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Guidance for ASMF holders and MA holders on Providing Regulatory Information in Electronic Format

# Harmonised Technical Guidance for ASMF Submissions in eCTD format in the EU

**Version 2.1**

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## 1. Introduction/Background

The purpose of the document is to provide guidance on the use of eCTD for the submission of Active Substance Master Files (ASMF), and should be read in conjunction with the already-available guidance on the eCTD and ASMF procedure handling as well as with other applicable guidelines for all European marketing authorisation procedures (CP, MRP, DCP, NP).
This guidance should be used in case submission in electronic format for ASMF is accepted or required in eCTD format. For a mandatory date of usage please refer to the esubmission website or national Competent Authorities' websites.

For further practical information on the general requirements for eCTD and general guidance as to how to build an eCTD, Active Substance Master Files holders and Applicants should also refer to:

- Harmonised Technical Guidance for eCTD submissions
- Harmonised Technical Guidance for Non-eCTD electronic Submissions
- The ICH eCTD specification V3.2.2
- The EU M1 eCTD Specification
- EMA presubmission Guidance, question 21

Active Substance Master File Holders and Applicants should treat this guidance as complementary to the current regulatory guidance relating to ASMF (available on EMA website).

In the above referenced documents the terms 'applicant' and 'application' are commonly been used. In the context of this guidance document, the applicant for an ASMF is the ASMF holder and the application is equivalent to the ASMF being managed by the ASMF holder.

For information on eCTD format requirements in CEP submissions please refer to EDQM.

## 2. General Principles

Although the prescribed eCTD structure can accommodate the submission of data required for the ASMF, it should be clarified that the eCTD ASMF dossier remains, from a technical perspective, a *standalone* dossier and is distinct from the marketing authorisation dossier and lifecycle. The eCTD ASMF dossier will be submitted with its applicant part and restricted part by the ASMF holder and will have its own lifecycle.

The marketing authorisation application and the ASMF may not have the same format. However, if the MAA is in eCTD format then the applicant part of the ASMF should be included also in eCTD format.

### 2.1 ASMF submission types:

#### 2.1.1 National Submissions – For National, MRP, DCP applications

The ASMF holders are encouraged to submit the ASMF dossier in eCTD format if not otherwise communicated by the NCA. . It depends from procedure and NCA policy whether a dossier number needs to be requested in advance.

#### 2.1.2 EU ASMF submissions - For NAPs (NP, MRP, DCP), CAPs or mixed

The voluntary EU ASMF worksharing process is applicable to new ASMFs (not formerly assessed as part of an EU procedure), submitted as part of a new marketing authorisation, or a variation application, through the Centralised, Mutual Recognition or Decentralised procedure, where a full assessment report will be prepared by a Competent Authority. This enables assessors to harmonise reports and avoid duplication. A 'work sharing ASMF' is an ASMF that requires an EU/ASMF reference number (EU/ASMF/xxxxx). This is obtainable from the Member States (RMS) or from the EMA. In case of any future submission, this number always has to be referred to in the Letter of Access, the eCTD envelope (optional high level submission number element and mandatory procedure tracking number element as well) and in the submission cover letter where applicable. The ASMF holder is also responsible to inform the relevant MAH of this number.

It is not possible to combine EMA & Country specific envelopes while combining the centralised & national DCP/MRP procedures.

Please use the eCTD tracking table to maintain/have better visibility of the eCTD sequences used in two parallel lifecycles.

### 2.1.3 EMA ASMF submissions – For CAPs only

ASMFs submitted to the EMA for CAPs must have an EMEA/ASMF number. This is to simplify the processing and assessment and reduce the burden of multiplication of ASMF submissions of same substances that are contained in multiple centrally authorised products.

ASMF holders are advised not to interchange the use of EU/ASMF/xxxxx and the EMEA/ASMF/1xxxxx numbers as it can lead to non-acceptance and negative validation.

Requirements when submitting an ASMF for a product that has one or more existing pharmaceutical product eCTD life-cycle(s):

- The ASMF holder should select which life-cycle they wish to carry on with. The previously submitted versions most often have different eCTD sequence numbers depending on the date of authorisation of the related CAP. The suggestion is to carry on with the 'highest' sequence number as it would have the most information on the same substance. The EMEA/ASMF/1xxxx number requesting letter should contain this information and list all the CAPs relating to this ASMF.
- Once the ASMF holder is **submitting an update or new version to the ASMF**, they have to do so **with this new,** EMEA/ASMF/1xxxx **number**. The ASMF holder will have to prepare a **new sequence** (using the next number in the eCTD lifecycle) in which (in the module 1, cover letter) they declare that the previously submitted ASMF version has not been modified since it was last submitted. The related CAPs have to be listed. At this time the previously submitted other dossiers will become redundant and the dossier will be renamed as per the EMEA/ASMF/1xxxx number, covering all listed CAPs.
- If there have been modifications (new version) since the last ASMF submission, the relevant modules within this new eCTD sequence will also have to be updated.

