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# **GENERAL GUIDANCE DOCUMENT ON QUALITY, SAFETY AND EFFICACY REQUIREMENTS FOR BIOLOGICAL MEDICINES**

This guideline is intended to provide guidance to applicants wishing to submit new application for registration of biological medicines. 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.

## **Document History**

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## 1. INTRODUCTION

The Biological Medicines Unit of SAHPRA is adopting the EMA ICH guidelines for quality, safety and efficacy (QSE) and endorses the principles contained therein.. All relevant sub guidelines included in the specific sections of the adopted ICH QSE guidelines that are applicable to biological medicines are also adopted. The adopted EMA ICH guidelines listed in Section 5 below should be read in conjunction with the current SAHPRA guidelines listed in Section 4 below and other relevant SAHPRA guidance document.

**Please note:** Unless mentioned otherwise, where ICH/EMA guidelines adopted in South Africa include references to European Union (EU) legislation, the requirements contained in the referenced EU legislation are not applicable to the evaluation of medicines by SAHPRA. South African legislation will apply wherever relevant and current.

## 2. SCOPE

This guideline is applicable to all new application for registration of all biologicals medicines including but not limited to vaccines, monoclonal antibodies, hormones, proteins and plasma derived medicines.

## 3. LEGAL BASIS

Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended and the relevant Regulations.

## 4. APPLICABLE SAHPRA GUIDELINES TO BE READ IN CONJUNCTION WITH NEWLY ADOPTED ICH GUIDELINES

The SAHPRA guidelines listed below are to be read in conjunction with the newly adopted guidelines for quality, safety and efficacy requirements. The latest published (i.e. non-draft) version should always be referred to. Other relevant SAHPRA guidance documents not listed below but available of SAHPRA website should also be consulted.

- a. 2.38\_International Metric System (SI) Guideline [https://www.sahpra.org.za/wp-content/uploads/2020/01/2.38\\_SI\\_Metric\\_System\\_Mar19\\_v3.pdf](https://www.sahpra.org.za/wp-content/uploads/2020/01/2.38_SI_Metric_System_Mar19_v3.pdf).
- b. 2.58\_Guidance for the submission of regulatory information in eSubmission format. [https://www.sahpra.org.za/wp-content/uploads/2020/02/2.58\\_Submission-in-eSubmission-format\\_Jul19\\_v1-1.pdf](https://www.sahpra.org.za/wp-content/uploads/2020/02/2.58_Submission-in-eSubmission-format_Jul19_v1-1.pdf)
- c. 2.24\_Guidance for the submission of the South African CTD/eCTD –General & Module 1 Guideline [https://www.sahpra.org.za/wp-content/uploads/2020/02/2.01\\_Guidance\\_General\\_Module\\_1\\_May19\\_v6-1.pdf](https://www.sahpra.org.za/wp-content/uploads/2020/02/2.01_Guidance_General_Module_1_May19_v6-1.pdf)

- d. 2.60\_Biological Medicines Stability Guideline <https://www.sahpra.org.za/wp-content/uploads/2021/02/stability-guidelines-biologicals-v1.docx.pdf>
- e. 2.30\_Biosimilar guideline with annexure. <https://www.sahpra.org.za/wp-content/uploads/2020/08/sahpra-biosimilars-medicines-guidance.pdf>
- f. 2.14\_Guideline for Patient Information Leaflet for Human medicines (Category A and D) [https://www.sahpra.org.za/wp-content/uploads/2020/02/2.14\\_Guideline-for-Patient-Information-Leaflet-for-Human-Medicines-Categories-A-and-D\\_Jul19\\_v2-1.pdf](https://www.sahpra.org.za/wp-content/uploads/2020/02/2.14_Guideline-for-Patient-Information-Leaflet-for-Human-Medicines-Categories-A-and-D_Jul19_v2-1.pdf)
- g. 2.16\_Guideline for Professional Information for Human medicines (Category A and D) [https://www.sahpra.org.za/wp-content/uploads/2020/02/2.16\\_Guideline-for-Professional-Information-for-Human-Medicines-Categories-A-and-D\\_Jul19\\_v2-1.pdf](https://www.sahpra.org.za/wp-content/uploads/2020/02/2.16_Guideline-for-Professional-Information-for-Human-Medicines-Categories-A-and-D_Jul19_v2-1.pdf)

