

GUIDELINE FOR THE API MASTER FILE (APIMF) PROCEDURE

JAN 2021

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines and variations. It represents the Authority's current thinking on the safety, efficacy and quality of medicines. It is not intended as an exclusive approach. SAHPRA reserves the right to request any additional information to establish the safety, efficacy and quality of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The Authority is committed to ensure that all registered medicines will be of the required safety, efficacy and quality. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available on the SAHPRA website: www.sahpra.org.za

Document History

Version 1 draft for comment	October 2019
Final Guideline for implementation	1 June 2020
Version 2 final guideline for implementation	21 January 2021

List of abbreviations and definitions

API	Active Pharmaceutical Ingredient
APIMF	Active Pharmaceutical Ingredient Master File
API manufacturer	A party involved in the manufacturing chain of the API.
APIMF number	A unique reference number allocated to the APIMF upon receipt of applications
APIMF record	SAHPRA's record of an approved API + manufacturer combination, evidenced by a unique APIMF reference number.
Applicant	The applicant can also be called the proposed holder of the certificate of registration.
Category A	Medicines which are intended for use in humans and which are, without manipulation, ready for administration, including packaged preparations where only a vehicle is added to the effective medicine.
Category C	Medicines intended for veterinary use which are, without further manipulation, ready for administration, including packaged preparations where only a vehicle is added to the effective medicine.
Category D	Complementary medicines intended for use in humans and animals, which are, without manipulation, ready for administration, including packaged preparations where only a vehicle is added to the effective medicine.
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
Closed part of the APIMF	An applicant generally does not have access to this information, which is confidential intellectual property of the API manufacturer, including individual steps of the manufacturing method and manufacturing quality control procedures.
CTD	Common Technical Document
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
FPP	Finished Pharmaceutical Product
GPS	Global Positioning System
HCR	Holder of certificate of registration

Manufacturing chain	A clear flow chart or written text explaining the manufacturing and distribution route of the API from the first starting materials to the final API as delivered to the applicant/HCR.
ME&R	Medicines Evaluation and Research
Open part of the APIMF	The applicant must have access to this information, and it must be sufficient for the applicant to ensure the suitability of the API used in the finished pharmaceutical product.
QOS	Quality Overall Summary
Quality	The suitability of either an API or FPP for its intended use. This term includes such attributes as the identity, strength and purity.
RRA	Recognised regulatory authority
SAHPRA	South African Health Products Regulatory Authority
SCoRE	Summary of Critical Regulatory Elements
SMF	Site Master File

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1. Introduction

1.1. Background

An Active Pharmaceutical Ingredient Master File (APIMF) contains all the required information for the quality¹ evaluation of an API. The APIMF is comprised of two parts:

- **The open part²:** The applicant must have access to this information, and it must be sufficient for the applicant to ensure the suitability of the API used in the finished pharmaceutical product (FPP)
- **The closed part³:** The applicant does not have always access to this information, which is confidential intellectual property of the API manufacturer, including a detailed description of the manufacturing process (with individual steps⁴), manufacturing quality control procedures, process validation etc.

Please see Appendix 1 of this document for a high-level overview from the European Medicines Agency (EMA) on content guidelines for the open part versus the closed part of the APIMF.

Generally, API manufacturers share only the open part of the APIMF with the applicants to whom they supply the API. Applicants therefore only submit the open part of the APIMF in a new registration application. However, SAHPRA requires both the open and closed part of the APIMF to evaluate an API's quality. Previously, obtaining the closed part necessitated back-and-forth communication with the API manufacturer through the applicant.

Going forward, SAHPRA will have an APIMF Procedure in place to avoid this, and to achieve other objectives.

1.2. Objectives

The objectives of the APIMF⁵ Procedure are as follows:

- a. To ensure that the API manufacturer's proprietary information is managed confidentially end-to-end:
 - Communication on the closed part of the dossier is kept separate from that of the open part (i.e. the applicant will not receive queries on the closed part, which could contain sensitive information). The applicant will be notified that questions to the APIMF holder have been submitted.
 - A SAHPRA submission portal with strict access permissions for submission of the APIMF and restricted parts
 - The APIMF will be stored electronically, with strict access permissions.
- b. To allow one evaluation of an API from a specific manufacturing site to be used across multiple finished pharmaceutical product (FPP) evaluations, reducing quality evaluation timelines.

1.3. Scope

Until further communication is issued, the APIMF Procedure will apply exclusively to Category A medicines. This does not preclude a modified APIMF Procedure being applied to Category C or Category D medicines in the future.

