The worksharing procedure for the assessment of Active Substance Master File (ASMF)

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1. INTRODUCTION AND GENERAL COMMENTS

The Active Substance Master File (ASMF) procedure allows valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, whilst at the same time allowing the Applicant or Marketing Authorisation (MA) holder to take full responsibility for the medicinal product, including the quality of the active substance. Competent Authorities 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.

Active substance manufacturers often supply their active substances to multiple MA holders. Active substances can also be used in different medicinal products either on their own or in combination with other active substances. As a result, identical ASMFs are often submitted as part of new marketing authorisation or variation\(^1\) applications through any of the authorisation routes in Europe (Centralised procedure, Decentralised procedure, Mutual Recognition procedure and national authorisation procedures).

This may result in a situation where the same ASMF can be assessed by different Competent Authorities, leading to unnecessary duplication of assessment, inconsistency in decision making, frequent and numerous updating of the ASMF (often at the request of Competent Authorities) and an increased regulatory burden on the ASMF holder and Applicants/MA holders, alike, as well as the Competent Authorities.

It is acknowledged that the assessment of an ASMF is intrinsically linked to the nature of the drug product, in which the active substance will be used, and that it will need to be ensured that the quality of the active substance is appropriate for the specific product in which it will be used – this means that some level of MA/drug product-specific review of ASMFs may be required. However, there is broad agreement that a worksharing procedure should be put in place to avoid unnecessary duplication of assessment and optimise the consistency of the assessment process.

In order to address this situation, a Working Group on Active Substance Master File (ASMF) procedures has been established to develop a worksharing procedure for the coordinated sharing and harmonised use of ASMF assessment reports.

2. SCOPE OF THE ASMF WORKSHARING PROCEDURE

The regulatory history and lifecycle of an ASMF can be complicated since an ASMF may be submitted as part of new marketing authorisation or variation applications through any of the authorisation routes in Europe (Centralised, Decentralised, Mutual Recognition and national procedures).

Therefore, it is proposed to adopt a step-wise approach in rolling out a worksharing procedure, starting with simple situations and then increasing in complexity in the future.

Currently, it is only intended to include new ASMFs, submitted as part of a new marketing authorisation or variation application through the Centralised or Decentralised procedure only, where a full assessment report will be prepared by a Competent Authority.

For the purpose of the ASMF worksharing procedure, a ‘new ASMF’ is defined as an ASMF that has not been previously assessed by a Competent Authority as part of a Centralised, Decentralised or Mutual

\(^1\) Type IA, IB and II variations always refer to human medicinal products and variations requiring assessment (VRAs)/variations not requiring assessment (VNRAs) always refer to veterinary medicinal products.
Recognition new marketing authorisation or variation application - it is accepted that a ‘new ASMF’ may have been assessed as part of a national application. As a result, the ASMF is considered to have little or no regulatory history within Europe, and should be regarded as the ‘baseline’.

Full information on the ASMF can be found in the Submission Details Form (see section 3.1), which should be submitted along with the ASMF by the ASMF holder. The Submission Details Form will state whether the ASMF has been issued an EU/ASMF Reference Number and whether the ASMF has been previously assessed in Europe (see Administrative Information In Relation To Other Marketing Applications/Authorisations)

To ensure the future lifecycle of the ‘worksharing ASMF’ is captured, the scope of the worksharing procedure will also include any subsequent updates, submitted as part of a new marketing authorisation application or variation through the main authorisation routes in Europe.

Currently, it is only possible to follow the ASMF Worksharing procedure from the start of the procedure. It is not possible to switch to the worksharing procedure during the clock-stop of a procedure.

A ‘worksharing ASMF’ is an ASMF that has an EU/ASMF reference number and is being/has been assessed within the worksharing procedure.

Following a review of the experience gained post authorisation with EU/ASMFs accepted for use, the scope of the worksharing procedure may be extended.

The ASMF worksharing procedure described in this document is intended to be used in conjunction with the EU numbering system for ASMFs (see Appendix 1) and the ASMF assessment report (ASMF AR) repository.

3. PROCEDURE FOR WORKSHARING ASMF ARs

3.1. Introduction

To date, where Competent Authorities have been able to identify when the same version of an ASMF has been submitted in different European procedures, they have pragmatically adopted an informal worksharing procedure to harmonise the assessment of the ASMF.

The proposed worksharing procedure is a natural enhancement of this current working practice. Although the procedure attempts to co-ordinate such practice, it should not replace communication amongst Competent Authorities, which is strongly encouraged.

A basic requirement for any worksharing procedure is the ability to identify conclusively where the same version of the ASMF is submitted in different procedures in Europe.

Therefore, the following systems have been specifically developed with this in mind:

- The EU/ASMF numbering system for ASMFs (see Appendix 1)
- The ASMF-AR repository (https://asmf.cts-mrp.eu/)

Together, these systems contain all the necessary information to identify where the same ASMF has been submitted in different procedures.
The worksharing procedures for ASMF should be followed in conjunction with other procedural guidance. All efforts were made when designing the WS procedure to avoid procedural inconsistencies. The ASMF worksharing should not lead to any delay to marketing authorisation procedures or variations.

3.2. **The ASMF assessment report**

3.2.1. **Assessment report templates**

In order to facilitate the sharing of ASMF assessment reports amongst Competent Authorities, it is important that the latest ASMF assessment report templates should be used, which are published on the CMDh and EMA websites:

- Decentralised ASMF assessment report templates:
  [http://www.hma.eu/334.html](http://www.hma.eu/334.html)
- Centralised ASMF assessment report templates:

The templates contain the same information but have different document formats. Separate templates are available for the Restricted and Applicant’s Part of the ASMF. The templates can be used interchangeably; the template used will be dependent on the parent procedure responsible for originally drafting the report.

Where the ASMF uses the CTD format, the above assessment report templates should be used (the submission of the same ASMF in different formats is discouraged).

The structure of the ASMF assessment report template is described as an ‘add on’ report, which contains the preliminary assessment of the ASMF plus assessment of the responses at the various stages of the procedure. This ensures the evaluation of the ASMF remains fully transparent, which is important if the ASMF is used in other procedures (as it avoids repetition of points).

In the exceptional situation where the ASMFs uses the VNees format (exclusively for veterinary applications), appropriate national assessment report templates should be used. The reports should include the assessment of the initial ASMF and responses to deficiency questions.

3.2.1.1. **Assessment report templates for updates to worksharing ASMFs**

During the development of the EU numbering system for ASMFs (see Appendix 1) and the ASMF worksharing procedure, it was acknowledged and agreed that an assessment report would need to be produced for an update to a worksharing ASMF (in case the update is subsequently used in other procedures).

All variations submitted to an ASMF should be listed in the variation table of the ASMF Summary. The ASMF Summary is an internal document for NCA’s to be uploaded in the repository.

Where an ASMF update contains single or grouped changes, the description of all changes submitted should be added to the table of changes in the ASMF Summary, and the summary data should be updated accordingly.

For MRP or national procedure, if an ASMF update contains a single or grouped Type IB changes, the ASMF Type IB Variation Assessment report template should be used:
This template could also be used for a Type II change, depending on the nature of the change.

For CAP, the relevant template is sent to the Rapporteurs at the start of procedure.

For ASMF updates containing a considerable number of changes, the initial assessment report template (section 3.2.1) should be used (the previous full ASMF assessment report could be used as a basis for the evaluation of the update).

