

CEFIC/APIC POSITION PAPER:

CEFIC/APIC Position on Post-Approval Change Authorization Procedures (PACAPs) relating to the manufacture of APIs

Changes relating to the manufacture of APIs may be necessary or even unavoidable for a variety of reasons, such as:

- To meet new environmental requirements
- To meet new regulatory requirements
- To increase the safety in the manufacturing plant
- To increase the quality of the product
- To lower the production costs / market price
- To replace obsolete technologies by state of the art technologies
- To correct for unforeseen process drifts of various origins, such as those related to ageing of manufacturing equipment
- To accommodate for a change in availability of raw materials of a specific quality

In many cases, a combination of several of the above reasons forms the driving force behind the need to implement such a change. Such situations often occur after the authorisations / approvals of the medicinal product(s) manufactured from the API have been granted.

Provided that the quality, safety and efficacy (QS&E) of the derived medicinal product(s) will remain secured - or will improve, as often is the case - the effects of a change implemented for one or more of the above reasons are either beneficial to the end-user, or to society as a whole or both. The terms improvement and process optimisation are therefore appropriate ones to use for such changes.

For the above reasons, it is CEFIC/APIC's view that PACAPs relating to APIs should be designed in such a way that manufacturers will not unnecessarily be blocked in implementing improvements. While on the one hand PACAPs should secure the medicinal product's QS&E, their procedural characteristics should on the other hand be such that authorisation of the improvement is feasible. This should also be the case if one or more manufacturing steps in the API production process are being performed by producers other than the final medicinal product manufacturer itself.

Certain existing PACAPs do not meet the requirement that the authorisation of an improvement is a feasible target to attain. This is notably the case when the improvement results in the amendment of the content of a Drug Master File (DMF) (*) that has been cross-referenced by several or even many Marketing Applications (MAs) for medicinal products. Because the authorisation of the improvement in the API manufacturing process can exclusively be obtained through regulatory actions of the MA holders, the manufacturer wishing to implement the improvement is confronted with the situation that the power to decide on requesting authorisation does not reside in its own hands but in the hands of several or even a large number of manufacturers downstream.

Furthermore, authorisation can then only be obtained when each and every one of those companies downstream will agree to prepare and submit the authorisation requests (Supplements / Variations).

Taking into account that the preparation of such supplementary submissions is quite time- and money consuming, it comes as no surprise that APIC members' experience has shown that the implementation of improvements in API manufacture is frequently blocked by the very nature of the PACAPs: Companies downstream will often not be willing to spend the required efforts and money.

It is APIC's position that the following set of principles should be applied in designing (or re-designing) PACAPs, in order to avoid the unnecessary and unreasonable blocking of improvements in API manufacture:

- Regulatory approval (**) of an improvement should be requested by and granted to the company that will implement the improvement
- Companies downstream in the manufacturing chain should not delegate to the authorities their responsibilities for dealing with companies upstream regarding intended improvements
- 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
- PACAPs or any other registrational procedures only contribute to the safety of patients if they are linked to adequate inspection systems and -procedures

In conclusion:

It is CEFIC/APIC's position that a dedicated system is required for the assessment and approval (**) of regulatory submissions on APIs and subsequent changes therein. The approved status will normally imply that the API has been found suitable and safe for use in any medicinal product. However, should specific and concrete reasons justify this, the approval may be limited to one or more specific classes of dosage forms.

Through mutual recognition agreements or through centralisation, an ideal situation should be pursued in which such API approvals will have worldwide validity.

In order to ensure that the system contributes to the safety of patients, adequate inspection systems and -procedures should be in place

(*) See also CEFIC/APIC's Position Paper on the CEP Procedure versus the DMF Procedure.

(**) Approval could also be in the form of authorisation or certification.