PART XII

EAC PROCEDURE ON EVALUATION OF QUALITY OF ACTIVE PHARMACEUTICAL INGREDIENTS

1. Introduction

Evaluation of Active Pharmaceutical Ingredients (API) is an obligatory part of the overall assessment of quality, safety and efficacy of a medicinal product. Alternate procedures for submission of API information are described in the *Guideline for Submission of Documentation for Registration of Medicinal Products* including:

a) Submission of the reference number and details of the WHO-prequalified API, together with additional supporting information.
b) Submitting a copy of the relevant Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) issued by the European Directorate for the Quality of Medicines and HealthCare, together with additional supporting information
c) Submitting a complete ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) module 3.2.S for the API, as part of the FPP dossier submitted for evaluation. As stated in the EAC guidelines (www.mrh.eac.int)

As a means of increasing efficiency and to avoid duplication of work the EAC MRH Programme has decided to initiate an API certification procedure. This will enable manufacturers to procure EAC certified APIs and thus reduce the burden of compilation of dossiers for applications for registration of new medicinal products.

This document has been prepared in order to provide guidance on supportive documents that are to be submitted in order for an API manufacturer to apply for certification of their respective APIs.

API certification should not be confused with the API master file procedure (APIMF) where by an API manufacturer is invited to provide its APIMF in support of an application for registration of FPP or a stand – alone submission.

1. Active Pharmaceutical Ingredients certification

1.1 Certification of active pharmaceutical ingredients (APIs) will be an independent procedure that identifies APIs that are of good quality and manufactured in compliance with WHO Good Manufacturing Practices (GMP). If a certified API is used in the manufacture of a finished pharmaceutical product (FPP) for which EAC registration is sought, evaluation of that FPP will be greatly facilitated by abbreviation of evaluation of the API information.

1.2 In order to become certified an API must be of good quality and manufactured in accordance with WHO Good Manufacturing Practices (GMP).

1.3 Evaluation of an API for registration has two components: assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and verification that the site(s) of API manufacture comply with WHO GMP requirements.

1.4 Registration of an API is made with specific reference to the manufacturing details and quality controls described in the EAC APIMF submitted for assessment.

1.5 A certified API is therefore clearly identifiable with a specific APIMF version. An APIMF version may be altered during registration assessment, or as a result of post-registration changes. Therefore, the version number of the current APIMF will be included on the EAC List of registered Active Pharmaceutical Ingredients, to serve as a reference for the production and quality control of that API.

1.6 In addition to the registered API(s) being included in the EAC List of certified Active Pharmaceutical Ingredients, successful applicants will receive an EAC Confirmation of Active Pharmaceutical Ingredient Certification for each API for which they attain certification. The confirmation will contain information on the accepted active ingredient specifications as well as the assay and related substances test methods. It may be provided by the applicant to interested parties.

1.7 There are three possible routes to API certification;

a) Full assessment of an APIMF not previously assessed by WHO.
b) Abridged assessment of a WHO prequalified API.
c) Abridged assessment of APIs that have CEPs.

2. Evaluation of API information

2.1 Under the following conditions the assessment of the API shall be limited to verification of the identity, source of API and parameters relevant to the specific dosage form:
a) In case the assessment report from the accepted APIMF is available; or
b) In case the APIMF is not (yet) accepted but API has been fully evaluated in a product approved by EAC not more than 3 years ago.

2.2 For products that have been recently submitted for registration, for which APIMF evaluation is also under way the outstanding concerns from the APIMF evaluation report shall be taken into consideration during evaluation of the FPP.

2.3 For the rest of products, i.e. for which APIMF is not submitted, the FPP evaluation shall include full evaluation of the related API(s) according to the CTD format.

2.4 APIs cannot be classified into two categories – high and low risk APIs by any single criteria, but the extent of effort and detail required for their assessment depends mainly on the track record of this API source in the EAC context.

2.5 In case pharmacopoeia monograph is available, the evaluation should include, whether the monograph used is actually suitable to control the quality of the substance in the context of the related medicinal product and the API manufacturing process specific to each source

2.6 Evaluation of submitted APIMFs shall be done based on the principle of First In First Out, however priority may be given to an APIMF that is used in support for multiple products submitted for registration.

3. API Master File (APIMF) Procedure

Information on the preparation, control and stability of an active pharmaceutical ingredient (API) intended for use in a finished pharmaceutical product (FPP) can be provided by the API master file (APIMF) procedure. This procedure has advantage over other options of submitting the API information in that it preserves the confidentiality of the API information.

3.1 How the APIMF procedure works

3.1.1 The FPP applicant submits the open part (non-confidential information) (OP) of the APIMF as part of the application for registration of the FPP. In so doing the applicant demonstrates that it has at least basic knowledge about the API used in the manufacture of its product.

3.1.2 The FPP applicant requests the API manufacturer to provide a Letter of Access granting the NMRA permission to review the restricted part (RP) (i.e. containing confidential information) of the APIMF when evaluating the relevant FPP applied for registration.

