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Annex 4

Guidelines on active pharmaceutical ingredient master file procedure[1,2]

[1] These guidelines are based on the approach described in the *Consultation draft guideline on active substance master file procedure*. London, European Medicines Agency, 2005 (document CPMP/QWP/227/02 Rev 2).

[2] The APIMF procedure guidelines do not apply to biological APIs.

1. Introduction

The main objective of the Active Pharmaceutical Ingredient Master File (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 for prequalification or prequalification variation (from now on named in the text as the applicant) to take full responsibility for the finished pharmaceutical product (FPP) and the quality and quality control of the API. The WHO Prequalification Programme thus has access to all the information necessary for an evaluation of the suitability of the use of the API in the FPP.

The APIMF procedure is a possibility offered to applicants for WHO prequalification of medicinal products and the manufacturers of their APIs. Other means of submission of scientific data on the API include:

— a valid certificate of suitability of pharmacopoeial monographs with which the API complies with all appendices, and adding information which is not covered by the certificate;
— by submitting scientific information on the API to the extent available and organized according to the current guidance documents, available on the WHO Prequalification web site (http://www.who.int/prequal/). In this case, the API manufacturer should provide a signed declaration that the synthesis and subsequent purification is conducted in accordance with what is presented in the dossier.

In addition, the WHO pharmaceutical starting materials certification scheme (SMACS) can be used to attest the relevant data as covered in the scheme. (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report.* Geneva, World Health Organization, 2004. WHO Technical Report Series, No. 917, Annex 3.)

2. Scope

These guidelines are intended to assist applicants in the compilation of the information on APIs in their dossiers for prequalification or when submitting a variation to a dossier on a prequalified product (named in the text from now on as product dossier) when the APIMF procedure is used. It is also intended to help APIMF holders in the compilation of their APIMFs.

3. Content of the active pharmaceutical ingredient master file

The APIMF should contain detailed scientific information as indicated in Section 2. Active pharmaceutical ingredient(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", available on the WHO Prequalification web site at: http://www.who.int/prequal/.

The information required should be organized and presented in the structure and format described in these guidelines, which follows that of the Common Technical Document (CTD), agreed in November 2000 within the framework of the International Conference on Harmonisation (ICH, see web site: www.ich.org).

The scientific information in the APIMF should be physically divided into two separate parts, namely the open part (OP) and the restricted part (RP). In addition to the OP and RP, the APIMF should contain a table of contents and a separate quality summary for the OP and the RP. The OP and RP should each have a version number given by the APIMF holder. The structure of the version numbers should be unique and the following structure is suggested:

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

3.1 Open part of APIMF

The OP contains the information that the APIMF holder regards as non-confidential to the applicant, whereas the RP contains the information that the APIMF holder regards as confidential. It is emphasized that the OP is still a confidential document that cannot be submitted to third parties without the written consent of the APIMF holder. In all cases the OP should contain sufficient information to enable the applicant 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.

For the OP, at least those aspects listed below must be covered by appropriate documentation in the APIMF.

General information

- nomenclature
- structure
- general properties.

Manufacture

- manufacturer(s)/site of manufacture
- description of the manufacturing process and process controls
  A *flow chart and brief outline of the manufacturing process is regarded as sufficient, if detailed information is presented in the RP. However, full*

validation data on the sterilization process may be requested in the OP (in cases where there is no further sterilization of the final product).

- control of critical steps and intermediates
  in so far as the information is also relevant for the applicant to prequalification.

Characterization

- elucidation of structure and other characteristics
- impurities.

Control of API

- specification
- analytical procedures
- validation of analytical procedures
- batch analysis
- justification of specification.

Reference standards or materials

Container closure system

Stability

- stability summary and conclusion
- post-approval stability protocol and stability commitment
- stability data.

3.2 Restricted part of APIMF

The RP should contain the remaining information, such as a detailed description of the individual steps of the manufacturing method (reaction operating conditions, data on validation and evaluation of critical steps) and the quality control during the manufacturing method of the API. Information relevant to the applicant such as that on impurities should be discussed in the RP, but it may be also submitted in the OP if considered necessary to enable the applicant to take full responsibility for its product.

