

CLINICAL GUIDELINE

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of Human Medicines containing specified substances. In addition to this guideline, SAHPRA reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. SAHPRA is committed to ensure that all registered medicines will be of the required quality, safety and efficacy.

Guidelines and application forms are available from the office of the Chief Executive Officer and the website.

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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
Amendments	Used interchangeably with the term 'variations'
API	Active Pharmaceutical Ingredient
CHMP	Committee for Medicinal Products for Human Use
EA	Extension Application
EMA	European Medicines Agency
EU	European Union
ICH	The International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
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 (United Kingdom)
NCE	New Chemical Entity
ME&R	Medicines Evaluation and Research
Package Leaflet	Equivalent to PIL: Patient Information Leaflet
PBRER	Periodic Benefit-Risk Evaluation Report
PSUR	Periodic Safety Update Report
RRA	Recognised Regulatory Authorities – a term used to refer to the list of regulatory authorities with which SAHPRA aligns itself
SAHPRA	South African Health Products Regulatory Authority
SmPC: Summary of Product characteristics	Equivalent to PI: Professional Information
The Authority	Relevant regulatory authority, in this case SAHPRA
TGA	Therapeutic Goods Administration (Australia)
US FDA	United States Food and Drug Administration

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1 INTRODUCTION

Guidelines are constantly evolving as a result of scientific developments and harmonisation of the requirements of the major international regulatory authorities. SAHPRA endeavours to keep abreast of such developments and keep its application requirements and evaluation policies in line with best international practice. As an Observer country to The International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), South Africa uses and applies information provided in the ICH and European Union (EU) guidelines for safety, efficacy and quality requirements. Specific guidelines from ICH and EMA will be communicated from time to time, and should be read in conjunction with relevant sections of some of the current as well as revised SAHPRA guidelines where necessary.

This guideline outlines SAHPRA's evaluation pathways for Clinical and the associated documentation/data requirements, and provides guidance on Clinical and Pre-clinical studies. Furthermore, this guideline contains additional information on some of the harmonisation initiatives with the European Medicines Agency (EMA) to aid the transition. A key change from the previous version of this guideline is that SAHPRA will no longer be requiring a Summary Basis for Registration (SBRA) document to aid clinical evaluation. The SBRA has been replaced by the clinical overviews and summaries, as well as the SCoRE document.

The following guidelines should be read together with this guideline where applicable:

- 2.01 General Information Guideline
- 2.08 Variations Addendum for Human and Veterinary Medicines
- 2.16 Guideline on Professional Information for Human Medicines (Categories A and D)
- 2.20 Guideline on Standardised Text for Professional Information
- 2.30 Biosimilar Medicines Guideline
- EMA Guideline on clinical development of fixed combination medicinal products (except for HIV, Malaria and TB medicines where the SAHPRA guideline applies)
- 2.31 SAHPRA Fixed Drug Combination Guidelines for HIV, TB and Malaria
- EU variations classification guidelines

1.1 REVISED PROFESSIONAL INFORMATION (PI) AND PATIENT INFORMATION LEAFLET (PIL) GUIDELINES

The latest PI format is adopted from the EMA SmPC as-is, using both the stipulated EMA numbering and headings (with exception to section 7, labelled 'Holder of Certificate of Registration' in accordance with South African legislation). "Scheduling Status", however, has not been covered in the EMA SmPC. SAHPRA requires applicants to include this item above the "Name of the Medicine" section. The "Scheduling Status" will not have its own number (please refer to the 2.16 Guideline on Professional Information for Human Use).

For example, PI/SmPC format will follow:

SCHEDULING STATUS

1. NAME OF THE MEDICINE
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For “Pharmacological Classifications”, SAHPRA intends to adopt the Anatomical Therapeutic Chemical (ATC) Classification System once Regulation 9 has been amended to accommodate this change. (The ATC classification system divides medicines into different groups according to the organ or system on which they act and according to their chemical, pharmacological and therapeutic properties). Until such time as Regulation 9 is amended, SAHPRA will continue to use the current pharmacological classification system.

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.

