EUROPEAN DRUG MASTER FILE PROCEDURE FOR ACTIVE SUBSTANCES

Guideline Title	**European Drug Master File Procedure for Active Substances**
Legislative basis	**Directive 75/318/EEC as amended**
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Previous titles/other references	***Use of the European DMF Procedure* III/5370/93 which included and replaced III/3500/91 and III/3499/91 and the previous guidance *Drug Master Files on Active Ingredients* III/3836/89**
Additional Notes	**This note for guidance describes the legal basis and possible way of presenting the documentation required in Part 2 C and F of the Annexes to Directive 75/318/EEC as amended and Directive 81/852/EEC as amended.**

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This compilation has been prepared in order to help applicants for marketing authorisations and manufacturers of active substances when using the European Drug Master File procedure in the preparation of dossiers for application for marketing authorisations. It does not have any legal force and in case of doubt, applicants should refer to the original texts of the directives.

The words "medicinal products" cover both products for use in humans and veterinary medicinal products

Contents:

1. Legal basis of the procedure: annexes to Directives 75/318/EEC as amended and 81/852/EEC as amended, Part 1 C 1, "Control of starting materials".
2. Note for guidance *Use of the European Drug Master File Procedure*, adopted by the Committee for Proprietary Medicinal Products (CPMP) on 12.5.1993 and revised on 16.6.1993, and by the Committee for Veterinary Medicinal Products (CVMP) on 23.3.1994, with immediate entry into operation.

A. LEGAL BASIS OF THE PROCEDURE: EXTRACT FROM THE ANNEX TO DIRECTIVE 75/318/EEC AS AMENDED, (*) AND TO DIRECTIVE 81/852/EEC AS AMENDED, (**) "CONTROL OF STARTING MATERIALS"

Controls of starting materials

In the case of:

– an active substance not described in the European Pharmacopoeia or in the pharmacopoeia of a Member State, or

– an active substance described in the European Pharmacopoeia or in the pharmacopoeia of a Member State, when prepared by a method liable to leave impurities not mentioned in the pharmacopoeial monograph and for which the monograph is inappropriate to adequately control its quality, which is manufactured by a person different from the applicant, the latter may arrange for the detailed description of the manufacturing method, quality control during manufacture and process validation to be supplied directly to the competent authorities by the manufacturer of the active substance. In this case, the manufacturer shall however provide the applicant with all the data which may be necessary for the latter to take responsibility for the medicinal product. The

(*) as modified by Directive 91/507/EEC of 19 July 1991, Official Journal n° L 270 of 26.6.1991

(**) as modified by Directive 92/18/EEC of 20 March 1992, Official Journal N° L 97/1 of 10.4.1992

manufacturer shall confirm in writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing the applicant. Documents and particulars supporting the application for such a change shall be supplied to the competent authorities.

B. EUROPEAN DRUG MASTER FILE PROCEDURE

Note for guidance concerning a possible way of presenting the documentation required in Part 2 C and F of the Annex to Directives 75/318/EEC as amended and 81/852/EEC as amended. The documentation needed is described in detail in the "Notice to Applicants for marketing authorisations for medicinal products for human use in the Member States of the European Union" Part II, C 1 and F 1 and in the same document dealing with veterinary medicinal products and in the note for guidance *Chemistry of Active Substances.*

1. INTRODUCTION

The European Drug Master File (DMF) procedure may be used when the active substance manufacturer (ASM) is not the applicant for a product marketing authorisation (applicant), with a view to protecting valuable know-how on the manufacture of the active substance.

A DMF is a document containing the information required to demonstrate that the quality of the active substance is adequately controlled by the specification proposed by the applicant. The applicant must, therefore, collaborate with the person submitting a separate DMF to ensure that all relevant information required is supplied. Furthermore it must be ensured that the applicant's part of the DMF (cf. below) contains all information needed for the applicant to take full responsibility for the preparation, including the suitability of the active substance (as supplied) for the intended route of administration.

It is not a requirement to present information on the active substance in the form of a DMF. The information may also form part of the application for authorisation to place a medicinal product on the market.

Three types of active substances may be described in a European DMF.

A. New active substances still covered by a patent, not described in the European Pharmacopoeia or in the pharmacopoeia of a Member State.

B. Active substances off-patent, not described in the European Pharmacopoeia or the pharmacopoeia of a Member State.

C. Active substances described in the European Pharmacopoeia or in the pharmacopoeia of a Member State when prepared by a method liable to leave impurities not mentioned in the pharmacopoeial monograph and for which the monograph is inappropriate to adequately control their quality (Directives 75/318/EEC as amended and 81/852/EEC as amended).

