SAHPRA
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

GUIDELINE FOR THE API MASTER FILE (APIMF) PROCEDURE

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 from the office of the Chief Executive Officer and the website.

Version 1	
Date of implementation	1 December 2019
Date of compulsory implementation (with exceptions)	1 May 2020

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 quality[1] evaluation of an API. The APIMF is comprised of two parts:

- **The open part**[2]: 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 part**[3]**:** 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 steps[4]), 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 APIMF[5] 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).
- Dedicated email address for APIMF submissions, with strict access permissions.
- The APIMF will be stored electronically, with strict access permissions.
- Once the closed part has been uploaded to SAHPRA's server, the physical copy of the information (CD / DVD / flash drive) can be returned to the API manufacturer, or it will be destroyed.

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).

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.

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 can also 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.

2. New registrations

Please note that the APIMF Procedure will be compulsory except for final pharmaceutical product applications occupied by the Restricted Part from 1 January 2020 for all 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 appended to the validation template in Module 1.

- 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)
- Module 1.4.1: Information about the experts
- Module 2.3.S: Quality Overall Summary (relevant section)
- Module 3.2.S: Quality information (relevant section)

The APIMF submission does not need to comply with eSubmission or eCTD criteria 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 authorities[7] (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.

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 API manufacturer can submit the submission form and APIMF (the documents) to SAHPRA via one of three methods:

a. The documents can 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.

b. The documents can be shared with SAHPRA via a secure link to an online document repository. The link should be sent to the following email address: APIMF@sahpra.org.za. The subject line of the email should clearly reference the associated FPP application.

c. The documents can be delivered to SAHPRA on a correctly-labelled CD / DVD / flash drive at the following address:

The Chief Executive Officer
South African Health Products Regulatory Authority
Building 38a
CSIR
Meiring Naude Road
Brummeria
Pretoria
South Africa

The labelling should include:

- Relevant FPP application number
- Proposed name of FPP
- Name of API manufacturer
- Name of API
- APIMF reference number

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.

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.

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 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
- 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.

Please note that 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 existing APIMF record.

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 3.1.1 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.

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.

3.2.2. No existing APIMF record

If a registered product does not have an associated APIMF number, evaluation of a variation application follows the exact requirements of the latest relevant guidelines:

- Variations Addendum for Orthodox Medicines
- Quality and Bioequivalence Guideline

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.2.2	Analytical procedures	x	
3.2.S.4.3	Validation of analytical procedures	x	
3.2.S.4.4	Batch analysis	x	
3.2.S.5.5	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	

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).

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

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 holder[9] on headed paper

The Chief Executive Officer

South African Health Products Regulatory Authority

Building 38a

CSIR

Meiring Naude Road

Brummeria

Pretoria

South Africa

[Date]

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]

9. API manufacturer

Appendix 3: Submission form template

From APIMF holder[10] on headed paper

Attention: South African Health Products Regulatory Authority (SAHPRA)

[Date]

Submission of documents relating to an APIMF for [Name of API]

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]:

Name of product: [Fill in here]

Required information:

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))	[Fill in here]
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	[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	☒

10. API manufacturer

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.

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.]

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?	☐ [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)	☐
Are assessment reports for the APIMF included in this submission? (Module 1.10)	☐

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]