### 3.2.2. ASMF Summary

When the ASMF is accepted for use and the final assessment reports will be uploaded to the ASMF-AR repository an ASMF Summary document needs to be written. The ASMF Summary is an internal document for NCA’s to be uploaded in the repository. A template for the ASMF Summary is available to the NCA’s.

#### 3.2.2.1. ASMF Summary update for updates to worksharing ASMFs

All variations submitted to an ASMF, including VNRAs for veterinary medicinal products, should be listed in the variation table of the ASMF Summary.

Where an ASMF update contains a single or grouped changes, the description of the changes submitted should be added to the table of changes in the ASMF Summary, and the summary data should be updated accordingly.

In case a consolidated assessment report is written for a type II variation or for a VRA for veterinary medicinal products (see section 3.5.1.5.) this will be mentioned in the variation table and the ASMF Summary will be updated. In the variation table it should be made clear that a consolidated AR has been written, but the previous variations still need to be kept included in the table as this gives a comprehensive overview of all submitted variations.

### 3.2.3. Using the ASMF-AR repository to share assessment reports

In their Letter of Access to the ASMF, the ASMF holder acknowledges that the EEA National Competent Authorities, 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 ASMF assessment reports amongst themselves.

The ASMF-AR repository and the EU/ASMF reference number have been developed to facilitate the sharing of ASMF assessment reports amongst Competent Authorities. Therefore, it is important that the most up to date ASMF assessment report is uploaded onto the ASMF-AR repository as soon as possible, so that other Competent Authorities benefit from the assessment already performed. When other Competent Authorities use an ASMF assessment report from the ASMF-AR repository they should circulate it “as is” and without making any changes to the details in the report.

A reference that the ASMF is a worksharing ASMF (as indicated by the EU/ASMF repository number) should be included in the main Quality assessment report and Overview. Product specific and member state specific information should be avoided (e.g. MA or procedure reference numbers, applicants, product names, assessor details, member state/authority raising comments); however, if needed, such information should only be included in the ASMF assessment report relating to the Restricted Part. This avoids disclosing commercially confidential information from one application in another application.
The uploading of the ASMF assessment report onto the repository or reference to the EU/ASMF reference number does not replace the requirement for the RMS/Rapporteur to circulate the ASMF assessment report amongst Competent Authorities and other relevant parties involved in a particular marketing authorisation or variation procedure.

If a Competent Authority wishes to use a consolidated ASMF assessment report, or a package of assessment reports including add-on reports, that has been uploaded onto the repository in a (new) procedure, it should assure itself that the report is suitable to describe the quality of the active substance in relation to the medicinal product in which it is used.

### 3.2.4. Status of the ASMF in the ASMF-AR repository

After the ASMF-holder has requested an EU/ASMF-number a record will be created in the ASMF-AR repository. The ASMF will then have the status number reserved. Once the ASMF has been submitted and the procedure has started the status will change to under evaluation. After the evaluation has been finalised the status can change to either accepted, on hold or withdrawn.

**Number reserved:** The ASMF holder has requested the EU/ASMF-number and a record has been created in the ASMF-AR repository by the Rapporteur.

**Under evaluation:** The ASMF has been submitted and the initial procedure is included in the record. Detailed information is included in the record.

**Accepted:** The assessment of the ASMF (in a marketing authorisation application or variation application) has resolved all issues and the conclusion of the Rapporteur is that the information in the ASMF is sufficient to be used in support (or to be referred to?) in a given marketing authorisation. The ASMF and the assessment reports can be used, in principle, for future procedures without further assessment unless otherwise justified by critical points raised by daughter procedures RMS/CMSs.

**On hold:** During a marketing authorisation application or variation application procedure Questions have been raised and the applicant has decided to withdraw the complete application or the ASMF in the specific application, but the ASMF has not been withdrawn by the ASMF-holder. The ASMF will not be further assessed but can be re-activated for a new marketing authorisation or variation application.

**Withdrawn:** The ASMF-holder has decided to withdraw the ASMF from the worksharing procedure. This ASMF will not be further evaluated or re-activated.

### 3.3. The worksharing procedure for a New ASMF

The following section will describe the worksharing procedure for the assessment of a new ASMF. In this context the following definitions are important:

**Parent procedure:** The procedure involved in the ASMF WS which will need to circulate an ASMF assessment report at the earliest time point.
Parent RMS/Rapporteur: The RMS/Rapporteur of the Parent procedure, which will be responsible for assessing the ASMF and preparing an assessment report

Parent CMS/CxMP members: The CMS/CxMP members of the parent procedure

Daughter procedure: A procedure involved in the ASMF WS which will need to circulate an ASMF assessment report later than the Parent procedure

Daughter RMS/Rapporteur: The RMS of Daughter procedures which will use the ASMF assessment report prepared by the Parent RMS/Rapporteur

Daughter CMS/CxMP members: The CMS/CxMP members of the daughter procedure(s)

ASMF Summary: Report containing up to date summary information of the ASMF and its lifecycle (table of changes).

New ASMF: ASMF that has not been previously assessed by a Competent Authority as part of a Centralised, Decentralised or Mutual Recognition new marketing authorisation or variation application - it is accepted that a ‘new ASMF’ may have been assessed as part of a national application.

3.3.1. When a new ASMF is used in a single Centralised or Decentralised procedure.

Where a new ASMF is used in a single Centralised or Decentralised procedure, it follows that the ASMF assessment may not benefit from a worksharing procedure. However, since the same version of the ASMF could be used in another procedure at a later date, the worksharing procedure as described in section 3.3.2 should still be followed.

In the context of the ASMF worksharing procedure, a single Decentralised or Centralised procedure is defined as one having a common RMS/Rapporteur and common timetable, e.g. duplicate procedures.

3.3.2. When a new ASMF is used in more than one Centralised/Decentralised procedure

Where a new ASMF is used in more than one Centralised/Decentralised Procedure with different RMSs/Rapporteurs, and/or different timetables, the ASMF assessment will benefit from the worksharing procedure.

3.3.2.1. Reserving the EU/ASMF reference and assessment report number (see Appendix 1)

Before a new ASMF is submitted, the ASMF holder should request an EU/ASMF reference number from the RMS of the associated Decentralised procedure or from the EMA if the associated procedure is Centralised. Ideally, the procedure number should be quoted in the number request form; however, if the procedure number is not known, the EU/ASMF number can still be reserved. Competent Authorities have the discretion to refuse reservation of numbers in certain situations e.g. block reserving of numbers.

The number request form should be submitted shortly before the submission of the ASMF, the timing of which should be in line with the ASMF guidance.
The Competent Authority should ensure that EU/ASMF numbers requests are promptly dealt with so that the EU/ASMF reference number is available for reference in the marketing authorisation application.

The ASMF-AR repository will assign a new sequential EU/ASMF reference number to the ASMF (i.e. EU/ASMF/XXXXX) and an assessment report number (i.e. YYYYY) to the particular version of the ASMF - see Appendix 1 for further information.

The Competent Authority will then communicate this EU/ASMF reference number to the ASMF holder, which should then be quoted in all subsequent correspondence with Applicants/MAHs and Competent Authorities, relating to the particular version of the ASMF.

When submitting an ASMF that has an EU/ASMF reference number, the ASMF holder should clearly state this in the Submission Details Form (see CHMP/QWP/227/, EMEA/CVMP/134/ Guideline on Active Substance Master File Procedure, Annex 3), Letter of Access and application form for MAA or MAV.

