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Committee for Medicinal Products for Human Use (CHMP)
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Guideline on Active Substance Master File Procedure

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This guideline replaces guideline CPMP/QWP/227/02 Rev 4 (EMEA/CVMP/134/02 Rev.4).

Keywords	***Active substance master file, ASMF, letter of access, submission letter***

Note:

* The correction concerns a clarification in Annex 2, detailing that sharing assessment reports between the EEA National Competent Authorities includes sharing the assessment outcomes with UK competent authorities for procedures concerning medicinal products authorised in the territory of Northern Ireland, in which EU Law applies to the extent foreseen in the Protocol on Ireland/Northern Ireland included in the Agreement on the withdrawal of the UK from the EU.

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Executive summary

1. Introduction (background)

The main objective of the Active Substance Master File (ASMF) procedure, formerly 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. National 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.

2. Scope

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 ASMF holders in the compilation of their ASMFs.

ASMF Procedure and herbal substances/preparations

In accordance with Directive 2001/83/EC as amended, the quality of traditional herbal medicinal products for human use has to be documented in accordance with existing European legislative requirements. These criteria are laid down in the following guidelines (which are applicable for all Human and Veterinary Herbal Medicinal products): 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products' (CPMP/QWP/2819/00, EMEA/CVMP/814/00, in their latest revisions) and the 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/ traditional herbal medicinal products' (CPMP/QWP/2820/00, EMEA/CVMP/815/00, in their latest revisions).

It should be noted that the principles which are outlined in table 3 of Annex 1 in relation to traditional herbal medicinal products are equally applicable to other herbal medicinal products, both for Human and Veterinary use, which do not follow the simplified registration procedure.

References:

1. 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products' (CPMP/QWP/2819/00, EMEA/CVMP/814/00, in their latest revisions);
2. 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/ traditional herbal medicinal products' (CPMP/QWP/2820/00, EMEA/CVMP/815/00, in their latest revisions);
3. 'Guideline on summary of requirements for active substances in the quality part of the dossier' (CHMP/QWP/297/97, EMEA/CVMP/1069/02, in their latest revisions).

3. Legal basis

Annex I to Directive 2001/83/EC as amended Part I, 3.2 Basic principles and requirements, (8) Active Substance Master File (for Human medicinal products) and Annex I to Directive 2001/82/EC as amended, Part 2.C.1 General Requirements, 1.1. Active Substances (for Veterinary medicinal products).

4. Content of the Active Substance Master File

The overall content of the ASMF 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).

ASMFs linked to human medicinal products should be presented in the format of the Common Technical Document (CTD), see Annex 1 table 1.

ASMFs linked to veterinary medicinal products should normally be presented in accordance with the format given in Annex 1 table 2, however in accordance with Parts 1.C and 2 of Directive 2001/82/EC as amended, all parts of such ASMFs (AP, RP, and their summaries) may be presented in the CTD format in the following circumstances[1]:

- Where the active substance has been included in a medicinal product for human use authorised in accordance with the requirements of Annex I to Directive 2001/83/EC as amended;
- In the case of any application for an animal species or for indications representing smaller market sectors;
- Where the competent authority has publicly announced this possibility.

The scientific information in the ASMF should be physically divided into two separate parts, namely the Applicant's Part (AP) and the Restricted Part (RP). The AP contains the information that the ASMF holder regards as non-confidential to the Applicant/MA holder, whereas the RP contains the information that the ASMF 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 ASMF 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 specification 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 of the active substance. The National Competent Authorities/EMA may not accept that particular information has not been disclosed to the Applicant/MA holder. In such cases, the National Competent Authorities/EMA may ask for an amendment to the AP.

In addition to the AP and RP, the ASMF should contain a table of contents, and separate summaries for both the AP and the RP. In cases where the ASMF is provided in the CTD format, both summaries should be presented as a Quality Overall Summary (QOS). In cases where the veterinary NtA format is used, they should be detailed and critical summaries. Each version of the AP and RP should have unique and independent version control numbers.