¹ Can be referred to as Chemistry, Manufacturing and Controls (CMC).

² Can be referred to as the Applicant's Part (AP).

³ Can be referred to as the Restricted Part (RP).

⁴ This can include starting materials, intermediates, reaction conditions, temperature, test methods, data of critical steps, in-process control procedures and process validation data.

⁵ Can be referred to by different documents or regulators as the DMF (Drug Master File), DSMF (Drug Substance Master File) and ASMF (Active Substance Master File)

The APIMF Procedure is non-applicable to the following categories of medicines:

- **Pre-evaluated APIs:**
 - APIs with a certificate of suitability of monographs of the European Pharmacopoeia (CEP) from the European Directorate for the Quality of Medicines (EDQM)
 - APIs that are pre-qualified by the World Health Organisation (WHO)
- **Biological active substances:**
 - The concept of the APIMF is non-applicable to biological active substances. In line with EMA's view (see Annex 5 of EMA's [Guideline on Active Substance Master File Procedure](#)), the characterisation and determination of a biological active substance's quality requires extensive knowledge of the manufacturing process and its controls, and the applicant therefore requires full and transparent access to all quality-related data.

The APIMF Procedure should always be associated with a new registration or variation application, i.e. SAHPRA will not create an APIMF record for an API that is not part of an FPP intended to be registered in South Africa. Please note that the APIMF Procedure may or may not be used when there is no confidentiality issue between the applicant / FPP manufacturer and the API manufacturer, i.e. when they are the same company. Should the company want to use the APIMF for future submissions then it is advised that they apply for the APIMF procedure.

2. New registrations

Please note that the APIMF Procedure will be applicable within 6 months of the publication of this guideline for new registration applications that fall within the scope of the APIMF Procedure. This does not apply to applications with API(s) pre-qualified by the WHO PQ or with a CEP from the EDQM, or applications for biological products.

2.1. Submission requirements

Prior to submitting a new registration application, the applicant must obtain the following from the API manufacturer:

- A copy of the latest version of the open part of the APIMF
- A copy of the QOS of the latest version of the open part of the APIMF
- Letter of access (Appendix 2 of this document)
- APIMF number, if allocated

2.1.1. Existing APIMF record

The applicant must include the letter of access and reference to the APIMF number in their new registration application to SAHPRA:

- The letter of access should be included in module 1.2.2.6.
- The APIMF number should be referenced in the application letter, as well as in the relevant parts of the Summary of Critical Regulatory Elements (SCoRE) document.
- SAHPRA's other submission requirements must be adhered to, and the full dossier must be submitted, including the open part of the APIMF.

2.1.2. No existing APIMF record

If the API manufacturer has not been allocated an APIMF number for that specific API, this means that an APIMF record has not been created by SAHPRA for the specific API + manufacturer combination.

In this case, the applicant should still include the letter of access in their new registration application. In addition, the applicant must request the API manufacturer to submit the following directly to SAHPRA:

- Submission form (Appendix 3 of this document)
- If applicable, reliance documentation (detailed in Appendix 3 of this document)
- The APIMF (both open and closed parts)

The Common Technical Document (CTD) structure applies to the APIMF. The granularity and placement of documents should follow SAHPRA's existing guidelines. For the submission of an initial APIMF, the relevant modules are as follows:

- Module 1.0: Submission letter (in place of application letter) as per Appendix 3
- Module 1.4.1: Information about the experts
- Module 2.3.S: Quality Overall Summary (relevant section)
- Module 1.10: Reliance documentation (if applicable)
- Module 3.2.S: Quality information (relevant section)

The APIMF submission may be submitted in electronic or eSubmission format, as stipulated in SAHPRA's guidelines, but documents should be clearly labelled as closed part (CP) or open part (OP)⁶.

Reliance can be used for the APIMF. If the same APIMF is on record with one of SAHPRA's recognised regulatory authorities⁷ (RRAs), the API manufacturer can submit relevant documentation (approval letters, assessment reports) for the APIMF in Module 1.10 to expedite the evaluation process.

A situation may arise where multiple applicants submit applications for the same new API + manufacturer combination (i.e. where there is no existing APIMF record) at a similar time. If an API manufacturer has submitted the submission form and APIMF, but has not yet received an APIMF reference number, the date of submission can be referenced in the letter of access for subsequent applicants until the APIMF reference number is created.

It is the API manufacturer's responsibility to notify the applicants and SAHPRA about any changes to the open and/or closed part of the APIMF, so that applicants can update all affected dossiers accordingly.

