FAQ: Active Pharmaceutical Ingredient Master Files (APIMFs)

Electronic Formatting

Will electronic signatures be accepted?

Electronic signatures will be accepted on the basis that they form part of the submission and are therefore covered by declarations made by the applicant at the time of submission, i.e. that all information provided in the application is accurate and truthful.

What if a single file is greater than the recommended 50 MB size?

There are a number of steps that can be taken to reduce the size of a file. These include changing the file format, reducing resolution of any inserted pictures, and dividing the document into sub-documents. A document larger than 50 MB with no internal subdivisions should simply be divided into two documents and labelled accordingly (part 1 and part 2).

To what level of detail should PDF bookmarks be taken in submitted documents?

PDF bookmarks should be present to the sub-heading level at a minimum, i.e. 3.2.S.X.X , but applicants are encouraged to add further bookmarks if they feel this will make navigation easier. Any stand-alone documents, such as validation reports or annexes, should also be bookmarked.

Is it permissible to use of abbreviated names to avoid lengthy path lengths?

Yes, although judicious naming of documents would be a better strategy for reducing overall path length.

Document Formatting

How should APIMF version numbers be applied to revised sections of an APIMF submitted as part of a response to a request for information?

Since changes to an APIMF are invariably requested during review, WHO prefers that a complete and revised APIMF only be submitted by the applicant following completion of the assessment. WHO discourages submissions of revised versions of an APIMF by the applicant before all issues have been resolved

However, if a revised subsection is requested prior to the submission of a final APIMF version, this should be labelled with a version number in the same manner as for amendments, e.g.

Artemether/OP/00/Feb-2013/Amend-01-June-2013

Procedural Issues

Can changes be made to API details whilst the APIMF is under assessment?

While this is not prohibited, the introduction of changes will complicate the evaluation and delay acceptance of the APIMF. The additional time required will depend on the nature of the change and how well the change is explained and supported by the applicant.

In this situation, the applicant should consider whether it be preferable to follow the amendment procedure after the APIMF has been accepted.

APIMF Content

What information should be provided for the API starting material in section 3.2.S.2.3?

There are several acceptable ways to arrange information regarding the starting material(s) (SM) in section 3.2.S.2.3, provided that complete information is submitted for each SM from each supplier. The following organization of information is suggested but not mandatory. The detail or additional information provided should be judged on a case-by-case basis. This information is also relevant for post-approval changes (amendments) in SM suppliers.

The SM section of an APIMF should be introduced by a summary clearly identifying the molecules nominated as the SMs and summarizing the name and manufacturing address for each manufacturer. Each nominated SM can then be discussed within its own subsection.

For each SM, an introductory section should justify the choice of API SM in line with the principles of ICH Q11. This section is obligatory and should describe the justification and rationale for the choice of SM.

For each supplier of the SM the following should be provided.

- A characterization report; the degree of detail will depend on the molecule in question;
- A summary of the preparation of the API SM should be sufficiently detailed to support the choice of API SM and to permit a judgement to be made over the suitability of the SM specifications. Typically, this description will consist of a synthetic scheme that includes the reagents, catalysts and solvents that are used.
- Certificates of analysis for at least one batch of the API SM issued by each of the suppliers; and the corresponding certificates of analysis for the API SM as tested upon receipt by the API manufacturer.

The API SM specifications as applied by the API manufacturer should be listed, with a statement that the specifications are applied to all sources of the API SM that are received.

A justification for the specifications should cover the suitability of the specifications to control the API SM received from all proposed manufacturers, given their methods of preparation.

Finally, in section 3.2.S.4.4, batch analysis should be provided for batches of API produced using API SM from each of the proposed suppliers.

To better illustrate the suggested layout, the example below includes there are two proposed SMs (SM-1 and SM-2), each with two suppliers. The overall organization of the information would follow this structure.

1. **3.2.S.2.3.1 - Starting materials (SMs)**

   Introduction: listing each of the SMs and the names and addresses of each SM supplier.

2. **SM Information: SM-1**

   Introduction: Molecular structure, name, justification for the choice of SM, API manufacturer's specifications for SM-1, test method description and validation (as necessary); justification for the SM specifications. Comparative batch analysis for batches of SM-1 from each supplier, as tested upon receipt by the API manufacturer.

   a. SM-1, Supplier 1: Name of supplier
      i. Characterization report, summary of the preparation of the API SM; the SM suppliers' and the API manufacturer's certificates of analysis for received batches of the SM.

   b. SM-1, Supplier 2: Name of supplier
      i. Characterization report, summary of the preparation of the API SM; the SM suppliers' and the API manufacturer's certificates of analysis for received batches of the SM.

3. **Starting Material Information: SM-2**

   Introduction: Molecular structure, name, justification for the choice of SM, API manufacturer's specifications for SM-1, test method description and validation (as necessary); justification for the SM specifications.