### 2.1.4 Submission channels

The submission channels do not deviate from common requirements.

All ASMF submissions directed to EMA for Centrally Authorised Products have to be uploaded via eSubmission Gateway and it will be shared through the Common Repository. Please refer to the respective guidance documents.

ASMF submission submitted to NCAs will in most cases be accepted via CESP. Please refer to detailed national information at the CMDh website and the CESP website.

## 3. Structure of the eCTD Dossier for the ASMF

The CTD structure applies to the ASMF. The granularity and placement of documents should follow the existing guidance's and Q&As from ICH and EU. For an initial ASMF, the relevant modules are M1, M2.3 and M3.2.S, and these modules should be populated as follows:

- M1 includes the Cover Letter with the Letter of Access, Submission Letter and Administrative Details, and Withdrawal of Letter of Access (Annex 4 of the ASMF Guideline), where applicable, as one annex, in 1.0, and Information about Expert in 1.4.1. It may include an Application Form in 1.2, depending on national requirements.
- M2 includes Summary information in 2.3.S
- M3 includes relevant quality information in 3.2.S

Not all modules may apply for subsequent submissions and some additional sections may need to be used (e.g. for responses to lists of questions). Please consult EMA Presubmission guidance Q&A no. 21 for more information on the data to be submitted at the different stages of the procedure or lifecycle of the ASMF. The same principles apply for nationally submitted ASMF eCTD sequences.

When there is any change to the ASMF data, in line with general eCTD principles, only updated documents should be submitted with the respective eCTD operators.

## 3.1 Differentiation between Applicant's Part/Restricted Part

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).

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 (a correlation table should also be provided for ASMFs for Veterinary applications presented in the CTD format):

- 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.

The ASMF should be submitted as one eCTD sequence, where sections 2.3.S and 3.2.S branch into two parts, first the Applicant's Part and then the Restricted Part. The eCTD meta-data should be used to distinguish the two parts.

The prefix 'AP or 'RP' should be added to the <substance> meta-data value, and in addition the prefix 'AP' or 'RP' should be added to every leaf title in the respective section.

It is recommended that the suffix 'ap'/'rp' is also applied to the file names.

In some cases in where the ASMF is used to support applications in a number of different procedures or where the API is used in different formulations, the requirements for one MAA may require additional documentation to be included into the ASMF eCTD dossier[1]. These documents

[1] In these cases the participation in the ASMF AR WS is strongly recommended.

can be included within the ASMF eCTD by adding an extension to the file name to identify the procedure or MAA application (see Figure 3 below) and by including some specific information about this as part of the prefix in the leaf title , after the "ap" or "rp".

