South African Health Products
Regulatory Authority
Building A
Loftus Park
Arcadia
Pretoria

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QUALITY AND BIOEQUIVALENCE GUIDELINE

This guideline is intended to provide recommendations to applicants wishing to submit new registration applications as well as variations. It represents the South African Health Product Regulatory Authority's (SAHPRA)'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 SAHPRA website.

Document History

Final Version	Reason for Amendment-i think we may remove the amendments from last 10 years QMS may confirm	Effective Date
1	First publication released for implementation and comment	May 2003
	Release for additional comments	November 2003
	Deadline for comment	November 2003
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2	Amendment of sections 2, 2.1, 2.1.1 c) h), 2.1.2 a) d) i) j) k) l) m), 2.1.3 b), 3, 3.1, 3.2, 3.3, 3.4, 3.5.3, 3.5.4, 3.6, 3.7, 3.8, List of acronyms, Terminology	June 2006
	Deadline for comment	14 August 2006
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3	Renumbering of section 2.1.3, amendment of section 2.1.3.2.a) & ii) and addition of section 2.1.3.2 c) re foreign reference products, amendment of section 3.5.4 re validation	April 2009
	Date of implementation	June 2009
4	2.1.1 f)	June 2010

	2.1.2 & 2.1.3 renumbering, regrouping and clarification of confirmations required and justification of reference products, 2.1.2.4, 2.1.2.6, 2.1.2.7 e), 2.1.3.2; 3.1.3, 3.1.4, 3.1.5 d) f) i) j) l) m) q), 3.1.6, 3.1.7 c) d) e), 3.1.10; 3.2.1, 3.2.3 b), 3.2.16; 3.3.1, 3.3.5, 3.3.10, 3.3.11, 3.3.12, 3.3.14; 3.4.9; 3.5.1 – 4; 3.6.1, 3.6.4, 3.6.6, 3.6.7, 3.6.9; 3.7; 3.8.2 a) b) d); References	
	Date of implementation	June 2010
5	Amended in line with comments received on P&A guideline for CTD; replaced “drug” with “API” in Terminology; indicated FPRR in IFD	March 2011
	Sections 1, 2.1.1, 2.1.1 f), 2.1.2.1 e), 2.1.2.4 a), b), c); 2.1.2.5, 2.1.2.6, 2.1.2.7 + table; 3.1.1, 3.1.4, 3.1.5 d) e) i) j) k) l) 3.1.6, 3.1.7 c), 3.1.8, 3.1.10 3.2.1, 3.2.7, 3.2.8, 3.2.9, deleted 3.2.16 3.3.1, 3.3.2, deleted 3.3.10 3.4.1, 3.4.2, 3.4.5, 3.4.8 3.5.1, 3.5.2, 3.5.3, 3.5.4 3.6.1, 3.6.4, 3.6.5, 3.6.6, 3.6.11 3.8.2 List of Acronyms	
	Date of implementation	March 2011
6	Additions to 2.1.1, 2.1.2.1, and 3.8.2 b) for clarification	June 2011
	Date of implementation	June 2011
7	Publication for comment	April 2019
	Date of implementation	July 2019

8	- Periodic review of documents - Updated to align with current regulatory terms - Updated to align with new guideline format change - New version number issued from 2.02 to SAHPGL-PEM-02_v8 - Updated section 3 to include legal provision (section 15 (1) – (3) of the Act) -SCoRE document obsolete -Add Quality overall summary & Quality information summary (QOS & QIS) under list of forms. - Section 7.5 Documentation required for reliance-based evaluation: Delete information specific to Backlog requirements -Hyperlink all mentioned documents -Update Section 8 South Africa Specific Requirements to include requirements for 3.2.S.4.1 Specification, 3.2.S.7 & 3.2.P.8 Stability -update to include a reference statement to guideline to refer to in a case of a rolling review - Dissolution guideline is obsolete - Stability guideline is obsolete - Biostudies guideline is obsolete - Replace Amendments guideline with Variations addendum -Updated section 9 to include validity -Update Appendix 1: In vitro Studies-Dissolution profile comparison to include table 3: Change in inactive pharmaceutical ingredient (IPI) range: - Immediate release solid oral dosage form -Modified release solid oral dosage form (only non-release controlling IPIs) - Delete Appendix 3: Declaration for previous P&A Committee approval/PEM Approval	May 2023
9	-Update to remove the use of old medicines as a reference product in BE studies, to align with current practice	October 2025

	-Update to include CEP 2.0 requirements	

DR BOITUMELO SEMETE-MAKOKOTLELA
CHIEF EXECUTIVE OFFICER

Contents

Glossary

Abbreviation/ Term	Meaning
API	Active Pharmaceutical Ingredient
BCS	Biopharmaceuticals Classification System
BTIF	Bioequivalence Trial Information Form
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CoA	Certificate of Analysis
CPQ	Certificate of Pre-qualification
CTD	Common Technical Document
EMA	European Medicines Agency
FPP	Finished Pharmaceutical Product
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRP	Good Regulatory Practice
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPRP	International Pharmaceutical Regulators Programme
LOD	Limit of Detection
PEM	Pharmaceutical Evaluations and Management
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
NCE	New Chemical Entity
P&A	Pharmaceutical and Analytical

PD	Product Dossier
Ph.Eur	European Pharmacopoeia
Post-reg.	Post-registration
PPL	Periplakin (protein coding gene)
PQ	Pre-qualification
Pre-reg.	Pre-registration
PSF	Product Summary File
QIS	Quality Information Summary
QOS	Quality Overall Summary
RRA	Recognised Regulatory Authority
RSA	Republic of South Africa
SADC	Southern African Development Community
SAHPRA	South African Health Products Regulatory Authority
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TGA	Therapeutic Goods Administration (Australia)
US FDA	United States of America Food and Drug Administration
USP	United States Pharmacopoeia
WHO	World Health Organization

1. INTRODUCTION

The South African Health Products Regulatory Authority (SAHPRA) has decided to harmonise certain organisational medicine policies and procedures with those of the European Medicines Agency (EMA). These in turn are aligned to the framework of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). By doing so, SAHPRA will reflect global best practice in terms of the safety, quality, and efficacy of health product regulation.