2 CLINICAL REVIEW TYPES

A clinical application will follow one of the following review types, namely:

- a) Full Review
- b) Abridged Review
- c) Verified Review
- d) Recognition

Review types (b), (c) and (d) represent reliance pathways, which SAHPRA will be implementing to reduce evaluation times. To qualify for a reliance pathway, an application must have received prior approval from a RRA. Reliance pathways are applied independently for Clinical and ME&R, with differing requirements (e.g., Clinical may follow a verification procedure while ME&R follows a full review based on the quality of documents submitted).

RRAs include: US FDA, EMA (Centralised and Decentralised Procedures only), MHLW (Japan), Health Canada, Swiss Medic, TGA (Australia), and MHRA (UK). Two additional procedures can be used for reliance / collaborative review, which are not strictly regulatory authorities: World Health Organisation Prequalification (WHO PQ) and Zazibona collaborative procedure. In order for an application to be considered for a reliance evaluation, additional documentation must be submitted with the application. The document/data requirements are listed in section 4 of this document.

The final evaluation pathway decision for an application is at the discretion of SAHPRA, 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.

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.

2.1 FULL REVIEW

A full review involves a thorough review of all aspects of the dossier, particularly the pre-clinical and clinical data submitted under CTD modules 4 and 5 (and summarised in module 2).

All NCE and biological medicine applications, generic applications with clinical data, Type II 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:

2.1.1 Monocomponent medicines

- For a monocomponent NCE (new chemical entity) not registered by a RRA
- For a monocomponent multisource medicine/generic/API not registered by a RRA, and where clinical data generated with the generic has been supplied in support of the application
- Biological medicine not registered by a RRA

2.1.2 Multicomponent medicines

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

2.1.3 Type II variations

- For Type II variations where the amendment applied for has not been approved by a RRA

2.1.4 Extension applications

- For all EAs which have not yet been approved by SAHPRA or by a RRA for a given molecule

2.2 ABRIDGED REVIEW

The Abridged Review is initiated to limit the evaluation time of medicines that are registered by RRAs.

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. The abridged review process does not involve an abbreviated **application** – the full CTD module structure should be submitted by the applicant. Evaluators may still wish to review pre-clinical and clinical data in modules 4 and 5 as required.

Applicants need to draft and sign a Letter of Access, allowing SAHPRA to request un-redacted reports from the associated RRA(s). Only one Letter should be signed covering both ME&R and Clinical access to the un-redacted 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. This is a minimum requirement in order for an application to be considered for an abridged review (see point 4.2.3 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 SAHPRA with the un-redacted reports directly. SAHPRA 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 with clinical data, Type II variations and EAs that have prior approval from a RRA will be considered¹ for an abridged review. In addition, all applications for biosimilar medicines will be considered¹ for an abridged review.

An abridged review is indicated specifically for the following types of applications:

2.2.1 Monocomponent medicines

- For registration of a NCE already approved by a RRA
- 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
- For a monocomponent multisource medicine / generic registered by a RRA, and where clinical data generated with the generic has been supplied in support of the application
- Biological medicine registered by a RRA
- Biosimilar medicine where the reference biological medicine has already been registered by SAHPRA

2.2.2 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

2.2.3 Type II variations

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

2.2.4 EAs

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

¹ Provided the correct documentation (as per Section 4 of this guideline) has been submitted

2.3 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:

2.3.1 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

2.3.2 Multicomponent medicines

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

2.3.3 Type IB variations

- For all Type IB variations reviewed by SAHPRA

2.3.4 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)²

2.4 RECOGNITION

SAHPRA is currently in the process of exploring recognition agreements with selected regulatory authorities. 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 regulatory authorities with which SAHPRA shares a recognition agreement may not need to

² 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)

be evaluated separately by SAHPRA.

Please note that this is not to be confused with collaborative / work-sharing procedures (e.g., Zazibona).

3 PRE-CLINICAL AND CLINICAL STUDIES

3.1 PRE-CLINICAL STUDIES (CTD MODULES 2.4, 2.6 & 4)

The details of results from tests shall depend on the state of scientific knowledge at the time when the application is lodged. Any interim and final results of ongoing studies should be submitted as soon as these data become available.

A new route of administration, or an increased daily dose, or different inactive pharmaceutical ingredients, may result in the need for additional pharmaco-toxicological data.

