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Committee for Medicinal Products for Human Use (CHMP)

Additional guidance on documents relating to an active substance master file

Additional guidance on completing the Annex 2-letter of access, Annex 3-submission letter and administrative details for documents relating to an active substance master file and Annex 4-withdrawal of access letter of the active substance master file procedure guidance (CHMP/QWP/227/02 Rev 3, EMEA/CVMP/134/02 Rev 03)

Introduction and general comments

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 (NCA) / European Medicines Agency (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 document is intended to provide additional guidance for ASMF holders on completing the Annex 2-Letter of Access, the Annex 3-Submission Letter and Administrative Details for Documents relating to an Active Substance Master File (referred to as the Submission Details Form throughout this document), and the Annex 4-Withdrawal of Access Letter of CPMP/QWP/227/02 Rev 3/ EMEA/CVMP/134/02 Rev 3 Guideline on Active Substance Master File Procedure. Therefore, this document should be read in conjunction with the guideline. It is intended to update this document, as and when required.

This additional guidance will also be useful information for MA holders.

The objective of the aforementioned Annexes is to assist NCA/EMA identify and track where the same ASMF is used in multiple European (Centralised, Decentralised or Mutual Recognition) procedures and/or Member States, and to facilitate sharing of the ASMF assessment report, with the ultimate aim of improving harmonisation of decision making and reducing the regulatory burden on ASMF and MA holders alike.

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When should each Annex be submitted?

Annex 2-Letter of Access and Annex 3-Submission Details Form

Initial submission of an ASMF in a MA or Marketing Authorisation Variation (MAV) application:

The ASMF holder should provide:

- Letter of Access to the NCA/EMA
- a copy of the Letter of Access to the MA holder for inclusion in the annexes to their MA/MAV application form
- a Submission Details Form to the NCA/EMA

Subsequent updates to an ASMF where the information in the form is the same for all applications:

The ASMF holder should provide to the NCA/EMA:

- a single Submission Details Form, covering all MAs (which should be listed)

Note: ASMF holders are strongly encouraged to harmonise updates to an ASMF across all MAs using the active substance, wherever feasible and as soon as possible.

Note: The Letter of Access will be valid for the initial ASMF submission and for any update, until the ASMF is no longer used in conjunction with the MA; therefore, it only needs to be provided with the initial ASMF submission.

Response to deficiency letters:

The ASMF holder should provide to the NCA/EMA:

- a Submission Details Form (updated, if applicable) with the responses so that they can be assigned to the correct ASMF. This is especially important where the ASMF holder holds more than one ASMF for a particular active substance, e.g. for different polymorphic forms.

Administrative change to the ASMF:

The ASMF holder should provide to the NCA/EMA:

- a Submission Details Form documenting the change

Note: This is for information only, and will help identify and track where the same ASMF is used in multiple procedures and Member States. The MA holder is still responsible for submitting MAV applications to gain regulatory approval of these changes.

Annex 4- Withdrawal of Access Letter

Where the active substance is no longer supplied to the MA holder or the corresponding ASMF is replaced by a Ph. Eur. Certificate of Suitability (CEP), the ASMF holder should provide a Withdrawal of Access Letter to the NCA/EMA.

Note: This is for information only and will help identify and track where the same ASMF is used in multiple procedures and Member States. The MA holder is still responsible for submitting MAV applications to gain regulatory approval of these changes.

Annex Templates

The templates for the Letter of Access, Submission Details Form and Withdrawal of Access Letter are available on the EMA website:

(http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500129998)

The Annexes should be printed on the ASMF holder's company headed paper and provided to each NCA/EMA involved in the MA/MAV procedure.

All information fields should be completed, unless otherwise instructed and authorised by the NCA/EMA. Changes to the text, format and layout of the Letter of Access, the Submission Details Form or the Withdrawal of Access Letter should not be made, unless otherwise instructed and authorised by the NCA/EMA.

Guidance on completing the letter of access (Annex 2)

The Letter of Access is an important document in that it authorises the NCA/EMA to refer to and review the ASMF in support of a MA/MAV application. The letter also notifies the NCA/EMA that the ASMF holder is informed and accepts that assessment reports of the ASMF may be shared amongst the NCA, EMA (including CHMP/CVMP members and experts) and the Certification of Substances Division of the EDQM. The letter also confirms that the ASMF holder commits to ensure batch to batch consistency and to inform the MA holder of any changes to the ASMF.

The EU/ASMF reference number will help identify and track where the same ASMF is submitted in multiple European procedures and/or Member States. It will be required for an ASMF used in MA/MAV applications submitted using the Centralised, Decentralised or Mutual Recognition Procedures. Consequently, it will not be necessary to provide national ASMF reference numbers.

