South African Health Products
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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.

Document History

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A. LIST OF ABBREVIATIONS AND TERMINOLOGY

Abbreviation / Acronyms	
CTD	Common Technical Document
CEP	Certificate of Suitability (Ph Eur monograph)
EMA	European Medicines Agency
EU	European Union
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
PIL	Patient Information Leaflet
PI	Professional Information
QSE	Quality, Safety and Efficacy
SAHPRA	South African Health Products Regulatory Authority
US FDA	United States of America Food and Drug Administration
WHO	World Health Organization

B. DEFINITIONS

Some of the definitions below were modified (compared to those provided in other documents) to reflect the meanings as used in this guidance.

Biological Medicine: all medicines that contain a living organism or are derived from a living organism or biological processes. They include, but are not limited to the following:

i. Plasma-derived and animal products e.g., Clotting factors, immunosera, antivenoms;

ii. Vaccines.

iii. Biotechnology-derived medicines (recombinant DNA products) e.g., rHu-anti-haemophilic factors, hormones, cytokines, enzymes, monoclonal antibodies, erythropoietins, nucleic acids;

iv. Products developed for Human Gene therapy

Well-characterized, low-molecular mass, medicinal biological compounds, may be excluded by specific regulatory decision from biological medicine status, and in that case, will not be reviewed through the biological medicines review process.

Biosimilar application: This is synonymous with follow-on biologics and similar biotherapeutic products (SBP). A biosimilar application is for a biological medicine that is similar, but not necessarily identical, in terms of quality, safety and efficacy to an already registered reference biological medicine

Comparability: The activities, including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable. In addition to routine analyses performed during production and control of the active biological ingredient or final product, these evaluations typically include further characterization studies. In some cases, non-clinical or clinical data might contribute to the conclusion

Final Product: A finished dosage form (e.g., tablet or solution) that contains an Active ingredient generally, but not necessarily, in association within Active ingredients. It is also referred to as Finished Product or Drug Product in other documents.

Manufacturer: means a person manufacturing a medicine (Final Product) or manufacturing of the active ingredients and includes a manufacturing plant

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges or other criteria for the tests described. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by the regulatory authorities

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 EMA 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 biological 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 on 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.

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

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

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

g. 2.16_Guideline for Professional Information for Human medicines (Category A and D) https://www.sahpra.org.za/document/2-16-guideline-for-professional-information-for-human-medicines/

h. 2.22_South African eCTD validation criteria eCTD_Validation_Criteria_Sept16_v2.1 https://www.sahpra.org.za/33020f622-22_ectd_validation_criteria_sept16_v2-1/

i. 2.23_Guidance for the submission of regulatory information in eCTD format https://www.sahpra.org.za/2-23_submission-in-ectd-format_jul19_v3/

j. 2.01_General information guideline. https://www.sahpra.org.za/document/2-01-general-information-guideline/ .

k.2.66_ Guideline for Lot release of human vaccines. https://www.sahpra.org.za/document/2-66-guideline-for-lot-release-of-human-vaccines/

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 provided below with available links; 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, EMA, 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 review pathway for biological medicines will include both full review and the reliance review pathway where applicable as per SAHPRA 5.08_Reliance guideline: https://www.sahpra.org.za/document/5-08-reliance-guideline/

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. The risk management plan should take into consideration South African specific issues such as HIV, Tuberculosis and e.t.c).

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 in the working documents folder as described in the eCTD [2.23] and eSubmission [2.58] guidelines.

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.

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 Active Pharmaceutical Ingredient (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 active ingredient 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 active ingredient Prequalification (CPQ)

3.2.R.4 Multiple active ingredient 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 active ingredient, the following should be submitted, in addition to Module 3.2.S for each active ingredient:

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 the active ingredient reported 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 (active ingredient 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 active ingredient 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
01 February 2022	New	Version 1