2. CONTENT OF THE EUROPEAN DRUG MASTER FILE

2.1 Overall content

Detailed information should be provided 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" – Part II C, Control of starting materials – active substances and Part II F, Stability – stability tests on active substances.

2.2. Applicant's part and ASM Restricted Part of a European DMF

The DMF contains information which includes valuable know-how which should be kept confidential and submitted to the authorities only. Therefore, it should be divided into 2 parts – an applicant's part and an ASM Restricted Part. The applicant's part of a DMF is provided by the ASM to the applicant directly and becomes part of the application for marketing authorisation. Both the applicant's part and the ASM Restricted Part of the DMF are submitted to the competent authorities. The applicant's part of the DMF is still a confidential document which cannot be submitted to third parties without the written agreement of the ASM.

a) Applicant's part of a DMF

The applicant must be supplied by the ASM with sufficient information to be able to take responsibility for an evaluation of the suitability of the active substance specification to control the quality of the substance. This normally includes a brief outline of the manufacturing method, information on potential impurities originating from the manufacturing method, from the isolation procedure (natural products) or from degradation and, where applicable, information on the toxicity of specific impurities.

b) ASM Restricted Part of DMF

Detailed information on the individual steps of the manufacturing method such as reaction conditions, temperature, validation and evaluation data for certain critical steps of the manufacturing method, etc. and on quality control during manufacture may contain valuable know-how. Such information may therefore be supplied to the authorities only.

An example is provided in the Table below of the division of the information which should be included in the applicant's part and the ASM Restricted Part, respectively. However, the type of information should always be adapted to the manufacturing method and the characteristics of the individual active substance. The figures in brackets refer to sections in Part II C or II F in the Notice to Applicants.

TABLE

	ASM Restricted Part	Applicant's part
Name(s) and site(s) of manufacturer(s)	+	+
Specification and routine tests (C.1.1.)		+
Nomenclature (C.1.2.1.)		+
Description (C.1.2.2.)		+
Manufacturing method (C.1.2.3.)		
- brief outline (flow chart)		+
- detailed description	+	
QC during manufacture (C.1.2.4.)	+	
Process validation and evaluation of data	+	
Development chemistry (C.1.2.5.)		
- evidence of structure (if needed)		+
- potential isomerism		+
- physico-chemical characterisation		+
- analytical validation		+
Impurities (C.1.2.6.)		+
Batch analysis (incl. impurities) (C.1.2.7.)		+
Stability (where necessary) (F.1.)		+

2.3. Discussion of potential toxicology of impurities

The ASM should, where applicable, include in the applicant's part of the DMF available information on the potential toxicology of impurities by reference to literature or by the presentation of data to justify the proposed limits. If the information is incomplete, the applicant for the product marketing authorisation needs to supply additional information.

3. INFORMATION ACCOMPANYING AN EDMF

The ASM should give permission to the competent authorities to assess the data in his DMF on behalf of a specified applicant in the form of a 'Letter of access'. Such a letter should include the following information:

– name and address of the applicant;

– name of product and, if possible, date of application;

– name and address of the ASM;

– name and address of the importer of the active substance, where applicable;

– name and address of the distributor (agent or broker), where applicable.

A written assurance that there is a formal agreement between the ASM and the applicant which ensures that if there is a significant change in the manufacturing method (likely to alter the quality or safety of the product) or in active substance specification, this information will be communicated to the applicant and to the authorities. It is the responsibility of the applicant to consider any necessary changes in his specification and to inform the competent authorities accordingly.

A 'letter of access' must be lodged by the ASM for every application for marketing authorisation.

4. CRITICAL APPRAISAL OF DOCUMENTATION OF THE EDMF

The applicant for the product marketing authorisation has the full responsibility for the inclusion in the Expert Report of the required critical evaluation of the dossier. However, as information in the ASM Restricted Part of the DMF is not available to the applicant, a critical appraisal should be included in the ASM Restricted Part of the DMF on specific items important for the quality of the active substance. In particular this section should consider:

– the manufacturing method and discuss how it will consistently guarantee material of the desired quality;

– batch analyses and whether these show consistency of manufacture;

– demonstration of how the specification and routine tests in the applicant's part is justified in relation to the ASM Restricted Part.

5. GLOSSARY OF TERMS

European Drug Master File: EC procedure where information can be provided to the authorities and the applicant, where the active substance manufacturer is not the applicant for a product marketing authorisation, with a view to protecting valuable manufacturing know-how.

ASM: Active Substance Manufacturer.

Applicant's part of a DMF: Section of the European DMF given to the applicant to include in the application for a product marketing authorisation.

ASM Restricted Part of DMF: Section of the European DMF given by the ASM only to the authorities.

Letter of Access: Letter of authority from the ASM to allow the competent authorities to assess the European DMF on behalf of a specified applicant.

