APIC POSITION PAPER

ACTIVE SUBSTANCE MASTER FILE CERTIFICATE

PROPOSAL FOR A DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL ON THE UNION CODE RELATING TO MEDICINAL PRODUCTS FOR HUMAN USE, AND REPEALING DIRECTIVE 2001/83/EC AND DIRECTIVE 2009/35/EC

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General comments

- APIC strongly agrees with the principle of the active substance master file (ASMF) certificate. The lifecycle of a European ASMF is often complicated, especially when supporting multiple marketing authorisations, therefore single assessment is seen as the only workable solution for both industry and the National Competent Authorities to avoid duplication of assessment and reduce workload.

- The scope of the proposed AMSF certificate procedure should be clarified. Clause 93 refers to reliance "on an active substance master file certificate or a monograph of the European Pharmacopeia, instead of submitting the relevant data as required in accordance with Annex II" whereas Article 25 refers to reliance "on an active substance master file, an active substance master file certificate … or a certificate confirming that the quality of the active substance concerned is suitably controlled by the relevant monograph of the European Pharmacopeia." These sections are not aligned in their meaning.

- It should be confirmed that the ASMF certificate procedure will only be applicable to active substances with no European Pharmacopoeia (Ph Eur) monograph. For active substances with a Ph Eur monograph, the Certification of Suitability to the monographs of the European Pharmacopoeia (CEP) procedure, run by the EDQM, remains an option. In both cases, it is important that an ASMF may also be used, as it is currently, to avoid any delays in submission of MAAs while applications for certificates (both ASMF certificates and CEPs) are being assessed.

- It is not clear if the application for an ASMF certificate will be a stand-alone procedure (like a CEP application) or if it must be linked to a MAA/MAV.

- It is stated that the ASMFcertificate will be granted by the European Medicines Agency. It should be stated that CEPs are granted by the EDQM.

- The CEP procedure is a proven certification system for assessing active substances. The ASMF certification procedure should be fully aligned with this procedure.

- This leads to the question – what is the rationale for choosing EMA to be the agency responsible for the ASMF certification procedure? EDQM would seem the logical choice given their knowledge and experience in the assessment of active substances.

- CEPs are recognised by an increasing number of authorities outside the EU. Extension of this procedure to cover non-pharmacopoeial substances would be beneficial to European companies selling in global markets.

- APIC is strongly opposed to the MA holder receiving access to the full ASMF assessment report. The ASMF procedure was developed to protect the active substance manufacturer's valuable intellectual property. This objective must be upheld in any new procedure.

Comments on the proposed text

(93)	**To optimise the use of resources for both applicants for marketing authorisation and competent authorities and avoid duplication of assessment of chemical active substances of medicinal products, marketing authorisation applicants should be able to rely on an active substance master file certificate or a monograph of the European Pharmacopeia, instead of submitting the relevant data as required in accordance with Annex II. An active substance master file certificate may be granted by the Agency when the relevant data on the active substance concerned is not already covered by a monograph of the European Pharmacopeia or by another active substance master file certificate. The Commission should be empowered to establish the procedure for the single assessment of an active substance master file. To further optimise the use of resources, the Commission should be empowered to allow use a certification scheme also for additional quality master files i.e. for active substances other than chemical active substances, or for other substances present or used in the manufacture of a medicinal product, required in accordance with Annex II, e.g. in case of novel excipients, adjuvants, radiopharmaceutical precursors and active substance intermediates, when the intermediate is a chemical active substance by itself or used in conjugation with a biological substance.**

- Regarding the wording of clause 93, are the words in blue missing (to align with Article 25, point 1)?

  … should be able to rely on an active substance master file certificate or a Certificate of Suitability to the monograph of the European Pharmacopeia, instead of submitting the relevant data as required in accordance with Annex II.

