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MULTIPLE APPLICATIONS GUIDELINE

This guideline is intended to provide recommendations to applicants wishing to submit multiple applications for the registration of medicines. It represents the South African Health Products Regulatory Authority's (SAHPRA) current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. SAHPRA reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. SAHPRA is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. 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 on the website, www.sahpra.org.za.

Document History

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3	Published for Implementation • new applications • Applications in the System	December 2015 With immediate effect
4	Change from MCC to SAHPRA Changes to Section 1.2, 5 (old 6) and 7 (old 5) Section 5 moved to 7 New section 6	May 2019
5	Update to new SAHPRA guideline template Added sections 1.2, 2, 3.3, 5 & 6. Changes to Section 4.1, 4.5, 4.6, 4.7 & 4.8.2. Deleted sections 4.4, 4.8.1, 4.8.3, 4.8.4 & 5.	December 2023 Implementation date: 01 January 2024

DR BOITUMELO SEMETE-MAKOKOTLELA
CHIEF EXECUTIVE OFFICER

Contents

Glossary

Abbreviation/ Term	Meaning
API	Active Pharmaceutical Ingredient (also known as Drug Substance)
Clone	Application submitted by the HCR of the innovator as a copy of its own product under a different proprietary name at any stage during the product life cycle of the registered product.
Duplicate or Multiple	Two or more applications submitted simultaneously by the same applicant, which are identical in every aspect except for the proposed proprietary name(s) and include duplicate or multiple applications of innovator and generic products.
eCTD	Electronic Common Technical Document
FPP	Finished Pharmaceutical Product
HCR	Holder of Certificate of Registration
Master dossier	Is the first or original application submitted for registration on which the duplicate, clone and replica applications is based.
NCE	New Chemical Entity
QIS	Quality Information Summary
QOS	Quality Overall Summary
Replica	A copy of an already registered generic product, submitted by the same or by another applicant at any stage during the product life cycle of the registered product.

1. INTRODUCTION

Applicants often submit multiple applications for the same product under different proprietary names.

Generally, in practice the first application is compiled by the applicant and then additional applications for the additional product names are prepared by replacing the proprietary name of the first, or master application, with each of the additional proprietary names.

These types of submissions are generally referred to as 'duplicates' / 'multiples' or in Europe as 'clones' and should not be confused with the applications for the same molecule from different Applicants, final product (FPP) and active pharmaceutical ingredient (API) manufacturers.

Sometimes the additional applications are not submitted together with the first or master application but can be submitted many years later.

1.1 Purpose

The aim of this guideline is to assist applicants wishing to submit multiple applications for the registration of medicines including post-registration variations. The types of medicine, which this guideline refers to, include applications for a new chemical entity (NCE), new biological medicine, a multisource (generic) product or a biosimilar product, including clones and replicas.

1.2 Scope

A **duplicate** application may be for an innovator or a generic or a biosimilar product.

A duplicate application must be submitted at the same time as the master application. If, for example, an application is submitted days, months or years after the master, it is regarded as **not** being linked to a master and would follow the normal evaluation process.

An application for a **clone or replica** is submitted after the registration of the original product.

2. LEGAL PROVISION

There are no legal provisions for this guideline.

3. GENERAL

3.1 Process for duplicate applications

3.1.1 A single "master" dossier for an application for registration or to support the submission of post-registration variations is required with a module 1.2.1 for each proprietary name. The application must be accompanied by photographs of all dimensions of the sample in the final primary packaging and of the sample itself and a *single* professional information and patient information leaflet where the product name is indicated as [PRODUCT NAME]. A list of all the proposed proprietary names must be included in module 1.5.3. The application must be accompanied by the applicable application fees for each application.

3.1.2 The applicant must indicate which proprietary name should be regarded as the "master"; if not indicated the invented name will usually be regarded as the master.

3.1.3 Additional product applications (same API and source, same indications, same FPP manufacturer)

not linked to the master will not be handled as a duplicate application. In this case, each application will stand on its own, and be evaluated on its own, and a Technical Evaluation Unit query letter on one product may not be applied and responded to for the other applications.

An application number is allocated to the master dossier, and for each of the additional proprietary names.

3.1.4 The single master dossier is fully evaluated by all the relevant Technical Evaluation Units and all the proposed proprietary names for the master and duplicate dossiers are reviewed by the Names and Scheduling Unit.

3.1.5 When approved by all Technical Evaluation Units the master product and all the duplicates are registered.

3.1.6 A registration certificate is issued for each approved proprietary name.

3.1.7 Pre- and Post-registration changes are affected to and reviewed only for the single master dossier and is implemented across all the duplicate/clone/replica dossiers, as applicable.

3.1.7.1 If an application is made for a variation which is *not intended* to be implemented across all the duplicate/clone/replica dossiers, the affected dossier must be delinked/submitted separately and will be a stand-alone dossier. Such an application requires submission of a complete approved baseline dossier, sequence 0000 together with the relevant variation and the applicable fee(s) in sequence 0001.