SAHPRA is adopting the EMA, ICH and Southern African Development Community (SADC) guidelines for quality and bioequivalence requirements and endorses the principles contained therein. The EMA guidelines adopted in Section 5 below should be read in conjunction with currently applicable SAHPRA guidelines stipulated in Section 4 below.

Please note: Unless mentioned otherwise, where 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 new applications for small molecule NCEs, generics and post registration applications. Biological, complementary medicines and medical devices are not covered in this guideline.

3. LEGAL PROVISION

Section 15(1)-(3) of the Act states:

(1) Every application for the registration of a medicine, medical device or IVD shall be submitted to the Chief Executive Officer in the prescribed form and shall be accompanied by-
(a) the prescribed particulars;
(b) samples of the relevant medicines;
(c) where practicable, samples of medical devices or IVDs; and
(d) the prescribed registration fees.

(2) As soon as possible after receipt by the Chief Executive Officer of an application contemplated in subsection (1), he or she shall inform the applicant in writing that the application is being considered.

(3)
(a) If after consideration of any such application and after any investigation or enquiry which it

may consider necessary the Authority is satisfied that the medicine, medical device or IVD in question-

(i) is suitable for the purpose for which it is intended;

(ii) complies with the prescribed requirements; and

(iii) is safe, efficacious and of good quality and, in the case of a medical device and IVD, performs as intended,

the Authority shall issue the applicant with a certificate of registration to that effect.

4. APPLICABLE SAHPRA GUIDELINES TO BE READ IN CONJUNCTION WITH NEW GUIDELINES

The SAHPRA guidelines/ forms listed below are to be read in conjunction with the adopted guidelines for quality and bioequivalence requirements. The latest published (i.e., non-draft) version should always be referred to.

List of Guidelines

SAHPGL-PEM-04	International Metric System (SI) Guideline
SAHPGL-HPA-07	General Information Guideline
SAHPGL-PEM-03	Guideline for the APIMF Procedure
2.24	Module 1 Guideline
SAHPL-CRO-02	Reliance guideline

List of forms

GLF-PEM-02D	Quality overall summary (QOS)
GLF-PEM-02C	Quality information summary (QIS)
OF-PEM-PRE-01H	Additional strength biowaiver application form
OF-PEM-PRE-01I	Biopharmaceutics classification system (BCS) based biowaiver application form
OF-PEM-PRE-01J	Bioequivalence trial information form BTIF
OF-PEM-PRE-01P	Abridged review reliance template
OF-PEM-PRE-01Q	Verified review reliance template

5. ADOPTED GUIDELINES

The below list of adopted guidelines should be referred to for quality and bioequivalence requirements for new registrations and variations to currently registered products.

Current versions are 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 recognise guidance from the WHO, United States of America Food and Drug Administration (US FDA) and other regulatory authorities with which SAHPRA aligns itself. However,

applicants are advised to prepare submissions in line with the new guidelines, read in conjunction with applicable SAHPRA guidelines listed in Section 4.

Quality guidelines:

- SADC quality guideline
- ICH quality guidelines
    - ICH Q1A – Stability testing of new drug substances and products
    - ICH Q1B – Stability testing: Photostability of new drug substances and products
    - ICH Q1C – Stability testing for new dosage forms
    - ICH Q1D – Bracketing and matrixing designs for stability testing of new drug substances and products
    - ICH Q1E – Evaluation of stability data
    - ICH Q2 – Analytical validation
    - ICH Q3A – Impurities in new drug substances
    - ICH Q3B – Impurities in new drug products
    - ICH Q3C – Guideline for residual solvents
    - ICH Q3D – Guideline for elemental impurities
    - ICH Q6A – Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances
    - ICH Q8 – Pharmaceutical development
    - ICH Q11 – Development and manufacture of drug substances
    - ICH Q14 – Analytical procedure development

- *EMA Quality guidelines are provided for:*
    - Active substance
    - Manufacturing
    - Impurities
    - Specifications, analytical procedures, and analytical validation
    - Excipients
    - Packaging
    - Stability
    - Pharmaceutical development
    - Quality by design
    - Specific types of products

- Lifecycle management
- EMA excipient labelling guideline

Bioequivalence guidelines

- Bioanalytical method validation, presentation of biopharmaceutical and bioanalytical data, and pharmacokinetic and clinical evaluation of modified release dosage forms
- ICH M9 guideline on biopharmaceutics classification system-based biowaivers
- ICH M10 Bioanalytical method validation and study sample analysis
- M13A-C EWG Bioequivalence for immediate- release solid oral dosage forms
- EMA Comment on bioequivalence for fixed combination products
- EMA Questions and answers – Clinical pharmacology and pharmacokinetics
- EMA Questions and answers – Pharmacokinetics Working Party
- EMA reflection paper on the dissolution specification for generic oral immediate release products
- SADC Bioequivalence guideline

6. VARIATIONS

SAHPRA has adopted the EU variation classification guidelines for orthodox human and veterinary medicines[1] in full, but with specific exceptions. Please see SAHPRA's Variations Addendum for Orthodox medicines for more information about the application of the EU variation classification.

The QOS & QIS documents should be submitted with all applications in PDF, M 3.2.R.8, and word in the working folder. The QIS should be submitted with all applicable variations. An updated QOS should be submitted for new API source changes and extensive type II changes which results in major changes to the dossier.

7. REVIEW PATHWAYS

7.1. A Pharmaceutical Evaluations and Management (PEM) evaluation will follow one of the following review pathways:

[1] Any guidance regarding complementary and biological medicines, as well as medical devices, referenced in the EU variations guidelines is not applicable to SAHPRA – existing guidelines will apply

a) Full review

b) Abridged review

c) Verified review

d) Recognition

Review pathways (b), (c) and (d) represent reliance-based evaluations. Please see SAHPRA's Reliance Guideline for further information. 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."