5. Use of the Active Substance Master File Procedure

An ASMF 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 ASMF 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

[1] A correlation table should also be provided for ASMFs for Veterinary applications presented in the CTD format.

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 ASMF.

The ASMF procedure can be used for the following active substances, including herbal active substances/preparations. 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. Pharmacopeial active substances included in the Ph. Eur. or in the pharmacopoeia of an EU Member State.

The ASMF procedure cannot be used for biological active substances, see Annex 5.

The ASMF holder may have an ASMF as well as a Certificate of Suitability (CEP) issued by EDQM for a single active substance. Generally, it is however not acceptable that the Applicant/MA holder refers to an ASMF as well as to a CEP for a single active substance of a particular MAA/MAV. In cases where the CEP contains too little information (e.g. stability) the National 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 ASMF and a CEP.

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

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

- a copy of the latest version of the AP (and, if applicable, responses to deficiency letters on the AP from a NCA/EMA if not already incorporated into the AP);
- a copy of the QOS or detailed and critical summary, as appropriate, on the latest version of the AP;
- a copy of the Letter of Access where this letter has not been submitted earlier for the product concerned.

In addition, it is an essential requirement that the ASMF holder should submit to all National Competent Authorities/EMA involved in the MAA/MAV procedure:

- the ASMF (and, if applicable, responses to deficiency letters from a NCA/EMA if not already incorporated into the ASMF), accompanied by a Submission Letter and Administrative Details, see Annex 3. This also applies to the ASMF holder's responses to deficiency letters from a NCA/EMA;
- the Letter of Access where this letter has not been submitted earlier for the product concerned.

The ASMF holder should submit the ASMF to the National Competent Authority/EMA either for each MAA and each MAV or only once according to national requirements. The submission of the relevant documentation by the ASMF holder to the National Competent Authority/EMA must be synchronised to arrive at approximately the same time as the MAA or the MAV i.e. not more than one month before and not after the intended MAA/MAV submission date.

Where the ASMF procedure is used, the Applicant/MA holder should submit the MAA or MAV to the National Competent Authorities/EMA together with the Letter of Access where this Letter has not been submitted earlier by the MA holder/Applicant himself or by the ASMF 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 ASMF holder should submit identical documentation to every National Competent Authority/EMA. Consequently, the National Competent Authorities/EMA may require that

any ASMF updates made in relation to one MA should apply to all. It is the ASMF holder's responsibility to notify the MA holders and National Competent Authorities/EMA concerned about any changes to the AP and/or RP, so that the MA holders can update all affected MAs accordingly. The ASMF holder may consider using an ASMF worksharing procedure[2] (when applicable).

6. Content of the MA-dossier when the Active Substance Master File Procedure is used

The Applicant/MA holder is responsible for ensuring that they have access to all relevant information concerning the current manufacture of the active substance, in order to ensure that they are capabale of taking full responsibility for the quality of the active substance in the medicinal product.

The specification used by the Applicant/MA holder to control the correct quality of the active substance should be laid down unambiguously in the MA dossier (CTD format section 3.2.S.4.1 and 3.2.S.4.2 or old human/or veterinary NtA format part 2.C.1). It should be acknowledged that certain additional tests may need to be included in the specification of the Applicant/ MA holder to ensure a suitable quality of the active substance for use in a specific medicinal product e.g. particle size, sterility, bacterial endotoxins. However, as such tests may not be relevant to the ASMF holder, these do not need to be included in the specification in the ASMF.

In the case of a single supplier and where the ASMF procedure or CEP procedure is used, the specification for the active substance provided by the Applicant/MA holder in the MA dossier should be identical to that of the ASMF or the CEP holder, unless otherwise justified. For example, the Applicant/MA holder does not need to adopt any superfluous tests in the specification, unnecessarily tight specification limits and/or outdated analytical methods, differences should be justified.

In case where there is more than one supplier, the Applicant/MA holder should adopt one single compiled specification that takes into account the different impurity profiles of 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.