C. USE OF THE EUROPEAN DRUG MASTER FILE (EDMF) PROCEDURE

A practical guide to implementation by the chemical industry (manufacturers of active substances) and the pharmaceutical industry (applicants for marketing authorisations).

1. Where is the procedure described?

The possibility of submitting confidential data to the competent authorities directly from an Active Substance Manufacturer (ASM) who is different from the applicant for the marketing

authorisation, is provided for in Directives 75/318/EEC as amended and 81/852/EEC as amended. Details of the procedure are given in the note for guidance *European Drug Master File Procedure for Active Substances*.

2. Is the procedure mandatory?

The EDMF procedure is a possibility offered to the industry, it is not a requirement.

If there is no problem of confidentiality between the ASM and the applicant for a marketing authorisation or if the ASM and the applicant can come to an agreement safeguarding confidentiality, all of the information on the active substance should be given directly in the application for the marketing authorisation.

3. When to submit an EDMF?

An EDMF may only be submitted if it is referred to in a marketing application for a medicinal product. It should be submitted shortly after the submission of the application, so that the reference number given by the competent authority to the application for marketing authorisation can be given in the letter of access. The EDMF may be submitted at the same time as the application, provided an unambiguous reference to the application can be given.

4. Who can submit an EDMF ?

Only ASMs and their authorised representatives (e.g. importers) may submit an EDMF.

If an applicant for a marketing authorisation wants to rely on alternative suppliers of the active substance, he should refer to this situation in the application.

5. Where and how to submit an EDMF?

5.1 One copy of the complete EDMF, comprising the 2 parts (applicant's part and ASM's restricted part) should be sent by the ASM directly to each of the competent authorities concerned.

5.2 A copy of the applicant's part should be supplied in advance by the ASM to the applicant. This applicant's part should be included in the application for marketing authorisation.

6. How to include additional specifications for certain dosage forms?

Specific quality requirements for certain dosage forms may be included in the application for marketing authorisation. Such requirements will not form part of the EDMF. They should be described in a formal contract between the ASM and the applicant and included in the application for marketing authorisation.

7. If a DMF has been previously assessed by the competent authority, what information should be given with a new DMF on the same active substance?

7.1 If an EDMF has been updated since the previous assessment, the changes should be clearly identified (particularly those in the method of manufacture and in the specifications of the active substance).

7.2 If a DMF was not presented in accordance with the current guideline on EDMFs (prior to 1992 for human medicinal products and prior to May 1993 for veterinary medicinal products), it should be re-arranged into the 2-part format, and the different parts sent to the authorities and to the applicant as described above.

8. Are EDMFs to be approved by the authorities?

An EDMF will never be approved as such, it may only be accepted in relation to a specific application for marketing authorisation. No claims should therefore be made by any ASM as to his EDMF having been "approved".

9. If further questions need to be answered before the assessment on an EDMF can be completed, how will this be done?

One of the major objectives of the EDMF procedure is to ensure that the applicant is always fully aware of any aspects of the active substance which could impact on its safety, quality or efficacy. Thus, all deficiencies in the EDMF will normally be addressed by the competent authorities to the applicant for the marketing authorisation. When asking such questions, rather general terms will be used to avoid any disclosure of confidential data from the ASM restricted part. The applicant will then ask the ASM to supply the further data to the concerned competent authorities and also to ensure that his part of the EDMF is completed.

10. Will an ASM be advised of the results of the assessment of his EDMF?

The competent authority will not inform the Active Substance Manufacturer that his EDMF has been accepted in relation to a particular application for marketing authorisation. This information should be sought by the ASM from the applicant.

11. Need for identical specifications between the application and the EDMF

The specification of the active substance should be identical in the application and in the applicant's part of the EDMF. Any proposal from the applicant to use a different test procedure for the purity tests must be fully validated in relation to the procedure used by the active substance manufacturer, in particular as regards the precision and accuracy of the results of the tests, including the limits of detection for all possible impurities.

12. How to inform the interested parties when an ASM wants to modify the ASM restricted part or the applicant's part?

12.1 If the only change to be made is in relation to the contents of the ASM restricted part of the file, this information should only be given to the authorities. A prerequisite for such procedure is that there is no change in specification and no change in impurity profile.

12.2 If changes are to be made in the applicant's part of the EDMF, this information must also be given to any other applicant or holder of a marketing authorisation referring to this EDMF. All the applicants involved will then need to seek to change their marketing authorisation dossier (using the appropriate variation procedures).

13. Fees to be paid to the competent authorities

13.1 Fees, if any, for the EDMF assessment are to be paid by the applicant for a marketing authorisation according to the instructions given by the relevant competent authority.

13.2 Variations to marketing authorisations because of changes to the EDMF attract the relevant fee, to be paid by the holder of the authorisation.