REG–79 version 1 ACTIVE SUBSTANCE MASTER FILE

This Guideline supersedes guideline REG-79 with the effect from 3 June 2011.

This guideline is based upon guideline CPMP/QWP/227/02 (EMEA/CVMP/134/02) "Guideline on Active Substance Master File Procedure", issued on February 11, 2004 and effective within the European Union as of August 31,2004 (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002814.pdf). This guideline lays down details of the procedure for submission of the Active substance master file within the marketing authorisation/variation to marketing authorisation procedure.

Pursuant to Annex 1 to Decree No 288/2008 Coll., on the marketing authorisation of medicinal products, as amended, an application for marketing authorisation of a medicinal product shall be accompanied by detailed information about the active substance and its manufacture. Where the manufacturer of the active substance is not identical with the manufacturer of the product, the information shall be provided in the form of a separate document submitted by the manufacturer of the active substance directly to the State Institute for Drug Control (hereinafter referred to as the "Institute"), as the Active Substance Master File (Základní dokument o léčivé látce). An application for marketing authorisation shall be regarded incomplete, unless this information on the active substance is submitted to the Institute.

1. INTRODUCTION

The main objective of the procedure governing the Active Substance Master File, ASMF (Základní dokument o léčivé látce), which is generally known as the European Drug Master File (EDMF), is to allow confidential data or "know-how" of the manufacturer of the active substance to be protected and, at the same time, allow the applicant for marketing authorisation or the marketing authorisation holder to take full responsibility for the medicinal product and for the quality and quality control of the active substance. This will ensure that the Institute has access to the complete information necessary for the assessment of the suitability of use of the active substance in the product concerned.

The purpose of this guideline is to help applicants for marketing authorisation or marketing authorisation holders in the preparation of the marketing authorisation (MA) dossier submitted together with the Marketing Authorisation Application/Marketing Authorisation Variation for a medicinal product.

2. CONTENT OF THE ACTIVE SUBSTANCE MASTER FILE (ASMF, EDMF)

The Active Substance Master File should include detailed scientific information as indicated in the various chapters of the Notice to Applicants for Marketing Authorisations for Medicinal Products in the Member States of the European Union (NtA Vol 2B CTD - http://ec.europa.eu/health/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf). EDMFs linked to human medicinal products shall be submitted in the CTD format (Common Technical Document) - Annex 1 refers.

Data contained within the EDMF should be divided into two separate parts, one part available to the MA applicant or holder and to the Institute, so called Applicants Part (AP) and the other available only to the Institute, i.e. the Restricted Part (RP). The AP contains information which the EDMF holder does not consider confidential in respect to the MA applicant or MA holder, while the RP contains information which the EDMF holder considers confidential (Annex 1 refers). It should be emphasised that the AP is still a confidential document which must not be disclosed to any third party without the written approval of the EDMF holder. In any case, the AP should contain such information which shall be sufficient for the MA applicant to be able to take full responsibility for the quality control of the active substance in the manufacture of the given medicinal product. The RP shall then contain the remaining information, such as details of the individual steps of the manufacturing process (reaction conditions, temperature, validations, critical steps evaluation, etc.), and information on the quality control during the manufacture of the active substance. In some cases the Institute may not accept that an essential piece of information was not disclosed to the Applicant or MA Holder and in such cases the Institute shall request an amendment to the AP.

Apart from the AP and RP, the EDMF should also include the Table of Contents and a separate AP and RP summaries. Where the EDMF is presented in the CTD format, both summaries should be presented as a Quality Overall Summary, see CTD, NtA). Where the "old" NtA format is used (applications within MRP commenced before April 30, 2005), each summary should be made in the form of a written and tabulated Expert Report. . Both the AP and RP should be labelled with a version number. Once the EDMF is received by the Institute, it shall be allocated number which shall be then communicated to the EDMF holder. This number shall be unique and shall follow a logical order. The allocated numbers shall have the following structure:

3. USE OF THE EDMF PROCEDURE

An EDMF may only be submitted in support of a Marketing Authorisation Application/Marketing Authorisation Variation for a medicinal product. Although the EDMF procedure has been developed with the intention to maintain the protection of confidential data or "know-how" of the active substance manufacturer, it may be applied also in situations where the confidentiality issues between the MA holder/applicant and the manufacturer is not applicable (e.g. where the manufacture of the active substance is conducted by the MA applicant/holder himself).

The EDMF procedure may be used for all active substances, i.e.:

A. New active substances;
B. Known active substances not included in the European Pharmacopoeia (Ph.Eur.) or in EU Member States pharmacopoeias;
C. Pharmacopoeial active substances included in Ph.Eur. or in EU Member States pharmacopoeias.