3.1.3 In the Letter of Access the API manufacturer should commit to informing the NMRA of any changes it has made to the details of either the OP or restricted part (RP) of the APIMF, and to inform the FPP applicant of any changes made or likely to be made to the preparation, control and/or stability of the API.

3.1.4 Thereafter the API manufacturer provides NMRA with both the OP and the RP of the APIMF for review.

3.1.5 It is the responsibility of the FPP applicant to ensure that the API manufacturer provides the NMRA with the complete APIMF (i.e. both the OP and the RP).

3.1.6 NMRA shall contact the APIMF holder directly if it has any questions arising from its assessment of the RP, or requires any further information about the APIMF. Once assessment has been completed (i.e. the APIMF is considered to be acceptable), the APIMF details are considered to form part of the FPP dossier.

3.1.7 Reassessment of the APIMF shall not be required when other applications for registration of FPPs using the same API are submitted provided that the API manufacturer consents and provides a Letter of Access allowing their APIMF to be used in support of a specified FPP application.

4. General considerations

4.1 Both the APIMF procedure and the API certification procedure may be used in support of an FPP application, and both procedures make extensive use of APIMFs.

4.2 API certification is a stand-alone procedure for API manufacturers and does not need to be applied when an application for FPP registration is made.

4.3 Acceptance of an APIMF within the APIMF procedure does not mean that the API is certified. However, APIMF holders who have had their APIMF accepted within the APIMF procedure may wish to build upon this acceptance and apply for API certification.

4.4 The same APIMF can be used as part of a submission for API certification and as part of a submission of an application for FPP registration.

5. Inspection of API Manufacturers

All manufacturers of APIs used in approved medicinal products should comply with GMP. API Manufacturing site requirements are as follows:

5.1 All applicants must submit a site master file (SMF) for each manufacturing site of each API and intermediate involved in the preparation of the API for which registration is sought. An SMF is a document prepared by the manufacturer containing information with respect to the production and/or control of pharmaceutical manufacturing operations carried out at a named site, and to any closely integrated operations at adjacent and/or nearby buildings. If only part of the API production is carried out at a site — such as analysis or packaging — the SMF need describe only that operation.

5.2 Each API or intermediate manufacturing site must comply with EAC GMP guidelines. Manufacturers who submit an application for registration should therefore request inspection by EAC of the relevant manufacturing site(s) so that compliance with EAC GMP can be assessed. However, applicants whose manufacturing site(s) have already undergone a WHO Prequalification GMP inspection, or inspection within the past three years by a member of the Pharmaceutical Inspection Co-operation Scheme (PICs), evidence of this can be submitted inspection as part of their application for API prequalification, in lieu of a request for inspection by EAC.

5.3 By definition, if an API manufacturer is rated unacceptable with regard to GMP compliance, there is a risk to public health and safety. The degree of risk will depend on the nature of the GMP deficiencies and the type of API and medicinal product.

5.4 New medicinal products should not be approved by EAC unless all API manufacturers have been determined to comply with EAC GMP guidelines with respect to the manufacture of the specific API(s). An exception to this may be considered when the health benefits from a product being available are greater than the risk to public health and safety resulting from GMP non-compliance. A risk-based decision will be made on a case-by-case basis and documented.

5.5 EAC approval of existing medicinal products should be suspended if an API manufacturer is found to have an unacceptable level of GMP compliance. An exception to this may be considered when the health risk due to product unavailability is greater than the risk to public health and safety resulting from GMP non-compliance. A risk-based decision will be made on a case-by-case basis and documented.

5.6 As a default, all manufacturers of APIs used in EAC approved medicinal products should be inspected by the EAC. An inspection by the EAC may be omitted when other acceptable evidence of GMP compliance is provided by the API manufacturer.

5.7 An inspection by another acceptable organization, such as the EDQM, a PIC/S member country, the US FDA, WHO or an EAC Member state, may be considered in lieu of a EAC inspection when:

a) The inspection was conducted within the last 3 years, and
b) The scope of the inspection covered the specific API in question, and
c) The API manufacturer submits a copy of the last inspection report for review by the EAC. The review must determine that the inspection was comprehensive and that the inspection report supports the final outcome.
d) Irrespective of the above, the EAC reserves the right to inspect any API manufacturer if considered necessary on a risk basis.

5.8 Whether inspected by the EAC or GMP compliance is based on an inspection by another acceptable organization, on-going GMP compliance must be confirmed at least every 3 years.

5.9 API inspection conducted by the EAC should be prioritized on a risk basis. The following order is provided for guidance in determining priorities:

a) Sterile APIs
b) The API is used in a number of products
c) The API is produced by fermentation
d) The sole supplier of an API
e) A new API manufacturer when the product approval process may be held up by lack of GMP evidence for the API manufacturer
f) Re-inspection when it is more than 12 months past the re-inspection due date