Details (published or unpublished) of the results of any trials or experiments carried out in man or in the animal target species, or carried out in other animals, that establish and confirm the safety of the medicine, with particular reference to the Posology and method of administration for use, should be included.

Pharmacology

The Pharmacology of the medicine should be addressed.

Pharmacodynamic properties:

- a) The primary effects of the medicine, with results in different animal species (ED50 values if possible), should be addressed.
- b) Comparison of the effects of the medicine with that of reference product(s), is valuable information.
- c) Where relevant, the pharmacology of significant metabolites should be investigated.
- d) Other pharmacodynamic effects, especially those that might be of significance for adverse effects of the medicine, should be studied and described.

Interaction studies, where **relevant**, should be included.

Pharmacokinetic properties:

- a) To assist in the interpretation of toxicological studies, it is important to compare the exposure of the animals used in the toxicity testing with that anticipated in patients given the proposed therapeutic dose regimen data, which includes C_{max} (after a single dose and at steady state) and AUC
- b) MODULE 4 should, therefore, include comparative pharmacokinetic data for the parent substance and major/active metabolite(s), where relevant, in human and all species used in the toxicity, carcinogenicity and reproduction studies.
- c) These data should preferably be obtained from the toxicity studies.
- d) Other information (for example, t_{1/2} and clearance) may be of value where

important differences have been shown between animals and man.

Toxicology:

For medicines other than biological medicines the Toxicology of the medicine should be addressed.

- a) A summary, or Expert Report, should be submitted for each animal species studied, with information on the sex of the animals, number of animals, dosage, route of administration, duration of study and toxic manifestations.
- b) Important points to consider that pertain to pre-clinical toxicity, are:
 - Dose-response relationship
 - Time-response relationship
 - Species specificity
 - Consistency of findings across studies with different species
 - Target organ specificity
 - Reversibility/irreversibility of toxic effects.
- c) Medicines that show specific toxicological effects, such as immunotoxicity, teratogenicity, nephrotoxicity hepatotoxicity or neurotoxicity, should be investigated further, taking into account the points under b) above.
- d) New medicines, which belong to classes that are known to produce a particular toxic effect, should be tested appropriately.
- e) The possible mechanism(s) underlying the changes observed in toxicity studies need to be investigated and addressed.
- f) Due to the local climatic conditions, the phototoxic potential of a medicine should be considered.
- g) The points to address in the reproduction studies include: fertility, embryonal toxicity, teratogenicity, peri- and post- natal effects.

3.2 CLINICAL STUDIES (CTD MODULES 2.5, 2.7 & 5)

The following items should be addressed in conducting, and presenting the findings from, clinical studies:

- a) The clinical data should be presented in a manner that allows easy cross-referencing to the index, other studies and the professional information.
- b) Data presented in support of the safety and efficacy of the medicine should be derived from clinical trials conducted in compliance with internationally accepted GCP guidelines. The studies should be properly designed and conducted, and should be of acceptable statistical power. (Refer to the SA clinical trial guidelines, and any other ICH-approved clinical trial guidelines referenced therein). Where relevant, results published in peer reviewed

scientific journals, should be submitted in full.