To minimise the workload of the Competent Authority at this stage, the ASMF-AR repository record should only be populated with sufficient information to avoid duplication of repository records for the same version of the ASMF.

The following information is considered sufficient:

- International Non-proprietary Name plus salt form of the active substance;
- ASMF holder;
- Version numbers of the Applicant’s and Restricted Parts.

Where the ASMF holder already holds an ASMF that has been assigned an EU/ASMF reference number and wishes to register another ASMF for the same active substance, e.g. a substantially different route of synthesis (see Appendix 1 Assignment of a new ASMF Reference Number), this should also be clearly stated in the Submission Details Form.

The ASMF-AR repository has been designed to highlight possible duplicate records when entering data. When creating the ASMF-AR repository record, all possible care should be taken to avoid creating a duplicate record for the same ASMF, particularly when the ASMF holder registers more than one ASMF for the same active substance, e.g. a substantially different route of synthesis (see Appendix 1 Assignment of a new ASMF Reference Number).

Full information on the ASMF can be found in the Submission Details Form, which should be submitted along with the ASMF by the ASMF holder.

As soon as the CTS record for each associated MA procedure is created it should be linked to the ASMF-AR repository record, to ensure that the Revision Sheet contains an accurate list of procedures using the ASMF and that the parent and daughter procedures can be determined.

Since there is currently no equivalent link between SIAMED and the ASMF-AR repository, timetables of Centralised procedures will need to be manually entered onto the ASMF-AR repository record by EMA.

3.3.2.2. Determining the parent procedure for the First Stage assessment of the ASMF

When more than one Decentralised and/or Centralised procedures use the same ASMF, the parent RMS/Rapporteur is responsible for preparing the ASMF assessment report. Consequently, the other procedures using the ASMF are known as the daughter procedures.

The Revision Sheet in the ASMF-AR repository can be used to sort the different procedures with respect to their timetables. The Repository automatically assigns the applicable parent procedure by
the earlier calendar date of the Day 70 and/or Day 80 of the MAA procedure or Day 40/30 of the variation procedure.

**Example:**

IE/H/9690/01/DC (CMS: AT, DE, IT & CZ) - Day 70 is 17/01/2013
CZ/H/9878/01/DC (CMS: DE, DK, IE & SE) - Day 70 is 28/01/2013
FR/H/9798/01/II/023 (CMS: BE, CZ, NL, PL & SK) - Day 40 is 24/03/2013
DE/H/9987/01/DC (CMS: AT, ES, FR & SE) - Day 70 is 31/04/2013

The parent procedure is IE/H/9690/01/DC as IE is the first RMS that will need to prepare an ASMF assessment report at Day 70. The other procedures are defined as daughter procedures.

Where more than one procedure has identical timetables and uses the same ASMF, which can occur more frequently with Centralised Procedures since timetables are harmonised with CxMP meetings, then the respective RMS/Rapporteur & EMA procedure managers should agree who will be designated parent RMS/Rapporteur. In these cases, it is imperative that procedure information is entered onto the ASMF-AR repository and the parent RMS/Rapporteur designated as soon as is practically possible.

As soon as the Parent RMS/Rapporteur is identified, they should complete the ASMF-AR repository record, using the information contained in the Submission Details Form.

### 3.3.2.3. First stage assessment of the ASMF

Before starting the assessment of the ASMF, the parent RMS/Rapporteur should re-check that the ASMF is not a duplicate record of an ASMF that is undergoing or has been previously assessed.

Once the preliminary assessment of the ASMF is complete, the ASMF assessment report should be uploaded onto the ASMF-AR repository by the parent RMS/Rapporteur as per the timelines in section 3.3.2.2.

The timelines in section 3.3.2.2 are chosen as the first date to upload the ASMF assessment report, in case there are other procedures that need to circulate an ASMF assessment report before Day 105/120/60 of the parent procedure. The ASMF AR should be sent to the ASMF Holder and applicant (AP and RP, as applicable) as per SOP of DCP and CP.

Daughter procedures that need to circulate an ASMF assessment report before Day 105/120/60 of the Parent procedure should be aware that the List of Questions (LoQ) may change at Day 105/120/60; consequently, they should inform the Applicant that the ASMF is part of the worksharing procedure and that the LoQ may change at Day 105/120/60 of their procedure.

The assessment report filename should use following format to identify clearly the ASMF, active substance and stage of assessment:

"EU_ASMF_XXXXX_0001 <ASMF holder, active substance> First stage AR"

#### 3.3.2.3.1. Quality assurance review of the First Stage ASMF-AR

In order that other Competent Authorities can rely on the First Stage ASMF-AR, it has been decided to introduce a quality assurance (QA) review of the report to ensure that the assessment is robust and identifies as many quality critical deficiencies as possible.

During the preparation of the First Stage ASMF-AR (i.e. Day 0-70 of a DCP; Day 0-80 of a CP; Day 0-40 of a variation; Day 0-30 for veterinary CP variations), the parent RMS should discuss and agree
which Parent CMS will be responsible for carrying out the QA review of the ASMF assessment report. The assignment of the QA reviewer should be made by Day 0. The country and reference of the associated procedure related to the QA reviewer should be recorded in the ASMF AR repository by the RMS of the parent procedure.

Priority criteria for deciding the Quality Assurance reviewer:

1. Parent CMS/CxMP member and Daughter RMS/Rapporteur of next procedure using the ASMF
2. Daughter RMS/Rapporteur of next procedure using ASMF
3. Parent CMS/CxMP member

In the above example, CZ should agree to carry out the QA review.

Note: Where the Parent Procedure is a Centralised Procedure and the ASMF is being assessed jointly by the Rapporteur and Co-rapporteur, there is no need to nominate an additional QA reviewer.

The QA review is a risk-based, targeted review of the ASMF assessment report to ensure that it covers all relevant quality aspects for the active substance. The quality assurance review should not be a re-assessment of the ASMF data, although the QA reviewer may have to carry out an evaluation of the data if the report is unclear.

There is no need for the QA reviewer to provide an evaluation of the ASMF assessment report or to hold teleconferences to discuss issues (unless this is required as part of the regulatory procedure). The QA reviewer should only raise additional points that are critical to quality of the active substance using the appropriate CMS/CxMP members comments template (there is no specific QA review template).

The Quality Assurance review does not remove the responsibility of each Competent Authority to ensure that the active substance is suitable for use in the associated medicinal product; therefore, Competent Authorities may raise additional points that are critical to the quality of the active substance. However, points that do not improve the quality of the active substance, e.g. updating the description of the properties of a well-known active substance, should not be raised.

QA reviewer should send comments at Day 100 of the Centralised/Decentralised parent procedure or at Day 55 of a variation procedure (Day 43 for veterinary CP variations).

3.3.2.3.2. Parent CMS/CxMP members comments on the First Stage ASMF-AR

Parent CMS/CxMP member should only raise additional points that are critical to the quality of the active substance using the appropriate comments template. The comments will be added onto the ASMF-AR to improve transparency of the assessment procedure and avoid Daughter procedures from raising the same or similar points. It is acknowledged that this will not avoid raising duplicate comments when the Daughter Procedures are running less than 30 days behind the Parent procedure.

Where the Parent procedure is a Decentralised Procedure, the Parent RMS should simply add a list of the various comments to the D70 ASMF AR onto the ASMF-AR file. The updated D105 ASMF AR should be uploaded onto the ASMF-AR repository by Day 105. The RMS should submit the revised ASMF AR with the revised LoQ to the ASMF holder.

