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| **COVER LETTER ON CLINICAL GUIDELINE** |

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| This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines and variations. 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.Guidelines and application forms are available from the office of the Chief Executive Officer and the website. |

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**SECTION A – OVERVIEW OF CLINICAL GUIDELINES**

As an Observer country to ICH, South Africa uses and applies information provided in The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and European Union (EU) guidelines for safety, efficacy and quality requirements. Specific guidelines from ICH and EU 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.

For technical clinical requirements for new registration and variations, refer to the:

1. **General Information guidelines**

The 2.0 General Information Guideline still stands, except for references to the original SAHPRA/MCC PI, PIL and Clinical guidelines which are currently under revision. In addition, references to regulation 9 and 10 have now been replaced by regulation 11 and 12 respectively. Notably, applicants are required to adhere to the working codes as per page 28 of the General Information guideline for a clinical evaluation.

*Document reference: 00 Start here General Information guide / 2.0 General Information Guidelines (for reference)*

1. **Additional guidelines for reference**

Please refer to the following additional SAHPRA/MCC guidelines where required upon resubmission: Co-packing guideline, Human Reproduction guideline, FDC guideline (HIV, Malaria and TB), biosimilar guidelines, and Standardised Text for Human Medicine guideline.

Please refer to the following additional EU guidelines where required upon resubmission: FDC guideline (except for HIV, Malaria and TB medicines where the SAHPRA guideline applies), EU variations guidelines, as well as any EU guidelines referred to in the P&A cover letter.

*Document reference: 01. Guidelines / 02. Clinical guidelines*

1. **Revised Professional Information (PI) & Patient Information Leaflet (PIL) guidelines**

For all backlog resubmissions, applicants are required to submit the proposed PI and PIL in the European Medicines Agency (EMA) format. In parallel, the relevant regulations to Act 101 of 1965, as amended, will be changed to reflect the new format.

The PI format will be 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 abovethe “Name of the Medicine” section. The “Scheduling Status” will not have its own number (please refer to the PI guideline).

For example, PI/SmPC format will follow:

SCHEDULING STATUS

1. NAME OF THE MEDICINE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For “Pharmacological Classifications”, SAHPRA will adopt the Anatomical Therapeutic Chemical (ATC) Classification System. (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). Note that the Pharmalogical Classification will no longer form part of the registration number. Details surrounding new registration numbering will be communicated separately.

For PI/PIL content, SAHPRA will be using reliance where applicable. Refer to reliance pathways and documentation required in Section B of this letter.

Upon resubmission, SAHPRA also requests all backlog applicants to provide the latest approved (and attainable) PI/PIL from a recognized regulatory authority if applicable. If the PI/PIL has been previously approved by the EMA Centralised Procedure, it must be provided as the default. If not approved by EMA, the applicant can provide an approved PI/PIL from any other regulatory authority with which SAHPRA aligns itself.

*Document reference: 01. Guidelines / 02. Clinical guidelines*

1. **Clinical variations**

SAHPRA is adopting the EU variations classification guidelines in full, and will publish exceptions for codes, procedures and data requirements facing different treatment in South Africa. This will take the format of a SAHPRA variations guideline / addendum letter to the EU guidelines, largely simplifying and replacing the content of the previously-published Clinical Variations guideline. This new document will be accompanied by another comment period, with more information to be communicated shortly.

Applicants will be required to consolidate and resubmit all backlog variations according to the EU procedure types (e.g. Type II, Type IB or Type IA). Urgent Safety Restriction Notifications (USRN) guidelines are incorporated in the addendum letter to the EU variations guidelines. Former Safety Related Package Insert Notifications (SR-PIN) guidelines have been withdrawn.

Beyond variations, SAHPRA’s PI, PIL, and Clinical guidelines have been adopted from EU guidelines and adapted to the South African context where applicable.

*Document reference: 01. Guidelines / 02. Clinical guidelines*

**SECTION B – RELIANCE PATHWAYS & DOCUMENTATION**

SAHPRA will be using reliance where applicable to reduce evaluation processing times:

* Abridged Review (Abbreviated Medicines Registration Process)
* Verification Review
* Mutual Recognition (where applicable through Zazibona)

Recognized authorities include: FDA, EMA, MHLW (Japan), Health Canada, Swiss Medic, TGA (Australia), MHRA (UK), and Zazibona (products registered prior 2016, post 2016 – mutual recognition). In order for an application to be considered for a reliance evaluation, additional documentation must be submitted with the application. The required additional documentation is listed on the technical screening checklists and guideline documents. In the absence of a suitable reliance pathway, applications will follow a Full Review.

See below a summary of the clinical evaluation pathways. The final evaluation pathway decision for an application is at the discretion of SAHPRA, and will depend on the quality of reliance documentation submitted. More information on reliance pathways can be found in the Clinical guideline.

1. Full review

All applications that do not have adequate reliance documentation will follow the full review pathway.

All NCE applications that do not have prior registrations with regulatory authorities with which SAHPRA aligns itself will be evaluated via a full review.

1. Abridged review

NCE applications that have approval(s) from a RA(s) with which SAHPRA aligns itself will be considered for an abridged review.

Generic applications that have approval(s) from a RA(s) with which SAHPRA aligns itself, but where the API has yet to be registered by SAHPRA, will be considered for an abridged review.

[Note: Applicants need to sign a letter of access, allowing SAHPRA to request un-redacted reports from regulatory authorities with which SAHPRA aligns itself. This is a minimum requirement in order for an application to be considered for an abridged review.]

1. Verified review

Generic applications for APIs already registered by SAHPRA will be considered for a verified review.

1. Mutual recognition

Applications that have been previously registered by Zazibona (post 2016) will qualify for mutual recognition.

Note: All applications, including applications that qualify for reliance, should have all relevant CTD documentation submitted. Reliance documentation should be submitted in addition to all standard documentation. Applicants should refer to the Clinical and variations guidelines for all documentation/data requirements for SAHPRA’s evaluation pathways.