An EDMF holder may have both an EDMF and Ph.Eur. certificate of suitability (CEP) for a single active substance. It is, however, generally not acceptable that the MA applicant/holder refers both to the EDMF and CEP for a single active substance of a particular MA application.. Where the CEP does not include certain important information (e.g. on stability), the Institute may request submission of additional data. Only in such a case it shall be acceptable to refer both to the EDMF and CEP.

An EDMF holder should give the Institute his consent for assessment of data contained in the EDMF in relation to a specific Marketing Authorisation Application/Marketing Authorisation Variation in the form of a Letter of Access (please refer to Annex 2).

An EDMF holder should provide the MA applicant/holder with the following documents:

- a copy of the latest version of the AP;
- a copy of the Quality Overall Summary or Expert Report for the latest version of the AP;
- the Letter of Access, unless it has been submitted previously.

An EDMF holder shall submit to the Institute:

- the EDMF (both the AP and RP) together with the Covering Letter (please refer to Annex 3);
- the Letter of Access, unless submitted earlier;
- a copy of the Quality Overall Summary, or Expert Report for the latest version of the RP.

An EDMF holder may submit the EDMF to the Institute either for each individual Marketing Authorisation Application/Marketing Authorisation Variation separately, or he may present one common EDMF for several MA applications/variations. The submission of the relevant documentation by the EDMF holder to the Institute should be synchronised so that all the above mentioned documents are delivered to the Institute at approximately the same time as the Marketing Authorisation Application/Marketing Authorisation Variation.

Where the EDMF procedure is applied, the MA applicant/holder should submit the Marketing Authorisation Application/Marketing Authorisation Variation to the Institute together with the Letter of Access, unless the letter has been submitted previously for the given product either by the MA applicant or MA holder or by the EDMF holder.

Where the same active substance of the same manufacturer is used in the manufacture of several different products in one or more Member States, the EDMF holder shall submit identical documentation to each Competent Authority/EMEA. The Competent Authorities/EMEA may, subsequently, request that any updates made to the EDMF in relation to a single application should apply to the MA of all products containing the given active substance of the particular manufacturer. Responsibility for the notification of any changes to the AP or RP to the MA holders and Competent Authorities/EMEA shall lie with the EDMF holder. This ensures that MA applicants/holders can update all MAs to which the given change applies, as appropriate.

4. THE CONTENT OF THE MA DOSSIER WHERE THE EDMF PROCEDURE IS APPLIED

The MA applicant/holder is responsible for ensuring that he has access to any necessary information concerning the current manufacture of the active substance.
The specifications used by the MA applicant/holder for the quality control of the active substance should be clearly specified in the MA dossier. A copy of the AP shall be included by the MA applicant/holder in the MA

[1] The active substance code and active substance manufacturer code shall be allocated by the Institute.

dossier. The MA dossier should contain the latest version which should be identical with the AP provided to the Institute by the EDMF holder as part of the EDMF. The MA applicant/holder shall include all relevant information from the AP in the Quality Overall Summary or Expert Report for the MA dossier. Where the data contained in the EDMF pertain only to the given product, information on this data should be part of the Quality Overall Summary or the Expert Report for the MA dossier.
Where a single manufacturer of the active substance is concerned and the EDMF or CEP procedure is applied, the specifications of the MA applicant/holder contained in the MA dossier should be essentially identical to those of the EDMF/CEP holder. The MA applicant/holder, however, does not need to accept outdated analytical methods. Where the MA applicant/holder applies a different analytical method than the one described in the EDMF he shall perform validation of the method. Specifications implied by the pharmaceutical form of the medicinal product which are not a normal part of the EDMF (e.g. particle size) should be included in the MA applicant's / holder's specifications.
Where several manufacturers of the active substance are concerned, one specification should be drafted, which shall be common for all manufacturers. In this event, the specification may give several acceptance criteria/analytical methods for a single parameter, with the statement "if tested" e.g. for residual solvents).

5. CHANGES AND UPDATES OF EDMF

EDMF holders should keep the content of their EDMFs updated in respect of the actual process of synthesis/production. Quality control procedures should be constantly kept in line with current regulatory and scientific requirements. EDMF holders may not change the contents of their EDMFs (e.g. manufacturing process for an active substance or specifications) without informing the MA applicant/holder and the Institute. Before any change to the EDMF is made it shall be necessary for each MA holder whose products contain the given active substance to notify the change to the Institute by means of an application for the appropriate variation to the marketing authorisation. Besides the application, a Covering Letter should be provided to the Institute. . If the EDMF cannot be changed for a certain period of time due to other procedures (e.g. particularly due to pending MRP procedures) the EDMF holder shall still provide the above mentioned data to the MA holder and to the Institute and shall point out to this reason and request a postponed submission of the application.

