**Certification of Substances Department**

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# Certification of suitability to the Monographs of the European Pharmacopoeia

## API-Mix (or mixtures) and CEPs

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## 1. Introduction

This document describes the approach to be taken regarding applications for CEPs for API-mix, which are mixtures of drug substances (API-active pharmaceutical ingredient) with excipients, following the publication in April 2016 of Questions and Answers (Q&A) on this subject by the Quality Working Party of the European Medicines Agency (EMA):

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001524.jsp&mid.

These Q&A provide information on how to deal with API-mix, and to identify situations where it will be acceptable to use the ASMF/CEP procedures and perform manufacture under EU GMP Part II (except for the manufacturing steps such as sterilisation activities and the steps after sterilisation where EU GMP Part I is mandatory).

Typical situations for API-mix are the addition of an antioxidant to a drug substance, or the introduction of a drug substance into a matrix. Drug substances in solution are also considered as API-mixes.

The Q&A also clarify that where there is an existing Ph. Eur. monograph for an API-mix, a CEP can be granted. Examples are potassium clavulanate diluted (where the potassium clavulanate is mixed with an excipient), simvastatin (where there is a statement under Definition that "A suitable antioxidant may be added") and chlorhexidine digluconate solution where the active substance is present in aqueous solution.

Additionally the Q&A make clear that a statement in Ph. Eur. monograph, such as "A suitable antioxidant may be added", is considered sufficient and acceptable per se as a justification for the use of an API-mix. However, additional justification on the choice and level of antioxidant needs to be provided, and a control test is required for the antioxidant in the API-mix.

## 2. Acceptance of applications for CEPs

From 1 December 2016, where there is a Ph. Eur. monograph which covers an API-mix, a CEP application can be accepted.

Where the Ph. Eur. monograph describes the excipients which may be used (generally in the Definition section), the monograph requirements should be complied with in the CEP application. If the API-Mix does not meet the requirements of the monograph with regards the qualitative and/or quantitative composition, the CEP application will not be accepted.

## 3. Assessment of CEP applications for API-mix

The CEP dossier should contain all relevant information on the mixing process, qualitative and quantitative composition of the mixture and on the control strategy.

Data supporting the choice and the amount of the excipient(s) should be provided, unless they are covered by the Ph. Eur. monograph and this also applies to the quality and amounts of antioxidants where these are allowed by the monograph but not identified (i.e. .. a suitable antioxidant may be added...). The guideline on "Excipients in the dossier for application for marketing authorisation of a medicinal product" (EMEA/CHMP/QWP/396951/2006) is applicable; therefore the CEP application should include data to support the changes to the content of the antioxidant and the API-mix impurity profile at release and after storage (i.e. stability data).

A re-test period for the API-mix can be accepted, if justified. If appropriate, the stability data should include details of the levels of the additives such as antioxidants during the programme.

4. Information included on a CEP for API-mix

If there is a labelling section in the Ph. Eur. monograph, this is reflected on the CEP. The presence of an antioxidant is generally highlighted in the subtitle for the substance on the CEP.

The following information is mentioned on the CEP for an API-mix, unless it is already included in the Ph. Eur monograph:

- The name of any excipient used
- The amount (range) of any excipient used
- For the control of antioxidants, an appropriately validated control method is annexed to the CEP