

CEFIC/APIIC POSITION PAPER

CEFIC/APIIC Position on the “Procedure for the Certification of Suitability to the Monographs of the European Pharmacopoeia” (CEP Procedure) versus the “Drug Master File Procedure” (DMF Procedure)

CEFIC/APIIC has recognized the importance as well as the benefits of the CEP Procedure from the moment it was introduced in the early 1990s. After a decade of experience with using this procedure, APIIC has come to the conclusion that especially for dedicated API manufacturers it is the most attractive- *and in particular in multi-customer environments even the only workable* regulatory submission procedure for compendial APIs. This conclusion relates both to the initial submission and assessment and - even more strongly - to the further post-approval maintenance of the filed information.

Nevertheless, CEFIC/APIIC recognizes the need for maintaining the other two API submission routes available in the EU as alternative options for compendial substances: Full content disclosure through Part IIC and IIF of a Marketing Application (when there is no issue of confidentiality of this API information) or the use of the European DMF procedure.

Especially the delay in the approval of MAAs or Variations of more than one year that may in certain situations be caused by the CEP procedure as compared to the other two options mentioned above, clearly illustrates the need for avoiding that use of the CEP procedure would become mandatory. Such delays would have negative consequences for public health in the EU and would in addition have detrimental effects on the pharmaceutical industry.

However, in comparison with the European DMF Procedure, the CEP procedure offers many significant advantages to industry as well as to the competent authorities. The latter have officially confirmed this through the issuance of the “CPMP Note for Guidance on Summary of Requirements to Active Substances in Part II of the Dossier” (CPMP/QWP/297/97, 28 January 1998) in which the preference for use of the CEP Procedure for compendial APIs is firmly stated.

The major advantages of the CEP Procedure versus the DMF Procedure, as identified by APIIC are:

- One single, centralised assessment of submitted information, at initial submission as well as for further maintenance and updating, instead of duplication of assessment by the individual national authorities. This results in preventing unacceptable, but avoidable workloads and in important savings for the public health system
- The CEP system provides for a uniform standard as opposed to duplication of assessment which often results in widely differing requests from each national authority for additional information from the API manufacturer and thus - ultimately - in a whole range of mutually differing DMFs, each to be separately maintained by the DMF holder thereafter
- In situations that one CEP supports several or many Marketing Applications: One single, centralised assessment of any subsequent changes to submitted information instead of duplication of assessment of (much more extensive) Variations to all the involved Marketing Applications

- One single time schedule for assessment instead of widely differing ones at different national authorities
- Strict control over and adherence to the safeguarding of confidentiality of the submissions at the EDQM premises
- Classification of Variations to Marketing Applications in relation to CEPs as maximally Type I (*)
- The upgrading of Ph.Eur. monographs through the submitted information, thus significantly increasing the relevance and value of the Ph.Eur. both to industry and to the authorities

In APIC's view, aspects of the CEP procedure that still offer room for improvement are:

- The lack of an adequate inspection procedure and -system. This lack originates from the overall EU regulatory situation regarding all APIs - except for those involved in the EU's centralised procedure - irrespective which API submission procedure is being used (**).
As long as neither inspection of the adherence to information submitted in CEP dossiers, nor inspection of adherence to GMP principles are carried out on a routine basis in relation to the CEP Procedure, it cannot be regarded as a procedure in which compliance is secured and enforced. Therefore, APIC emphasizes that the implementation of such an inspection system, a task that falls within the responsibilities of the EU authorities, should receive the very highest possible priority within the pharmaceutical program of the European Commission. APIC will also support the acceptability of API inspections performed by authorities with which the EU will have a mutual recognition agreement covering such inspections.
- CEFIC/APIC regrets that the period required for the assessment of CEP dossiers and other CEP submissions has increased in recent years in such a way that the official timelines are routinely exceeded with a significant number of months. Reduction of these periods to the length to which EDQM has committed itself through Resolution AP-CSP (99) 4 should receive high priority. Too long assessment periods may well lead to decisions to use the EDMF procedure instead, because for customers of CEP holders timing is often a primary concern.
- National authorities in certain cases still request information from CEP holders that was already reviewed during assessment of the CEP dossier. Therefore, these authorities should continuously be made aware that this should not occur unless for very specific, good and exceptional reasons.
- Further steps are needed to provide a waterproof safeguard against the unauthorised use of copies of CEPs. CEFIC/APIC sees as the optimal solution for this issue that the authorities will include in their assessment procedure an action to send letters to CEP holders, notifying them of all MAAs received and/or authorised that include the holder's CEP.

APIC highly appreciates the opportunities offered by EDQM and the Ph. Eur. Commission to provide input, based on APIC members' experience, with the aim of further improving various practical aspects of the procedure. During the past decade such interactions have already resulted in the implementation of many important improvements to the procedure.

It is APIC's view that (preferably in a form including the above mentioned, to be improved aspects) the CEP Procedure should be used by all authorities throughout the world as a model for the development of (more) adequate procedures for - both compendial and non-compendial - API submissions. Furthermore, possibly as a first step towards that goal, APIC would fully endorse the expansion of the scope of the CEP procedure to non-compendial APIs, thus establishing the option in Europe of a centralised assessment of all APIs. Ideally, and after an adequate period allowing for such transition, CEPs would in due time become world wide accepted documents that adequately cover all aspects of the safety and quality of APIs within registration dossiers for medicinal products.

Decades of experience with regulatory procedures have confirmed that the only workable API regulatory system is one in which approval is granted to manufacturers which are performing the to be approved operations - and subsequent changes therein - themselves. In addition to this, however, the crucial dialogue on intended improvements in API manufacture should take place at the interface between the manufacturer intending to implement the improvement and the company that purchases its product. Only through this dialogue can all aspects of significant change in relation to the safety of the final medicinal product be adequately addressed.

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(In February 2002 the European Commission issued drafts for the revision of the EU Variation Regulations. This drafted revision proposes to re-classify many Variations involving CEPs as major ones (Type II B). Should this become reality then the usefulness of the CEP Procedure would be largely destroyed: Most post-approval changes that affect the CEP would be classified in an identical way as when EDMFs are involved. In addition, applying for new CEPs would become extremely unattractive because the time needed to obtain a CEP (on average in the range of one year) will then practically always have to be followed by the period needed for authorisation of a major Type II B Variation. Use of the EDMF procedure would therefore lead to saving one full year in the approval process, because the Variation involving a new EDMF can be filed immediately.*

In its comments to these draft regulations, submitted to the European Commission in March 2002, APIC has stressed the crucial importance of maintaining the status of minor variations for changes involving CEPs.

*(**) The EDQM initiative to perform inspections independently from yet to be developed EU systems is very much appreciated by APIC.*