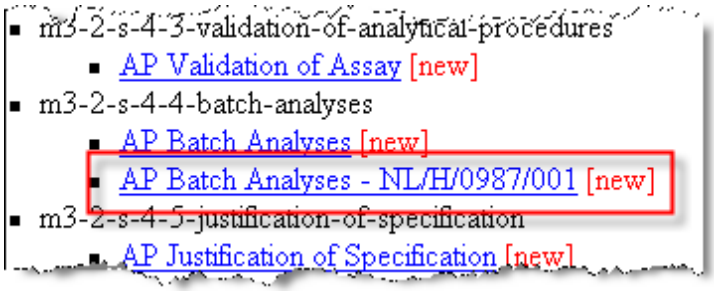



**Figure 1: ASMF AP leaf title sample**

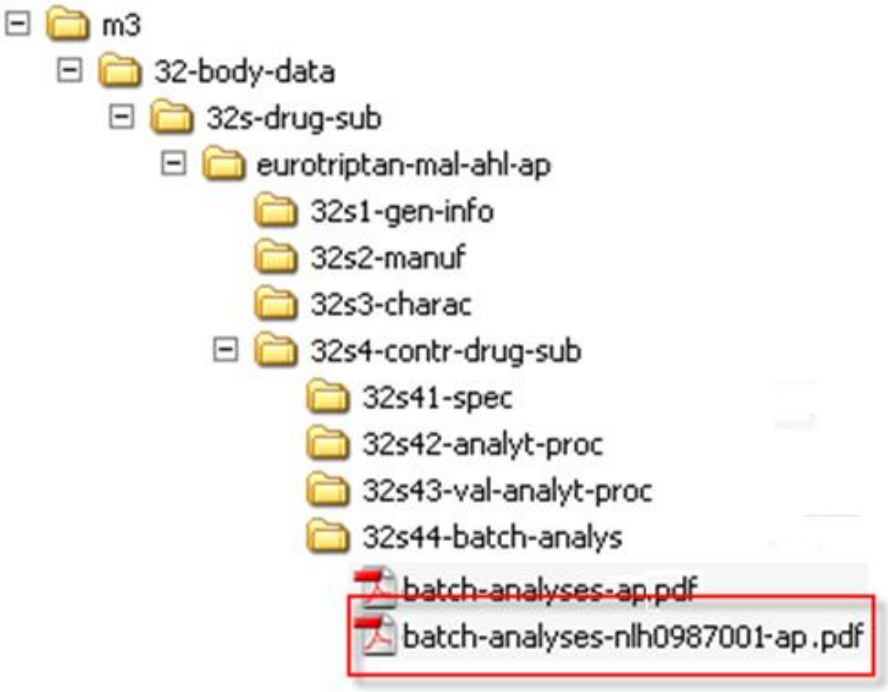



**Figure 2: ASMF AP file name sample**

Documents that are the same in both the AP and RP sections should be included only once and placed in the AP section of the folder structure. The leaf in the RP section will therefore point to the file in the AP section folder.

## 3.2 Example eCTD Structure for the ASMF

The example below shows a possible stylesheet view of an eCTD ASMF submission:

- DTD nodes (e.g. m3-2-body-of-data) appear in **black** as in the official stylesheet. Note that all module 1 section titles are displayed by the m1 stylesheet, whether the section is populated or not; in other modules, the section title is only displayed if the section is populated with file(s).

- Leaves are references to files in the eCTD, and each leaf has a leaf title which is not the same as the underlying PDF file name. Leaves appear in blue (because of the hyperlink to a PDF file). It is the suggested eCTD leaf title that is attributed to the file, *not* the underlying PDF filename, which is displayed in the example. The leaf titles displayed in the examples are intended as a guide only – other leaf titles can be used as appropriate.

- Some leaves illustrated may not be applicable for all ASMF submissions.

Submissions should otherwise be built in line with the eCTD guideline for MAAs as regards structure/placement, envelope elements and metadata.

## eCTD DTD version 3.2

- m1-administrative-information-and-prescribing-information
  - EU Regional Information [new]

- m2-common-technical-document-summaries
  - m2-3-quality-overall-summary
    - m2-3-s-drug-substance [manufacturer: ASMF Holders Ltd] [substance: AP eurotriptan maleate]
      - AP Drug Substance [new]
    - m2-3-s-drug-substance [manufacturer: ASMF Holders Ltd] [substance: RP eurotriptan maleate]
      - RP Drug Substance [new]
- m3-quality
  - m3-2-body-of-data
    - m3-2-s-drug-substance [manufacturer: ASMF Holders Ltd] [substance: AP eurotriptan maleate]
      - m3-2-s-1-general-information
        - m3-2-s-1-1-nomenclature
          - AP Nomenclature [new]
        - m3-2-s-1-2-structure
          - AP Structure [new]
        - m3-2-s-1-3-general-properties
          - AP General Properties [new]
      - m3-2-s-2-manufacture
        - m3-2-s-2-1-manufacturer
          - AP Manufacturer(s) [new]
        - m3-2-s-2-2-description-of-manufacturing-process-and-process-controls
          - AP Description of Manufacturing Process and Process Controls - Flow Chart of the Synthesis [new]
          - AP Description of Manufacturing Process and Process Controls - Brief Description of the Synthesis [new]
      - m3-2-s-3-characterisation
        - m3-2-s-3-1-elucidation-of-structure-and-other-characteristics
          - AP Elucidation of Structure and Other Characteristics [new]
        - m3-2-s-3-2-impurities
          - AP Impurities [new]
      - m3-2-s-4-control-of-drug-substance
        - m3-2-s-4-1-specification
          - AP Specification [new]
        - m3-2-s-4-2-analytical-procedures
          - AP Assay [new]
        - m3-2-s-4-3-validation-of-analytical-procedures
          - AP Validation of Assay [new]
        - m3-2-s-4-4-batch-analyses
          - AP Batch Analyses [new]
        - m3-2-s-4-5-justification-of-specification
          - AP Justification of Specification [new]
      - m3-2-s-5-reference-standards-or-materials
        - AP Reference Standards or Materials [new]
      - m3-2-s-6-container-closure-system
        - AP Container Closure System [new]
      - m3-2-s-7-stability
        - m3-2-s-7-1-stability-summary-and-conclusions
          - AP Stability Summary and Conclusions [new]
        - m3-2-s-7-2-post-approval-stability-protocol-and-stability-commitment
          - AP Post-approval Stability Protocol and Stability Commitment [new]
        - m3-2-s-7-3-stability-data
          - AP Stability Data [new]

- m3-2-s-drug-substance [manufacturer: ASMF Holders Ltd] [substance: RP eurotriptan maleate]
  - m3-2-s-2-manufacture
    - m3-2-s-2-2-description-of-manufacturing-process-and-process-controls
      - RP Description of Manufacturing Process and Process Controls [new]
    - m3-2-s-2-3-control-of-materials
      - RP Control of Materials - Starting Material - Specification [new]
      - RP Control of Materials - Starting Material - Assay [new]
      - RP Control of Materials - Reagent [new]
      - RP Control of Materials - Solvent [new]
    - m3-2-s-2-4-controls-of-critical-steps-and-intermediates
      - RP Controls of Critical Steps and Intermediates [new]
    - m3-2-s-2-5-process-validation-and-or-evaluation
      - RP Process Validation and/or Evaluation [new]
    - m3-2-s-2-6-manufacturing-process-development
      - RP Manufacturing Process Development [new]

**Figure 3: Samples of additional metadata of the leaf**

## 3.3 Example Envelope Elements and Metadata for ASMF Dossiers

This section describes how the envelope elements should be used in the eCTD when submitting ASMF dossiers submitted by the ASMF holder.

