Active Substance Master File (ASMF) worksharing procedure

Updates to a worksharing ASMF: Submitting a variation

Dr Elspeth Gray
Joint Working Group on ASMF Procedure & Pharmaceutical Assessor, Medicines and Healthcare Products Regulatory Agency (MHRA), UK
October 2017
Changes to a worksharing ASMF

• As for all ASMF, updates to a worksharing ASMF may only be agreed in the context of a marketing authorisation for a medicinal product.

• This may occur as:
  
  – An ASMF update submitted during the assessment of an MAA. (This may arise when major changes are required to the ASMF as a result of initial assessment e.g. redefinition of starting materials)

  – An ASMF update submitted as a post-authorisation variation to an approved MA.
Do the variation regulations differ?

• **No** - in common with **all** changes concerning an ASMF:
  
  – the Classification Guideline should be consulted to determine whether the proposed change(s) should be submitted as a single or grouped, type 1A, type 1B or type II variation. The CMDh has also published guidance to submitting updates to ASMF.

  – Where the update involves multiple changes, these may be grouped, and the procedure categorised according to the highest individual change

  – It’s important to declare the ASMF / Version number in the variation application form (under “present vs. proposed”) and to reference this in all correspondence. …For a worksharing ASMF, this will comprise the EU/ASMF/XXXXX/YYYY assessment number.
Are there any additional considerations?

• Assessment of updates to a worksharing ASMF can be more complex owing to different regulatory routes (MAA/MAV, Decentralised/Centralised), different submission timings and potential divergence in the variation classification by the MAH/Applicant).

• Some MAH may choose not to submit variation(s) for all changes in certain circumstances e.g. nature of change not critical to the quality of the pharmaceutical form such as a change to polymorphic form of drug substance to an oral solution.

• However - the parent RMS/Rapporteur will assess all changes submitted by the ASMF holder, regardless of whether the MAH has presented variations for all the changes.
What will the ASMF Holder do?

• The ASMF Holder will:
  – Define a new sequential assessment number (EU/ASMF/XXXXX/YYYY) for each worksharing ASMF update (regardless of whether the change impacts the Applicant’s Part, Restricted Part or both).

    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

  – Submit a consolidated version of the updated ASMF, including all changes approved by the RMS/Rapporteur during the initial procedure. As with all ASMF updates, a Table of Changes (Annex 3 of ASMF Guideline), should highlight the proposed amendments in the updated version.

  – Ideally, use eCTD, NeeS (or equivalent veterinary formats) for submission!
What will the Parent RMS / Rapporteur do?

• The Parent RMS/Rapporteur will:

  – add the description of changes to the table of changes in the ASMF Summary, and update the summary data.

  – Update the ASMF-AR repository to indicate that an updated version of the ASMF is under review. At the end of the relevant procedure (assuming the changes are accepted); the status of the repository record will be further updated to “Accepted for use in a Marketing Authorisation”.

  – Confirm the sequential assessment number (EU/ASMF/XXXXX/YYYY) for the associated procedure at the time of circulation of the ASMF-AR (type IB & type II procedures).

  – Upload an ASMF-AR at procedure end where necessary – the choice of template will depend upon the type of variation (see later slides).
Keeping order: Determining the parent procedure

- Particularly where a worksharing ASMF is registered to many MA / MAA, determining the parent procedure may not be straightforward. However, the same principles that guide assessment of an initial ASMF are employed:

- The parent procedure should be the procedure that is first required to prepare an assessment report on the ASMF update e.g.

  UK/H/9098/01/II/001 - Day 40 is 07/02/2017 (parent procedure)
  AT/H/9999/01/DC – Day 70 is 28/03/2017 (daughter procedure)

  - In the case of national MAA or variations, the NCA should specify a date on which the ASMF-AR will be prepared. Depending upon the principles above, this may then becomes the “parent” procedure and the NCA takes on the responsibilities of “RMS” for updates to ASMF Summary reports and repository information.
Specific guidance: Types of variations: Type 1A IN (Immediate Notification) only

- The Classification Guideline classifies five changes to the active substance as Type IA immediate notifications.

- With the exception of a change in the name of the active substance, these changes will require immediate updates to be made to the ASMF.
Specific guidance: Types of variations: Type 1A “Do & Tell” Notifications only

- Type IA variations do not require prior approval, however 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 the 12 month timepoint to allow the MAH to submit the variation(s).

- Ideally, type IA changes should be grouped with other type IB or type II changes. This will help to ensure timely submission and aid consistent variation classification.

- Due to time constraints, this may not always be possible, therefore the ASMF holder should:
  - provide a list of all the Type IA variations implemented within a defined period, along with any updated CTD sections to Applicant/MAH so they can submit the appropriate variations.
  - submit the updated ASMF to the Competent Authorities.
Specific guidance: Types of variations: Type 1B &/or type II variations

• Type 1B and II changes are classed as “substantial” and require prior approval from the Competent Authority before they can be implemented by the ASMF holder.

• On rare occasions, the class of variation may be interpreted differently by MAH or NCA, leading to differences in procedure timetables for the same update. Careful attention to the Table of Changes should minimise this.

• For ASMF updates solely containing Type IB variations:
  – The Parent RMS/Rapporteur is responsible for assessing and determining the ASMF update, without consultation with CMS.
  – The ASMF Type IB Variation Assessment report template should be used: http://www.hma.eu/334.html
    For a Centralised Procedure, the relevant template will be provided at procedure start.
  – The ASMF AR should be uploaded onto the ASMF-AR repository by Day 30 of the associated procedure and circulated to Parent CMS, the MAH and the ASMF Holder. If a Notification with Grounds is sent on day 30, the ASMF-AR should be uploaded following the second round of assessment.
Specific guidance: Types of variations: Type II variations only

- The parent RMS/Rapporteur will provide an ASMF-AR for upload to the repository by Day 40 of the associated procedure, together with the PVAR / FVAR. This is then circulated to the Parent CMS for comments.

- The assessment report filename should adopt the following format: “EU/ASMF/XXXXX/YYYY <PVAR or FVAR> <[ASMF holder, active substance]> Type II (grouped)”

- The choice of template will depend upon the extent and complexity of the change(s) – either a type 1B or initial AR template may be used.

- Daughter procedures should circulate the ASMF-AR without making changes, unless there are critical quality issues.
End of Presentation