For the RP, at least those aspects listed below must be covered by appropriate documentation in the APIMF.

Manufacture

- manufacturer(s)/site of manufacture
- detailed description of the manufacturing process and process controls
- control of materials
- control of critical steps and intermediates

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;
- process validation and/or evaluation
- manufacturing process development.

Characterization

- impurities
  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.

Control of API

- justification of specification
  in so far as the information is related to the detailed description of the manufacturing process, control of materials and process validation.

4. Use of the APIMF procedure

An APIMF can only be submitted in support of a product dossier or a variation to a product dossier and is only reviewed in connection with that product dossier. An APIMF is never approved as such, it can be only accepted in relation to an FPP dossier.

The relationship between the quality of the API and its use in the FPP needs to be justified in the relevant product dossier. Although the APIMF procedure is developed to keep the intellectual property relating to the API confidential, it is also permissible to use the procedure when there is no confidentiality issue between the applicant and the API manufacturer, e.g. when the applicant for prequalification manufactures the API itself.

Preferably, the API manufacturer should be the holder of the APIMF. It is, however, permissible for the APIMF to be submitted by another party, considered as the holder. In this case, a formal letter of authorization should be available from the manufacturer of the API.

The APIMF procedure should be used for APIs where a professed standard is declared, i.e. where no monograph exists in *The International Pharmacopoeia*, *European Pharmacopoeia*, *United States Pharmacopeia* or *Japanese Pharmacopoeia*, or where a monograph exists but a manufacturer's in-house standard is declared. The APIMF procedure can also be used when APIs are described in *The International Pharmacopoeia*, *European Pharmacopoeia*, *United States Pharmacopeia* or *Japanese Pharmacopoeia*.

A Drug Master File (DMF) of an API (active substance) assessed by a drug regulatory authority in the International Conference on Harmonisation

(ICH)-participating and associated countries can be accepted without further evaluation provided that:

— the complete drug master file is submitted to the WHO Prequalification Programme;

and

— the corresponding assessment report from ICH or the associated authorities is made available through a mechanism of sharing of information;

or

— the manufacturer is able to prove that the API is used in an FPP-approved, in an ICH-participating, or associated country. In this respect, a certificate according to the WHO pharmaceutical starting materials certification scheme (SMACS) issued by a competent regulatory authority can be submitted, if available.

The holder of the DMF should also declare in writing that there have been no changes to the manufacture of batches of API to be supplied for WHO prequalification and to the DMF content since its acceptance by the ICH-participating or associated countries.

5. Steps of the APIMF procedure

The APIMF holder (manufacturer of the API or its authorized representative) should provide the APIMF to WHO only once, independently of the number of applicants and the number of FPP dossiers submitted. The submission of the relevant documentation by the APIMF holder to WHO must be synchronized to arrive at approximately the same time as the first product dossier is received from the FPP manufacturer that refers to the APIMF.

Where the APIMF procedure is used, the applicant for prequalification should submit to WHO the product dossier together with the "letter of access". The APIMF holder should give permission to WHO, in the form of a "letter of access", to assess the data in the APIMF in relation to a specific product dossier (see Appendix 1).

The APIMF holder should submit to WHO:

- the APIMF accompanied by a covering letter (see Appendix 2);
- quality summaries on the RP and the OP;
- the letter of access (see Appendix 1).

In addition, the APIMF holder should submit to the relevant FPP applicant(s):

- a copy of the latest version of the OP;

- a copy of the quality summary on the latest version of the OP;
- the letter of access.

WHO requires that any APIMF updates made in relation to one prequalification dossier should apply to all other FPP dossiers referencing that specific APIMF. It is the responsibility of the APIMF holder to notify the applicants and WHO about any changes to the OP and/or RP, so that the applicants can update all affected prequalification dossiers accordingly and file the appropriate variation(s) with WHO as necessary.