Where the EU/ASMF reference number has not been allocated or if an ASMF is used in national applications only, a national ASMF reference number should be provided.

The EU/ASMF reference number (or the national ASMF reference number) will be used for administrative purposes by the NCA/EMA. It is not an ASMF version control number, and does not replace the ASMF holder's responsibility to implement a document/version control system for their ASMF.

The name of the product and the Applicant/MA holder should be stated, along with the MA number (if known) and the planned date of submission of the MA/MAV application (if known).

The Letter of Access should be signed by an appropriately authorised representative of the ASMF holder's company, and their name and function clearly stated.

Guidance on completing the submission details form (Annex 3)

The Submission Details Form provides all the necessary administrative information that NCA/EMA will use to identify and track where the same ASMF is used in multiple European procedures and Member States, and to facilitate the sharing of the ASMF assessment report.

The Submission Letter and Administrative Details for Documents relating to an Active Substance Master File are not separate documents, and should always be submitted together.

Submission Letter

The name of the active substance and the EU/ASMF reference number (when available) or national ASMF reference number, as appropriate, should be clearly stated in the subject heading.

The name of the product and the European procedure or national marketing authorisation number should be provided. The intended date of submission of the MA/MAV application should be stated, if known.

The Submission Letter should be signed by the authorised contact person for the ASMF holder. Their name, address (if different to the ASMF holder's address stated at the top of the letter) and position should be clearly stated.

Administration Details for the Documents Relating to an ASMF

First Information Box – recipients of the ASMF submission, the EU/ASMF or national reference number, ASMF version number, active substance name and internal (active pharmaceutical ingredient (API)) code

The ASMF holder should confirm, by checking the appropriate box, that they have sent the ASMF to all NCA/EMA involved in the MA/MAV procedure stated in the Submission Letter.

The EU/ASMF reference number or national ASMF reference number, as appropriate, should be clearly stated.

In accordance with Part II, section 6 of EU GMP guidance for active substances, the ASMF holder should employ a document control system for all documents related to the manufacture of intermediates or the API. This includes the ASMF. Since the ASMF is physically divided into an Applicant's Part (AP) and a Restricted Part (RP), each Part can be independently updated and therefore should have an individual and unique version number. The ASMF holder's version control numbers for both AP and RP should be clearly stated, as it will help identify where the same ASMF is used in multiple procedures and/or Member States.

ASMF holders are free to choose the format of the version control number for the AP or RP; however, in order that the number is individual and unique, and can unambiguously identify the version of the AP or RP, it is strongly recommended that it includes the following identifying components: (1) active substance reference (e.g. common name or API code or INN or modified INN, etc); (2) reference to the AP or RP; (3) version number; (4) date of issue of the version.

Updates to an AP or RP should not be re-issued with the same version number and a different date, e.g. OZP/AP/01/2012-01-28 should not be updated to OZP/AP/01/*2012-04-10*, but rather a new version OZP/AP/*02/2012-04-10.*

It is also recommended that the ASMF holder provides the version numbers of the Quality Overall Summaries of the AP and/or RP, where appropriate.

The CTD sections of eCTD and NeeS format ASMFs can be individually updated (and thus version controlled), and the individual updates provided to the NCA/EMA.

Guidance on lifecycle management and sequencing of eCTD format ASMFs has been published and should be followed. The guidance can be found in Practical Guidelines on the Use of the eCTD Format for ASMFs for Active Substance Master File Holders and Marketing Authorisation Holders (http://esubmission.emea.europa.eu/doc/index.html).

The Sequence Tracking Table is a key component in the lifecycle management of eCTD ASMFs. This tracking table is not available for NeeS submissions, so a tabulated list of the version control numbers of the individual CTD sections may need to be provided for clarity.

Each Part (AP and RP) of the eCTD or NeeS format ASMF should, nevertheless, be assigned an overall version control number.

The International Non-proprietary Name, common name and Active Substance Manufacturer's internal API code (if applicable) should be clearly stated. The active substance name should clearly indicate if the active substance is a sterile grade.

Second Information Box – contact details of ASMF holder and companies responsible for manufacturing and quality control

The ASMF holder's full company name and administrative address (including any postal/zip codes and country) should be clearly stated. The authorised contact person should be provided, together with their telephone number and email address.

For all companies involved in the manufacture of the active substance, the full company name, site address (including postal/zip codes and country), DUNS number (if registered) and GPS co-ordinates of the main entrance (or other specified entrance) should be clearly stated. The manufacturing function(s) of the company should be clearly stated. The authorised contact person for the manufacturing site should be provided, together with their telephone number and email address.