The API manufacturer can submit the submission form to SAHPRA via the following method:

- a) The submission form should be shared with SAHPRA via email, at the following email address: APIMF@sahpra.org.za. The subject line of the email should clearly reference the associated FPP application as follows: Application number of FPP_Applicant name_API name_e.g. 123456 by XYZ Pharmaceuticals_Dolutegravir Sodium
- b) The documents will then be shared with SAHPRA via a secure SAHPRA submission portal. Information on using this portal will be shared with the APIMF holder once the Submission form has been received or by contacting APIMF@sahpra.org.za.

⁶ Documents can also be labelled applicant's part (AP) and restricted part (RP).

⁷ Please see section 5.2 of SAHPRA's Quality and Bioequivalence Guideline for the list of RRAs.

The applicant must ensure that SAHPRA receives the submission form and the APIMF to arrive at approximately the same time as the registration application, i.e. not more than one month before and not later than one week after the application is received. If the aforementioned documents are not received within this timeframe, the application could be rejected. Note that SAHPRA will no longer receive any hard copies or couriered mail of the restricted part and complete APIMF.

2.2. Evaluation process

2.2.1. Existing APIMF record

The full dossier (including the open and closed parts of the APIMF) will undergo screening to ensure that all the required documents listed under 2.1.1 *Existing APIMF record* have been submitted.

Upon evaluation of the API, SAHPRA will reference the APIMF number in evaluating Module 3.2.S. The APIMF number reference will be sufficient proof that the API + manufacturer combination has been previously evaluated and quality evaluation of the API (Module 3.2.S) can be bypassed.

2.2.2. No existing APIMF record

The dossier will undergo screening to ensure that all the required documents listed under 2.1.2 *No existing APIMF record* have been submitted. SAHPRA will communicate directly with the API manufacturer regarding screening queries on the closed part of the APIMF.

SAHPRA will evaluate the API (Module 3.2.S) in a separate report to the rest of the dossier. This evaluation report will be stored securely by SAHPRA. Evaluation queries for the closed part of the APIMF will be sent directly to the API manufacturer. Evaluation queries for the open part of the APIMF will be sent to the applicant and the APIMF holder.

Once the API + manufacturer combination has been evaluated, SAHPRA will send an outcome letter to the API manufacturer, with a unique APIMF number for the specific API. The API manufacturer will be responsible for sharing this APIMF number (in the letter of access) with other applicants whose products use the API in question.

3. Variations

The APIMF holder, i.e. the API manufacturer, is responsible for keeping the content of their APIMF updated with respect to the actual synthesis / manufacturing process and controls. The quality control methods should be kept in line with the current regulatory and scientific requirements.

The applicant, on the advice of the APIMF holder, will submit a variation to SAHPRA. If the variation is contained in the closed part of the APIMF, the applicant must send the variation and advise the APIMF holder to submit the detail directly to SAHPRA.

The APIMF holder shall not make any changes to the content of the APIMF that may affect the quality or performance of the FPP without informing each relevant applicant and/or HCR, as well as SAHPRA. The notification to SAHPRA should be done through email to APIMF@sahpra.org.za, referencing the APIMF number, if allocated.

It is the applicant's and/or HCR's responsibility to ensure that these changes have been approved by SAHPRA prior to using the API in the manufacture of the FPP. For a post- registration change that affects the APIMF, it is the responsibility of each individual HCR to submit a variation application to SAHPRA.

3.1. Submission requirements

3.1.1. Existing APIMF record

All variations to a product with an existing APIMF record must include a reference to the APIMF number. Apart from the APIMF number reference, the variation application submission follows the exact requirements of the latest relevant guidelines:

- Variations Addendum for Orthodox Medicines [2.08],
- Quality and Bioequivalence Guideline [2.02]

The application should clearly indicate the change being proposed in the Tabulated Schedule of Amendments in Module 1.5.2.1. These guideline may be accessed here: <https://www.sahpra.org.za/orthodox-medicines/>

Note: No variation application for a registered product with an APIMF number will be considered for evaluation without direct reference to the APIMF number in the application.

3.1.2. No existing APIMF record

If a registered product does not have an associated APIMF number, the variation application submission follows the exact requirements as outlined in 2.1.2 above and the latest relevant guidelines:

- Variations Addendum for Orthodox Medicines
- Quality and Bioequivalence Guideline

The application should clearly indicate the change being proposed in the Tabulated Schedule of Amendments in Module 1.5.2.1.

