GUIDELINE ON
ACTIVE PHARMACEUTICAL INGREDIENT MASTER FILE
(APIMF) PROCEDURE

(The APIMF procedure guideline does not apply to biological APIs.)

TABLE OF CONTENTS

1 INTRODUCTION................................................................................................................... 2
2 SCOPE ............................................................................................................................. 2
3 MAIN GUIDELINE TEXT .................................................................................................... 2
   3.1 Content of the APIMF ................................................................................................. 2
   3.2 Use of APIMF Procedure .......................................................................................... 2
   3.3 Content of the PD when the APIMF Procedure is Used .............................................. 3
   3.4 Changes and updates to the APIMF .......................................................................... 4
ANNEX 1 - OVERVIEW APIMF CONTENTS .................................................................. 5
ANNEX 2 - TEMPLATE LETTER OF ACCESS ................................................................. 7
ANNEX 3 - PART OF COVERING LETTER ....................................................................... 8
ANNEX 4 - LIST OF ABBREVIATIONS ........................................................................... 9
ANNEX 5 - GLOSSARY .................................................................................................. 10

---

1 This guideline is based on the approach described in the document CPMP/QWP/227/02 Rev 2 Consultation draft GUIDELINE ON ACTIVE SUBSTANCE MASTER FILE PROCEDURE (London, 27 April 2005) of the European Medicines Agency
1 INTRODUCTION

The main objective of the APIMF procedure is to allow valuable confidential intellectual property or "know-how" of the Manufacturer of the active pharmaceutical ingredient (API) to be protected, while at the same time allowing the Applicant or holder of Prequalification Dossier (PD) to take full responsibility for the finished pharmaceutical product (FPP) and the quality and quality control of the API. The Prequalification Team thus has access to the complete information that is necessary for an evaluation of the suitability of the use of the API in the FPP.

2 SCOPE

This Guideline is intended to assist Applicants/PD holders in the compilation of the API information of their dossiers for a prequalification dossier application (PDA) or a prequalification dossier variation (VPD) of a FPP. It is also intended to help APIMF holders in the compilation of their APIMFs.

3 MAIN GUIDELINE TEXT

3.1 Content of the APIMF

The overall content of the APIMF should contain detailed scientific information as indicated in Section 2. ACTIVE PHARMACEUTICAL INGREDIENT(s) [API(s)] of the “Guideline on Submission of Documentation for Prequalification of Multi-source (Generic) Finished Pharmaceutical Products (FPPs) Used in the Treatment of HIV/AIDS, Malaria and Tuberculosis”.

The scientific information in the APIMF should be physically divided into two separate parts, namely the Open Part (OP) and the Restricted Part (RP). The OP contains the information that the APIMF holder regards as non-confidential to the Applicant/PD holder, whereas the RP contains the information that the APIMF holder regards as confidential, see Annex 1. It is emphasized that the OP is still a confidential document that cannot be submitted by anyone to third parties without the written consent of the APIMF holder. In all cases the OP should contain sufficient information to enable the Applicant/PD holder to take full responsibility for an evaluation of the suitability of the specifications for the API to control the quality of this API for use in the manufacture of a specified FPP.

The RP shall contain the remaining information, such as detailed information on the individual steps of the manufacturing method (reaction conditions, temperature, validation and evaluation data of critical steps) and the quality control during the manufacturing method of the API. Information that is relevant to the Applicant/PD holder (see notes 2 and 5 of ANNEX 1 regarding residual solvents and impurities, respectively) should be discussed in the RP but should also be submitted in the OP.

In addition to the OP and RP, the APIMF should contain a table of contents, and a separate summary for the OP and the RP. Both summaries should be presented as a Pharmaceutical Quality Information Form (PQIF). The OP and RP should each have a version number. The structure of the version numbers should be unique and follow a logical order. Preferably the following structure is used:

Name APIMF holder / Name active pharmaceutical ingredient/ OP or RP/ version number / date in yyyy-mm-dd.

3.2 Use of APIMF Procedure

An APIMF can only be submitted in support of a PDA or VPD. The relationship between the quality of the API and its use in the FPP needs to be justified in this PDA or VPD. Although the APIMF procedure is developed to keep intellectual property of the API confidential, it is also permissible to use the procedure when there is no confidentiality issue between the Applicant/PD holder and the API manufacturer (e.g. when the Applicant/PD holder manufactures the API itself). It is expected that the API manufacturer is also the holder of the APIMF.

The APIMF procedure should be used for APIs where a professed standard is declared (namely no monograph exists in the Ph. Eur., Ph. Int. or USP), or where a monograph exists but a manufacturer’s
in-house standard is declared. The APIMF procedure can also be used when APIs are included in the Ph. Eur., Ph. Int. or USP.

A Drug Master File of an API (active substance, drug substance) assessed by a drug regulatory agency in the International Conference on Harmonization (ICH) regions and associated countries - including among others the EU, Japan and USA - is accepted without further evaluation as a prequalified APIMF on condition that evidence of such regulatory acceptance has been submitted. The holder of the DMF should also declare in writing that there have been no changes to the DMF content and manufacture of batches of API to be supplied for Applicants/PD holders.