The Covering Letter submitted to the Institute by the EDMF holder should contain the following information (if available):

- A tabular list summarising changes made since the first compilation of the EDMF;
- An overview providing a comparison of the old and new content of the EDMF;
- Information as to whether the change has been approved, rejected or suspended in another Member State;
- Names of the relevant MA applicants/holders, and names of the medicinal products and their MA numbers, if applicable;
- New AP and/or RP parts, giving the new version number for each;
- Updated Quality Overall Summary or Expert Report, if applicable.

As part of the 5-yearly renewal procedure for a medicinal product, the MA holder shall submit a declaration stating that the quality of the product in terms of manufacturing procedures and in-process controls has been regularly updated by means of submitted applications for variations to the MA with respect to technical and scientific progress, and that the product complies with the current guidelines. The MA holder shall also declare that no changes have been made to the product particulars other than those approved by the Institute.

MA holders should verify with relevant EDMF holders whether such declaration may be issued with respect to the active substance data. Where a change has not been notified to the MA holder or the Institute, a relevant application for variation to the MA should be submitted without delay.

For better practical application the Annexes to this guideline are provided in English.

Overview of EDMF Contents

Table 1	NtA CTD format	Applicants Part	Restricted Part
3.2.S1	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	Manufacturer(s)	x	
3.2.S.2.2	Description of manufacturing process and process controls	1)	2)
3.2.S.2.3	Control of materials		x
3.2.S.2.4	Control of critical steps and intermediates	3)	4)
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	5)
3.2.S.4	Control of drug substance	x	
3.2.S.4.1	Specifications	x	
3.2.S.4.2	Analytical procedures	x	
3.2.S.4.3	Validation of analytical procedures	x	
3.2.S.4.4	Batch analysis	x	
3.2.S.4.5	Justification of specification	x	6)
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	

1) Flow chart and short description 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 Applicants Part /in case 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/MA holder.
4) In so far as the information is related to the detail description of the manufacturing process and in so far as this information is not relevant for the Applicant/MA holder.
5) In so far as the information is related to the detail description of the manufacturing process and in so far the EDMF holder sufficiently justifies that there is no need to control these impurities in the final active substance.
6) In so far as the information is related to the detailed description of the manufacturing process, control of materials and process validation.

Specimen Letter of Access

[Address of Competent Authority/EMEA]

[Date and place]

LETTER OF ACCESS

Number of Active Substance Master File: [if known, or to be given by the Competent Authority/EMEA or procedure reference number/community reference number in Centralised Procedure]

Manufacturing site: [name and address]
Active Substance Master File holder: [name and address]

The aforementioned Active Substance Master file holder hereby authorises the [name of Competent Authority/EMEA including all CPMP Members and their experts] to refer to and review the above mentioned Active Substance Master File in support of the following Marketing Authorisation Application(s) or Marketing Authorisation Variation(s)[1] submitted by [name/Marketing Authorisation Holder/Applicant] on [planned date of submission]:

[Name of product and Marketing Authorisation number, if known]
[Name of Applicant or Marketing Authorisation Holder]

The aforementioned Active Substance Master File holder commits to ensure batch to batch consistency and to inform [name of Marketing Authorisation holder/Applicant] and Competent Authority/EMEA of any change in Active Substance Master File.

Signature for Active Substance Master File holder
[Name and address]
[Signature]

[1] i.e. To introduce a new EDMF from a new AS manufacturer.

Specimen Covering Letter

This Active Substance Master File is submitted in relation to the Marketing Authorisation Application/Marketing Authorisation Variation:

[Number of national, centralized or mutual recognition procedure]
[Name of product in national, centralized or mutual recognition procedure]
[Name of Applicant/Marketing Authorisation holder for the application concerned]
[Concerned Member States in mutual recognition]

And describes <changes to> the manufacturing process and specifications of the (or one of the) active substance(s) of this Marketing Authorisation Application or Marketing Authorisation Variation.

[Name active substance]

The version number of Active Substance Master File is
Applicants part: version [version number]
Restricted part: version [version number]

This Active Substance Master File has previously been submitted for assessment in combination with a Marketing Authorisation Application/Marketing Authorisation Variation for a medicinal product within the European Union:

- ❑ No
- ❑ Yes, within the following National, Centralised or mutual recognition procedure:

[Number of National, Centralised or Mutual recognition procedure]
[Name of product in National, Centralised or Mutual recognition procedure]
[Authorisation number and date of approval of the products concerned]
[Rapporteur or Reference Member State]
[Concerned Member States in Mutual recognition]
[Version number Applicants part]
[Version number restricted part]

Note:
Information in *italic font* can be left blank if not known.
Information in normal font is always required.