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**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)
COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS
(CVMP)**

GUIDELINE ON ACTIVE SUBSTANCE MASTER FILE PROCEDURE

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Note:

Clarifications have been attached to this document (see last page) in relation to its applicability to well-defined active substances only and its non-applicability to biological active substances. In addition, corrections are introduced in the Annex 1, sections 3.2.S.2 and 3.2.S.2.1. These changes have been endorsed by CHMP and CVMP at their March and April 2005 meetings.

Public

GUIDELINE ON ACTIVE SUBSTANCE MASTER FILE PROCEDURE

1. INTRODUCTION

The main objective of the Active Substance Master File (ASMF) procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the Applicant or marketing authorisation (MA) holder to take full responsibility for the medicinal product and the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary for an evaluation of the suitability of the use of the active substance in the medicinal product.

This Guideline is intended to assist Applicants/MA holders in the compilation of the active substance section of their dossiers for a marketing authorisation application (MAA) or a marketing authorisation variation (MAV) of a medicinal product. It is also intended to help EDMF holders in the compilation of their EDMFs. This Guideline is not intended to give instructions to the Competent Authorities/EMA in the administrative and scientific handling of EDMFs and related MAAs and MAVs.

2. CONTENT OF THE ACTIVE SUBSTANCE MASTER FILE

The overall content of the EDMF should contain detailed scientific information as indicated under the various headings of the relevant Notice to Applicants for Marketing Authorisations for Medicinal Products in the Member States of the European Union (NtA). EDMFs linked to human medicinal products should be presented in the format of the Common Technical Document (CTD), see Annex 1 table 1. EDMFs linked to veterinary medicinal products should be presented in accordance with Annex 1 table 2. EDMFs for veterinary medicinal products may also be presented in CTD format after consultation with the Competent Authorities/EMA.

The scientific information in the EDMF should be physically divided into two separate parts, namely the Applicants Part (AP) and the Restricted Part (RP). The AP contains the information that the EDMF holder regards as non-confidential to the Applicant/MA holder, whereas the RP contains the information that the EDMF holder regards as confidential, see Annex 1. It is emphasized that the AP is still a confidential document that cannot be submitted by anyone to third parties without the written consent of the EDMF holder. In all cases the AP should contain sufficient information to enable the Applicant/MA holder to take full responsibility for an evaluation of the suitability of the specifications for the active substance to control the quality of this active substance for use in the manufacture of a specified medicinal product. The RP may 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 manufacture method of the active substance. The Competent Authorities/EMA may not accept that particular information has not been disclosed to the Applicant/MA holder. In such cases, the Competent Authorities/EMA may ask for an amendment to the AP.

In addition to the AP and RP, the EDMF should contain a table of contents, and a separate summary for the AP and the RP. In cases where the EDMF is provided in the CTD format, CPMP/QWP/227/02 rev 1 and EMA/CVMP/134/02 rev 1

both summaries should be presented as a Quality Overall Summary (QOS). In cases where the old human or current veterinary NtA format is used, each summary should be made in the form of a written and tabulated expert report (ER). The AP 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 EDMF holder / Name active substance / AP or RP/ version number / date in yyyy-mm-dd.

3. USE OF THE ACTIVE SUBSTANCE MASTER FILE PROCEDURE

An EDMF can only be submitted in support of an MAA or MAV. The relationship between the quality of the active substance and its use in the medicinal product needs to be justified in this MAA or MAV. Although the EDMF procedure is developed to keep intellectual property of the ASM confidential, it is also permissible to use the procedure when there is no confidentiality issue between the Applicant/MA holder and the ASM (e.g. when the Applicant/MA holder synthesises the active substance himself). It is expected that the ASM is also the holder of the EDMF.

The EDMF procedure can be used for the following active substances (except biological active substances, see the CHMP procedural announcement at the last page of this Guideline), i.e.:

- A. New active substances
- B. Existing active substances not included in the European Pharmacopoeia (Ph. Eur.) or the pharmacopoeia of an EU Member State
- C. Pharmacopoeial active substances included in the Ph. Eur. or in the pharmacopoeia of an EU Member State

The EDMF holder may have an EDMF as well as a CEP for a single active substance. Generally, it is however not acceptable that the Applicant/MA holder refers to an EDMF as well as to a CEP for a single active substance of a particular MAA. In cases where the CEP contains too little information (e.g. stability) the Competent Authorities/EMA may decide that additional information should be provided in the dossier. In such case it may be acceptable to refer both to an EDMF and a CEP.

The EDMF holder should give permission to the Competent Authorities/EMA to assess the data in the EDMF in relation to a specific MAA/MAV, in the form of a 'Letter of Access', see Annex 2.

