

How to use a Certificate of suitability to the Monographs of the European Pharmacopoeia (CEP) in the context of a Marketing Authorisation Variation

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Use of a CEP

Types of CEPs

Certificate for chemical purity and microbiological quality (“Chemical CEP”)

Certificate for herbal drugs and herbal drug preparations (“Herbal CEP”)

- Certifies that the quality of the substance is suitably controlled by the Ph. Eur. monograph and any supplementary tests in line with ICH and EMA guidelines (included on the CEP).

TSE Certificate (“TSE CEP”)

- Certifies that the substance complies with the Ph. Eur. General Chapter 5.2.8 on minimising the TSE risk.

Format of CEPs

“Old CEP”

Paper document with wet signature.

“CEP 2.0” / “Hybrid CEP”

- EMA SPOR/OMS ORG_ID and LOC_ID for all companies involved in Certification of suitability (Holders & manufacturing sites).
- Letter of access.
- Electronic document with electronic signature.

DO NOT FORGET!

✓ **A CEP does not replace a certificate of analysis.**

✓ **A CEP does not replace the QP declaration**

✓ **A CEP is not a GMP certificate**

Submission, Update or Deletion of a CEP

Q.III.1 (a) EUROPEAN PHARMACOPOEIAL CERTIFICATE OF SUITABILITY TO THE RELEVANT PH. EUR. MONOGRAPH

Q.III.1.a.1	IAin	New certificate of suitability (CEP) (including replacement or addition).
Q.III.1.a.1	IA	Update of an approved certificate of suitability (CEP).
Q.III.1.a.1	IA	Deletion of certificate(s) of suitability (CEP).
Q.III.1.a.1	IB	New certificate of suitability (CEP) for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free.
Q.III.1.a.1	IB	New or updated certificate of suitability (CEP) for a herbal active substance.

For APIs supported by a CEP, a separate variation is required under category Q.I. scope in the following scenarios:

Q.I.a

To register or amend sites (e.g. micronisation or control/testing sites) if these sites are not included on the CEP.

Q.I.b

To register or amend in-house analytical procedures used by finished product manufacturer if these analytical procedures are not included on the CEP.

Q.I.d

To register or amend a re-test period if the re-test period is not included on the CEP.

Main changes of the revised Variation Guideline

Conditions

- Scopes have been merged to simplify and improve readability.
- A note has been included to explain situations in which additional variations are required.
- Condition 1: Strengthened to put emphasis on MAH/FPM responsibilities and include reference to change in composition (API-Mix).
- Conditions 2&3: Revised for better clarity.

Documentation

- Letter of access for CEP 2.0 is included in documentation 1.
- More detailed explanation (eCTD dossier sections expected) is added.
- Addition of CEP for herbal APIs.



MAHs are **ultimately responsible** for the quality of APIs used in their finished product

QWP Questions and answers

How to use a CEP in the context of a Marketing Authorisation Application (MAA) or a Marketing Authorisation Variation (MAV)

3.2.R: A copy of the most recent version of the CEP with the declaration of access to the MAH/ applicant on the CEP, or a Letter of access for CEP 2.0 filled and signed.

S.2.1. Manufacturer(s): all active substance manufacturing sites should be stated, including sites used for quality control/testing of the active substance.

Check out [the guide](#)
for more details

QWP Questions and answers

S.3.2. Information on any impurity containing vulnerable amines (e.g. secondary or tertiary amines) that may trigger formation of nitrosamine impurities should be provided.

S.4.1. The specification should clearly indicate which parameters/acceptance criteria, and analytical methods are included from the Ph. Eur. monograph, the CEP and any additional specific attributes.

If there is more than one supplier of the active substance, the MAH/ applicant/finished product manufacturer should adopt one single compiled specification for the active substance that takes into account the different impurity profiles of each supplier or source.

QWP Questions and answers

S.4.2 & S.4.3: Analytical methods used must be described; if they correspond to the Ph. Eur. monograph, a declaration is sufficient. If the same methods as those used by the CEP holder are applied, they only need to be referenced and no validation data is required. However, if in-house methods or additional finished product-specific parameters are used, their description and corresponding validation data must be included to demonstrate suitability.

GENERAL - APPLICABLE TO ALL SECTIONS

In each individual eCTD section, where no additional information is provided because it is identical to that included in the CEP, this should be clearly stated. Reference should be made to the CEP number and its revision number.

Submission, Update or Deletion of a CEP

Submission Obligation: *A variation is required whenever a new or updated CEP is implemented in the manufacturing process of the active substance or the finished product.*

HANDLING OF VARIATIONS

In cases where the same holder applies for one or several Type IA variations to the terms of a single marketing authorisation, these should be submitted as a single notification: Grouping of type IA variations concerning one MA: **ANNUAL UPDATE.**

One or several variations Type IA and/or type IAin variations to the terms of multiple marketing authorisations held by the same holder may be submitted as a single notification: **SUPER-GROUPING APPLICATION** of type IA variation(s) concerning more than one MA.

Do you need **support with Variations?**

Contact us:
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