7.2. SAHPRA's recognised regulatory authorities

To qualify for a reliance evaluation pathway, a product being applied for must be registered by one or more of the recognised regulatory authorities (RRAs) with which SAHPRA aligns itself. SAHPRA will leverage evaluation efforts done by RRAs in order to make its evaluation process more efficient and enhance market access. **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)
- European Union Mutual Recognition Procedure
- European Union National Procedure
- Health Canada
- Medicines and Health Products Regulatory Agency, UK (MHRA)
- Ministry of Health, Labour, and Welfare (MHLW), Japan
- Swiss Agency for Therapeutic Products (Swissmedic)
- Therapeutic Goods Administration, Australia (TGA)

US Food and Drug Administration (US FDA)

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

- World Health Organisation Prequalification (WHO CRP PQ and SRA)
- Zazibona collaborative procedure
- African Medicines Agency (AMA)
- EU-Medicines for *all (*EU-M4all)

7.3. Principles of reliance-based evaluation

Reliance-based evaluation will be based on the following principles:

- Reliance is applicable for both new registration and variation applications (Type I and Type II).

- Reliance for Clinical and PEM is applied independently, i.e., the review types selected by the units could differ based on unit-specific document requirements and the availability thereof.

- 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.

- All decisions regarding final evaluation pathway (i.e., full review or reliance-based review) as well as the extent of reliance on the RRA's evaluation of the product being applied for are at the discretion of SAHPRA, based on the documents (and quality thereof) available for reliance- based evaluation.

- All decisions regarding approval and final registration will be made by SAHPRA, in consideration of multiple factors including an RRA registration.

7.4. Definitions of review pathways

7.4.1 Full review

A full review involves a thorough review of all aspects of the dossier, including:

- Module 1: Regional administrative data (as required)
- Module 2: Relevant summaries
- Module 3: Quality data
- Module 5: Efficacy data (for generic medicines)

All applications for products/variations that have not been registered/approved by an RRA, or that lack sufficient reliance documentation, will be considered for a full review. To reiterate, both new registrations and Type I and Type II variations, for NCEs and generics, which meet these criteria will be considered for a full review.

7.4.2 Abridged review

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 and 3.2.R: Regional administrative information (as required).
- Evaluation of specific aspects of the dossier, depending on the type of application submitted

The abridged review process does **not** involve an abbreviated application – all data and information required for a full review should be submitted, i.e., the full CTD module structure, as well as the QOS & QIS document. Evaluators may still wish to review data in the dossier as required.

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 in Expression of Interest-WHO Pre-Qualification Collaborative Registration Procedure

iii. For a Type II variation where the variation applied for has already been approved by an RRA and assessment reports are provided.

7.4.3 Verified review

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 and 3.2.R: Regional administrative information (as required).

The verified review process does **not** involve an abbreviated application – all data and information required for a full review should be submitted, i.e., the full CTD module structure, as well as the QOS & QIS document. Evaluators may still wish to review data in the dossier 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 I variation where the variation applied for has already been approved by an RRA and assessment reports are provided.

7.4.4 Recognition

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. Currently, there are no existing recognition agreements with RRA's that SAHPRA aligns itself with. The recognition pathway will be considered in the future once a framework has been developed.

7.5. Documentation required for reliance-based evaluation

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
• Completed abridged review template (OF-PEM-PRE-01P)
• Completed verified review template (OF-PEM-PRE-01Q)

• Full, initial scientific 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/or approval of the variation/s, • SmPC, a copy of the patient information leaflet (PIL) and label of the product that has been registered by the RRA, and • If available: 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. This does not include the data package filed with the RRA
• Letter of approval from the RRA
• Declaration: Sameness (Appendix 2)

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 CRP PQ and SRA products are detailed in SAHPRA's process for the WHO Collaborative Registration Procedure Expression of Interest-WHO Pre-Qualification Collaborative Registration Procedure.

Additional documentation requirements for Zazibona's procedure are detailed in SAHPRA's process for Zazibona's registration procedure.

Additional documentation requirements for reliance-based review of variations' applications are detailed in SAHPRA's Variations Addendum for Orthodox Medicines.

7.5.1 Full assessment/evaluation reports

- Please note that if the full assessment/evaluation reports from the RRA where the product is registered are in a language which is not English, certified translated versions need to be provided as per SAHPRA guidelines.

- Please note that full assessment/evaluation reports from the RRA where the product is registered should at least include safety, efficacy and quality report(s) prepared by the RRA upon which the registration decision for the health product was based.

- If full assessment/evaluation reports from the RRA are not provided by the applicant, the application in question will most likely default to a full review.

8. South African Specific Requirements

The following guidelines contain information pertaining to the regional requirements specific to South Africa for quality and bioequivalence. Refer to the General Information Guideline (SAHPGL-HPA-07) and Module 1 Guideline (2.24) for additional South Africa specific requirements.

8.1. Module 3.2.S Active substance

8.1.1. 3.2.S.4.1 Specification

Please note that all specifications included from the API and FPP manufacturer in the submission will only be accepted if version controlled, dated, and signed.

8.1.2 3.2.S.6. Container Closure System

Please note that primary and secondary packaging specifications must be signed, dated and version controlled.

8.1.3 3.2.P.4.1 Specification (Inactive Pharmaceutical Ingredient)

Please note that excipient specifications if in-house must be signed, dated and version controlled.

Excipient specification must include the grade and a once off functionality test.

8.1.43.2.P.5.1 Final product specifications

Please note that all specifications included in the submission will only be accepted if version controlled, dated, and signed.

8.1.5 3.2.P.7 Container Closure System

Please note that primary and secondary packaging specifications must be signed, dated and version controlled.

8.2. Stability

8.2.1. 3.2.S.7 Drug substance & 3.2.P.8 Drug product

South African Development Community (SADC), and ICH stability guidelines are applicable.

Applicants may choose to follow the requirements of SADC or ICH Stability Guideline, as long as this is clearly stated in the Stability Protocol. This does not apply to products applied for through reliance on the Zazibona collaborative process for evaluation. In this case, the SADC Stability Guideline must be adhered to.

Regarding the requirement for stability data for generics, a minimum of 6 months' long-term and 3 months' accelerated stability data should be made available at the time of submission. However, SAHPRA would

prefer that 12 months' long-term and 6 months' accelerated stability data is included in the new registration application to facilitate retest periods.

For New chemical entities (NCEs), a minimum of 12 months' long term and 6 months' accelerated stability data should be made available at the time of submission.

For variations, refer to the Variations Guideline (EU variation classification guidelines).

In case of a rolling review and Public Emergency review, refer to the Public Health Emergency guideline.