## 5. NEWLY ADOPTED QUALITY, SAFETY AND EFFICACY GUIDELINES

The newly adopted guidelines listed below should be utilized and referred to for quality, safety and efficacy requirements for new application for registrations of biological medicines. The current versions of the adopted guidelines are showed and linked below; however, these are subject to updates and the latest published non-draft version should always be referred to. At its discretion, SAHPRA may recognize guidance from the WHO, US FDA and other regulatory authorities with which SAHPRA aligns itself. However, applicants are advised to prepare submissions in line with the newly adopted guidelines, read in conjunction with applicable SAHPRA guidelines listed in Section 4 above. The adopted quality, safety and efficacy guidelines are shown in section 5.1, 5.2 and 5.3 below:

- 5.1. **ICH M4Q Common technical document for the registration of pharmaceuticals for human use – quality.** <https://www.ema.europa.eu/en/ich-m4q-common-technical-document-registration-pharmaceuticals-human-use-quality>
- 5.2. **ICH M4S Common technical document for the registration of pharmaceuticals for human use – safety.** <https://www.ema.europa.eu/en/ich-m4s-common-technical-document-registration-pharmaceuticals-human-use-safety>
- 5.3. **ICH M4E Common technical document for the registration of pharmaceuticals for human use – efficacy.** <https://www.ema.europa.eu/en/ich-m4e-common-technical-document-registration-pharmaceuticals-human-use-efficacy>

## 6. REVIEW PATHWAYS FOR BIOLOGICAL MEDICINES:

The reliance pathway is currently not fully adopted for biological medicines. Nonetheless, the inclusion of the unredacted assessment reports from other regulatory authorities that SAHPRA aligns itself with will reduce the evaluation time lines as some section of the dossier may not need to be reassessed by SAHPRA.

## 7. SOUTH AFRICA SPECIFIC REQUIREMENT IN CERTAIN SECTION OF THE DOSSIER

The following sections contain information pertaining to the regional requirements specific to South Africa for quality, safety and efficacy. Refer to the General Information Guideline and Module 1 Guideline for additional South Africa specific requirements.

### 7.1 Module 1:

The information presented in Module 1 should be as per SAHPRA Module 1 Guideline (2.24). However, section 7.1.1 and 7.1.2 below highlights the additional requirements that must be provided for biological medicines applications.

#### 7.1.1 Module 1.13: Risk management plan:

All applications for the registration of the biological medicines should be accompanied by the risk management plan.

#### 7.1.2 Module 1.3.1 and 1.3.2 (PI and PIL)

The format and content of the PI and PIL should be as per SAHPRA latest PI and PIL guideline and relevant regulation. Applicant should also submit the working documents for PI and PIL in Microsoft Word format.

### 7.2 Module 3.2.S.4.1: Specifications of the active biological substance (release and stability specifications)

The proposed release and stability specifications of the active biological substance should be signed, dated and version controlled.

### 7.3 Module 3.2.S.7: Stability data of active biological substance:

Applicants should refer to Biological medicines stability guideline. For vaccines applicants should refer to WHO "Guidelines on stability evaluation of vaccines".

### 7.4 Module 3.2.P.5.1: Specifications of the final product (release and stability specifications)

The proposed release and stability specifications of the final product should be signed, dated and version controlled.

7.5 Module 3.2.P.8: Stability data of the final product

- Applicants should refer to Biological medicines stability guideline <https://www.sahpra.org.za/wp-content/uploads/2020/04/Stability-guideline-biologicals.pdf>.
- For vaccines applicants should refer to WHO “Guidelines on stability evaluation of vaccines [https://www.who.int/biologicals/publications/trs/areas/vaccines/stability/Microsoft%20Word%20-%20BS%202049.Stability.final.09\\_Nov\\_06.pdf](https://www.who.int/biologicals/publications/trs/areas/vaccines/stability/Microsoft%20Word%20-%20BS%202049.Stability.final.09_Nov_06.pdf).

## 7.6 **MODULE 3.2.R: REGIONAL INFORMATION**

### **PREAMBLE:**

The granulation for Module 3.2.R. indicated in this guidance document is as per currently approved SAHPRA requirements for Module 3.2.R. .Nonetheless, the Biosimilar analytical comparability studies should be included under section 3.2.R.8.

**N.B:** For biosimilar applications, applicants should comply with the requirements stipulated in SAHPRA Biosimilar guideline.