The EDMF holder should submit to the Applicant/MA holder:

- a copy of the latest version of the AP.
- a copy of the QOS/ ER on the latest version of the AP
- the letter of access where this letter has not been submitted earlier for the product concerned.

In addition, the EDMF holder should submit to the Competent Authorities/EMA:

- the EDMF accompanied by a covering letter, see Annex 3.

- the Letter of Access where this letter has not been submitted earlier for the product concerned.

The EDMF holder should submit the EDMF to the Competent Authority/EMEA either for each MAA and each MAV or only once according to national requirements. The submission of the relevant documentation by the EDMF holder to the Competent Authority/EMEA must be synchronised to arrive at approximately the same time as the MAA or the MAV.

Where the EDMF procedure is used, the Applicant/MA holder should submit the MAA or MAV to the Competent Authorities/EMEA together with the Letter of Access where this Letter has not been submitted earlier by the MA holder/Applicant himself or by the EDMF holder for the product concerned.

Where the same active substance is used in a number of applications for different products in one or more Member States, the EDMF holder should submit identical documentation to every Competent Authority/EMEA. Consequently, the Competent Authorities/EMEA may require that any EDMF updates made in relation to one MA should apply to all. It is the EDMF holder's responsibility to notify the MA holders and Competent Authorities/EMEA concerned about any changes to the AP and/or RP, so that the MA holders can update all affected MAs accordingly.

4. CONTENT OF THE MA DOSSIER WHEN THE ACTIVE SUBSTANCE MASTER FILE PROCEDURE IS USED

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

The specifications used by the Applicant/MA holder to control the correct quality of the active substance should be laid down unambiguously in the MA dossier (NtA CTD format section 3.2.S.4.1 and 3.2.S.4.2 or old human/veterinary NtA format part IIC1). The Applicant/MA holder should include a copy of the AP in the MA dossier (NtA CTD format section 3.2.S or NtA old human/veterinary format part IIC1). The version of the AP in the MA dossier should be the most recent and it should be identical to the AP as supplied by the EDMF holder to the Competent Authority/EMEA as part of the EDMF. The Applicant/MA holder should include all relevant details from the AP in the QOS/ER of the MA dossier. Issues of the EDMF that are specifically relevant to the product under consideration should be highlighted in the QOS/ER of the MA dossier.

In the case of a single supplier and where the EDMF procedure or CEP procedure is used, the specifications of the Applicant/MA holder in the MA dossier should in principle be identical to those of the EDMF holder or the CEP holder. The Applicant/MA holder does however not need to accept redundant specifications, unnecessarily tight specification limits or outdated analytical methods. In cases where the Applicant/MA holder uses a different analytical method than that described in the EDMF, both methods should be validated. Technical specifications relevant for the medicinal product, which are normally not part of the specifications in the EDMF (e.g. particle size), should be part of the specifications of the Applicant/MA 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 'if tested' (e.g. in case of residual solvents).

5. CHANGES AND UPDATES TO THE ACTIVE SUBSTANCE MASTER FILE

As for medicinal products, EDMF holders should keep the content of their EDMFs 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. EDMF holders shall not modify the contents of their EDMF (e.g. manufacturing process or specifications) without informing each Applicant/MA holder and each Competent Authority/EMEA. Before implementation, any change to the EDMF should be reported by every MA holder to the relevant Competent Authority/EMEA by means of an appropriate variation procedure. A covering letter should be provided. In cases where the contents of the EDMF cannot be changed for a certain period of time because of other procedural provisions (i.e. mainly because of ongoing MRP procedures), the EDMF holder should still provide the aforementioned data to the MA holder and Competent Authorities/EMEA making reference to this reason and requesting a later date of implementation.

The EDMF holders' covering letter to the Competent Authorities/EMEA should contain the following information (if available):

- A tabular list summarising the changes carried out since the first compilation of the EDMF.
- An overview comparing the old and new content of the EDMF.
- Information as to whether the change has already been accepted, rejected or withdrawn by another Member State.
- The names of the relevant Applicants, MA holders and MAs.
- The new AP and/or RP with each the new version number.
- An updated QOS/ER if relevant.

At the occasion of the 5-yearly renewal of a medicinal product, MA 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 CPMP/CVMP quality guidelines. They will also declare that no changes have been made to the product particulars other than those approved by the Competent Authority/EMEA.

MA holders should therefore verify with their EDMF holders whether the above declaration can be met in respect to the active substance particulars. In case changes have not been notified to the MA holder and Competent Authority/EMEA, the necessary variation procedure should be initiated without delay.