In cases where the Applicant/MA holder uses the same analytical method as described in the ASMF, either a clear reference to the sections 3.2.S.4.2 and 3.2.S.4.3 of the ASMF should be included in the respective sections of the MA dossier, or the Applicant/MA holder should copy the relevant sections from the ASMF in its MA dossier. In cases where the Applicant/MA holder uses a different analytical method than that described in the ASMF, both methods should be validated, by the respective owner of the tests.

In both cases, batch analysis data from the Applicant/MA holder in support of the proposed active substance specification need to be provided in section 3.2.S.4.4, as well as a justification of the specification in section 3.2.S.4.5. Information regarding reference standards used by the Applicant/ MA holder are required in 3.2.S.5.

In addition to the above, the Applicant/MA holder should include a copy of the AP in the MA dossier (CTD format section 3.2.S or veterinary NtA format part 2.C.1). 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 ASMF holder to the National Competent Authority/EMA as part of the ASMF.

[2] The worksharing procedure for the assessment of Active Substance Master File (ASMF) (EMA/CMDh/CMDv/308/2013)

The Applicant/MA holder should include all relevant details from the AP in the QOS/detailed and critical summary of the MA dossier. Issues of the ASMF that are specifically relevant to the medicinal product under consideration should be highlighted in the QOS/detailed and critical summary of the MA dossier.

7. Changes and updates to the Active Substance Master File

As for medicinal products, ASMF holders should keep the content of their ASMFs 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.

ASMF holders shall not modify the contents of their ASMF (e.g. manufacturing process or specifications) without informing each Applicant/MA holder and each National Competent Authority/EMA. This obligation remains valid until the Letter of Access has been withdrawn by the ASMF holder, see Annex 4. ASMF holders should provide the updated ASMF to all interested parties with reference to the revised version number.

Any change to the ASMF should be reported by every MA holder to the relevant National Competent Authority/EMA by means of an appropriate variation procedure. A Submission Letter should be provided (Annex 3).

In cases where the contents of the ASMF cannot be changed for a certain period of time because of other procedural provisions (i.e. mainly because of on-going MRP procedures), the ASMF holder should still provide the aforementioned data to the MA holder and National Competent Authorities/EMA making reference to this reason and requesting a later date of implementation.

At the occasion of the 5-year 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 CHMP/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/EMA.

MA holders should therefore verify with their ASMF 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 National Competent Authority/EMA, the necessary variation procedure should be initiated without delay.

ANNEX 1

OVERVIEW ASMF CONTENTS

Table 1	CTD format	Applicant's 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)[3]	x	
3.2.S.2.2	Description of Manufacturing Process and Process controls	a)	b)
3.2.S.2.3	Control of Materials		X
3.2.S.2.4	Control of critical steps and intermediates	c)	d)
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	e)
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	f)
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	

[3] Including all companies involved in the manufacture of the active substance, including quality control/ in process testing sites, intermediate manufacturers, milling and sterilisation sites.

Table 2	NtA veterinary format	Applicant's Part	Restricted Part
2.C.1	Name(s) and site(s) of ASM	x	X
2.C.1.1	Specifications and routine tests	x	
2.C.1.2.1	Nomenclature	x	
2.C.1.2.2	Description	x	
2.C.1.2.3	Brief outline of the manufacturing route (flow chart)	x	
2.C.1.2.3	Detailed description manufacturing method		X
2.C.1.2.4	QC during manufacture	c)	d)
	Process validation and evaluation of data		X
2.C.1.2.5	Development Chemistry	x	
	Evidence of structure	x	
	Potential Isomerism	x	
	Physiochemical characterisation	x	
	Analytical validation	x	
2.C.1.2.6	Impurities	x	e)
2.C.1.2.7	Batch analysis	x	
2.F.1	Stability	x	

a) 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 Applicant's Part (in cases where there is no further sterilisation of the final product).

b) Detailed information.

c) As far as the information is also relevant for the Applicant/MA holder.

d) As far as the information is related to the detailed description of the manufacturing process and as far as this information is not relevant for the Applicant/MA holder.

e) In so far as the information is related to the detailed description of the manufacturing process and in so far as the ASMF holder sufficiently justifies that there is no need to control these impurities in the final active substance.

f) As far as the information is related to the detailed description of the manufacturing process, control of materials and process validation.