Generic information on the eCTD envelope and the mandatory/optional elements are provided in the EU eCTD module 1 specification.

The information provided in the envelope is very important and it is used to identify, display and group the individual eCTD submission dossiers, and is also automatically extracted by the review tools (software) for dossier display.

Some of the key envelope elements must be populated using a pre-defined pick-list of values. Others allow the inclusion of free-text.

**Table 1: Envelope Meta-Data (based on EU M1v3.0.1)**

| Element | Attribute | Notes on Usage |
|---|---|---|
| eu-envelope | | |
| Envelope | | |
| | country | For CP EMA, for all other countries the respective value from the pick list should be selected. |
| Identifier | | The UUID will be assigned by the ASMF holder. As it is an identifier for the dossier, the same UUID will be used for all sequences of an eCTD ASMF dossier. |
| submission | | |
| | type | All ASMF applications and updates or responses to questions should use the value "asmf" in all cases even this is a baseline (Note: This is an exemption from rule for human medicinal products). |
| | mode | Not to be used with the ASMF |
| number | | Not required |
| procedure-tracking | number | For submissions related to Centralised (EMEA) and Worksharing procedures (EU), this section should ALWAYS contain the EMEA/ASMF/xxxxx or EU/ASMF/xxxxx numbers. *See EMA Presubmission guidance Q&A no. 21 and ASMF Working Group webpage*<br><br>For other procedures, if a specific ASMF number has not yet been allocated by the NCA the term "To be advised" should be used. |
| submission-unit | | The initial ASMF application should use the value "initial". Follow-up sequences submitted as part of an ASMF procedure should always use the value "response" (e.g. |

| | | |
|---|---|---|
| | | responses to deficiency letters, responses to questions and also for all amendments and/or updates to the ASMF initiated by the ASMF holder). Due to a normally slow life cycle this recommendation simplifies the selection without requiring specific rules as well as not confusing the receiving agencies.<br>In case of submitting other information (could include, for example, missing files) "additional-info" should be used and only, if "response" is not suitable.<br>If a baseline ASMF is being provided for future lifecycle activities then the value "reformat" should be used. |
| applicant | | The **ASMF Holder** name should be used |
| agency | | |
| | code | For CP EU-EMA, for all other agencies the respective value from the pick list should be selected. |
| procedure | | |
| | type | For CP use "centralised"<br>For all other instances (MRP, DCP and NP), in case the ASMF is submitted to only one agency, use "national".<br>In case the ASMF is sent out to more than one agency, use "mutual-recognition".<br><br>Please note that the use of "mutual-recognition" is independent of the application type of the drug product and will cover decentralised procedures as well. It only indicates if the ASMF has been sent to more than one agency. Using this procedure type makes sure, that a validation error is not detected. |
| invented-name | | The ASMF holder is recommended to include their own ASMF specific internal code and/or internally used name<br>Please be as precise as possible - for example, include any codes to identify the specific route of synthesis, manufacturing site, quality (particle size, grade, etc.).<br>If no code or name is available use the value "Not available". |
| inn | | Refer to the EU Module 1 specification. |
| sequence | | Refer to the EU Module 1 specification. |
| related-sequence | | For ASMF submissions this will always be 0000, both for the initial sequence and for all subsequent submissions. There is only one reference required. |
| submission-description | | This element is also used to provide a free text description of the sequence.<br>This element can be used to provide the date and/or version number of the applicant part and the restricted part of the ASMF. |

### 3.3.1 Sample ASMF eCTD envelope in Centralised Procedure

The figures below show an example set of envelope information for a Centralised Procedure ASMF both in the source XML and also when viewed using the EU stylesheet in a standard internet browser application. Note: the XML shows that the related sequence has not been used, although the standard stylesheet automatically creates an entry for this information, even when the field remains empty.

```
<eu:eu-backbone xmlns:eu="http://europa.eu.int" xmlns:xlink="http://www.w3c.org/1999/xlink" dtd-version="3.0.1">
    <eu-envelope>
        <envelope country="ema">
           <identifier>d714ca40-1890-11e6-8fb8-0002a5d5c51b</identifier>
            <submission type="asmf" mode="">
                <number></number>
                <procedure-tracking>
                    <number>EMEA/ASMF/xxxxx</number>
                </procedure-tracking>
            </submission>
            <submission-unit type="initial"/>
            <applicant>ASMF Holders Ltd.</applicant>
            <agency code="EU-EMA"/>
            <procedure type="centralised"/>
            <invented-name>Not Available</invented-name>
            <inn>eurotriptan maleate</inn>
            <sequence>0000</sequence>
            <related-sequence>0000</related-sequence>
            <submission-description>ASMF for eurotriptan maleate made 'ASMF Holders Ltd.'</submission-description>
        </envelope>
    </eu-envelope>
```