Where the Parent procedure is a Centralised Procedure, the Day 120 consolidated ASMF-AR should be sent to the ASMF Holder and Applicant, as applicable, and uploaded onto the ASMF-AR repository.

Where the Parent procedure is a variation procedure, the Parent RMS should simply add a list of the various comments to the PVAR ASMF AR onto the ASMF-AR file. The updated ASMF AR should be
uploaded onto the ASMF-AR repository by Day 60. The RMS should submit the revised ASMF AR with the revised LoQ to the ASMF holder.

The combined comments/consolidated List of Questions should be named as follows:
"EU_ASMF_XXXXX_0001 <ASMF holder, active substance> First Stage LoQ"

If the ASMF assessment is ready to be accepted for use, the remaining daughter procedures should be contacted to confirm agreement with the acceptability of the ASMF.

In the event that the ASMF is found to be acceptable to the parent RMS/Rapporteur and parent CMSs/CxMP members without any further amendment, then its parallel assessment in another pending daughter procedures should not prevent it from being accepted for use in a medicinal product.

However, the daughter RMS of any pending daughter procedure should be contacted to allow commenting on whether there remain critical issues that would affect the assessment in relation to the parent procedure. Consequently, the status of the ASMF-AR repository record should be changed from 'PENDING' to 'ACCEPTED FOR USE IN A MARKETING AUTHORISATION' and the revision file should be closed.

3.3.2.3.3. Circulation of the First Stage ASMF-AR in the daughter procedures

Competent Authorities involved in the daughter procedures should be able to rely on the ASMF assessment report of the parent procedure, since the Community pharmaceutical legislation fully harmonises the standards for quality and safety. Furthermore, the assessment report has also undergone a QA review to ensure the assessment is robust and quality critical deficiencies have been identified.

Daughter procedures should only raise additional points that are critical to the quality of the active substance. Additional points raised by the daughter RMS/Rapporteur should be circulated as a separate document in the Daughter procedure. Where a Daughter CMS/CxMP member raises other concerns, the daughter RMS/Rapporteur should consult with the CMS/CxMP member whether the concerns raised are critical or not. If they are not critical, the concerns should be withdrawn, and the daughter RMS/Rapporteur should notify the ASMF holder and, where relevant, Applicant/MAH that they do not need to be addressed.

Any additional issues raised in the Daughter procedure should be forwarded to the parent RMS/Rapporteur for amendment of the ASMF AR and the ASMF holder notified of the additional issue(s). The up-dated ASMF AR should be named as follows: "EU_ASMF XXXXX 0001 <ASMF holder, active substance> First Stage LoQ Daughter". If no comments are received that would lead to the change of the ASMF AR, the file is not updated.

Daughter RMS/Rapporteur should circulate the First Stage ASMF assessment report and the First stage LoQs, without making any further amendments to avoid creating different duplicate versions, in their own procedures. This ensures that the ASMF holder can submit the same set of responses in all procedures using the ASMF.

If on Day 70/80/40/30 of the daughter RMS/Rapporteur procedures, the First Stage LoQ is not available (pre D105/D120/D60) from the Parent procedure, the daughter RMS/Rapporteur should circulate this LoQ to the CMS/CxMP members as soon as available as this will help identify whether a particular deficiency has been raised.

3.3.2.4. Second Stage Assessment of ASMF

The following situations may arise at the second stage assessment of the ASMF:
1. The parent RMS does not change from the first stage to the second stage (ideal).

2. A daughter procedure from the first stage becomes the parent procedure for the second stage, as a result of (a) delays to or (b) withdrawal of the parent procedure (first stage).

In situation 2, the Daughter procedures should check the ASMF-AR repository and inform the parent RMS (first stage) that they intend to take over as parent RMS (second stage). The parent RMS (first stage) then has the option of following situation 2 or electing to carry out the second stage assessment of the responses (in which case the report should be uploaded to the repository and circulated to all concerned daughter procedures MSs”). In either case, the Parent RMS (first stage) should communicate their intentions to the RMS of the other procedures.

In situation 2, the Revision Sheet in the ASMF-AR repository should be used to sort the different procedures with respect to their timetables.

The parent RMS/Rapporteur of the second stage should include the assessment of the responses to all the First Stage LoQ, as an ‘add on’ report to the First Stage ASMF-AR and uploaded onto the ASMF-AR repository by Day 120 for a Decentralised parent procedure, Day 150 for a Centralised parent procedure (Day 160 for veterinary CP) or Day 60 for a DCP variation (D75 for human CP variations, D74 for veterinary CP variations), in addition to circulating it to the parent CMSs/CxMP Members, ASMF Holder and applicant, as applicable.

For easy identification and clarity, the assessment report filename should be in the following format to reflect the stage of assessment: “EU_ASMF_XXXXX_0001 <ASMF holder, active substance> Second Stage AR”.

3.3.2.4.1. Quality assurance review of the Second Stage ‘add-on’ assessment report

A Quality Assurance review of the second stage assessment of response should only be performed if PSRPH/Major Objection were raised in the First Stage; in which case, the QA review should follow the steps described above in section 3.3.2.3.1.

3.3.2.4.2. Parent CMS comments on the Second Stage ASMF-AR

Since the ASMF has been robustly assessed during the first assessment and subsequent QA review, it is not anticipated that there will be new additional points. If new points are raised or if the responses do not fully address the deficiency points, then parent CMS/CxMP members should send comments by day 145 for a Decentralised parent procedure, Day 170 for a Centralised parent procedure or Day 80 for a variation procedure (D79 for veterinary CP variations).

The same procedure described in section 3.3.2.3.2. should be followed concerning combining/consolidating the comments and uploading the second stage List of Questions/List of Outstanding Issues onto the ASMF-AR repository. The combined comments/consolidated LoQ/LoOI should be named as follows: “EU_ASMF_XXXXX_0001 <ASMF holder, active substance> Second Stage <LoQ or LoOI>”.

3.3.2.4.3. Circulation of the Second Stage ‘add-on’ assessment report in the daughter procedures

Daughter RMS/Rapporteurs should circulate the Second Stage ASMF assessment report and the Second Stage LoQ/LoOI, without making any further amendments to avoid creating slightly different duplicate versions, in their own procedures. This ensures that the ASMF holder can submit the same set of responses in all procedures using the ASMF.
If the Second Stage LoQ/LoOI is not available, the Daughter RMS should circulate it as soon as available as this will help identify whether a particular deficiency has been raised.

3.3.2.5. Third, fourth, etc Stage Assessment of ASMF

Ideally, the first set of responses should resolve all outstanding deficiency points concerning the ASMF. Where this is not the case, the same procedure as described in section 3.3.2.4. should be followed according to the timetable of the associated MAA procedure.

The assessment report filename should be in the following format to identify clearly the ASMF, active substance and stage of assessment: “EU_ASMF_XXXXX_0001 <ASMF holder, active substance> Third/Fourth/etc Stage AR”. The List of Questions filename should be in the following format: “EU_ASMF_XXXXX_0001 <ASMF holder, active substance>\(X\) Third/Fourth/etc Stage LoQ”

3.3.2.6. Concluding the assessment of the ASMF

When the assessment of the ASMF is completed, the final ‘add on’ assessment report and ASMF Summary should be uploaded onto the ASMF-AR repository regardless of the procedure timetable.

However, there may be instances where the parent RMS/Rapporteur may wish to prepare a consolidated assessment report from the ‘add on’ report, e.g. to make the assessment report more readable. The consolidated assessment report should maintain the audit trail of the assessment to ensure that any resolved points are not re-raised by other Competent Authorities.