It is recommended that a regularly accessed general email and telephone number are provided, rather than a personal email and telephone number, in case the authorised contact person is unavailable. However, personal telephone numbers and/or emails for the contact person may be additionally provided.

This contact information should be kept up to date by the ASMF holder to ensure that the NCA/EMA is able to contact the ASMF holder or the manufacturing companies quickly. Furthermore, electronic communication by email is preferred as this will avoid possible delays in delivery or loss of paper correspondence.

Third Information Box – type of submission

The ASMF holder should confirm, by ticking the appropriate box, whether the submission is a new ASMF in the NCA/EMA, an update to a previously evaluated ASMF or a response to a deficiency letter.

The same versions of the AP & RP (= ASMF) should be submitted to all NCA/EMA involved in the MA/MAV application. Where the ASMF is used in multiple procedures, the ASMF should be submitted only once, unless otherwise directed by the submission requirements of competent authorities.

Where the ASMF is considered new in some NCA/EMA and an update in others, both boxes should be checked. A complete version of the ASMF should be submitted in all NCA/EMA involved in the procedure, together with a Table of Changes describing the changes made to the previous versions of the AP and RP.

Where the submission is a response to a deficiency letter, the complete response to both the AP and RP questions should be submitted directly to each NCA/EMA, with a copy of the AP responses sent to the MA holder for inclusion in their own responses. The ASMF and MA holders are encouraged to discuss the responses to the AP before submission.

Since the Annexes will help identify where the same ASMF is used in multiple procedures and Member States, and facilitate sharing of the assessment report, it is anticipated that the number of issued

deficiency letters will be reduced. Consequently, the ASMF holder may be able to submit the same set of AP and/or RP responses for all procedures.

If the ASMF holder wishes to inform the NCA/EMA of an administrative change to the ASMF, this again should be confirmed by ticking the appropriate box.

Fourth Information Box – format of the ASMF Submission

The format of the ASMF submission should be confirmed by ticking the appropriate box. It is strongly recommended that ASMF holders use the eCTD format for applications for human medicinal products, or if applications using that ASMF are likely to be made for both human and veterinary medicinal products. However, other formats may be accepted, and the ASMF holder is strongly advised to consult the submission requirements of competent authorities.

Where the ASMF is submitted in eCTD format, it is essential that the Sequence Number and Sequence Tracking Table should be provided, allowing easy navigation through the different sequences.

The ASMF holder should not switch between different submission formats, unless they are deciding to upgrade to the eCTD format.

The number of volumes or media units should be stated so that it can be verified that the full ASMF has been received. It is recommended that media units, such as CD, DVDs, USB sticks, etc be identified by the following information: EU/ASMF reference number (when available) or national ASMF reference number, AP and/or RP version number (as appropriate), active substance name, ASMF holder's name and submission date.

Fifth Information Box – list of submitted documents

The ASMF holder should confirm they have provided the required documents by ticking the appropriate boxes.

A copy of the NCA/EMA deficiency letter(s) should only be provided with any submitted response.

Table of Changes between Different Versions of the AP and/or RP of the ASMF

When an update to an AP and/or RP is submitted, it is strongly recommended that a Table of Changes, describing the changes made from the present to the proposed version of the AP or RP, is provided as this will facilitate the assessment process. Changes that have been previously authorised in a national or European procedure should be annotated with the procedure reference number.

The Table of Changes should be submitted as a separate document to the Submission Details Form, in a format that can be edited by the NCA/EMA, e.g. Word. It is permissible to send separate Tables of Changes for the AP and RP, if desired.

Table 1. Example 1

TABLE OF CHANGES		
CTD section	PRESENT	PROPOSED
	API Ltd/CPT-MeOH/AP/01/2009-04-12	API Ltd/CPT-MeOH/AP/02/2010-05-23
	Current situation	Description of change
3.2.S.1	pka = 4.5	Correction of typographical error in pKa constant: pKa = 5.4
3.2.S.3	-	Correction of general typographical errors, no change in data
3.2.S.4.1	Water content = 0.5%	Updated to widen acceptance limits: water content = 1.0%

TABLE OF CHANGES		
3.2.S.4.4	-	Updated batch results
3.2.S.4.5	-	Updated justification of specification for water content specification
3.2.S.7	-	Updated stability data.