**EU Module 1**

DTD version 3.0.1

| **Envelope for EMA** | |
|---|---|
| Identifier: | d714ca40-1890-11e6-8fb8-0002a5d5c51b |
| Submission: | Type: Active Substance Master File |
| Procedure Tracking Number(s): | EMEA/ASMF/xxxxx |
| Submission Unit: | Type: Initial submission to start any regulatory activity |
| Applicant: | ASMF Holders Ltd. |
| Agency: | EMA - European Medicines Agency (EU-EMA) |
| Procedure: | Centralised |
| Invented Name: | Not Available |
| INN: | eurotriptan maleate |
| Sequence: | 0000 |
| Related Sequence: | 0000 |
| Submission Description: | ASMF for eurotriptan maleate made 'ASMF Holders Ltd.' |

**Figure 4: Samples of the XML part and display of the envelope for centralised procedures**

### 3.3.2 Sample ASMF eCTD envelope in National Procedures

The figures below show an example for an ASMF used on a national basis in three countries (Austria, France and Sweden). The figures illustrate the view of the envelope elements in the XML backbone (eu-regional.xml) and the same information when viewed using the standard EU Module 1 stylesheet.

```
<eu:eu-backbone xmlns:eu="http://europa.eu.int" xmlns:xlink="http://www.w3c.org/1999/xlink" dtd-version="3.0.1">
    <eu-envelope>
        <envelope country="at">
            <identifier>25635f23-a3a4-c4e0-b994-99c5f074960f596</identifier>
            <submission type="asmf" mode="">
                <number></number>
                <procedure-tracking>
                    <number>EU/ASMF/xxxxx</number>
                </procedure-tracking>
            </submission>
            <submission-unit type="initial"/>
            <applicant>ASMF Holders Company Ltd.</applicant>
            <agency code="AT-BASG"/>
            <procedure type="mutual-recognition"/>
            <invented-name></invented-name>
            <inn>eurotriptan maleate</inn>
            <sequence>0000</sequence>
            <related-sequence>0000</related-sequence>
            <submission-description>ASMF for Eurotriptan Maleate made by ASMF Holders Company Ltd. for submission
in Austria</submission-description>
        </envelope>
    </eu-envelope>
    <eu-envelope>
        <envelope country="fr">
            <identifier>25635f23-a3a4-c4e0-b994-99c5f074960f596</identifier>
            <submission type="asmf" mode="">
                <number>To be advised</number>
                <procedure-tracking>
                    <number>EU/ASMF/xxxxx</number>
                </procedure-tracking>
            </submission>
            <submission-unit type="initial"/>
            <applicant>ASMF Holders Company Ltd.</applicant>
            <agency code="FR-AMSN"/>
            <procedure type="mutual-recognition"/>
            <invented-name></invented-name>
            <inn>eurotriptan maleate</inn>
            <sequence>0000</sequence>
            <related-sequence>0000</related-sequence>
            <submission-description>ASMF for Eurotriptan Maleate made by ASMF Holders Company Ltd. for submission
in France</submission-description>
        </envelope>
    </eu-envelope>
    <eu-envelope>
        <envelope country="se">
            <identifier>25635f23-a3a4-c4e0-b994-99c5f074960f596</identifier>
            <submission type="asmf" mode="">
                <number></number>
                <procedure-tracking>
                    <number>EU/ASMF/xxxxx</number>
                </procedure-tracking>
            </submission>
            <submission-unit type="initial"/>
            <applicant>ASMF Holders Company Ltd.</applicant>
            <agency code="SE-MPA"/>
            <procedure type="mutual-recognition"/>
            <invented-name></invented-name>
            <inn>eurotriptan maleate</inn>
            <sequence>0000</sequence>
            <related-sequence>0000</related-sequence>
            <submission-description>ASMF for Eurotriptan Maleate made by ASMF Holders Company Ltd. for submission
in Sweden</submission-description>
        </envelope>
    </eu-envelope>
```

