • Statistical review(s) • Clinical pharmacology biopharmaceutics review(s) • Risk assessment and risk mitigation review(s) • Administrative document(s) and correspondence • Cross discipline team leader review • Office Director memo • Summaries of meetings with the US FDA (including presubmission advice, where relevant) • Summary review • Complete response letter • Approval letter

	• Post marketing reviews

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.

Please note, public assessment reports will not be accepted.

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 recognized regulator AND
- The activities applied for by the applicant are the same activities that have been approved by the recognized regulator.

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

8. CLINICAL TRIAL APPLICATION

Clinical Trial data is crucial in supporting the safety and efficacy of the product intended for registration. During the review process the Authority considers 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-centre trials, the Authority will further take into consideration proper monitoring of trial and local conditions or prevalence of disease within the context of South Africa.

9. PHARMACOVIGILANCE

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. To ensure that the Authority fulfils its mandate of monitoring the benefit-risk profile of the health products, the Authority will consider the safety information communicated or actions taken by other Recognised Regulatory Authorities. The Authority considers and gives significant weight to assessments performed by Recognised Regulatory Authorities in reaching its own regulatory decision. Furthermore, SAHPRA is an independent Authority and is, therefore, responsible and accountable for the decisions taken, even when it relies on the decisions and information from other Regulatory Authorities.

10. REFERENCES

The following related documents are referenced:

SAMENESS DECLARATION FOR RELIANCE-BASED EVALUATION MODELS: APPENDIX 2 TO SAHPGL-PEM-02 QUALITY AND BIOEQUIVALENCE GUIDELINE

11. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision and replaces the 5.08 Reliance Guideline. It will be reviewed on this timeframe or as and when required.