The APIMF holder should give permission to WHO to assess the data in the APIMF in relation to a specific PDA/VPD, in the form of a 'Letter of Access', see Annex 2. The APIMF holder should submit to the Applicant/PD holder:

- a copy of the latest version of the OP.
- a copy of the PQIF on the latest version of the OP.
- the Letter of Access.

In addition, the APIMF holder should submit to WHO:

- the APIMF accompanied by a covering letter, see Annex 3.
- the Letter of Access.

The APIMF holder should provide the APIMF to WHO only once, independently from the number of the PD holders and the number of PDAs/VPDs. The submission of the relevant documentation by the APIMF holder to WHO must be synchronised to arrive at approximately the same time as the first PDA or the first VPD is received from the FPP manufacturer that references the APIMF.

Where the APIMF procedure is used, the Applicant/PD holder should submit the PDA or VPD to WHO together with the Letter of Access.

WHO requires that any APIMF updates made in relation to one PD should apply to all. It is the APIMF holder's responsibility to notify the PD holders and WHO about any changes to the OP and/or RP, so that the PD holders can update all affected PDs accordingly and file the appropriate variation(s) to WHO as necessary.

3.3 Content of the PD when the APIMF Procedure is Used

The Applicant/PD holder is responsible for ensuring that he has access to all relevant information concerning the current manufacture of the API.

The specifications used by the Applicant/PD holder to control the quality of the API should be laid down unambiguously in the PD. The Applicant/PD holder should quote the OP version number / date in yyyy-mm-dd, or should include a copy of the OP in the PD dossier.

The version of the OP in the PD dossier should be the most recent and it should be identical to the OP as supplied by the APIMF holder to WHO as part of the APIMF.

The Applicant/PD holder should include all relevant details from the OP in the PQIF of the PD dossier. Issues of the APIMF that are specifically relevant to the FPP under consideration should be highlighted in the PQIF of the PD.

In the case of a single supplier and where the APIMF procedure or CEP procedure is used, the specifications of the Applicant/PD holder in the PD dossier should in principle be identical to those of the APIMF holder or the CEP holder. The Applicant/PD holder does however not need to accept redundant specifications, unnecessarily tight specification limits or outdated analytical methods. In cases where the Applicant/PD holder uses a different analytical method than that described in the APIMF, both methods should be validated. Technical specifications relevant for the FPP, which are normally not part of the specifications in the APIMF (e.g. particle size), should be part of the specifications of the Applicant/PD holder.
In cases where there is more than one supplier, there should be one single compiled specification that is identical for each supplier. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a single parameter with the statement “for API from supplier X” (e.g. in case of residual solvents).

3.4 Changes and updates to the APIMF

As for FPPs, APIMF holders should keep the content of their APIMFs updated with respect to the actual synthesis / manufacturing process. The quality control methods should be kept in-line with the current regulatory and scientific requirements. APIMF holders shall not modify the contents of their APIMF (e.g. manufacturing process or specifications) and must inform each Applicant/PD holder and WHO when a change in an APIMF requires the filing of a VPD. Before implementation, any change to the APIMF should be reported by every PD holder to WHO by means of an appropriate variation procedure. A covering letter should be provided. In cases where the contents of the APIMF cannot be changed for a certain period of time, the APIMF holder should still provide the aforementioned data to the PD holder and WHO making reference to this reason and requesting a later date of implementation.

The APIMF holders' covering letter to WHO should contain the following information (if available):

- A tabular list summarizing the changes carried out since the first compilation of the APIMF.
- An overview comparing the old and new content of the APIMF.
- Information as to whether the change has already been accepted, rejected or withdrawn by another drug regulatory authority in the ICH region and associated countries.
- The names of the relevant Applicants and PD holders. The new OP and/or RP with each new version number.
- An updated PQIF, if relevant.
- A discussion of the potential impact on the quality of the API as a result of the change(s).

At the occasion of the 3-yearly renewal of a FPP, PD holders are required to declare that the quality of the product, in respect of the methods of preparation and control, has been regularly updated by variation procedure to take account of technical and scientific progress, and that the product conforms with current WHO/Prequalification quality guidelines. They will also declare that no changes have been made to the product particulars other than those approved by WHO.