# EU Module 1

DTD version 3.0.1

| **Envelope for AT** | |
|---|---|
| Identifier: | 25635f23-a3a4-c4e0-b994-99c5f074960f596 |
| Submission: | Type: Active Substance Master File |
| Procedure Tracking Number(s): | EU/ASMF/xxxxx |
| Submission Unit: | Type: Initial submission to start any regulatory activity |
| Applicant: | ASMF Holders Company Ltd. |
| Agency: | Austria - BASG- Austrian Federal Office for Safety in Health Care / Austrian Medicines and Medical Devices Agency (AT-BASG) |
| Procedure: | Mutual Recognition Procedure (MRP) |
| Invented Name: | |
| INN: | eurotriptan maleate |
| Sequence: | 0000 |
| Related Sequence: | 0000 |
| Submission Description: | ASMF for Eurotriptan Maleate made by ASMF Holders Company Ltd. for submission in Austria |

| **Envelope for FR** | |
|---|---|
| Identifier: | 25635f23-a3a4-c4e0-b994-99c5f074960f596 |
| Submission: | Type: Active Substance Master File<br>Number: To be advised |
| Procedure Tracking Number(s): | EU/ASMF/xxxxx |
| Submission Unit: | Type: Initial submission to start any regulatory activity |
| Applicant: | ASMF Holders Company Ltd. |
| Agency: | (FR-AMSN) |
| Procedure: | Mutual Recognition Procedure (MRP) |
| Invented Name: | |
| INN: | eurotriptan maleate |
| Sequence: | 0000 |
| Related Sequence: | 0000 |
| Submission Description: | ASMF for Eurotriptan Maleate made by ASMF Holders Company Ltd. for submission in France |

| **Envelope for SE** | |
|---|---|
| Identifier: | 25635f23-a3a4-c4e0-b994-99c5f074960f596 |
| Submission: | Type: Active Substance Master File |
| Procedure Tracking Number(s): | EU/ASMF/xxxxx |
| Submission Unit: | Type: Initial submission to start any regulatory activity |
| Applicant: | ASMF Holders Company Ltd. |
| Agency: | Sweden - Medical Products Agency (SE-MPA) |
| Procedure: | Mutual Recognition Procedure (MRP) |
| Invented Name: | |
| INN: | eurotriptan maleate |
| Sequence: | 0000 |
| Related Sequence: | 0000 |
| Submission Description: | ASMF for Eurotriptan Maleate made by ASMF Holders Company Ltd. for submission in Sweden |

**Figure 5: Samples of the XML part and display of the envelope for other procedures**

## 4. Lifecycle and Sequencing

The ASMF is a standalone dossier, separate from the marketing authorisation applications that are affected by it. The lifecycle of the ASMF should therefore be managed independently. When a variation application impacts the details related to the ASMF both Module 3 of the MA and the ASMF have to be updated to reflect the changes being requested. Whilst the MAH has to apply for a variation the ASMF Holder should submit the updated ASMF as "additional-info".

Leaf lifecycle management should be conducted in the same way as for MAAs, using the appropriate operation attribute values.

An already-submitted ASMF might be referred to by another MAA. In this case, the ASMF Holder should only update Module 1 in the eCTD sequence and submit it to the relevant Authorities, always quoting the assigned ASMF numbers (EU or EMEA or National). The new MAA holder also has to ensure that they refer to this number.

The Letter of Access should only be submitted once for a given MA applicant or holder. The Letter of Access may state more than one procedure number or more than one letter can be included if the ASMF is in use for different products. The ASMF holder should not submit the Letter of Access for the product dossier in addition. If at a later point in time additional Letters of Access need to be submitted, the next sequence number must be used for this content to maintain the ASMF dossier life cycle correctly. In all cases it is valuable to include the procedure number of the marketing authorisation application the ASMF will be used for.

### 4.1 eCTD Baseline Submission

The baseline eCTD submission should be sequence 0000[2], regardless of the current submission tracking, as this marks the beginning of the tracking of the lifecycle in the eCTD. The Cover Letter should clearly indicate that the baseline submission does not form part of a procedure as such and is not for review, but is merely provided as an eCTD 'baseline' and an aid to lifecycle management. The envelope element <submission type> chosen for this reformatted submission should be 'asmf' and the submission unit type needs to be 'reformat'. The <submission description> envelope element should be used to clearly indicate the baseline nature of the submission.

In the case of submission of a baseline sequence, a signed declaration from the ASMF Holder must be provided as an annex to the Cover Letter, stating that the content/data of the submitted modules in eCTD format is identical to the currently approved ASMF, and that there have been no changes to the dossier content as a result of the provision of an eCTD submission.

#### 4.1.1 Centralised Procedure

When converting from NeeS to eCTD, the EMA requires a sequence 0000 baseline conversion at the time of the update of the ASMF dossier. This should be submitted with the correct EMEA/ASMF/xxxxx number or EU/ASMF/xxxxx number. The ASMF holder has to apply for a procedure number in advance in any case.

The reformatted ASMF eCTD baseline submission will not be assessed if it is a stand-alone submission. It will merely be loaded into eCTD review tools to serve as a baseline as the name suggests, to facilitate future eCTD lifecycle management of the ASMF. A declaration in the cover letter should state that no changes have been introduced to the content of the previously accepted dossier.