The assessment report filename should be amended to the following format to identify clearly the ASMF, active substance and stage of assessment: “EU_ASMF_XXXXX_0001 <ASMF holder, active substance> FAR”.

The status of the ASMF-AR repository record should be changed from ‘PENDING’ to ‘ACCEPTED FOR USE IN A MARKETING AUTHORISATION’.

In the unusual situation where a potential serious risk to public health (major objection) concerning the ASMF has been raised in an associated procedure, it is likely that this will be pertinent to all procedures. However, the circumstances of an individual procedure may permit the ASMF to be accepted for use. Consequently special care should be taken in this situation, and considered on a case-by-case basis.

3.4. Use of an accepted ASMF in a new procedure

If the same version of the ASMF is later used in another procedure (new marketing authorisation procedure or variation application), then the Member States involved in this procedure should simply adopt the final ASMF assessment report. The new procedure should be recorded in the ASMF AR repository. No new or updated Assessment report or summary is considered necessary.

The same principle applies as during the initial worksharing procedure, i.e. only additional points that are critical to the quality of the active substance should be raised by the new RMS and CMS’s.

In case an amendment of the ASMF assessment report is required for the same ASMF version number (YYYY number), e.g. due to changes to the state of the art, the AR may still be amended by the RMS/Rapporteur of the new daughter procedure without changing the ASMFversion number at that moment, but with a new version of the ASMF-AR. In this case the updated AR and, if necessary, the summary need to be uploaded in the ASMF repository for future use in new procedures.
3.5. **Change to a worksharing ASMF**

The guidance in the following sections only applies to ASMFs that have been previously assessed in the ASMF worksharing procedure i.e. the ASMF has been issued an EU/ASMF/XXXXX reference number.

At this moment, updates to existing ASMFs that have not been issued a worksharing reference number and assessed in the worksharing procedure are outside the scope of this guidance.

Whilst the addition of an ASMF to the work sharing procedure is restricted to new ASMFs submitted by the Decentralised and Centralised procedures, in order to capture the full lifecycle of 'worksharing ASMFs', subsequent updates submitted as part of a new marketing authorisation application or variation through national, MRP, DCP or CP will be followed by the ASMF worksharing.

An update to the worksharing ASMF can only be submitted by the ASMF holder in relation to a MA or variation application. Where an update is submitted in a variation application, this may be classified as a Type IA, IB or II for human medicinal products and VNRA or VRA for veterinary medicinal products depending on the nature of the changes. Where the update involves multiple changes, these changes can be grouped, and the procedure will be categorised according to the highest individual change of the overall variation application submitted.

The EU/ASMF/XXXXX number should be declared in the application form of the variation procedure (under the present/proposed table).

Where an ASMF update contains single or grouped changes, the description of the changes submitted should be added by the Parent RMS/Rapporteur to the table of changes in the ASMF Summary, and the summary data should be updated accordingly.

Competent Authorities recognise that assessment of an update to a worksharing ASMF can be more complex than a new ASMF because of the different regulatory routes (MAA/MAV, Decentralised/Centralised), different submission timings and potential divergence in the variation classification of the ASMF update by the MAH/Applicant. Consequently, it would be very challenging to envisage every possible scenario; therefore, the following guidance will look at/provide examples of different regulatory scenarios and aims at facilitating the lifecycle management of ASMFs by ASMF Holders, MAHs and Competent Authorities.

It is also recognised that all changes to an ASMF are not always submitted by all MAHs using that ASMF (e.g. one change affecting the crystal form may not be submitted for an oral solution or the MAH is not marketing their product and is therefore not submitting a variation). Where a group of changes is assessed by the parent RMS/Rapporteur all changes submitted by the ASMF holder should be considered for the use of the active substance in a particular medicinal product, regardless whether the MAH has submitted variation(s) for all the changes.

When an ASMF is used in both Human and Veterinary Medicinal Products which variation procedure (human or veterinary) should be used will be decided on a case by case basis.

3.5.1. **Defining a new sequential assessment report number (see Appendix 1)**

An update can involve the Applicant’s Part, Restricted Part or both Parts of the ASMF. For each update of the ASMF, a new sequential YYYY should be defined by the ASMF holder, and confirmed by the RMS for the associated Decentralised, Mutual Recognition or National procedure or to the EMA for the associated Centralised procedure at the time of circulation of the ASMF-AR (in Type IB and Type II procedures or VRA for veterinary medicinal products) – see Appendix 1 for further information.
The ASMF holder should then quote the EU/ASMF reference number and assessment report number, i.e. EU/ASMF/XXXXX/YYYY, in the MAA/MAV application form and all correspondence to MAHs and Competent Authorities, regarding the particular updated version(s) of the ASMF.

It is anticipated that the worksharing procedure will lead to fewer updates to the ASMF, and these updates will most likely be instigated by changes requested by the ASMF holder, rather than Competent Authorities.

The ASMF-AR repository record should be created and populated, and linked to the CTS record of the associated MA or MAV procedure (if available), as described in section 3.3.2.1.

### 3.5.1.1. Determining the parent procedure

Due to the different regulatory routes that may be potentially associated with an ASMF update, it is acknowledged that determining the parent procedure may be more complex with updates to worksharing ASMFs. However, the same principles for determining the parent procedure for a new ASMF should still be used. The parent procedure should be the procedure that is required to prepare an assessment report on the ASMF update first (see section 3.3.2.2); for ASMF updates involving Type IA/IB changes or certain VRAs for veterinary medicinal products, this should be Day 30 of the procedure.

E.g.

- FR/H/9098/01/II/001 - Day 40 is 07/02/2013
- IE/H/9590/01/II/001 - Day 40 is 17/02/2013
- AT/H/9999/01/DC - Day 70 is 28/03/2013

The parent procedure is FR/H/9098/01/II/001; FR would be the first RMS needing to prepare an assessment report on the ASMF update. The other procedures are defined as daughter procedures.

Where the update to a worksharing ASMF is submitted in association with a National only MA application or variation, then the NCA will need to specify a date on which the ASMF-AR will need to be prepared in order to determine the parent procedure. Where it is certain that the National only procedure will not act as Parent procedure, then it does not need to be included in the ASMF-AR repository.

The parent RMS/EMA or the NCA in case of a national procedure will be responsible for fully completing the ASMF-AR repository record, using the information contained in the Submission Details Form.

### 3.5.1.2. Updates to a worksharing ASMF submitted in a NEW Marketing Authorisation Application

For an update to a worksharing ASMF submitted in a Decentralised or Centralised procedure, the same procedure described in section 3.3. should be followed.

In Mutual Recognition MAA procedures, the ASMF update would have been previously assessed and accepted for use as part of a variation (see below) to update the National marketing authorisation ahead of initiating a Mutual Recognition procedure.

Where the ASMF update is submitted as part of a National procedure, then the same general procedure described in section 3.3. should be followed and adjusted to account for the fact that there are no CMS.

A Quality Assurance review of the ASMF-AR for the update is not required. Additional major quality issues may be reported by the CMSs/CXMP members.
3.5.1.3. Updates to an worksharing ASMF submitted in a VARIATION APPLICATION to a marketing authorisation

3.5.1.3.1. The worksharing ASMF update ONLY contains Type IA IMMEDIATE NOTIFICATIONS

The Classification Guideline for variations currently classifies five changes to the active substance as Type IA immediate notifications (also see Appendix 2). Apart from the change in the name of the active substance, these changes will require immediate updating of the ASMF.