Table 3	NtA CTD format[4] Herbal Active Substances/ Preparations	Applicant's Part	Restricted Part
3.2.S.1	General information	X	
3.2.S.1.1	Nomenclature For herbal substance: Binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable) Parts of the plants Definition of the herbal substance Other names (synonyms mentioned in other Pharmacopoeias) Laboratory code For herbal preparations Binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable) Parts of the plants Definition of the herbal preparation Ratio of the herbal substance to the herbal preparation Extraction solvent(s) Other names (synonyms mentioned in other Pharmacopoeias) Laboratory code	X	
3.2.S.1.2	Structure - Physical form - Description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass). - Other constituent(s)	X	
3.2.S.1.3	General properties	X	
3.2.S.2	Manufacturer(s) For herbal substances The name, address, and responsibility of each supplier, including contractors each proposed site or facility involved in production/collection and testing of the herbal substance should be provided, where appropriate. For herbal preparations The name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation should be provided, where appropriate.	X	X
3.2.S.2.2	Description of critical steps and intermediates For herbal substances	Flow chart	Detailed information

[4] ASMFs for Veterinary herbal medicinal products should be presented in accordance with section 4.1 above.

	Information should be provided to adequately describe the plant production and plant collection, including: Geographical source of medicinal plant Cultivation, harvesting, drying and storage conditions For herbal preparations Information should be provided to adequately describe the manufacturing process of the herbal preparation, including: Description of processing Solvents, reagents Purification stages Standardisation		
3.2.S.2.3	Control of materials		X
3.2.S.2.4	Control of critical steps and intermediates	If also relevant for the MA holder/applicant	X
3.2.S.2.5	Process validation and/or evaluation	X	X
3.2.S.2.6	Manufacturing Process Development A brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phytochemical composition of the herbal substance(s) and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substance(s) and herbal preparation(s) where applicable described in S1 should be discussed, where appropriate.		X
3.2.S.3	Characterisation	X	
3.2.S.3.1	Elucidation of structure and other characteristics For herbal substances Information on the botanical, macroscopical, microscopical, phytochemical characterisation, and biological activity if necessary, should be provided: For herbal preparations Information on the phyto- and physicochemical characterisation, and biological activity if necessary, should be provided:	X	
3.2.S.3.2	Impurities	X	
3.2.S.4	Control of drug substance	X	
3.2.S.4.1	Specification	X	

3.2.S.4.2	Analytical procedure	X	
3.2.S.4.3	Validation of analytical procedure	X	
3.2.S.4.4	Batch analysis	X	
3.2.S.4.5	Justification of specification	X	X
3.2.S.5	Reference standards of 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	

ANNEX 2

(< FROM ACTIVE SUBSTANCE MASTER FILE HOLDER ON HEADED PAPER>)

TEMPLATE LETTER OF ACCESS

[Address of Competent Authority/EMA]

[Date]

Number of Active Substance Master File:

< EMEA/ASMF/XXXXX EU/ASMF/XXXXX[5] or National ASMF reference number[6]>

Name of Active Substance:
Internal API Code (if applicable):
Active Substance Master File holder: [name and address]

The aforementioned Active Substance Master File holder hereby authorises the <name of National Competent Authority> <EMA including all CHMP and 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)[7] submitted by [Name of Marketing Authorisation Holder/Applicant] on [planned date of submission]:

[Name of product[8] and Marketing Authorisation number (if known)]

[Procedure Number (for Centralised applications only)]

[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/EMA of any change in the Active Substance Master File.