- c) Clinical trials should be conducted with the formulation as applied for. Where studies have been conducted with different formulations, comparative equivalence studies are required to enable extrapolation to the formulation intended for the market.
- d) Normally individual patient data and case record forms from clinical trials need not be included in an application dossier (except in the case of bioequivalence studies where the individual plasma/serum concentrations concentration/time curves and derived pharmacokinetic data should be supplied). Tabulated individual patient data may be included in the application if the applicant considers it appropriate.
- e) Studies designed to demonstrate the pharmacodynamic properties of a medicine should address the effect of the medicine, duration of effect, dose-response and tolerance. Additional action on e.g. the central nervous system, respiration, circulation, blood chemistry, liver and kidney function should be considered at the proposed therapeutic dose(s).
- f) Pharmacokinetic studies should be conducted with the formulation as applied for. All relevant pharmacokinetic data shall be given, such as amount and rate of absorption after various routes of administration, plasma concentration, half-lives, drug clearance, drug metabolism, handling by transporters, as well as the routes and rates of excretion. Data on major/active metabolite(s) should be included if applicable.
- g) The pharmacokinetic studies should be carried out with both single dose and multiple doses to steady state within the recommended dosage range. Where applicable the plasma concentration(s) producing pharmacological and/or therapeutic effects as well as adverse effects, should be presented. Possible dose and time-dependent pharmacokinetic effects should be addressed. The consequences of genetic polymorphism on transporters and metabolic enzymes should be discussed, if applicable.
- h) The trial design of the relevant clinical studies should be such that the safety and efficacy of the medicine can be established in comparison to either a placebo and/or a medicine registered by a RRA.
- i) The description of the studies should include patient population size and diagnosis, in- and exclusion criteria, test and comparator / reference medicine dosage regimens and duration of therapy, parameters assessed for efficacy and safety, including results of special investigations.
- j) It should be noted that the randomised, double blind, placebo and/or active controlled trial design remains the gold standard for establishing the efficacy and safety of medicines.
- k) Detailed statistical results should be presented. The analysis conducted should be consistent with that pre-specified in the protocol and statistical analysis plan (SAP). The SAP must be finalised before unblinded trial data are available.
- l) The dosage of the active comparator/reference should be in line with that approved for the specific therapeutic indication.

- m) The patient drop-outs should be addressed, including the time of and reason(s) for withdrawal/drop-out.
- n) To enable evaluation of safety of the medicine it should be noted that the long-term safety, particularly for medicines proposed for chronic use, or where repeated treatment courses are to be used, should be addressed.
- o) Whilst the medicine is in the evaluation process Applicants should notify the Authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicine is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicine concerned.

4 DOCUMENT/DATA REQUIREMENTS FOR NEW REGISTRATION

This section outlines the new-registration document/data requirements for the various evaluation pathways. Clinical document/data requirements for *variation applications* can be found in the '2.08 Variations Addendum for Human and Veterinary Medicines.'

4.1 FULL REVIEW REQUIREMENTS

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

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

- 4.1.8 Overview of preclinical data (M2.4)
- 4.1.9 Synopsis of preclinical findings of relevance to humans (M2.6)
- 4.1.10 Preclinical data expert report from the applicant (M2.4)
- 4.1.11 Full preclinical data (M4)

Clinical data

- 4.1.12 Overview of clinical data (incl. safety, efficacy, pharmacology and benefit/risk analysis) (M2.5)
- 4.1.13 Clinical expert reports on safety and efficacy from the applicant (M2.5)

- 4.1.14 Synopsis of each clinical study included in the application (M2.7)
- 4.1.15 Full clinical study data with formulation as applied for (FAAF) (M5)
- 4.1.16 Studies demonstrating pharmacology including mechanism of action and pharmacotoxicology (M5)
- 4.1.17 Studies demonstrating pharmacodynamic properties (M5)
- 4.1.18 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)

4.2 ABRIDGED REVIEW REQUIREMENTS

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

- 4.2.1 Full review requirements 4.1.1 – 4.1.18
- 4.2.2 Un-redacted rapporteur assessment reports from RRAs, if available (M1.10)
- 4.2.3 Letter of access granting SAHPRA permission to receive un-redacted reports from RRAs (attached to cover letter – M1.0) [Not required in instances where the applicant supplies the un-redacted reports of RRAs to SAHPRA directly]
- 4.2.4 The relevant reference PI approved by a RRA (M1.10.3)
- 4.2.5 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)
- 4.2.6 Correspondence between the Applicant and other *reference* RRAs, concerning queries relating to safety, efficacy, risk/benefit and RMP issues (if not included in the un-redacted assessment report). Detailed explanation/reasons if registration/approval was refused by a Regulator with which SAHPRA aligns itself (M1.10)

4.3 VERIFIED REVIEW REQUIREMENTS

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

- 4.3.1 Full review requirements 4.1.1 – 4.1.5
- 4.3.2 Full review requirement 4.1.6, if/when applicable for specified molecules and indications
- 4.3.3 The relevant, primary reference innovator PI approved by SAHPRA (M1.3)
- 4.3.4 The relevant secondary reference PI approved by a RRA, if applicable in instances where the local innovator PI is materially outdated (M1.3)