The Parent RMS should record the procedure on the ASMF-AR repository and change the status of the repository record to ‘ACCEPTED FOR USE IN A MARKETING AUTHORIZATION’ by Day 30 of the associated variation procedure (see section 3.3.2.6. and 3.2.1.1. )

Where an ASMF update contains a single or grouped Type IA, IB and II changes, the description of the changes submitted should be added by the Parent RMS/Rapporteur to the table of changes in the ASMF Summary, and the summary data should be updated accordingly.

3.5.1.3.2. The worksharing ASMF update ONLY contains Type IA ‘Do and Tell’ notifications

Type IA variations do not require prior approval, but the MAH must notify the Competent Authority within 12 months following implementation ("Do and Tell procedure"). This means that the ASMF holder must notify the MAH of any Type IA changes earlier than 12 months so that the MAH complies with regulatory requirements. Since implementation of the change is not reliant on Competent Authority approval, there may not be a driver for the MAH to submit the notification in a timely manner.

Wherever possible, it is recommended that Type IA changes should be grouped with other Type IB or Type II changes, which require prior approval before implementation, to provide encouragement for MAHs to submit the appropriate variations in a timely manner and will avoid the potential for differing variation classifications.

If this is not possible, the ASMF holder need to provide a list of all the Type IA variations implemented within a defined period, along with any updates to the CTD sections of the ASMF, to the Applicant/MAH so they can submit the appropriate variations in accordance with Commission Regulation (EC) No 1234/2008. The ASMF holder will also need to submit the updated ASMF to the Competent Authorities.

The Parent RMS should record the procedure on the ASMF-AR repository and change the status of the repository record to ‘ACCEPTED FOR USE IN A MARKETING AUTHORIZATION’ by Day 30 of the associated variation procedure (see section 3.3.2.6. and 3.2.1.1. )

Where an ASMF update contains a single or grouped Type IA, IB and II changes, the description of the changes submitted should be added by the Parent RMS/Rapporteur to the table of changes in the ASMF Summary, and the summary data should be updated accordingly.

3.5.1.3.3. The worksharing ASMF update contains Type IB and/or Type II changes

These types of changes require prior approval from the Competent Authority before they can be implemented by the ASMF holder.

CMDh has already published guidance on submitting updates to an ASMF, the scope of which covers variations submitted using National and Mutual Recognition procedures:

**Question 3.4**

*How should a change to or update of an ASMF, which is part of Module 3 of a marketing authorisation, be submitted?*
Answer:
An update or change of an ASMF as such is not foreseen in the Pharmaceutical Legislation and can only be addressed in connection with a marketing authorisation. The type of the variation is dependent on the type of the single changes introduced in the updated version. The update – including changes of the open as well as the restricted part - can be submitted as a grouped application according to the highest type of the single changes, if condition 5 of Annex III of the Variation Regulation applies.
However, in case of substantial changes in the updated version of the ASMF it is recommended to submit a single variation of type II under category B.I.z. However, it is a prerequisite for the validation of these single variations that the section “present/proposed” is filled out completely and correctly.
In all cases, the updated ASMF must be submitted by the ASMF holder (open and closed part to NCA, open part to MAH), the variation as such has to be submitted by the marketing authorisation holder.

Unfortunately, the phrase “substantial changes” has not been suitably defined and can lead to an ASMF update being classified differently by the Applicants/MAHs and/or Competent Authorities, leading to different procedure timetables for the same update that can be problematic for the worksharing procedure, e.g. MAH 1 submits the ASMF update as a type IB grouped variation, whereas MAH 2 submits the same ASMF update as a type II variation.

In contrast, variations to update ASMFs used in Centralised Procedures have to individually list and classify every change made to the ASMF, such that, a grouped variation is submitted.

The ASMF holder should provide a completed Table of Changes (Annex 3 of ASMF Guideline), describing the changes made between the current and proposed versions of the ASMF; this can be used by the Applicant/MAH to determine the classification of each change.

For ASMF updates only containing Type IB variations:

The Parent RMS/Rapporteur is responsible for assessing and determining the ASMF update, without seeking comments from CMS, in line with current practice. The ASMF-AR (see also 3.2.1.1.) should be uploaded onto the ASMF-AR repository by Day 30 of the associated MAV procedure and circulated to Parent CMS, the MAH and the ASMF Holder. If a Notification with Grounds has to be sent on day 30 it will be necessary to upload and circulate an updated AR on the second round of assessment of the IB procedure.

For easy identification and clarity, the assessment report filename should be in the following format:
"EU/ASMF/YYYY/YYYY FVAR < [ASMF holder, active substance> Type IB (grouped)"

and in case of a Notification with Grounds:
"EU/ASMF/YYYY/YYYY PVAR < [ASMF holder, active substance> Type IB (grouped)"

Daughter procedures should circulate the assessment report without making any changes.

The assessment should be concluded as described in section 3.3.2.6.

For ASMF updates only containing Type II variations:

In addition to producing the PVAR and FVAR, the parent RMS/Rapporteur should also produce a separate ASMF-AR, which should be uploaded onto the repository by Day 40 of the associated procedure and circulated to the Parent CMS for comments (see section 3.3.2.3.2. and 3.2.1.1.). The ASMF-AR will be an add-on report only describing the variation or a consolidated AR (see section 3.5.1.5. when a consolidated AR needs to be written).

For easy identification and clarity, the assessment report filename should be in the following format:
"EU/ASMF/YYYY/YYYY <PVAR or FVAR> < [ASMF holder, active substance> Type II (grouped)"

Daughter procedures should circulate the assessment report without making any changes, unless there are critical quality issues (see section 3.3.2.3.3.).

The assessment should be concluded as described in section 3.3.2.6.

Where an ASMF update contains a single or grouped Type IA, IB and II changes, the description of the changes submitted should be added by the Parent RMS/Rapporteur to the table of changes in the ASMF Summary, and the summary data should be updated accordingly.
3.5.1.3.4. The worksharing ASMF update ONLY contains Variation not requiring assessment (VNRA) (for veterinary medicinal products)

The Commission implementing Regulation (EU) 2021/17 contains several changes to the active substance as VNRA. Apart from the change in the name of the active substance, these changes will require immediate updating of the ASMF.

The Parent RMS/Rapporteur should record the procedure on the ASMF-AR repository and change the status of the repository record to 'ACCEPTED FOR USE IN A MARKETING AUTHORISATION' by Day 30 of the associated variation procedure (see section 3.3.2.6. and 3.2.1.1).

3.5.1.3.5. The worksharing ASMF update contains variations requiring assessment (for veterinary medicinal products)

These types of changes require prior approval from the Competent Authority before they can be implemented by the ASMF holder.

CMDv has published guidance on submitting updates to an ASMF, the scope of which covers variations submitted using National and Mutual Recognition procedures:

**Question 3.3**

*How should an update to the active substance part of the dossier and/or related ASMF be submitted?*

**Answer**:

An update or change of an ASMF can only be addressed in connection with a marketing authorisation.

An updated version of the ASMF or of the active substance part of the dossier can be submitted as a grouped application which will be processed according to the longest timetable of the included variations. However, where the update implies substantial change(s), submission of a single variation under variation code F.I.f.1 is recommended. The electronic application form, including section "present/proposed", should be filled out completely and correctly. In all cases of updates of the ASMF these must be submitted by the ASMF holder (open and closed part to NCA, open part to MAH), the variation as such has to be submitted by the marketing authorisation holder.