The variation application and applicable fee for an amended registration certificate for the delinked dossier should be applied for after approval of the technical variation in a follow-up sequence. The approval letter of the technical variation should be included in the certificate variation application. This variation application should be addressed to both the Inspectorate and Certification Variation Units.

3.2 Clones

3.2.1 Where the original registered dossier is still in paper format, a submission in eCTD format will be required as for a baseline submission, as sequence 0000. The application for the clone will then be sequence 0001.

Refer to guideline SAHPGL-HPA-10 Submission in eCTD format.

Include copies of the latest Authority letters of

- approval of any variations or variation summary from the DVP to the registered product, including the PI and PIL,
- the allocation of the shelf-life of the product, and
- the allocation of the retest/shelf-life period of the API/s

as bookmarked annexes to the letter of application in section 1.0

At this stage different strengths should be combined into one dossier, with the first application number being used as the eCTD identifier.

An application for a clone should not be submitted if there are amendments to the registered product pending Authority approval.

3.2.2 For an existing eCTD of a registered product, the clone should be submitted in a similar manner to a duplicate application.

The letter of application (M1.0), M1.2.1, 1.2.2.1, 1.2.2.4, labelling (1.3.1.1, 1.3.2, 1.3.3) reflecting the proposed proprietary name as [PRODUCT NAME] and 1.5.3 reflecting all proprietary names should be submitted.

The name/s and application number/s of the clone/s should be included in the envelope under Multiple/Duplicate Applications.

3.2.3 The following documents for the clone application should be included in M1.10

- Declaration of sameness for the clone, signed and dated by a Commissioner of Oaths
- Registration certificate for the registered product

3.2.4 The updated QIS / QOS should be included in M3.2.R.8.

3.3 Replicas

3.3.1 Replica application from the same Applicant

3.3.1.1 Where the original registration dossier is still in paper format, a submission in eCTD format will be required as for a baseline submission, as sequence 0000. The application for the replica will then be sequence 0001.

Refer to guideline 2.23 Submission in eCTD format.

Include copies of the latest Authority letters of

- approval of any variations or variation summary from the DVP to the registered product, including the PI and PIL,
- the allocation of the shelf-life of the product, and
- the allocation of the retest /shelf-life period of the API/s

as bookmarked annexes to the letter of application in section 1.0

At this stage different strengths should be combined into one dossier, with the first application number being used as the eCTD identifier.

An application for a replica should not be submitted if there are amendments to the registered product pending Authority approval.

3.3.1.2 For an existing eCTD of a registered product, the replica should be submitted as for a duplicate application. The application for the replica will then be submitted in a follow-up sequence.

The letter of application (M1.0), M1.2.1, 1.2.2.1, 1.2.2.4, labelling (1.3.1.1, 1.3.2, 1.3.3) reflecting the proposed proprietary name as [PRODUCT NAME] and 1.5.3 reflecting all proprietary names should be submitted.

3.3.1.3 The following documents for the replica application should be included in M1.10

- Declaration of sameness for the replica, signed and dated by a Commissioner of Oaths
- Registration certificate for the registered product

3.3.1.4 The updated QIS /QOS should be included in M3.2.R.8.

3.3.2 Replica application from different Applicants

3.3.2.1 Where the original registration is still in paper format, a submission in eCTD format will be required as for a baseline submission, as sequence 0000.

Refer to guideline SAHPGL-HPA-10 Submission in eCTD format.

Include copies of the latest Authority letters of

- approval of any variations or variation summary from the DVP to the registered product, including the PI and PIL,
- the allocation of the shelf-life of the product, and
- the allocation of the retest /shelf-life period of the API/s

as bookmarked annexes to the letter of application in section 1.0

At this stage different strengths should be combined into one dossier, with the first application number being used as the eCTD identifier.

The application for a replica should not be submitted until all amendments applied for have been approved for the registered product.

3.3.2.2 The following documents for the replica application should be included in M1.10

Declaration of sameness for the replica, signed and dated by a Commissioner of Oaths
Letter of Permission from the applicant with the registered product allowing the second applicant to use their data.

- Registration certificate for the registered product

3.3.2.3 The QIS / QOS should be included in M3.2.R.8.

4. FEES PAYABLE

The application fee for multiple applications will be as follows:

4.1.1 The fee for the master application will remain as published.

4.1.2 The fee for the duplicates will be same as for the master.

4.1.3 The fee for the clone/replica will be the same as for the registered product, according to the current fees.

4.1.4 For variations related fees, refer to the Explanatory note on general fees payable to the Quality variations (Type 1A, 1B & II) for medicinal products for human use.

5. REFERENCES

The following related documents are referenced:

5.1 Related Guidelines

- SAHPGL-HPA-10 Submission in eCTD format
- SAHPGL-HPA-07 General Information Guideline

5.2 GLF-HPA-07A Declaration of Sameness letter

5.3 GLF-HPA-07B Letter of Permission

6. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision and replaces the Multiple_applications_May19_v4/2.40. It will be reviewed on this timeframe or as and when required.