8.3. Module 3.2.R: Regional information

3.2.R.1 Pharmaceutical and Biological availability

SCOPE

This module addresses the pharmaceutical and biological availability for generic applications and NCE line extensions with special reference to the purpose of the study(ies), the reference product(s) and the overall conclusion.

i) Partial exemption from the requirements of 3.2.R.1 and 5.3.1 may be applicable if efficacy and safety are intended to be established by clinical data (or for other reasons as determined by SAHPRA), provided that clinical trials have been conducted with the same formulation as the one being applied for, in which case:

- The pharmaceutical availability profile(s) of the API(s) in the final formulation being applied for, for which exemption or partial exemption is justified, should specifically be demonstrated, e.g., the dissolution profiles for solid oral, oral suspension and parenteral suspension products should be included in accordance with the reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action, and/or other relevant data provided to unequivocally characterise the formulation used in the clinical trials.

ii) If clinical evidence in support of efficacy is not submitted, or if the final formulation being applied for is not the same as that used in clinical trials, studies, and data to demonstrate the pharmaceutical and/or biological availability/equivalence of the product should be included.

iii) If in the opinion of the applicant no data is required to substantiate efficacy (e.g., parenteral solutions), clearly state the rationale for accepting safety and efficacy and

include a discussion on the excipients (refer to EMA guideline on the investigation of bioequivalence), and a comparison of final product characteristics in 3.2.R.1.4.2.

iv) One of the following methods depending on the relevancy may be used:

- Bioavailability
- Dissolution
- Disintegration
- Acid neutralising capacity
- Microbial growth inhibition zones
- Proof of release by membrane diffusion
- Particle size distribution
- Blanching test
- EU guidance on locally applied locally acting products
- EU guidance on locally acting products in the gut
- Any other method provided the rationale for submitting the particular method is included. The above methods are subject to change based on finalisation of EMA guidelines addressing specific routes of administration.

v) Data submitted should always be comparative, except as stated above under i), when product characterisation is submitted.

a) Bioequivalence and/or biowaivers

Refer to the EU Bioequivalence guideline and EMA reflection paper on the dissolution specification for generic oral immediate release products.

For new registration generic applications and applicable variations, SAHPRA requires the completion of a Bioequivalence Trial Information Form (BTIF), designed to provide a summary of a bioequivalence study submitted as part of a product dossier. The completed BTIF will be used by the evaluator to facilitate more rapid and effective evaluation of the bioequivalence study. If applicable, please include a completed BTIF in Microsoft Word format in the working documents folder.

b) In vitro dissolution

The studies should be carried out in accordance with the EMA bioequivalence guideline, reflection paper and ICH M9 guideline on biopharmaceutics classification system-based biowaivers specified above. However, the stringent EMA criteria with respect to time points after > 85% dissolution is achieved (i.e., required for both test and reference products) do not need to be adhered to.

c) Disintegration

Disintegration as proof of efficacy may be used in the following instances:

- Vitamins or vitamins and mineral combinations when a claim is made as a supplement.
- Sucralfate.

The disintegration test included for Nutritional Supplements in the USP, or in the Ph Eur should be used for the vitamins.

The general disintegration test included in the USP/Ph Eur may be used for the other substances.

d) Acid neutralising capacity

Acid neutralising capacity may be used as proof of efficacy for products with an antacid or acid neutralising claim. The acid neutralising capacity test included in the USP should be used.

e) Microbial growth inhibition zones

Microbial growth inhibition zones may be used as proof of efficacy for simple solution topical formulations with a bacteriostatic/bacteriocidal/antiseptic claim.

f) Proof of release by membrane diffusion

Proof of release by membrane diffusion will not be accepted as proof of efficacy alone, unless data are presented that show a correlation between release through a membrane and clinical efficacy.

Additional information can be found below: Quality and equivalence of topical products.

g) Particle size distribution

Particle size distribution may be used in support of proof of efficacy for inhalations. The Anderson sampler or equivalent apparatus should be used. In addition, appropriate information should be submitted to provide evidence of clinical safety and efficacy.

Additional information can be found below:

- Pharmaceutical quality of inhalation and nasal products
- Requirements for clinical documentation for orally inhaled products

h) Blanching test

The blanching test may be used as proof of efficacy for topical dosage forms containing topical corticosteroids. Additional information can be found at the link below:

Quality and equivalence of topical products

The rationale for any other particular method should be provided.

STUDY PRODUCTS

A sufficient number of retention samples of both test and reference products used in the bioequivalence or other studies, should be kept for one year in excess of the accepted shelf- life, or two years after completion of the trial or until approval, whichever is longer, in order to allow re-testing if so, required by SAHPRA. A complete audit trail of procurement, storage, transport, and use of both the test and reference products should be recorded.

(1) Batch Size

The batch used in the bioequivalence or other studies should satisfy the following requirements:

i) The batch size should be a minimum of 100 000 units or at least 10% of the production batch, whichever is greater. If the batch size is less than 100 000 units, the use of a smaller batch size should be motivated/justified.

ii) If the production batch size is smaller than 100 000 units, a full production batch should be used.

iii) A high level of assurance should be provided that the product and process used in the production of the product will be feasible on an industrial scale. If the product is subjected to further scale-up, this should be validated appropriately.

(2) Reference Products (comparators) *(see also EMA bioequivalence guideline)*

N.B. Products containing chemical entities/active moieties that are not registered in South Africa cannot be used as reference products in efficacy and safety studies submitted in support of an application.

Copies of the labelling (label(s) and patient information leaflet/professional information) for the reference as well as the innovator product marketed in South Africa should be provided in 3.2.R.1.2 except as under point a)(iii) below, in which case a SAHPRA approved patient information leaflet/professional information for a generic or similar product should be submitted if available.

If a different chemical form is used, it must be confirmed that the safety/efficacy profile is not altered (3.2.R.1.1.11). The confirmation may be documented/with bibliographical evidence. If well known (e.g., hydrochloride, maleate, nitrate, stearate), reference to a pharmacopoeia accepted by SAHPRA may be acceptable.

Product strengths not available in South Africa may be applied for and/or used in biostudies provided that the dose range is approved/registered in South Africa.

i) Selection of Reference Product

The reference product should be an innovator product registered by SAHPRA and should be preferably procured in South Africa. where the innovator product is not available, the market leader should be used as the reference (e.g., IMS database). Applicant must submit evidence to substantiate market leadership claim. The use of an old medicine is not acceptable.