If an ASMF holder has more than one eCTD life-cycle filed for the same substance, they will need to obtain an EMEA/ASMF/xxxxx number. They will also need to decide which existing life-cycle they wish to carry on with. After this the ASMF has to be submitted only once (and will relate to all the multiple CAPs that are listed in the M1 Cover letter.

#### 4.1.2 National Procedures

Although there is no obligation to do so, it is highly recommended that ASMF Holders converting the ASMF dossier to the eCTD format first submit a 'baseline' eCTD dossier to all MS as well as to the MAH, when applicable.

[2] In exceptional circumstances the sequence number may not be 0000, the ASMF holder will need to liaise with the NCAs in such cases.

The eCTD baseline submission would in these cases be the first officially submitted dossier in eCTD format for applications previously managed in paper or other electronic formats. The intent of the baseline submission is that it should contain the current ASMF certified data on which future lifecycle management changes can be made.

## 4.2 Lifecycle Management of the ASMF

### 4.2.1 Centralised Procedure

An ASMF used in a Centralised Procedure only should be produced following the general eCTD practical guidance published by the EMA.

The lifecycle should be managed as a single submission to the EMA, no other countries should be included in the envelope or country specific information. The tracking of sequences and the management of the relationships between submitted documents should follow the standard eCTD rules described in the ICH eCTD specification.

Where the ASMF is used for several products, the cover letter submitted to the EMA should list all of these products. A separate eCTD lifecycle is required for ASMFs used in the centralised procedure.

### 4.2.2 ASMFs used in Multiple Procedures

When ASMFs are submitted to multiple NCAs (but not EMA), ASMF holders may benefit from managing a consolidated lifecycle for the ASMF eCTD and sharing this lifecycle with the individual agencies. However, individual eCTDs for each agency may also be appropriate depending on the complexity of the life cycle. The ASMF holder should chose the most appropriate approach.

Reference is made to the CMD(h) Best Practice Guide for eCTD in MRP/DCP (http://www.hma.eu/277.html) for the principles of lifecycle management and to the diagrams illustrating the way in which the sequences are managed. The practices described in the CMDh BPG for MAA dossiers can also be applied to the management of the ASMF lifecycle across the agencies where the ASMF has been submitted.

When submitting the ASMF to countries that have not previously received the ASMF, the ASMF holder should follow the principles of the guidance about the Repeat Use Procedure in the CMDh BPG. Once confirmed with the agency the ASMF holder should submit identical copies of all previously submitted ASMF eCTD sequences to the new agency. They can then use the eCTD tools at their disposal to build a "current view" of the ASMF from the sequences previously submitted to other countries. This will serve as the basis for the initial approval in the new country and the future lifecycle management of the ASMF.

According to the eCTD specification, the Module 1 eCTD XML file (eu-regional.xml) contains an envelope element for every country/NCA that is going to receive that particular sequence. If a particular eCTD sequence has no content relevant for a particular country, the eCTD should not contain an envelope element for that country nor should they be sent a copy of that sequence. Note, when maintaining an eCTD lifecycle for multiple countries for an ASMF, the 'Procedure Type' entry in the envelope must be set to "mutual-recognition", because using 'national' would mean that only one country specific envelope would be allowed.

A key component of the dossier lifecycle management is the inclusion of a Tracking Table as a "common" country document in Module 1.0. This identifies the individual sequences and which countries received them. This allows the recipient to identify why they might have gaps in their individual sequence numbers, as they can quickly see which country received which sequence.

## 5. How should the ASMF Holder provide information to the MAH?

ASMF holders should inform the MAH of the assigned EU or EMEA numbers which has to be referred to in all applications. All other submission requirements should be communicated directly between the MAH and ASMF holder.