PD holders should therefore verify with their APIMF holders whether the above declaration can be met in respect to the API particulars. In case changes have not been notified to the PD holder and WHO, the necessary variation procedure should be initiated without delay.
## ANNEX 1 - OVERVIEW APIMF CONTENTS

<table>
<thead>
<tr>
<th>Table 1</th>
<th>PQIF format</th>
<th>Open Part</th>
<th>Restricted Part</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>General information from literature</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>2.1</td>
<td><strong>Nomenclature</strong></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>2.2</td>
<td><strong>Properties of API</strong></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>2.3</td>
<td><strong>Site(s) of manufacture</strong></td>
<td>x</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Manufacturer(s)</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>2.4</td>
<td><strong>Manufacturing process</strong></td>
<td>1)</td>
<td>2)</td>
</tr>
<tr>
<td></td>
<td>Control of materials</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control of critical steps and intermediates</td>
<td>3)</td>
<td>4)</td>
</tr>
<tr>
<td></td>
<td>Process validation and/or Evaluation</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Manufacturing Process Development</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Characterization</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elucidation of Structure and other Characteristics</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Selected physicochemical and other relevant properties</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impurities</td>
<td>x</td>
<td>5)</td>
</tr>
<tr>
<td></td>
<td>Control of API</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td><strong>Specifications</strong></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Analytical procedures</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Validation of analytical procedures</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Batch analysis</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Justification of specification</td>
<td>x</td>
<td>6)</td>
</tr>
<tr>
<td></td>
<td>Reference standards or Materials</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>2.6</td>
<td><strong>Container Closure System</strong></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>2.7</td>
<td><strong>Stability</strong></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stability summary and conclusion</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-approval Stability Protocol and Stability Commitment</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stability data</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>
1) Flow chart and textbook-level narrative is regarded as sufficient, if detailed information is presented in the Restricted Part. However, full validation data on the sterilization process may be requested in the Open Part (in cases where there is no further sterilization of the final product).

2) Detailed information.

3) In so far as the information is also relevant for the Applicant/PD holder.

4) In so far as the information is related to the detailed description of the Manufacturing process and in so far as this information is not relevant for the Applicant/PD holder.

5) 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.

6) In so far as the information is related to the detailed description of the Manufacturing process, control of materials and process validation.
ANNEX 2 - TEMPLATE LETTER OF ACCESS

[Address of WHO]

[Date and place]

LETTER OF ACCESS

Number of Active Pharmaceutical Ingredient Master File:

Manufacturing site: [name and address]

Active Pharmaceutical Ingredient Master File holder: [name and address]

The aforementioned Active Pharmaceutical Ingredient Master File holder hereby authorizes the [WHO including all PQ Team Members and their experts] to refer to and review the above mentioned Active Pharmaceutical Ingredient Master File in support of the following Prequalification Application(s) or Prequalified Dossier Variation(s) submitted by [name / Prequalification holder / Applicant] on [planned date of submission]:

[Name of product and prequalification code number, if known] [Name of Applicant or PD holder]

The aforementioned Active Pharmaceutical Ingredient Master File holder commits to ensure batch-to-batch consistency and to inform [name of PD holder/Applicant] and WHO of any change in the OP or RP parts of the Active Pharmaceutical Ingredient Master File.

Signature for the Active Pharmaceutical Ingredient Master File holder [Name and address]

[Signature]
ANNEX 3 - PART OF COVERING LETTER

This Active Pharmaceutical Ingredient Master File is submitted in relation to the PDA / VPD:

[Name of product in prequalification procedure]
[Name of Applicant/PD holder for the application concerned]
and describes <changes to> the manufacturing process and specifications of the (or one of the) active pharmaceutical ingredient(s) of this PDA or VPD.

[Name active pharmaceutical ingredient]
The version number of this Active Pharmaceutical Ingredient Master File is
Open part: version [version number]
Restricted part: version [version number]

This Active Pharmaceutical Ingredient Master File has previously been submitted for assessment in combination with a PDA / VPD for a pharmaceutical product within the prequalification project:
Refer to the prequalification code and name of the FPP and the FPP manufacturer.
ANNEX 4 - LIST OF ABBREVIATIONS

API   Active Pharmaceutical Ingredient
APIMF Active Pharmaceutical Ingredient Master File
CEP   European procedure for a certificate of suitability of monographs of the European pharmacopoeia (here on chemical purity)
ICH   International Conference on Harmonization
OP    Open (Applicants) Part of the APIMF
PD    Prequalification dossier
PDA   Prequalification Dossier Application (including line extensions)
Ph. Eur. European Pharmacopoeia
Ph. Int. International Pharmacopoeia of WHO
PQIF  Pharmaceutical Quality Information Form
RP    Restricted Part (of APIMF)
USP   United States Pharmacopoeia
VPD   Variation to a prequalified dossier
WHO   World Health Organization
ANNEX 5 - GLOSSARY

Active pharmaceutical ingredient manufacturer
A party involved in the Manufacturing chain of the active pharmaceutical ingredient, including agents, brokers, traders, distributors, repackers or relabellers.

Active pharmaceutical ingredient Master File holder
This is the company that has the ultimate responsibility for the Active pharmaceutical ingredient Master File.

Applicant
This is the company requesting prequalification for a pharmaceutical product.

Prequalification dossier holder
This is the company that is responsible for the pharmaceutical product on the market

Manufacturing chain
A clear flow chart or written text explaining the Manufacturing and distribution route of the active pharmaceutical ingredient from the first starting material

Quality
According to ICH Q6A that is “The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength and purity.”

Specification
According to ICH Q6A that is “A list of test, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges or other criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. Conformance to specifications means that the drug substance and/or drug product, when tested according to the listed analytical procedures will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the Manufacturer and approved by regulatory authorities.”