The following options for selection of the reference product are listed in order of preference:

i) the innovator product registered and procured in South Africa; or

ii) the innovator product, registered in South Africa, for which a marketing authorisation has been granted by the health authority of a country with which SAHPRA aligns itself (see SAHPL-CRO-02_ Reliance Guideline, section 2.1), and which is to be purchased from that market; or

iii) a product from the latest edition of the WHO international comparator products for equivalent assessment of interchangeable multisource (generic) products. The primary manufacturing site is indicated in the WHO comparator list, and the comparator is to be purchased in that country, or;

iv) in the case that no innovator product can be identified – within the context of (i)–(iii) above, the choice of the reference must be made carefully and must be comprehensively justified by the applicant.

j) Reference Products for Combination Products *(see also EMA bioequivalence guideline)*

Combination products should, in general, in accordance with a) above, be assessed with respect to bioavailability and bioequivalence of individual active substances:

- Either single entity products administered concurrently (in the case of clinically justifiable combinations), or
- Using an existing combination as the reference, which should be an innovator product registered by SAHPRA on safety and efficacy data.

In the former instance, immediate release oral dosage forms containing a single API may be used as the reference.

3.2.R.1.1 Overview

3.2.R.1.1.1 Country where developed, company developed by test product synonyms.

Give a brief introductory description of the development of the test product, the innovator and test product synonyms.

3.2.R.1.1.2 The type of study(ies) submitted as proof of efficacy, i.e., bioequivalence, dissolution, comparative dissolution, or other study(ies). Give a brief description of the rationale for the different studies.

3.2.R.1.1.3 The purpose of the study or studies (more than one may be applicable):

1) comparison of the formulation to be marketed versus the formulation used in clinical trials, or
2) proof of efficacy for a multisource (generic) new dosage form/new strength medicine application, or
3) proof of efficacy of new formulation (formulation change); or
4) proof of efficacy of products manufactured by new manufacturer (manufacturer different to that of the test product - or previously approved/registered - when relevant as per the Variations Addendum); or
5) biowaiver in accordance with:
    - Similarity (for additional strengths)
    - Biopharmaceutical Classification System (BCS)
6) characterisation of the clinical trial(s) test product being applied for.

3.2.R.1.1.4 The status of the reference product

- Clinical trial formulation
- Innovator product
- Current formulation (for change of formulation)

3.2.R.1.1.5 A description of the type of study(ies), bioequivalence, dissolution, comparative dissolution, or other study(ies).

3.2.R.1.1.6 Confirmation that the data submitted have been obtained with the formulation and manufacturing process being applied for.

If the formulation and or manufacturing process being applied for is different to that of the test product the relevant requirements in accordance with the Variations Addendum and EU variations guide should be complied, and the relevant dissolution, stability and validation data included in 3.2.R.1.4, 3.2.P.8 and 3.2.P.3.5 respectively.

Please note: If the product being applied for is not identical to the test product used in the biostudy (i.e., if changes have been made to the product), the applicant is required to submit data to confirm essential similarity between the product being applied for and the test product used in the bioequivalence study. The data should include, but not be limited to, the following:

- Unit formulation, manufacturing procedure and equipment
- Site of manufacture and source of the API
- Overall product specifications and any changes with respect to analytical methods

If the reference product is expired or is not available, a batch of the reference product procured from the same country and manufacturer as the biostudy reference product should be used for dissolution testing. Please note that redoing the biostudy is not required.

3.2.R.1.1.7 Confirmation that the test product (all strengths) was manufactured by the same manufacturer and site applied for.

If the manufacturer or site being applied for is different to that of the test product the relevant requirements in accordance with the Variations guideline should be complied, and the dissolution, stability and validation data included in 3.2.R.1.4, 3.2.P.8 and 3.2.P.3.5 respectively.

3.2.R.1.1.8 Confirmation that the test product was manufactured with API(s) manufactured by the same API manufacturer as being applied for.

Proof of physico-chemical equivalence is required if the manufacturer of the API is additional or different to that stated in 3.2.S and must be included in 3.2.R.4. The relevant requirements in accordance with the Variations guideline should also be complied with and the dissolution, stability and validation data included in 3.2.R.1.4, 3.2.P.8 and 3.2.P.3.5 respectively.

3.2.R.1.1.9 A statement whether *in vivo-in vitro* correlation from the data was obtained by the method(s) used, if applicable.

In vivo-in vitro correlation data should be included in 5.3.1.3.

3.2.R.1.1.10 Motivation for the use of the particular reference product *[Refer to Selection of Reference Products i above]* The choice of reference product should be justified by the applicant. **Reference products registered in South Africa but produced in another country, the health regulatory authority of which SAHPRA aligns itself with ("foreign" reference product).**

The following additional information should be supplied when the biostudy reference product used is registered but not procured in South Africa:

1) The name and address of the manufacturing site where the reference product is manufactured.

2) The qualitative formulation of the reference product.

3) Copies of the immediate container label as well as the carton or outer container label of the reference product.

4) For modified release, evidence of the mechanism of modified release of the reference product.

5) The method of manufacture of the reference product if claimed by the applicant to be the same.

6) Procurement information of the reference product:

- Copy of licensing agreement/s if relevant
- Distribution arrangements/agreement/s if relevant
- Copy of purchase invoice (to reflect date and place o f purchase) *3.2.R.1.2.*

3.2.R.1.1.11 Motivation for the use of a pharmaceutical alternative or lower strength

3.2.R.1.1.12 Tabular summary of the information pertaining to the study products.

To facilitate evaluation a tabular summary (example on the next page) of the following information pertaining to the study products, is required.

1) Full details of the reference product(s) used as the standard for reference purposes (including e.g., the applicant, proprietary name, lot number, expiry date).

2) If the reference product is registered but not procured in South Africa, the labelling/SmPC/patient information leaflet of the reference product translated into English if not in English, as well as the professional information/patient information leaflet of the relevant innovator product in South Africa.

3) Full details of the test product (including e.g., the applicant, proprietary name, lot number, expiry date).

4) Assay of test and reference products. The assay of the test and reference products should not differ by more than 5% in assay unless justified.

5) Dissolution profiles of test and reference products (EU guideline on the investigation of bioequivalence).

