APIC POSITION PAPER

EUROPEAN ACTIVE SUBSTANCE MASTER FILE (ASMF) SINGLE ASSESSMENT

Problem Statement

Active substance manufacturers often supply their active substances to multiple marketing authorisation (MA) holders for use in different medicinal products. As a result, the same ASMF may be submitted to multiple Member States as part of new MA or variation applications through any of the authorisation routes in Europe (Centralised, Decentralised, Mutual Recognition and national procedures).

It is acknowledged by both industry and the National Competent Authorities (NCA) that the lifecycle of a European ASMF may be complicated and can lead to duplicated assessment, divergent decisions, frequent ASMF updates (at the NCA request), reduced oversight of the ASMF and increased workload for all parties.

In a bid to address this issue, the European ASMF Worksharing Procedure was established. This was a welcome and important step forward in addressing the problems highlighted above. However, this is a voluntary procedure, applicable only to new ASMFs and certain authorisation routes. The procedure remains complex and, while APIC appreciates the considerable effort made by the CMDh to improve the situation, it is not a solution for the generic market.

Proposed Solution

Single, self-standing assessment of ASMFs in a "CEP-like" procedure, i.e., submission of the ASMF by the API manufacturer directly to one central European authority for a single, centralised assessment of the ASMF and its subsequent changes, similar to the CEP system.

The Certification procedure, established by EDQM over 25 years ago, allows the active substance manufacturer to submit a detailed dossier for self-standing evaluation, in which the manufacturer demonstrates that the quality of the active substance is suitably controlled by the relevant monographs of the European Pharmacopoeia. Additional supplementary tests may be submitted where necessary. Following assessment by EDQM, a successful application results in the granting of a Certificate of Suitability to the European Pharmacopoeia (CEP). A copy of this certificate is then provided to the MA applicant/holder by the CEP holder for inclusion in their MA/variation application. It is also the CEP holder's responsibility to provide additional information to the MA applicant/holder to allow them to perform a satisfactory quality evaluation of the active substance.

APIC
Rue Belliard 40 b.15 B-1040 Brussels Belgium
Tel. +32.475.27.05.71 pvd@cefic.be - www.apic.cefic.org
A sector group of Cefic
European Chemical Industry Council - Cefic aisbl
EU Transparency Register n° 64879142323-90

Subsequent changes to the CEP dossier are submitted to EDQM by the CEP holder. Depending on the nature of the change, this may or may not result in a revised CEP being issued by EDQM. The revised CEP is submitted to the NCA(s) by the MA holder in a variation (Type IA) to the MA.
EDQM is currently undertaking a major project to design the "CEP of the Future". The aim is to develop a new-look CEP that will better fit the current needs of all stakeholders, including the regulators. It will be more user-friendly and provide greater transparency of the information conveyed. EDQM also aims to reduce revisions and facilitate the handling of changes.

APIC strongly supports the introduction of a new, centralised procedure for the assessment of European ASMFs that closely mirrors the CEP procedure. It is envisaged that the ASMF will be submitted to a single authority for assessment, in the same way as the CEP dossier is currently. The assessment will determine if the quality of the active substance is suitably controlled by the specification proposed by the active substance manufacturer. A successful application will result in the granting of an "ASMF-Certificate", which will be used in the MA/variation application in the same way as a CEP. As in the CEP procedure, any attributes of the active substance essential to a specific medicinal product that are not covered by this assessment, e.g. particle size, sterility, bacterial endotoxins, will be included in the MA application. Subsequent changes to the ASMF will be submitted by the ASMF-Certificate holder in the same way as changes to the CEP dossier are submitted. The circumstances in which a revised ASMF-Certificate is issued will be the same as those in which a revised CEP (of the Future) is issued. The procedure for the issue of Letters of Access / Withdrawal by the ASMF-Certificate holder should be aligned with that proposed for the CEP of the Future. Similarly, it should be possible for the issuing authority to suspend or withdraw an ASMF-Certificate, as is the case with CEPs.

As in the CEP procedure, the proposed single assessment procedure for ASMFs will allow the active substance manufacturer to take more control over the lifecycle of the active substance by themselves submitting changes to the dossier, as opposed to the MA holder having to submit a variation, as in the current ASMF procedure. This does not mean that the MA holder should not be sufficiently informed of the change, but it will reduce the regulatory burden on the MA holder and prevent changes (often improvements) to the active substance dossier being blocked by the MA holder. The proposed procedure also means that the same change is submitted for assessment only once by the ASMF-Certificate holder and not multiple times by each MA holder. Only when a revised ASMF-Certificate is issued would a variation (Type IA) need to be submitted by the MA holder, as in the CEP procedure.

APIC believes that a centralised assessment procedure will not only benefit industry (both active substance manufacturers and MA holders), it will also benefit the NCAs, by significantly reducing workload and increasing oversight of the ASMF; and patients, by optimising submission procedures to enable quick access to high quality medicines.

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Responsibilities

The current guideline on the European ASMF procedure states that the main objective of the ASMF procedure is to allow valuable confidential intellectual property or "know-how" of the manufacturer of the active substance to be protected, while at the same time allowing the applicant or MA holder to take full responsibility for the medicinal product, including the quality of the active substance.

APIC acknowledges this, and the fact that active substance manufacturers should share necessary information with the MA holder in order for them to fulfil that responsibility.

However, the CEP procedure as it currently stands, and the proposed single assessment procedure for ASMFs, do not require the division of the active substance dossier into an Applicant's Part and Restricted Part as in the current ASMF procedure. This may lead some active substance manufacturers to misunderstand their role when it comes to providing necessary information to the MA holders. This should be clarified in the guidelines.

Having said that, it is imperative that any new guidance retains the concept of Restricted Part information, and it is clearly stated that the active substance manufacturer is allowed to protect confidential know-how and is not required to share confidential details regarding the manufacturing process and in-process controls with the MA holder. New guidelines should clearly define the roles and responsibilities of all parties, including the level of information that should be shared in order for the MA holder to take full responsibility for the medicinal product.
It should be noted that communication is a two-way street and that for a partnership between active substance manufacturer and MA holder to be effective, expectations and practices need to be unambiguously stated.

APIC believes that by developing a good relationship, through communication, establishing sufficiently detailed quality / technical agreements, and building trust between the parties, the appropriate level of information to be shared can be defined to the satisfaction of all parties. Active substance manufacturers and MA holders have the same goal – to bring good quality, safe and effective medicines to the market, in the most efficient and timely way possible.

Conclusion

APIC strongly supports a single, self-standing assessment of ASMFs in a "CEP-like" procedure.
We would be pleased to answer any questions or provide further information on this very important topic. We would very much welcome the opportunity to enter into dialogue with interested parties to discuss in more detail.

25 January 2023

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