Unfortunately, the phrase “substantial changes” has not been suitably defined and can lead to an ASMF update being classified differently by the Applicants/MAHs and/or Competent Authorities, leading to different procedure timetables for the same update that can be problematic for the worksharing procedure, e.g. MAH 1 submits the ASMF update as grouped variations requiring assessment following a reduced timetable whereas MAH 2 submits the same ASMF update as a single variation requiring assessment following a standard timetable.

The ASMF holder should provide a completed Table of Changes (Annex 3 of ASMF Guideline), describing the changes made between the current and proposed versions of the ASMF; this can be used by the Applicant/MAH to determine the classification of each change.

In addition to producing the PVAR and FVAR, the parent RMS/Rapporteur should also produce a separate ASMF-AR, which should be uploaded onto the repository by Day 40/30 of the associated procedure and circulated to the Parent CMS for comments (see section 3.3.2.3.2. and 3.2.1.1.). The ASMF-AR will be an add-on report only describing the variation or a consolidated AR (see section 3.5.1.5. when a consolidated AR needs to be written).

For easy identification and clarity, the assessment report filename should be in the following format: “EU/ASMF/YYYYYY <PVAR or FVAR> <[ASMF holder, active substance]> VRA”

Daughter procedures should circulate the assessment report without making any changes, unless there are critical quality issues (see section 3.3.2.3.3.).
The assessment should be concluded as described in section 3.3.2.6.

Where an ASMF update contains single or grouped changes, the description of the changes submitted should be added by the Parent RMS/Rapporteur to the table of changes in the ASMF Summary, and the summary data should be updated accordingly.

3.5.1.4. Updates to an existing worksharing ASMF submitted in parallel in a NEW Marketing Authorisation Applications and VARIATION applications to an EXISTING marketing authorisation

The situation where an update to a worksharing ASMF may be submitted in association with new Marketing Authorisation applications and variations to existing Marketing Authorisations is acknowledged as being complex due to the potential interaction of different regulatory procedures with markedly different timetables.

Because of this, it is difficult to lay down a definitive procedure at this time until further experience is gained in the initial phase. However, the principles and procedures laid out above should be followed, and adjusted for the different procedure timetable on a case-by-case basis. All efforts should be made to keep with the MAA and MAV procedural timetables.

The ASMF-AR repository should be used to determine the parent procedure, and Competent Authorities should use the repository to make themselves aware of the interacting procedures.

Although it has been previously stated, it should be remembered that the update concerns a worksharing ASMF which has undergone such a review, and the likelihood of the update including a major quality critical issue anticipated to be low. Therefore, any other procedures subsequently using the ASMF update may be able to rely solely on the assessment report of the parent RMS/Rapporteur.

3.5.1.5. Consolidation ASMF Assessment Report

When should the ASMF AR be consolidated?

A consolidated ASMF AR may be written upon discretion of the Rapporteur, but in a number of cases it will be mandatory to write a consolidated assessment report. It is mandatory to write a consolidated ASMF assessment report in case of major Type II Variations (or major VRA for veterinary products) or when these major changes are included in a new MAA-procedure:

- change of route of synthesis,
- change in specification,
- design space/post approval change management protocol.

What does it mean to consolidate an ASMF Assessment Report?

To consolidate the ASMF Assessment Report means to incorporate all variations (IA, IB and II; VRA and VNRA for veterinary medicinal products) since the last consolidation of the ASMF Assessment Report. The consolidated ASMF Assessment Report replaces the initial or previous full ASMF Assessment Report and all subsequent add-on ASMF Assessment Reports since then. The ASMF Summary (table of changes as well as the key information) will be kept and it will be clearly indicated that a consolidated assessment report has been written.
Appendix 1

The EU Numbering System for ASMFs

A basic requirement to establish an ASMF worksharing procedure is the ability to conclusively identify when the same ASMF is submitted in different Member States. Previously no defined European-wide numbering system for ASMFs was identified. Many national authorities assign national ASMF numbers to ASMFs on receipt, but the format used for such numbering is not harmonised and the numbering is performed on a purely national basis. Many ASMF holders often assign numbers to their ASMFs but again the numbering system is not uniform and is at the discretion of individual ASMF holders.

In addition ASMFs are regularly updated and there is no consistent approach to assigning version numbers to different versions of ASMFs. In some cases separate sequential version numbers are applied to the restricted and open part of the ASMFs whereas in others the version is denoted by reference to the version date.

The lack of consistency in relation to ASMF numbering and version control made it impossible for a Competent Authority to be certain that the same version of the same ASMF has been previously submitted to and assessed by another Competent Authority, which leads to potentially unnecessary reassessment of the same ASMF. Therefore a European system for the numbering of ASMFs was created, which would include version control to facilitate the sharing of ASMF assessment reports between Competent Authorities.

A. Format of the EU ASMF Reference Number

The Working Group on Active Substance Master File (ASMF) procedures has agreed that the following format will be used for the numbering of ASMFs:

EU/ASMF/XXXXX/YYYY

XXXXX is the reference number of the ASMF - assigned as a sequential number by the ASMF-AR repository in order of request and independent of the ASMF holder

YYYY is the sequential assessment report number (for type IB and type II procedures; VRA for veterinary medicinal products) or sequential change number (for type IA procedures; VNRA for veterinary medicinal products). The same number will apply to any ASMF updates submitted in response to a deficiency question; the number will only change when the assessment/procedure has been completed and the version of the ASMF has been accepted for use. This number will be assigned sequentially by the ASMF holder to new regulatory updates of the ASMF. The 0001 corresponds to the initial assessment of the ASMF. Editorial changes are not considered formal updates to the ASMF, only those changes leading to a regulatory update would up version the YYYY number (either Type IA, IB or II; VNRA or VRA for veterinary medicinal products).

A single assessment report number will apply to the entire ASMF regardless of whether the update has been made to the open and/or the restricted part of the ASMF (see section 3.5.1. ).

B. Assignment of new ASMF Reference Number (XXXXX)

ASMF holders are requested to note that each of the following non exhaustive list of examples is considered to represent a new ASMF for the purposes of the EU ASMF numbering system:

a) Different active substance
b) Different set of specification (except when finished product specific):
   • Different salt of an active substance
• Different complex of an active substance
• Different solvate or hydrate form of an active substance
• Different isomer or mixture of isomers of an active substance
• Opposite enantiomer of an active substance
• Racemate of an optically pure active substance

c) Introduction of a new substantially different route of synthesis
d) The active substance is used for both human and veterinary medicinal products and is controlled to different quality standards

Where an ASMF undergoes a change of ownership, the same EU/ASMF reference number will be retained.

The following examples will not necessarily be considered to represent a new ASMF and in most cases could be incorporated in a single combined ASMF with the same ASMF reference number:

a) Slightly different routes of synthesis which do not result in changes to important quality characteristics of the active substance, such as the qualitative and/or quantitative impurity profile requiring qualification or physico-chemical properties impacting on bioavailability

b) Different manufacturing sites using the same or similar routes of synthesis

c) Other changes which do not result in changes to important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification or physico-chemical properties impacting on bioavailability

d) Transfer of ownership of an existing ASMF from one ASMF holder to another

e) Change in the name and/or address of the existing ASMF holder

Please note that the above should not be considered to be exhaustive lists and if in any doubt an ASMF holder should contact an appropriate Competent Authority for guidance prior to submission of the ASMF.