6) Certificates of Analysis for the test and reference products analysed using the control procedures for description, assay, impurities, content uniformity and dissolution proposed in the submission for the test product. Include in 3.2.R.1.3.

7) A CoA of the API used in the test product study-batch.

8) The size of the study/test product batch.

Table 2: Tabular summary of study products

- *For example, a biostudy may be adapted as appropriate to include the innovator product in South Africa or other information.*
    - *If the biostudy reference product is not the innovator registered and on the market in South Africa, an extra column for the details of the innovator product in South Africa corresponding to that biostudy reference product is appropriate. Extra rows may be included as required to reflect, e.g., more detailed dissolution results or similarity factor values, or page numbers of documents.*

Product Information	Reference Product(s) of Biostudies	Corresponding RSA Reference product	Test product Formulation Applied For
Name			
Biostudy			
Batch no and expiry date			
HCR/PHCR			
Country where purchased/ manufactured			***
Manufacturing site			
Assay results*			
Impurities			
Dissolution results			
Comparative dissolution			
Batch no and expiry date			
Assay results %			
Comp. dissolution results			
Similarity f2			
Source of API	*if known/relevant*	*if known/relevant*	**
Batch size	*if known/relevant*	*if known/relevant*	

Product status	Clinical trial formulation *or* Innovator product *or* Current formulation (for change of formulation) *as the case may be*	Clinical trial formulation *or* Innovator product *or* Current formulation (for change of formulation) *as the case may be*	
CoAs, test and reference products and API of test product study batch	3.2.R.1.3 p	3.2.R.1.3 p	3.2.R.1.3 p
Patient information leaflet /Professional information / SmPC	3.2.R.1.2 p	3.2.R.1.2 p	Module 1.3

Product Information	Reference Product(s) of Biostudies	Corresponding RSA Reference product	Test product Formulation Applied For
Label	3.2.R.1.2 p		Module 1.3
Justification if the difference between test and reference is more than 5 %* * Proof of physical/chemical equivalence is required if the manufacturer is different to that in 3.2.S* **** Motivation and supporting data are required if the manufacturer and/or the site applied for is different to the manufacturer and/or site of the test product*			

3.2.R.1.1.13 The formulation of each of the dosage strengths of the test product(s) in tabular form in the case of an application for a biowaiver of proportionally similar dosage strengths.

3.2.R.1.1.14 A discussion and conclusion of the outcomes of each of the studies and other relevant information to support and justify acceptance of product efficacy.

3.2.R.1.1.15 An overall conclusion

It is important to include, in addition to the individual study conclusions, an overall conclusion of all the data submitted to support and justify product efficacy and where relevant, safety.

3.2.R.1.1.16 References

3.2.R.1.2 Reference product/s (local and foreign) (identification/documentation):

1) Package inserts
2) Label and carton
3) Qualitative formulation
4) Proof of procurement/invoice (foreign product)

3.2.R.1.3 Certificates of Analysis:

1) Biostudy reference product
2) RSA corresponding innovator
3) Biostudy test product and any other strength
4) API of the test product
5) Before and after formulation/manufacturer/API changes

3.2.R.1.4 Pharmaceutical availability studies

Please refer to Appendix 1 for relevant guidance on in vitro studies – dissolution profile comparison.

3.2.R.1.4.1 Dissolution studies, data, and reports:

1) Dissolution profiles of the test and reference products
2) Comparative dissolution between foreign reference product and RSA registered innovator product (if applicable)
3) Comparative dissolution between different strengths of the test product (biowaiver of additional strengths)
4) Comparative dissolution between test and reference products (BCS biowaiver)
5) Comparative dissolution data in support of:
    - additional or different API manufacturer (for low solubility APIs or when particle size or polymorphic form is critical to the bioavailability of the product)
    - additional or different FPP manufacturer and/or site
    - different formulation being applied for to that of the test product

3.2.R.1.4.2 1) Other

2) Motivation for exemption of data to substantiate efficacy.

If in the opinion of the applicant no data are required to substantiate efficacy (e.g., parenteral solutions), the rationale for accepting safety and efficacy should be clearly stated and include a discussion on the excipients (refer to EMA guideline on the investigation of bioequivalence), and comparison of final product characteristics.

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

1) If an identical route of synthesis, or manufacturing process of the PPL (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)

Option 1: Certificate of Suitability of the European Pharmacopoeia (CEP)

The CEP holder should issue a signed and dated CEP letter of access to the applicant/FPP manufacturer.

In addition, a written commitment should be included that the applicant will inform SAHPRA in the event of changes, or if the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP would require additional consideration of the API data requirements (full Module 3.2.S) to support the product dossier.

Along with the application being supported by a CEP, the applicant should supply the following information in the dossier, with data summarized in the QIS and QOS.

- 3.2.S.1.3 General properties - discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and Ph.Eur. monograph, e.g., solubilities and polymorphs as per guidance in this section.

- 3.2.S.3.1 Elucidation of structure and other characteristics - studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per guidance in this section.

- 3.2.S.4.1 Specification - the specifications of the FPP manufacturer including all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that are not

controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.

- 3.2.S.4.2 / 3.2.S.4.3 Analytical procedures and validation – for any methods used by the FPP manufacturer in addition to those in the CEP and Ph.Eur. monograph.

- 3.2.S.4.4 Batch analysis - results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.

- 3.2.S.5 Reference standards or materials – information on the FPP manufacturer's reference standards.

- 3.2.S.6 Container closure system - specifications including descriptions and identification of primary packaging components. Exception: where the CEP specifies a container closure system and the applicant / FPP manufacturer declares to use the same container closure system.

- 3.2.S.7 Stability - exception: where the CEP specifies a re-test period that is the same as or of longer duration, and storage conditions which are the same or higher temperature and humidity as proposed by the applicant.

In the case of sterile APIs, data on the sterilisation process of the API, including validation data, should be included in the dossier.

Option 2: Confirmation of API Prequalification document (CPQ)

A complete copy of the WHO Confirmation of API Prequalification document should be provided in this section, together with the duly filled out authorisation box in the name of the FPP manufacturer or applicant.

The applicant should supply the following information in the dossier, with data summarised in the QOS

- 3.2.S.1.3 General properties - discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the API manufacturer's specifications
  e.g., solubilities and polymorphs as per guidance in this section.