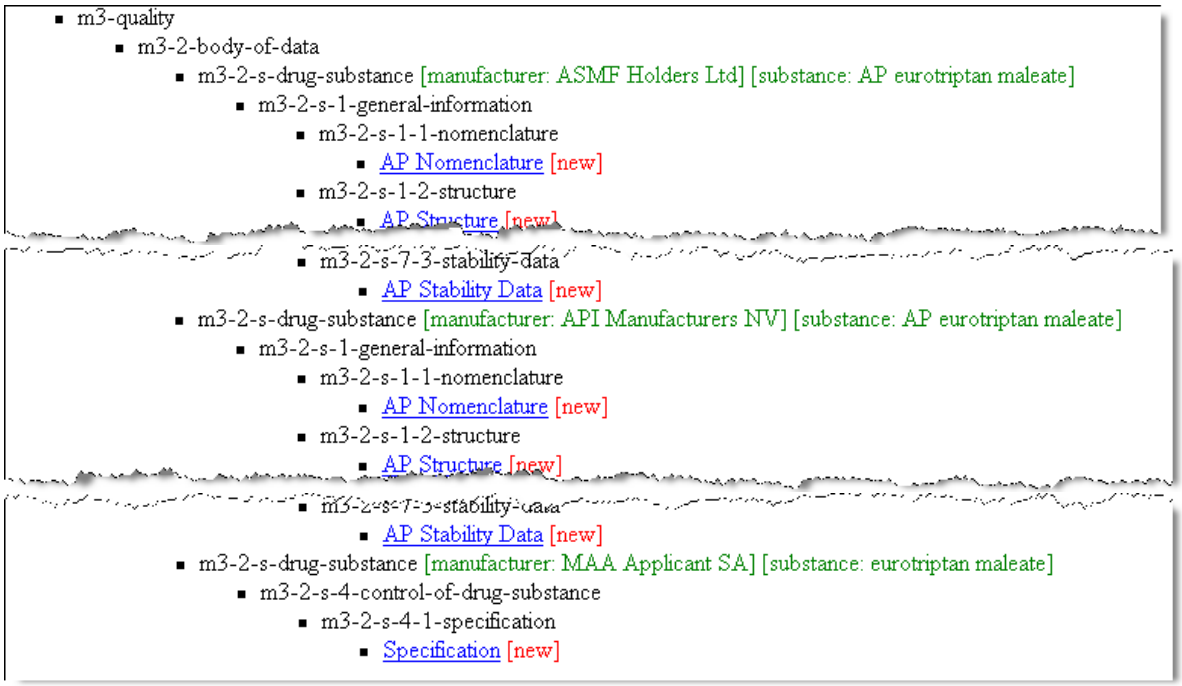
## 6. Including the Applicant's Part of the ASMF in a MA Dossier

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 clearly distinguished by the appropriate eCTD metadata values, leaf titles and file names (CTD format section 3.2.S.4.1 and 3.2.S.4.2 or old human/veterinary NtA format part 2.C.1). 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. 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 product under consideration should be highlighted in the QOS/detailed and critical summary of the MA dossier.

When the MAH incorporates the Applicant's Part of the ASMF into the MAA, there is no need to rename the leaf titles and files that were in the original ASMF.

For further procedural and regulatory details please refer to the Guideline on Active Substance Master File and the EMAs Presubmission guidance.

The figure below is an example of an MAA that refers to two different ASMF holders (ASMF Holders Ltd and API Manufacturers NV) as well as content from the applicant (MAA Applicant SA). These have been identified in the metadata and the naming of the folders.



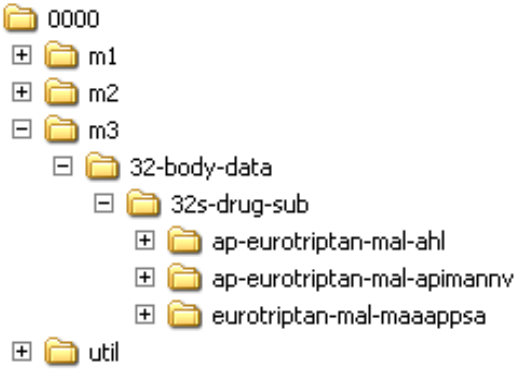



**Figure 6: Samples of the Table of Contents and folder structure in a MA dossier**

A copy of the "Letter of Access" addressed to the regulatory authority should be included in Annex 5.10 of the application form and be placed in the appropriate m1/eu/12-form/CC folder (i.e. in the respective folder for each concerned NCA).

Please note, that technically it is not possible for an MAH to refer/link/hyperlink to the ASMF holder's eCTD from within the MA dossier. Therefore, it is important that the appropriate Letter of Access is included so that the NCA receiving the MA Dossier can identify the relevant ASMF.

## 7. Glossary

Terms being used in this guidance document are defined and explained in the Harmonised Technical Guidance on eCTD which can be found here.

| Document Revision History | | |
|---|---|---|
| **Version** | **Date** | **Details** |
| 0.1 | December 2009 | Intial Draft for discussion |
| 0.2 | December 2009 | Updated draft following joint discussions between the European Medicines Agency/regulators/industry/ASMF holders 14/12/09 |
| 0.3 | January 2010 | Updated draft following written comments by European Medicines Agency/regulators/industry/ASMF holders |
| 0.4 | January 2010 | Updated following teleconference on 21st Jan, 2010 |
| 1.0 | January 2010 | First version for release |
| 1.1 | October 2012 | Draft for discussion |
| 1.1 | April 2015 | Draft for discussion |
| 1.2 | April 2016 | Update to cover EU M1 spec v3.0 changes. Discussion at Human Harmonisation Maintenance Group (HHMG) |
| 1.3 | April 2016 | First round of consolidating comments within HHMG |
| 1.4 | May 2016 | Finalising review and preparation for publication |
| 1.5 | June 2016 | Final draft for public consultation |
| 1.6 | September 2016 | Implementation of changes by HHMG based on public consultation comments |
| 2.0 | October 2017 | Second version for release after adoption by eSubmission CMB |