Note: API Ltd = ASMF holder; CPT = ASMF holder's active substance code; meoh = methanol synthesis route

Table 2. Example 2

TABLE OF CHANGES		
CTD section	PRESENT	PROPOSED
	Atenolol/O/01/2010-07-12	Atenolol/O/02/2011-10-10
	Current situation	Description of change
3.2.S.2.1	Manufacturing site: API Ltd, Building 6a, OneTown, OneCountry.	Addition of a new manufacturer: API International, Building 14, AnyCity, AnyCountry. *- Authorised in EMEA/H/C/9879*
3.2.S.2.3		Typographical corrections in method QC.A.145, no change in data *- Authorised in EMEA/H/C/9879*
	Method QC.B.45: mobile phase-acetonitrile	Change in mobile phase Method QC.B.45 – 95% isopropanolol:5% water Revalidation of method *- Authorised in EMEA/H/C/9879*

Note: o = open part (= applicant's part)

Table 3. Example 3

TABLE OF CHANGES		
CTD section	PRESENT	PROPOSED
	Atenolol/C/01/2010-07-12	Atenolol/C/02/2011-10-10
	Current situation	Description of change
3.2.S.2.1	Manufacturing site: API Ltd, Building 6a, Onetown, OneCountry.	Addition of a new manufacturer: API International, Building 14, AnyCity, AnyCountry. *- Authorised in EMEA/H/C/9879*

TABLE OF CHANGES		
3.2.S.4.4	-	Updated batch results for new manufacturing site *- Authorised in EMEA/H/C/9879*
3.2.S.7	-	Updated stability data for new manufacturing site *- Authorised in EMEA/H/C/9879*

Note: C = Closed Part (= restricted part)

Administrative Information in Relation to Other Marketing Authorisation Applications/Marketing Authorisation Dossiers

The ASMF holder should confirm by ticking the appropriate box whether current or a previous version of the ASMF has been previously submitted to a NCA/EMA.

If the ASMF has been previously submitted to the NCA/EMA, details of the procedure reference number, the EU/ASMF or national ASMF reference number and the ASMF holder's version control numbers of the AP and RP should be provided. Information on the approval status of the procedure, if known, would be beneficial,

Table 4. Example 1

Procedure Reference Number	EU or National Authority ASMF Number	ASMF holder's Version Number
UK/H/9567/01-10/DC (pending)	MFD-90879-1-8787	DHC/O/01/2009-04-10 DHC/C/01/2009-04-10
FR/H/8768/01-10/DC (pending)	DMF 2009-300	DHC/O/01/2009-04-10 DHC/C/01/2009-04-10

Note: DHC = ASMF holder's active substance code

The EU/ASMF reference number is not available so the national ASMF reference numbers in the Reference Member States (RMS) are provided. The two RMS can now work share the evaluation of the ASMF to prevent duplication of assessment and issuing of multiple deficiency letters.

Table 5. Example 2

Procedure Reference Number	EU or National Authority ASMF Number	ASMF holder's Version Number
UK/H/8795/01/DC (pending)	EU/ASMF/98798/0001	01136-AP.02-2011-12-01 01136-RP.02-2011-12-01
AT/H/9789/01/MR (approved)	ASMF11434	01136-AP.01-2010-08-27 01136-RP.01-2010-08-27

Note: 01136 = ASMF holder's active substance code

The EU/ASMF reference number is available and has been provided. However, the previous versions of the AP and RP were assessed before the EU/ASMF number was issued, so a national reference number was provided.

Procedure Reference Number	EU or National Authority ASMF Number	ASMF holder's Version Number
UK/H/7790/01/DC (pending)	EU/ASMF/88987/001	MFM-2/O/02/2011-06-15 MFM-2/C/01/2010-12-24
AT/H/6809/01-04/DC (refused)	ASMF11565	MFM-2/O/01/2010-12-24 MFM-2/C/01/2010-12-24

Note: MFM-2 = ASMF holder's active substance code

Refused procedures should also be provided, in addition to pending and approved procedures.

Guidance on completing the withdrawal of access letter (Annex 4)

Following a meeting with Interested Parties, the industry requested the creation of a Withdrawal of Access Letter to inform NCA/EMA when an ASMF is no longer used by the MA holder or has been replaced by a Ph. Eur. Certificate of Suitability (CEP).

It is important that the EU/ASMF reference number (or national ASMF reference number) is clearly and unambiguously stated, together with the name(s) of the medicinal product and the European procedure and/or national MA reference number(s). Separate letters are not required for each procedure.

The ASMF holder should confirm, by ticking one box only, the reason why access to the ASMF is being withdrawn for the respective marketing authorisation.

Where the active substance is no longer supplied to the MAH, the termination date of the supply agreement should be clearly stated.

The MAH should then submit appropriate MAV applications to gain regulatory approval of these changes, as soon as is reasonably practicable.