The Competent Authority will use the information in the EU/ASMF reference request form to create a record for the ASMF in the ASMF assessment report repository

C. Assignment of a new assessment number (YYYY)

A single assessment number YYYY will be sequentially defined by the ASMF holder for each update of the ASMF, regardless of whether the update has been made to the Applicant's Part, the Restricted Part or both Applicant’s and Restricted Parts of the ASMF. Editorial changes are not considered formal updates to the ASMF, only those changes leading to a regulatory update would up version the YYYY number.

e.g.

EU/ASMF/XXXXX/0001 - initial ASMF (AP & RP)

Applicant’s Part version: OZP/AP/01/2012-01-28

Restricted Part version: OZP/RP/01/2012-01-28

EU/ASMF/XXXXX/0002 – updated AP

Applicant’s Part version: OZP/AP/02/2012-04-10

Restricted Part version: (OZP/RP/01/2012-01-28)

EU/ASMF/ XXXXX /0003 – updated RP

Applicant’s Part version: (OZP/AP/02/2012-04-10)

Restricted Part version: OZP/RP/02/2012-10-16

EU/ASMF/ XXXXX /0004 – updated AP & RP
Applicant’s Part version: OZP/AP/03/2013-01-14

Restricted Part version: OZP/RP/03/2013-01-14

N.B. Applicant’s or Restricted Parts of the ASMF that are not being updated (i.e. the versions in parentheses in the above example) do not need to be re-submitted by the ASMF holder.

On receipt of an application to update an ASMF that already has an EU ASMF number, the lead competent authority for the regulatory procedure (EMA in the case of the Centralised procedure, RMS in the case of Decentralised and Mutual Recognition procedures or National Competent Authority in the case of national procedures) will update the ASMF-AR repository to indicate that an updated version of the ASMF is under review. The ASMF-AR repository will confirm the assessment report number which will then be listed in all assessment reports prepared by the parent RMS/Rapporteur. In addition, the ASMF holder should inform Competent Authorities of any ongoing applications involving the ASMF in the Submission Details Form.

ASMF holders should submit a consolidated version of the ASMF incorporating all changes proposed in the initial application that were approved by the lead competent authority, and any other changes that were agreed with the lead competent authority (Parent RMS/Rapporteur) during the regulatory procedure by the end of the procedure. This can be more easily achieved if the ASMF holder uses the eCTD or NeeS formats (or the equivalent veterinary formats) to submit their ASMF data, submitting the updated sections with the response to deficiency questions, and thus consolidating the ASMF during the procedure. If other submission formats are used in accordance with national requirements, then the ASMF holders are strongly encouraged to submit the updated sections of the ASMF with the responses.
Appendix 2

ASMF Assessment Report Naming Convention in MAA and MAV:

- “EU_ASMF_XXXXX_0001 <ASMF holder, active substance> First/Second/Third stage AR”
- “EU_ASMF_XXXXX_0001 <ASMF holder, active substance> First Stage LoQ”
- “EU_ASMF_XXXXX_0001 <ASMF holder, active substance> Second/Third/Forth Stage <LoQ or LoOI>”
- “EU_ASMF_XXXXX_0001 <ASMF holder, active substance> FAR”
- “EU_ASMF/XXXXX/YYYY <PVAR or FVAR> < [ASMF holder, active substance> Type IB (grouped)”
- “EU_ASMF/XXXXX/YYYY <PVAR or FVAR> < [ASMF holder, active substance> Type II (grouped)”
- “EU_ASMF/XXXXX/YYYY <PVAR or FxVAR> < [ASMF holder, active substance> VRA”
### Appendix 3

<table>
<thead>
<tr>
<th>ASMF related variation changes - Type IAn</th>
<th>Provision of updated CTD sections</th>
</tr>
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<tbody>
<tr>
<td><strong>A.3 Change in name of the active substance</strong></td>
<td>No</td>
</tr>
<tr>
<td>B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier</td>
<td>Yes</td>
</tr>
<tr>
<td>a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer.</td>
<td></td>
</tr>
<tr>
<td>B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance</td>
<td>Yes</td>
</tr>
<tr>
<td>a) Tightening of specification limits for medicinal products subject to Official Batch Release</td>
<td></td>
</tr>
<tr>
<td><strong>B.I.e.3 Deletion of an approved change management protocol related to the active substance</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>B.I.e.5 Implementation of changes foreseen in an approved change management protocol</strong></td>
<td>Yes</td>
</tr>
<tr>
<td>a) The implementation of the change requires no further supportive data</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ASMF related variation changes - Type IA</th>
<th>CTD sections affected by change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A.4 Change in the name and/or address of a manufacturer (including where relevant quality control sites) or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the product dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>A.7 Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)).</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>A.8 Changes to date of the audit to verify GMP compliance of the manufacturer of the active substance</strong></td>
<td>No</td>
</tr>
<tr>
<td><em>Note: This variation does not apply when the information has been otherwise transmitted to the authorities (e.g. through the so-called &quot;QP declaration&quot;).</em></td>
<td></td>
</tr>
<tr>
<td>B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier</td>
<td>Yes</td>
</tr>
<tr>
<td>f) Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place</td>
<td></td>
</tr>
<tr>
<td>i) Introduction of a new site of micronisation</td>
<td></td>
</tr>
<tr>
<td>B.I.a.2 Changes in the manufacturing process of the active substance</td>
<td>Yes</td>
</tr>
<tr>
<td>a) Minor change in the manufacturing process of the active substance</td>
<td></td>
</tr>
<tr>
<td>B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate</td>
<td>Yes</td>
</tr>
<tr>
<td>a) Up to 10-fold increase compared to the currently approved batch size</td>
<td></td>
</tr>
<tr>
<td>b) Downscaling</td>
<td></td>
</tr>
<tr>
<td>B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance</td>
<td>Yes</td>
</tr>
<tr>
<td>a) Tightening of in-process limits</td>
<td></td>
</tr>
<tr>
<td>b) Addition of a new in-process test and limits</td>
<td></td>
</tr>
<tr>
<td>c) Deletion of a non-significant in-process test</td>
<td></td>
</tr>
<tr>
<td>B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material /</td>
<td>Yes</td>
</tr>
<tr>
<td>B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td></td>
</tr>
<tr>
<td>a) Minor changes to an approved test procedure</td>
<td></td>
</tr>
<tr>
<td>b) Deletion of a test procedure for the active substance or a starting material/reagent/intermediate, if an alternative test procedure is already authorised.</td>
<td></td>
</tr>
<tr>
<td>c) Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B.I.c.1 Change in immediate packaging of the active Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Qualitative and/or quantitative composition</td>
</tr>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Tightening of specification limits</td>
</tr>
<tr>
<td>b) Addition of a new specification parameter to the specification with its corresponding test method</td>
</tr>
<tr>
<td>c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B.I.c.3 Change in test procedure for the immediate packaging of the active substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Minor changes to an approved test procedure</td>
</tr>
<tr>
<td>b) Other changes to a test procedure (including replacement or addition)</td>
</tr>
<tr>
<td>c) Deletion of a test procedure if an alternative test procedure is already authorised</td>
</tr>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B.I.d.1 Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Re-test period/storage period 1. Reduction</td>
</tr>
<tr>
<td>b) Storage conditions 1. Change to more restrictive storage conditions of the active substance</td>
</tr>
<tr>
<td>c) Change to an approved stability protocol</td>
</tr>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>