ANNEX 1: OVERVIEW EDMF CONTENTS

Table 1	NtA CTD format	Applicants Part	Restricted Part
3.2.S.1	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	Manufacture	x	X
3.2.S.2.1	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	Specification	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	

Table 2	NtA veterinary format / old human format	Applicants Part	Restricted Part
IIC.1	Name(s) and site(s) of ASM	x	X
IIC.1.1	Specifications and routine tests	x	
IIC.1.2.1	Nomenclature	x	
IIC.1.2.2	Description	x	
IIC.1.2.3	Brief outline of the manufacturing route (flow chart)	x	
IIC.1.2.3	Detailed description manufacturing method		X
IIC.1.2.4	QC during manufacture	3)	4)
	Process validation and evaluation of data		X
IIC.1.2.5	Development Chemistry	x	
	Evidence of structure	x	
	Potential Isomerism	x	
	Physiochemical characterisation	x	
	Analytical validation	x	
IIC.1.2.6	Impurities	x	5)
IIC.1.2.7	Batch analysis	x	
IIF1	Stability	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 sterilisation process may be requested in the Applicants Part (in cases where there is no further sterilisation 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 detailed 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 detailed description of the manufacturing process and in so far as 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.

ANNEX 2: TEMPLATE 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 or CVMP 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 the Active Substance Master File.

Signature for the Active Substance Master File holder

[Name and address]

[Signature]

¹ i.e. to introduce a new EDMF from a new AS manufacturer.

ANNEX 3: PART OF COVERING LETTER

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

[Number of national, centralised or mutual recognition procedure]

[Name of product in national, centralised 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 this 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.

ANNEX 4: LIST OF ABBREVIATIONS

Abbreviation	Full text
AP	Applicants Part (of EDMF)
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
CEP	European procedure for a certificate of suitability of monographs of the European pharmacopoeia (here on chemical purity)
CTD	Common Technical Document
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Evaluation Agency
ER	Written and tabulated expert report (refers to MA dossiers in old human or existing NtA veterinary format)
ICH	International Conference on Harmonisation
MA	Marketing Authorisation
MAA	Marketing Authorisation Application (including line extensions)
MAV	Marketing Authorisation Variation
NtA	Notice to Applicants
Ph. Eur.	European Pharmacopoeia
RP	Restricted Part (of EDMF)
QOS	Quality Overall Summary (refers to MA dossiers in NtA CTD format)

ANNEX 5: GLOSSARY

Item	Definition
Active Substance Manufacturer	A party involved in the manufacturing chain of the active substance, including agents, brokers, traders, distributors, repackers or relabellers.
Active Substance Master File holder	This is the company that has the ultimate responsibility for the Active Substance Master File.
Applicant	This is the company requesting a Marketing Authorisation for a medicinal product.
European Drug Master File	The old name of the Active Substance Master File
Marketing Authorisation holder	This is the company that is responsible for the medicinal product on the market
Manufacturing chain	A clear flow chart or written text explaining the manufacturing and distribution route of the active substance from the first starting materials to the final active substance as delivered to the Applicant/Marketing Authorisation holder.
New active substance	According to ICH Q6A new drug substance that is The designated therapeutic moiety, which has not previously been registered in a region or Member State (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved drug substance.
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.

- **Non applicability of Active Substance Master file (ASMF) concept to biological active substances**

Marketing Authorisation Holders (MAH) and applicants are advised that the concept of Active Substance Master files, as laid down in Directive 2001/83/EC, as amended, cannot be applied in the context of biological medicinal products.

The characterisation and determination of biological active substances' quality requires not only a combination of physico-chemical and biological testing, but also extensive knowledge of the production process and its control.

The MAH/applicant for a biological medicinal product could therefore not comply with the requirement to '*take responsibility for the medicinal product*' without having full and transparent access to these quality-related data. The use of an ASMF would prevent such access, and should therefore not be allowed for biological active substances.

In addition, active substances, which are present in certain medicinal products such as vaccines or cell-therapy medicinal products, do not fit with the concept of a '*well-defined*' active substance.

- **Non-applicability of ASMF concept of open and closed parts to Vaccine Antigen Master file (VAMF) and Plasma Master file (PMF)**

The legislation does not provide for the use of open/closed parts in the Vaccine Antigen Master file (VAMF) and Plasma Master file (PMF). The concept of open (non-confidential) and closed (confidential) parts is specific to the Active Substance Master file.

Regarding the VAMF the legislation specifies that the VAMF holder cannot differ from the MAH/applicant for the concerned medicinal product: there is hence no rationale for an 'open/closed' parts system.

For the PMF the legislation specifies that where the MAH/applicant differs from the holder of the PMF, the PMF shall be made available to the MAH/applicant for submission to the competent authority.