The aforementioned Active Substance Master File holder hereby is informed of and accepts that the EEA National Competent Authorities[9], the EMA including all CHMP and CVMP Members and their experts, and the Certification of Substances Division of the European Directorate for the Quality of Medicines & Healthcare may share the assessment reports of the above mentioned Active Substance Master File amongst themselves.

Signature for the Active Substance Master File holder

[Name and function]

[Signature]

[5] EU/ASMF/XXXXX reference number is allocated from the CTS ASMF assessment report repository (when available) by the Competent Authority/EMA
[6] The national ASMF reference numbers are allocated by the Competent Authority and should be used for national Marketing Authorisations only or when the EU/ASMF reference number is not allocated
[7] i.e. to introduce a new ASMF from a new AS manufacturer.
[8] If no invented name has been agreed at the time of submission for this product: it should be indicated 'INN + Marketing Authorisation Holder name'
[9] This includes sharing the assessment outcomes with UK competent authorities for procedures concerning medicinal products authorised in the territory of Northern Ireland, in which EU Law applies to the extent foreseen in the Protocol on Ireland/Northern Ireland included in the Agreement on the withdrawal of the UK from the EU.

ANNEX 3

(< FROM ACTIVE SUBSTANCE MASTER FILE HOLDER ON HEADED PAPER>)

Template Submission Letter and Administrative Details for documents relating to an Active Substance Master File (ASMF)[10]

From: <ASMF Holder name>

<ASMF Holder address>

<ASMF Holder address>

<ASMF Holder <Post code> Town>

<ASMF Holder Country>

To: <Name and Address of Competent Authority>

<Date>

<Reference>

Subject: Submission of documents relating to an ASMF

for <Name of Active Substance> - < EMEA/ASMF/XXXXX or EU/ASMF/XXXXX[11] or National ASMF reference number> [12]

Dear Sir or Madam:

This Active Substance Master File is submitted in relation to the following product:

Medicinal product	<Name of the medicinal product>[13]
Allocated procedure number (as applicable)	<EMEA/H/C/product reference number/procedure reference> <RMS/H/product reference number/procedure reference> <National Marketing Application/Authorisation Reference>
(Intended) Submission date of the marketing authorisation application or variation (if known)	<DD/MM/YYYY>

[10] To be submitted together with the ASMF in conjunction with every MAA/variation submission as one document

[11] EU/ASMF/XXXXX reference number is allocated from the CTS ASMF assessment report repository (when available) by the Competent Authority/EMA

[12] The national ASMF reference numbers is allocated by the Competent Authority and should be used for national Marketing Authorisations only or when EU/ASMF reference number is not allocated

[13] If no invented name has been agreed at the time of submission for this product: it should be indicated 'INN + Marketing Authorisation Holder name'

Administrative details for documents relating to an Active Substance Master file (ASMF)[14]

This submission letter should be used for an Active Substance Master File to be assessed in conjunction with a marketing authorisation application or variation for medicinal product for human/veterinary use, using either a national or mutual recognition or decentralised or centralised procedure.

This submission is also sent to: (as applicable)	☐ Rapporteur ☐ Co-Rapporteur ☐ All CHMP/CVMP members, as appropriate ☐ RMS ☐ All CMS ☐ <National Competent Authority> only[15]
ASMF reference number	< EMEA/ASMF/XXXXX or EU/ASMF/XXXXX[16] or national ASMF Reference number[17]>
ASMF holder's version (as included in this submission)	Applicants part: Version [version number]/date (dd-mm-yyyy) Restricted part: Version [version number]/date (dd-mm-yyyy)
Active substance name	<INN, common name> (+ salt/water content when applicable)
Active Substance Manufacturer's internal API code (if applicable):	<API internal code>
Additional information (as applicable, e.g. different route of synthesis, grade)[18]	

ASMF Holder	<ASMF Holder name> <Full ASMF Holder administrative address> <Country> Contact person: <name> Telephone: <telephone No.> e-mail: <e-mail>
Active Substance Manufacturer Manufacturing site(s)[19]	<Active substance manufacturer name> <Manufacturing site address(es)> <Country> <D-U-N-S number[20]> <GPS (WGS 84) coordinates of the site[21]> Contact person: <name> Telephone: <telephone No.> e-mail: <e-mail>