- 3.2.S.2 In the case of sterile APIs, data on the sterilisation process of the API, including validation data, should be included in the dossier, unless it is stated on the CPQ that the API is sterile.

- 3.2.S.3.1 Elucidation of structure and other characteristics - studies to identify polymorphs and

particle size distribution, where applicable, as per guidance in this section.

- 3.2.S.4.1 Specification - the specifications of the FPP manufacturer including all tests and limits of the API manufacturer's specifications and any additional tests and acceptance criteria that are not controlled by the API manufacturer's specifications such as polymorphs and/or particle size distribution.

- 3.2.S.4.2 / 3.2.S.4.3 Analytical procedures and validation – for any methods used by the FPP manufacturer in addition to those in the API manufacturer's specifications.
- 3.2.S.4.4 Batch analysis - results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.
- 3.2.S.5 Reference standards or materials – information on the FPP manufacturer's reference standards.
- 3.2.S.7 Stability - data to support the retest period if either the proposed retest period is longer or the proposed storage conditions are at a lower temperature or humidity to that of the Prequalified API.

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 utilised 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 Comparison of the APIs

- A report (desktop comparison) pointing out the differences in the routes used, where applicable, and the differences with regard to the impurity profiles and residual solvents unless justified. The specifications for the API should make provision for these impurities and residual solvents.

3.2.R.4.2 Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the active substance from the current and proposed manufacturers/sites.

3.2.R.4.3 Confirmation of compliance with guidelines

- Confirmation of compliance with the EU variation classification guideline, stating type and category (Module 1.5.2.1). Confirmation of compliance with the applicable Stability guidelines and identification and location of the relevant data in the dossier is required (Module 1.5.2.1).

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 administrative changes, annual notifications will suffice, and SAHPRA will not require submission of updated production documents. For minor changes e.g., batch size changes, updated production documents will be required.

3.2.R.7.1 Executed production documents

Copies of the executed production documents should be provided for the batches used in the comparative bioavailability or biowaiver studies. Any notations made by operators on the executed production documents should be clearly legible.

For solid oral dosage forms, the bio-batch should, at a minimum, be one-tenth that of full production scale or 100 000 tablets or capsules, whichever is the larger.

For dosage forms that do not require a comparative bioavailability study, 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 (including addition of a new FPP manufacturing site for variations) 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 or 100 000 tablets or capsules, whichever is the larger.

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 (e.g., mixing time, mixing speed, milling screen size, processing temperature range, granulation end-point, tablet machine speed (expressed as target and range));

f) list of in-process tests (e.g., appearance, pH, assay, blend uniformity, viscosity, particle size distribution, LOD, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity, filter integrity checks) and specifications;

g) sampling plan regarding the:

i. steps where sampling should be done (e.g., drying, lubrication, compression),

ii. number of samples that should be tested (e.g., for blend uniformity testing of low dose FPPs, blend drawn using a sampling thief from x positions in the blender),

iii. frequency of testing (e.g., weight variation every x minutes during compression or capsule filling);

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 QOS & QIS document.

9. Reference

The reference documents listed below are intended to provide additional information. However, it should be noted that documents identified do not represent a comprehensive list of all reference documents and may be further supplemented:

- "European Medicines Agency quality guidelines" EMA quality guidelines
- "European Medicines Agency Bioequivalence guidelines" https://www.ema.europa.eu/en/investigation-bioequivalence-scientific-guideline
- "European Medicines Agency variation classification guidelines for orthodox human and veterinary medicines" EU variation classification guidelines
- "International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use" https://www.ich.org/page/ich-guidelines
- "Southern African Development Community guidelines" https://zazibona.com/guidelines/
- "World Health Organisation" https://extranet.who.int/pqweb/

10.Validity

This guideline is valid for a period of 5 years from the effective date of revision and replaces SAHPGL-PEM-02_V8_ Quality-and-Bioequivalence-Guideline. It will be reviewed on this timeframe or as and when required.

Appendix 1: In vitro studies – Dissolution profile comparison

Please refer to the EMA Bioequivalence guideline for more information

For biowaiver purposes the dissolution profiles in three media (and the main/specification dissolution medium if not one of the three dissolution media, as described in the ICH M9 guideline), of the test and the reference product should be tested for similarity. The f_2 similarity factor should be used to compare dissolution profiles from different products and/or strengths of a product. An f_2 value ≥ 50 indicates a sufficiently similar dissolution profile such that further *in vivo* studies are not necessary. For an f_2 value < 50, it may be necessary to conduct an *in vivo* study. However, when both test and reference products dissolve 85% or more of the label amount of the API in ≤15 minutes similarity is accepted without the need to calculate f_2 values.

1. Proportionally similar formulations

a. Proportionally Similar Dosage Forms/Products

Pharmaceutical products are considered proportionally similar in the following cases:

- When all APIs and inactive pharmaceutical ingredients (IPIs) are in exactly the same proportion between different strengths (e.g., a 100 mg strength tablet has all API and IPIs exactly half of a 200 mg strength tablet and twice that of a 50 mg strength tablet).

- When the APIs and IPIs are not in exactly the same proportion but the ratios of IPIs to the total mass of the dosage form are within the limits defined by table 3 below.

- When the pharmaceutical products contain a low concentration of the APIs (e.g., less than 5%) and these products are of different strengths but are of similar mass. The difference in API content between strengths may be compensated for by mass changes in one or more of the IPIs provided that the total mass of the pharmaceutical product remains within 10 % of the mass of the pharmaceutical product on which the bioequivalence study was performed. In addition, the same IPIs should be used for all strengths, provided that the changes remain within the limits defined by table 3 below.