Comparative batch analysis for batches of M-1 from each suppler, as tested upon receipt by the API manufacturer.

a. SM-2, Supplier 1: Name of supplier
   i. Characterization report, summary of the preparation of the API SM; the SM suppliers' and the API manufacturer's certificates of analysis for received batches of the SM.

b. SM-2, Supplier 2: Name of supplier
   i. Characterization report, summary of the preparation of the API SM; the SM suppliers' and the API manufacturer's certificates of analysis for received batches of the SM.

4. **3.2.S.4.4**

Batch analysis for batches of API produced using API SM from each of the proposed suppliers.

What information should be provided for an API intermediate when the intermediate is obtained from an external supplier?

Externally-sourced intermediates are increasingly common in submitted APIMFs, or arise as a result of the request for redefinition of the API SM. The introduction of such a supplier invariably complicates the submitted APIMF and therefore attention must be given to presenting information on the intermediate in a clear and logical manner.

Two considerations include:

(a) The API manufacturer is responsible for all steps undertaken in the manufacturing process, from the introduction of the SM(s), and this should be reflected in the APIMF.

(b) It needs to be ensured that an API intermediate is of the same quality and controlled in a consistent manner whether supplied internally or externally.

With respect the first point above, the steps and controls undertaken by an external intermediate manufacturer must be integrated into the APIMF. Equally, the nomenclature of the various molecules and manufacturing steps may need to be revised to ensure the overall process and molecules are clear and consistent. Some examples of expectations are:

- That all intermediate suppliers are listed in section 3.2.S.2.1.
- A complete, terminologically consistent, and detailed manufacturing process description is supplied in section 3.2.S.2.2.
- Full information on all SM suppliers — whether these are supplying the API manufacturer directly or an external intermediate manufacturer — is provided and discussed in 3.2.S.2.3.
- All materials used in the preparation of the API, including by the intermediate supplier, should be provided in 3.2.S.2.3.
- In-process controls, critical steps and intermediate controls that are undertaken by the intermediate manufacturer are listed in section 3.2.S.2.4.

With respect to point (b), when an intermediate is sourced from an external supplier, information should be supplied in section 3.2.S.2.4 to illustrate that internally and externally sourced intermediate are of comparable quality and held to the same quality standards. Some examples of expectations are:

- The specification applied by the API manufacturer to batches of the intermediate is provided, together with a statement clearly stating that all batches of intermediate (both internally and externally sourced) are tested to this standard.
- The specifications applied by the intermediate suppliers at release are provided.
- A justification for the suitability of the API manufacturer's intermediate specifications is provided that considers all sources of the intermediate.
- Comparative batch analysis for batches of intermediate tested by the API manufacturer from all sources of the intermediate are provided.

Finally, in section 3.2.S.4.4 batch analysis should be carried out for batches of API produced using intermediate that is produced from each external manufacturer.

In many cases, supporting annexes are provided that contain detailed information regarding the externally sourced intermediate. This does not replace the need to ensure relevant information (as described above) is present in the body of the APIMF. It is not sufficient to simply incorporate the intermediate manufacturer's master file as an annex.

Can an APIMF include more than one method of preparation?

An APIMF generally includes information relating to a single method of preparation and control of the API to a single set of specifications (quality standard). The rationale is that the method of preparation determines to a large degree the impurity profile of the API, and consequently the acceptability of the API specifications.

This principle applies to new APIMF submissions and to requests for changes via the APIMF amendment procedure. There are occasions where combining more than one method of preparation in a single APIMF may be acceptable. If an applicant is considering the inclusion of any alternate process in their APIMF they should contact WHO prior to making any submission.

Generally, manufacturing processes that use different methods of synthesis different SMs or different reaction intermediates should not be proposed together in a single APIMF. Such differences can give rise to different impurity profiles, and complicate regulatory oversight and subsequent post-approval amendments.

Reprocessing or recovery processes, or recovered solvents, are not considered to be alternative methods of manufacture and therefore are permitted in the same APIMF.

Finally, there is a practical limit to the number of alternative methods of preparation that should be included in a single APIMF, even when the differences in alternative processes are minor. Such situations complicate the assessment of the APIMF or subsequent post-approval amendments.

How should applications address skip testing?

A skip test is a quality parameter that has been determined during assessment to present a sufficiently low chance of non-compliance that it does not need to be conducted routinely , with the understanding that those batches not being tested still must meet all acceptance criteria established. This contrasts with reduced testing, the practice in which a manufacturer may omit a test during the testing of a specific batch.

The appropriateness of designating a test as a skip test is part of the APIMF assessment process. Tests within specifications that are skip tests should be indicated as such within the specification itself. This can be done either by including the comment "skip test" in brackets or as a footnote.

In contrast, the frequency of skip testing is considered a GMP matter for the manufacturer to decide and is not evaluated during APIMF assessment. However, documentation explaining and justifying the frequency of testing should be developed and be available for inspectors. Finally, even after the frequency of skip testing has been set internally by the manufacturer, this frequency should not be applied blindly. The decision to skip test a parameter for any given batch should always be decided by the manufacturer on a batch to batch basis taking into account the specific circumstances relating to the manufacture of the batch in question. Accordingly, no indication of testing frequency should be included within the specifications.