[14] It is mandatory to complete all information fields

[15] For ASMFs used in national marketing authorisations only

[16] EU/ASMF/XXXXX reference number is allocated from the CTS ASMF assessment report repository (when available) by the Competent Authority/EMA, based on eligibility

[17] The national ASMF reference numbers is allocated by the Competent Authority and should be used for national Marketing Authorisations only or when EU/ASMF reference number is not allocated

[18] Applicable when an ASMF holder has more than one ASMF for the same active substance.

[19] All companies involved in the manufacture of the active substance, including quality control / in process testing sites, intermediate manufacturers, milling and sterilisation sites should be listed in separate boxes.

[20] A Data Universal Numbering System (D-U-N-S) for all manufacturing sites should be provided, if registered. The D-U-N-S system was developed by Dun & Bradstreet (D&B) which assigns a unique digit numeric identifier to a single business entity. It is used in this case to facilitate the identification of manufacturing sites outside of EEA

[21] Latitude (S or N) and Longitude (E or W) expressed in Degrees Minutes Seconds to 1 decimal place (Alternatively it can be expressed in Degrees to at least 5 decimal places or Degrees Minutes to at least 3 decimal places). If not main entrance, specify site.

Submission Type	☐ New submission ☐ Update to the ASMF ☐ Response to deficiency letter (both Applicant's and Restricted Parts, where applicable) ☐ Administrative change only (manufacturing site remains unchanged in all cases) ☐ Change of ASMF holder ☐ Change of name/address of ASMF holder ☐ Change of name/address of Active substance manufacturer

Submission Format	☐ eCTD[22] - <sequence No.> - [Related Sequence <Related sequence No.>] - ☐ History of the sequences (Sequence Tracking Table) is attached ☐ (V)NeeS ☐ CTD[23] ☐ NtA[24] ☐ paper submission and other electronic format
Number of Volumes of Paper Copy	<Number>
Number of Media Units	<Number>

Submitted Documents	☐ Letter of Access[25] ☐ A copy of the Expert's curriculum vitae ☐ QOS or detailed and critical summary, as appropriate ☐ Table of Changes (only for submission of an update to a currently authorised ASMF) ☐ A copy of the proposed ASMF holder's active substance specification (3.2.S.4.1 or part 2.C.1.1, as appropriate)[26] ☐ A copy of the ASMF Deficiency Letter sent by Competent Authority/EMA (only for submission of response documents) ☐ Correlation table[27] for CTD:NtA formats

Yours faithfully,

<Signature of authorised contact person>

<Name, address and position in company>

[22] From 1 January 2010, the mandatory format in the Centralised Procedure for applications for Human medicinal products in electronic submissions is eCTD only.
[23] For ASMFs used in applications for Veterinary medicinal products only
[24] For ASMFs used in applications for Veterinary medicinal products only
[25] see Annex 2
[26] Only where the ASMF has not been submitted in (V)NeeS or eCTD format
[27] For an ASMF provided in the CTD format for applications for Veterinary medicinal products

Table of Changes between different versions of the ASMF

This section should only be completed for updates to an already submitted ASMF.

The Table of Changes should be included as a separate document to the main Submission Cover Letter. The ASMF holder should use the following example templates for the table. If the changes have been previously authorised in a National or European procedure, the ASMF holder should annotate the table with the procedure number.

Table of Changes example template

TABLE OF CHANGES		
	PRESENT	**PROPOSED**
	ASMF holder's RP and/or AP Version Number [version number]/date (dd-mm-yyyy)	ASMF holder's RP and/or AP Version Number [version number]/date (dd-mm-yyyy)
Section (CTD or NtA, as appropriate)	Current situation	Description of change

Administrative Information In Relation To Other Marketing Applications/Authorisations Dossiers

Other Applications/Authorisations referring to the same ASMF

The ASMF has previously been submitted to a National Competent Authority or to the EMA	Yes ☐
	No ☐

If yes, please provide a list of Human/Veterinary medicinal products containing the drug substance manufactured in accordance with the details submitted in the ASMF. Use additional sheets if necessary. Include the 5 most recently submitted medicinal products or all medicinal products submitted under National or European procedures – Centralised, Decentralised and Mutual Recognition under the last 2 years, whichever is greater[28].