Note: SAHPRA may request a full APIMF (Open and Restricted part) for variations affecting the restricted part of the APIMF of a registered product.

3.2. Evaluation process

3.2.1. Existing APIMF record

The evaluation of a proposed change to the APIMF will be done for the first variation application. If more than one HCR submits the same variation application, it will not be re-evaluated in full. SAHPRA will verify the sameness of the variation applications, looking at the content and the APIMF reference number, and reject or approve the subsequent applications based on the initial evaluation.

If there are specific evaluation queries on the closed part, these will be sent directly to the API manufacturer. The APIMF report kept on record will be updated with the latest information (approved variations) for future reference.

3.2.1. No existing APIMF record

If a registered product does not have an associated APIMF number, evaluation of a variation application follows the evaluation process in point 2.2.2 above, as well as exact requirements of the latest relevant guidelines:

- Variations Addendum for Orthodox Medicines [2.08]
- Quality and Bioequivalence Guideline [2.02]

Appendix 1: Overview of APIMF contents

Module	Content	Open part	Closed part
3.2. S.1	General information	x	
3.2. S.1.1	Nomenclature	x	
3.2. S.1.2	Structure	x	
3.2. S.1.3	General properties	x	
3.2. S.2	Manufacture	x	x
3.2. S.2.1	Manufacturer(s) ⁸	x	
3.2. S.2.2	Description of manufacturing process and process controls	a)	b)
3.2. S.2.3	Control of Materials		x
3.2. S.2.4	Control of critical steps and intermediates	c)	d)
3.2. S.2.5	Process validation and/or evaluation		x
3.2. S.2.6	Manufacturing process development		x
3.2. S.3	Characterisation	x	
3.2. S.3.1	Elucidation of structure and other characteristics	x	
3.2. S.3.2	Impurities	x	e)
3.2. S.4	Control of drug substance	x	
3.2. S.4.1	Specification	x	
3.2. S.4.2	Analytical procedures	x	
3.2. S.4.3	Validation of analytical procedures	x	
3.2. S.4.4	Batch analysis	x	
3.2. S.4.5	Justification of specification	x	f)
3.2. S.5	Reference standards or materials	x	
3.2. S.6	Container closure system	x	
3.2. S.7	Stability	x	
3.2. S.7.1	Stability summary and conclusion	x	
3.2. S.7.2	Post-approval stability protocol and stability commitment	x	
3.2.S.7.3	Stability data	x	

⁸ Including all companies involved in the manufacture of the active substance, including control/in process testing sites, intermediate manufacturers, milling and sterilisation sites.

- a) Flow chart and short description is regarded as sufficient if detailed information is presented in the closed part. However, full validation data on the sterilisation process may be requested in the open part (in cases where there is no further sterilisation of the final product).
- b) Detailed information
- c) As far as the information is also relevant for the applicant.
- d) As far as information is related to the detailed description of the manufacturing process and as far as information is not relevant for the applicant.
- e) In so far as the information is related to the detailed description of the manufacturing process and in so far as the APIMF holder sufficiently justifies that there is no need to control these impurities in the final API.
- f) As far as information is related to the detailed description of the manufacturing process, control of materials and process validation.

Appendix 2: Letter of access template

From APIMF holder⁹ on headed paper

The Chief Executive Officer

South African Health Products Regulatory Authority

[Include address as per SAHPRA website, <https://www.sahpra.org.za/Contact>]

Letter of access for SAHPRA, in reference to APIMF record [APIMF number, if allocated]

Name of API: [Fill in here]

APIMF holder: [Fill in here]

The aforementioned APIMF holder hereby authorises the South African Health Products Regulatory Authority (SAHPRA) to refer to and review the aforementioned APIMF record in support of the following new registration application(s) or variation(s) submitted by [Name of applicant] on [planned date of submission]:

Name of product: [Fill in here]

Application number: [Fill in here]

The aforementioned APIMF holder commits to ensure batch-to-batch consistency and to inform [Name of applicant] and SAHPRA of any change in the APIMF.

The aforementioned APIMF holder is hereby informed of and accepts that SAHPRA may share the evaluation reports of the aforementioned APIMF record within the regulator.