6. Content of the product dossier when the APIMF procedure is used

The applicant for prequalification is responsible for ensuring that he or she has access to the relevant information concerning the current manufacture of the API.

The specifications used by the applicant to control the quality of the API should be unambiguously laid down in the product dossier. The applicant for prequalification should quote the *OP version number / date in yyyy-mm-dd*, or should include a copy of the OP in the prequalification dossier. The version of the OP in the prequalification 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 should include all relevant details from the OP in the Quality summary of the product dossier. Aspects of the APIMF that are specifically relevant to the FPP under consideration should be highlighted in this summary.

In the case of a single supplier/manufacturer of the API, and where the APIMF, a valid certificate of suitability of pharmacopoeial monographs or the WHO API prequalification procedure is used, the specifications of the applicant for the API in the product dossier should in principle be identical to those of the APIMF, the certificate of suitability or the prequalified API. The applicant does not, however, need to accept redundant specifications, unnecessarily tight specification limits or outdated analytical methods. In cases where the applicant uses a different analytical method to the one described in the APIMF, both methods should be validated. Technical specifications relevant to the FPP, which are normally not part of the specifications in the APIMF (e.g. particle size), should be part of the API specifications submitted by the applicant for prequalification in its product dossier.

In cases where there is more than one supplier/manufacturer of API using one of the APIMF, certificate of suitability or API prequalification procedures, there should be a core of one single set of specifications for

the API presented by the applicant for prequalification 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 specific single parameter with the statement "for API from supplier X" (e.g. in the case of residual solvents).

7. Changes and updates to the APIMF

As for FPPs, APIMF holders should keep their APIMFs up to date on the actual synthesis or manufacturing process. The quality control methods should be kept in line with the current regulatory and scientific requirements. APIMF holders should not modify the contents of their APIMF (e.g. manufacturing process or specifications) without informing each applicant and WHO when a change introduced requires the filing of a variation to the product dossier. Changes in the RP of an APIMF not requiring filing of a variation, should, however, be notified to WHO. Before implementation, any change to the APIMF should be reported to WHO by every applicant 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 applicant and to WHO, making reference to this reason and requesting a later date of implementation.

The covering letter sent by the APIMF holder to WHO should contain the following information:

- a tabular list summarizing the changes carried out since the the APIMF was first compiled;
- 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-participating and associated countries;
- the names of the relevant applicants;
- the new OP and/or RP with each new version number;
- an updated Quality summary, if relevant;
- a discussion of the potential impact on the quality of the API as a result of the change(s).

Appendix 1

Template letter of access

Letter of access

Reference number of active pharmaceutical ingredient master file (given by WHO Prequalification, if known):

Manufacturing site: *(name and physical address; specify the unit, block or plot (if applicable))*

Active pharmaceutical ingredient master file holder: *(name and address)*

The aforementioned active pharmaceutical ingredient master file holder hereby authorizes the (WHO relevant staff members and external experts) to refer to and review the above-mentioned active pharmaceutical ingredient master file in support of the following Prequalification application(s) or Variation application(s) submitted by *(name of the applicant)* on *(planned date of submission)*; *(name of FPP product and prequalification code/ reference number, if known) (name of applicant)*

The aforementioned active pharmaceutical ingredient master file holder is committed to ensuring batch-to-batch consistency and to informing *(name of the applicant to prequalification)* 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 *(Date, name and address)*

Appendix 2

Part of covering letter to be submitted by the APIMF holder to WHO

This active pharmaceutical ingredient master file is submitted in relation to the product dossier:

(Name of the FPP in WHO Prequalification Programme for medicinal products)

(Name of applicant for Prequalification 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 product dossier.

(Name active pharmaceutical ingredient)

The version number *(given by the APIMF holder)* 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 relation to a product dossier for an FPP within the WHO Prequalification Programme.

(Refer to the prequalification code/reference number and name of the FPP and the FPP manufacturer.)