Table 3: Change in inactive pharmaceutical ingredient (IPI) range:
- Immediate release solid oral dosage form.
- Modified release solid oral dosage form (only non-release controlling IPIs)

DESCRIPTION		DOCUMENTS WHICH MAY BE AFFECTED/REQUIRED
IPI (m/m) per total target dosage form mass	**% IPI**	Formulation; final product specifications and control procedures; manufacturing procedure.
Filler	≤ 5 %	
Disintegrant:		
Starch	≤ 3 %	
Binder	≤ 1 %	
Lubricant		
Ca/Mg stearate	≤ 0.25 %	
Other	≤ 1 %	
Glidant:		
Talc	≤ 1 %	
Other	≤ 0.1 %	
Film-coat	≤ 1 %	
The total effect of all IPI changes should not be more than 5 % *m/m* relative to the total dosage mass. Calculation example		
API	500mg	
Total IPIs	100 mg	
Total dosage mass	600 mg	
Lactose: change from 30 to 45 mg (=15/600)	=+2.5 %	
Cellulose: change from 50 to 35 mg (-15/600)	=-2.5 %	
Absolute total change	= 5 %	

A prerequisite for qualification for a biowaiver based on dose-proportionality of formulations is that:

- The multisource product at one strength has been shown to be bioequivalent to the corresponding strength of the reference product.
- The further strengths of the multisource product are proportionally similar in formulation to that of the studied strength.

When both criteria are met and all the dissolution profiles of the further dosage strengths are shown to be

similar to the one of the studied strengths on a percentage released vs. time basis, the biowaiver procedure can be considered for the further strengths.

b. Immediate release tablets

When the pharmaceutical product is the same dosage form but of a different strength and is proportionally similar in its API and IPIs, a biowaiver may be acceptable.

c. Modified Release Products

A *modified-release dosage form* is one for which the API release characteristics of time course and/or location are chosen to accomplish therapeutic, or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms. Delayed-release and extended-release dosage forms are two types of modified-release dosage forms.

Delayed-release dosage forms - A delayed-release dosage form is one that releases an API(s) at a time other than promptly after administration.

Extended-release dosage forms - An extended-release dosage form is one that allows at least a twofold reduction in dosing frequency or significant increase in patient compliance or therapeutic performance as compared to that presented as a conventional dosage form (e.g., as a solution or a prompt drug-releasing, conventional solid dosage form).

The terms-controlled release, prolonged action, and sustained release are used synonymously with extended release. This document uses the term extended release to describe a formulation that does not release an API immediately after oral dosing and that also allows a reduction in dosage frequency. This nomenclature accords generally with the USP definition of extended release but does not specify an impact on dosing frequency. The terms-controlled release and extended release are considered interchangeable in this guidance.

Modified release products include delayed release products and extended (controlled) release products. In general, bioequivalence studies are required. In addition to the studies required for immediate release products, a food-effect study is necessary. Multiple dose studies are generally not recommended.

Beaded Capsules - Lower Strength

For extended-release beaded capsules where the strength differs only in the number of beads containing the API, a single-dose, fasting BE study should be carried out on the highest strength. A biowaiver for the lower strength based on dissolution studies can be requested. Dissolution profiles in support of a biowaiver should be generated for each strength using the recommended dissolution test methods and media.

d. Tablets – Lower strength

For extended-release tablets when the pharmaceutical product is:

i. in the same dosage form but in a different strength, and

ii. is proportionally similar in its APIs and IPIs, and

iii. has the same drug/API release mechanism,

An *in vivo* BE determination of one or more lower strengths may be waived based on dissolution testing as previously described. Dissolution profiles should be generated on all the strengths of the test and the reference products.

When the highest strength (generally, as usually the highest strength is used unless a lower strength is chosen for reasons of safety) of the multisource product is bioequivalent to the highest strength or dose[2] of the reference product, and other strengths are proportionally similar in formulations and the dissolution profiles are similar between the dosage strengths, biowaiver can be considered to lower/ other strengths.

[2] Dose included in the dosage range of the SAHPRA-approved package insert of the innovator product registered in South Africa

2. Reference Products registered in South Africa but procured in another country, the regulatory authority of which SAHPRA aligns itself with

Bioequivalence studies submitted where a foreign reference product has been used, will require demonstration of equivalence between the foreign product and the innovator product marketed in South Africa. If the reference product is not the current innovator product available on the SA market, then the reference product may be procured from another country provided that it complies with the requirements specified.

Dissolution profiles of the test and reference products should be compared for similarity as described in the EMA Bioequivalence guideline for each of the three specified media irrespective of the solubility and/or stability profiles. Further evidence in the main/specification dissolution medium, if not one of the required dissolution media, should be provided.

3. Variations

Although this guideline comments primarily on registration requirements for multisource pharmaceutical products, in vitro dissolution testing may also be suitable to confirm similarity of product quality and performance characteristics with minor formulation or manufacturing changes after approval.

Appendix 2: Sameness declaration for reliance-based evaluation models

To be completed by the applicant:

Application for {Application number, if allocated} {Proposed product name}	{Name of recognised regulatory authority}
Registration date	
Date(s) of approval of post-registration variation(s) if applicable	

I, {Full name}, {Job title} at {Company's full legal name}, hereby confirm the following for application {Application number, if allocated} submitted to the South African Health Products Regulatory Authority (SAHPRA) on {Date of application submission}:

- The information and documentation provided in support of this submission for registration is true and correct.
- The product submitted for registration with SAHPRA is the same as the product registered with the above-specified regulatory authority or authorities.
- The technical information in the dossier submitted to SAHPRA for registration is the same as the technical information approved by the above-specified regulatory authority or authorities, taking into account all variations that the above-specified regulatory authority or authorities have approved since registration.

The "same" product is characterised by:

- The same product dossier content;
    - **Note**: For WHO PQ vaccines submitted to the WHO in Product Summary File (PSF) format, this content needs to be transferred to CTD format
- The same manufacturing chain, processes and control of materials and finished product, and in the case of vaccines also by the same batch release scheme;
- The same active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) specifications
- The same essential elements of product information for pharmaceutical products, and in the case of vaccines, by the same product information, packaging presentation and labelling.

Information which need not be the same:

- Module 1, i.e., region-specific administrative requirements
- Module 3.2.R, i.e., region-specific requirements to enable bioequivalence evaluation with a

country-specific comparator if required

Minor differences which are not considered essential may include differences in administrative information, brand name, format, and level of detail of product information as per regional requirements, labelling of internal and external packaging and language of product information.

I hereby confirm that if documents have been submitted by [*Insert full company legal name here*] which were received by the above-specified regulatory authority or authorities, these documents are complete and unredacted.

Full name of Responsible pharmacist / Person authorised to communicate with the authority: Job title, company:

Email address:
Telephone number:

Signature:

Date: Place:

https://www.sahpra.org.za/document/reliance-guideline/