Signature for the APIMF holder (above)

Name and function: [Fill in here] Appendix 3: Submission form template

From APIMF holder⁹ on headed paper

Attention: South African Health Products Regulatory Authority (SAHPRA)

[Include address as per SAHPRA website, <https://www.sahpra.org.za/Contact>]

[Date]

Submission of documents relating to an APIMF for [Name of API] [SAHPRA APIMF number, if allocated]

The APIMF (open and closed parts) is submitted in relation to the following new registration application submitted by [Name of applicant] on [planned date of submission]:

Required information:

[Final product Manufacturer]	
Name of Product	
Final Product Application number	
Name of FPP manufacturer	
Final Product applicant	
Application from Backlog pre-reg /BAU pre-reg /Backlog post-reg/ Backlog post-reg ¹⁰ (please tick)	<input type="checkbox"/> Backlog pre-reg <input type="checkbox"/> BAU pre-reg <input type="checkbox"/> Backlog post-reg <input type="checkbox"/> BAU post-reg
Type of application	<input type="checkbox"/> New application <input type="checkbox"/> Response to queries

APIMF holder	
APIMF holder name	[Fill in here]
Full APIMF holder administrative address	[Fill in here]
Site master file number (for API manufacturing site(s) located in South Africa)	[Fill in here]

⁹ API manufacturer

¹⁰ Pre-reg: Pre registration unit, post-reg: Post registration unit, BAU: Business as usual application.

APIMF holders APIMF number, version and	
Contact person	[Fill in here]
Telephone number	[Fill in here]
E-mail address	[Fill in here]

API manufacturing site(s)	
API manufacturer name	[Fill in here]
Manufacturing site name	[Fill in here]
Manufacturing site SMF (site master file) number (for API manufacturing site(s) located in South Africa)	[Fill in here]
Manufacturing site role ¹¹	[Fill in here]
Manufacturing site physical address (including block / unit / number)	[Fill in here]
GPS coordinates ¹² of manufacturing site	[Fill in here]
Manufacturing site contact person	[Fill in here]
Manufacturing site telephone number	[Fill in here]
Manufacturing site e-mail address	[Fill in here]
It is hereby confirmed that copies of the latest GMP certificate for manufacturer(s) and/or a copy of the appropriate manufacturing license(s) have been included	<input type="checkbox"/>

BCS classification of API	
Polymorphic form	
<i>Packaging</i>	
<i>Proposed retest period</i>	
<i>Proposed storage conditions</i>	

Please replicate this table for additional manufacturing sites. Manufacturing sites are all sites involved in the manufacture of the active substance, from the introduction of starting material(s), including quality control / in process testing sites, intermediate manufacturers, milling, micronisation and sterilisation. Each manufacturing site should be listed in a separate table and its role should be specified.

If the APIMF has been approved by one of SAHPRA's recognised regulatory authorities (RRAs), please complete the table below.

[Please check the tick-box for Yes, and leave it blank for No. Please duplicate the table for additional RRAs as required.]

¹¹ Please see text below this table for examples of manufacturing site roles.

¹² Latitude (S or N) and Longitude (E or W) expressed in Degrees Minutes Seconds to 1 decimal place, alternatively Degrees to at least 5 decimal places, or Degrees Minutes to at least 3 decimal places.

Name of RRA	{Insert name of RRA}
Date of submission	MM/YYYY
Is this APIMF identical to the APIMF on file in the above mentioned RRA?	<input type="checkbox"/> [If no, please provide an explanation of changes below.]
Are approval letters from the RRA for the APIMF included in this submission? (Module 1.10)	<input type="checkbox"/>
Are assessment reports for the APIMF included in this submission? (Module 1.10)	<input type="checkbox"/>

The undersigned hereby declares that all the information herein, and in the Annexes and Modules hereto, are correct and true and are relevant to this particular API, and that all existing data which are relevant to the quality, safety and efficacy of the API have been supplied in the dossier, as appropriate.

Signature for the APIMF holder (above)

Name and function: [Fill in here]

Amendment History

Version	Date	Reason for amendment
Version 1 Final Guideline	1 June 2020	
Version 2 Final guideline (update)	21 January 2021	<p>To amend the method of submission of the APIMFs and restricted parts to SAHPRA in section 2.1.2.</p> <p>To include the use of a specific subject line to use for communication on the APIMF email address.</p> <p>To include that the submission form should be sent to the APIMF email address to express interest in submitting the APIMF or restricted part</p> <p>To include the process of the submission of the APIMF or restricted part to SAHPRA’s FTP portal.</p> <p>To amend the submission form titled as Appendix 3 in this document.</p> <p>To include further details on the submission form regarding the associated product.</p> <p>To include further details to describe the characteristics of the API such as BCS class, stability and proposed storage conditions.</p>