**3.2.R.1 Not applicable for biosimilar applications.**

**3.2.R.2 Parent API manufacturer / DMF Holder with various sites**

- 1) If an identical route of synthesis, or manufacturing process of the Primary Production Lot (in case of Biological Medicines), including the purification step is used by each site of the same parent company or DMF Holder, a statement to this effect will suffice with regard to the route.
- 2) In this case include valid CoAs from the API manufacturer or manufacturer of the primary production lot (in case of Biological Medicines) for two batches issued by each site.

**3.2.R.3 Certificate(s) of suitability with respect the Ph.Eur. (CEPs) Confirmation of WHO API Prequalification (CPQ)**

**3.2.R.4 Multiple API manufacturers**

If more than one manufacturer of the API is being applied for (irrespective of the apparent similarity of the routes utilized by the different manufacturers), or when different routes of synthesis are used in the manufacture of the API, the following should be submitted, in addition to Module 3.2.S for each API:

**3.2.R.4.1** Comparability between the active biological ingredient batches manufactured at the proposed manufacturing sites with respect to physico- chemical characterization, biological activity, and impurity profile. Occasionally, bridging non- clinical and/or clinical studies may be required when quality data are insufficient to establish comparability. The extent and nature of non-clinical and/or clinical studies should be determined on a case-by-case basis taking into consideration the quality comparability findings, the nature and level of the knowledge of the medicine, existing relevant non- clinical and clinical data, and aspects of medicine use.

**3.2.R.4.2** Description of the batches and summary of in-process and batch release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive batches manufactured at each of the proposed manufacturing sites.

**3.2.R.4.3** Comparative results of at least 3 active biological ingredients batches manufactured at each of the proposed sites for key stability indicating parameters. The data should cover a minimum of 6 months testing unless otherwise justified

**3.2.R.4.4 Certificates of analysis**

- Provide certificates of analysis for each batch of API reported on in 3.2.R.4.2

**3.2.R.5 Medical devices**

Validation / calibration / specifications of medical device(s)

**3.2.R.6 Materials of animal / human origin**

All ingredients of animal origin (excluding products from porcine origin) should be BSE/TSE free. Include a declaration from FPP manufacturer that the materials used will always comply with BSE/TSE free requirements.

**3.2.R.7 Production documentation**

Copy of the batch manufacturing record including the ingredient (API and excipients) analytical reports, in process control tests reports, intermediate product test reports, reconciliation records and a certificate of analysis for the batch must be presented. Please note that if there is a major change in the production process that affects the quality evaluation of the product, e.g. changes to the process, in-process controls, or ingredients, updated production documents will be required by SAHPRA. For editorial or minor changes (Type 1A variations or administrative changes), annual notifications will suffice, and SAHPRA will not require submission of updated production documents.

**3.2.R.7.1 Executed production documents**

The executed production documents should be provided for the batches used in the product development.

Copies of executed manufacturing records should be in English, or translated into English where relevant.

**3.2.R.7.2 Blank / master production documents**

Copies of the FPP master production documents must be provided for each manufacturing site and should ideally be provided for each proposed strength and commercial batch size. Master production documents from a pilot scale batch will be sufficient if the process has not yet been scaled up to production scale. Please note that the pilot batch size should correspond to at least 10% of the production scale batch.

Where the EMA guidelines permit bracketing for commercial batch sizes, master production documents for the smallest and largest batches as validated will be sufficient.



The details in the master production documents should include, but not be limited to, the following:

- a) master formula;
- b) dispensing, processing and packaging sections with relevant material and operational details;
- c) relevant calculations (e.g. if the amount of API is adjusted based on the assay results or on the anhydrous basis);
- d) identification of all equipment by, at minimum, type and working capacity (including make, model and equipment number, where possible);
- e) process parameters
- f) list of in-process tests and specifications;
- g) sampling plan with regard to the:
  - i. steps where sampling should be done
  - ii. number of samples that should be tested
  - iii. frequency of testing
- h) precautions necessary to ensure product quality (e.g. temperature and humidity control, maximum holding times);
- i) for sterile products, reference to SOPs in appropriate sections and a list of all relevant SOPs at the end of the document;
- j) theoretical and actual yield;
- k) compliance with the GMP requirements.

If some of the required detail is contained in standard operating procedures (SOPs) and not in the master production document, the applicant should submit both the master production document and the relevant SOPs.

#### **3.2.R.8. Other**

Placeholder section for documents that do not have a specified location in the CTD folder structure, but which the applicant deems necessary for evaluation of the dossier. This includes the biosimilarity analytical comparability studies.

## 8. UPDATE HISTORY

Date	Reason for update	Version
October 2021	First draft for comments	V1