- Confirmation is needed that the following sentence is correct:

  An active substance master file certificate may be granted by the Agency when the relevant data on the active substance concerned is not already covered by a monograph of the European Pharmacopeia or by another active substance master file certificate.

  i.e. The ASMF certification procedure is not open to substances with a monograph in the European Pharmacopoeia. In this case, the manufacturer must use an ASMF or apply for a CEP?

(149) **In order to supplement or amend certain non-essential elements of this Directive, the power to adopt acts in accordance with Article 290 TFEU should be delegated to the Commission in respect of specifying the procedure for examination of application of active substance master file certificate, the publication of such certificates, the procedure for changes to the active substance master file and its certificate, access to the active substance master file and its assessment report …**

When developing the above procedures, the following points should be considered:

- The ASMF certification procedure should be fully aligned with the CEP procedure.
  The CEP procedure is a well-established system for the assessment of the active substance.
  The implementation of CEP 2.0 follows in-depth consultations with stakeholders, including the National Competent Authorities, to ensure it meets their needs. EDQM's knowledge and experience in active substance assessments should be utilised.
  There should be no discrepancies between the two certification procedures:
  - Assessments and timelines should be aligned.
  - The same level of information should be conveyed on the certificate.
  - Changes to the dossier should be managed in the same way:
    - The ASMF certificate holder should be responsible for submitting revisions.
    - The situations in which a revised ASMF certificate is issued should be the same as those in which a revised CEP (2.0) is issued.
    - The MA holder should only have to submit a variation to the MA when a revised ASMF certificate is issued, the same as when a revised CEP is issued.
  - The Letter of Access / Withdrawal system should be the same for both procedures.
  - The issuing authority should be able to suspend or withdraw an ASMF certificate, as with CEPs.
- Any new guidance on the use of ASMFs / ASMF certificates must retain the concept of Restricted Part information, i.e., as in the current AMSF procedure, it should state that the active substance manufacturer is allowed to protect their valuable know-how and is not required to share confidential details regarding the manufacturing process and in-process controls with the MA applicant / holder. The roles and responsibilities of all parties should be clearly defined, including the level of information that the ASMF certificate holder / CEP holder should share with the MA applicant / holder. This should be the equivalent of the Applicant's Part of an ASMF. While it is acknowledged that the MA holder requires sufficient information to take responsibility for the medicinal product, it is the role of the regulators to assess the confidential manufacturing details and ascertain if the proposed specifications are adequate. The MA applicant / holder should not require access to the Restricted Part information or the full ASMF assessment report. Inspections and audits by the relevant authorities and the MA applicant / holder should be the means for confirming compliance.

Article 25

Active substance master file certificate

1. **Marketing authorisation applicants may, instead of submitting the relevant data on a chemical active substance of a medicinal product required in accordance with Annex II, rely on an active substance master file, an active substance master file certificate granted by the Agency in accordance with this Article ('active substance master file certificate') or a certificate confirming that the quality of the active substance concerned is suitably controlled by the relevant monograph of the European Pharmacopeia.**
   Marketing authorisation applicants may only rely on an active substance master file if no certificate exists on the same active substance master file.

2. **An active substance master file certificate may be granted by the Agency in cases where the relevant data on the active substance concerned is not already covered by a monograph of the European Pharmacopeia or by an active substance master file certificate.**
   In order to obtain an active substance master file certificate, an application shall be submitted to the Agency. The applicant for an active substance master file certificate shall demonstrate that the active substance concerned is not already covered by a monograph of the European Pharmacopeia or an active substance master file certificate. The Agency shall examine the application and, in case of a positive outcome, shall grant the certificate that shall be valid throughout the Union. In case of centralised marketing authorisations, the application for an active substance master file certificate may be submitted as part of the marketing authorisation application for the corresponding medicinal product.
   The Agency shall establish a repository of active substance master files, their assessments reports and their certificates and ensure that personal data is protected. The Agency shall ensure that the competent authorities of the Member State have access to this repository.