Procedure Reference Number[29]	EU or National Authority ASMF Number	ASMF holder's Version Number (RP & AP)/Date

[28] More information may be submitted by the ASMF holder. Information on additional medicinal products concerned by this ASMF may be requested by the competent authorities

[29] RMS/H/XXXX, EMEA/H/C/XXXX, National Marketing Authorisation Reference. Country to be specified when a National Procedure

ANNEX 4

(< FROM ACTIVE SUBSTANCE MASTER FILE HOLDER ON HEADED PAPER>)

TEMPLATE WITHDRAWAL OF ACCESS LETTER

[Address of Competent Authority/EMA]

[Date]

Number of Active Substance Master File:

< EMEA/ASMF/XXXXX or EU/ASMF/XXXXX>[30] or <National ASMF Reference number[31]>

Name of Active Substance:
Internal API Code (if applicable):
Active Substance Master File holder: [name and address]

The aforementioned Active Substance Master File holder hereby informs the <name of National Competent Authority> <EMA including all CHMP and CVMP Members and their experts> that they no longer wish the above Active Substance Master File to be used in support of the following Marketing Authorisation Application[32], held by [Name of Marketing Authorisation Holder/Applicant]:

Medicinal product	<Name of the medicinal product>[33]
Allocated procedure number (as applicable)	<EMEA/H/C/product reference number/procedure reference> <RMS/H/product reference number/procedure reference> <National Marketing Application/Authorisation Reference>

The aforementioned Active Substance Master File holder hereby confirms that they have previously informed [Name of Marketing Authorisation Holder/Applicant] of this decision in line with the terms of their supply agreement.

☐ Active Substance manufactured in accordance with the above Active Substance Master File will no longer be supplied after [supply agreement termination date],

☐ Replacement of the Active Substance Master File by Certificate of Suitability, [CEP no]. A copy of the Certificate of Suitability is attached to this letter

Signature of the Active Substance Master File holder

[Name and function]

[Signature]

[30] EU/ASMF/XXXXX reference number is allocated from the CTS ASMF assessment report repository (when available) by the Competent Authority/EMA

[31] The national ASMF reference numbers is allocated by the Competent Authority and should be used for national Marketing Authorisations only or when EU/ASMF reference number is not available

[32] Separate Letters of Withdrawal should be submitted for different Marketing Authorisation Holders / Applicants

[33] If a Marketing Authorisation has not been granted for the product and an invented name not agreed at the time of submission for this product: it should be indicated 'INN + Marketing Authorisation Holder name'

ANNEX 5

Non-applicability of the Active Substance Master File (ASMF) concept

- **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 and Directive 2001/82/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 National Competent authority.

ANNEX 6

LIST OF ABBREVIATIONS

Abbreviation	Full text
AP	Applicant's Part (of ASMF)
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 and Healthcare
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency, currently known as EMA
ICH	International Conference on Harmonisation
MA	Marketing Authorisation
MAA	Marketing Authorisation Application (including line extensions)
MAH	Marketing Authorisation Holder
MAV	Marketing Authorisation Variation
NtA	Notice to Applicants
Ph. Eur.	European Pharmacopoeia
RP	Restricted Part (of ASMF)
QOS	Quality Overall Summary (refers to MA dossiers in CTD format)

ANNEX 7

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 a new drug substance 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. (See VICH GL39 for the equivalent definition of a new Veterinary drug substance.)
Quality	According to ICH Q6A/VICH GL39 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 tests, 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. (See VICH GL39 for the equivalent definition for a Veterinary specification.)