Point 1 of Article 25 indicates that, instead of submitting the relevant data in the MAA, applicants may rely on one of three options: (1) an ASMF; (2) an ASMF certificate, granted by the Agency; or (3) a CEP.
It should be stated that the CEP is granted by the EDQM.

Point 2 excludes substances with a Ph Eur monograph from the scope of the ASMF certification procedure. From this, it is concluded that, for substances not covered by a Ph Eur monograph, an ASMF may still be used, or an application for an ASMF certificate may be submitted. For substances covered by a Ph Eur monograph, the current situation will be unchanged – an ASMF may be used, or an application for a CEP may be submitted. This should be clearly stated in both clause 93 and Article 25.

It is not clear whether or not applications for ASMF certificates must be linked to a specific MA/MAA/MAV. For active substances that are not already a constituent of an approved medicinal product, the point at which an application for an ASMF certificate can be submitted must be defined. Must the ASMF certificate application be assessed and approved before the MAA is submitted, as in the CEP procedure, or will it be possible for the assessments to be done in parallel? It is stated that, in the case of the centralised procedure, the application for an ASMF certificate may be submitted as part of the MAA for the corresponding medicinal product. However, for other application types, assessment of the MAA and ASMF certificate application in parallel may not be feasible as more than one generic MAA using the same active substance may be submitted at the same time.

Holders of existing ASMFs for substances without a Ph Eur monograph that already support at least one approved MA should have the option to submit an application for an ASMF certificate at any time, in the same way they have the option to submit a CEP application at any time for substances with a Ph Eur monograph.

The situation whereby an ASMF certificate is granted for an active substance with no Ph Eur monograph, and a new Ph Eur monograph is subsequently implemented, should be considered, e.g., the possibility of a fast track procedure for transition to a CEP.

Regarding the ASMF assessment reports held in the repository, these should be available to EMA/EDQM/the National Competent Authorities only. The MA holder should not have access to the full ASMF assessment report.

Article 25

4. The active substance master file certificate holder shall be the manufacturer of the active substance.

APIC does not agree that the ASMF certificate holder should necessarily be the manufacturer of the active substance. Contract manufacture, multiple manufacturing sites, head office as holder, should be considered. This should be aligned with the CEP procedure.

Article 25

9. The Commission is empowered to adopt delegated acts in accordance with Article 215 to supplement this Directive by specifying, the following:

(a) the rules governing the content and format of the application for an active substance master file certificate;

(b) the rules for the examination of an application for an active substance master file certificate and for the granting of the certificate;

(c) the rules for making publicly available of active substance master file certificates;

(d) the rules for introducing changes to the active substance master file and the active substance master file certificate;

(e) the rules on access for competent authorities of the Member States to the active substance master file and its assessment report;

(f) the rules on access for marketing authorisation applicants and marketing authorisation holders relying on an active substance master file certificate to the active substance master file and to the assessment report.

Regarding point 9 (c), the level of information on ASMF certificates made available via a public database should be aligned with EDQM's certification database. Certificates should only be visible once they have been granted, as with CEPs. No confidential or commercially sensitive information should be accessible via this database.

Regarding point 9 (f), the full ASMF assessment report should not be available to MA applicants / holders. They do not require access to confidential information that is normally in the Restricted Part of an ASMF. As stated in the current guideline on the ASMF procedure, the main objective of an ASMF is to allow valuable confidential intellectual property of the active substance manufacturer to be protected, while at the same time allowing the MA applicant / holder to take full responsibility for the medicinal product. EMA / EDQM / the National Competent Authorities will 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. It is unnecessary for the MA applicant / holder to have the same access.

Conclusion

APIC welcomes the introduction of an ASMF certification procedure for non-pharmacopoeial substances. This should be fully aligned with the CEP procedure and preferably overseen by EDQM.
APIC supports the sharing of necessary information with the MA holder but strongly opposes the sharing of Restricted Part information and the full ASMF assessment report.

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