Lyfjastofnun
Icelandic Medicines Agency

How to use a CEP in a MAA/MAV

EDQM - How to read a CEP webinar

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Looking Back…

- The Certificate of Suitability to the Monographs of the European Pharmacopoeia (CEP) was introduced in 1994
- One of three possibilities to present information on the quality of the active substance in a MAA/MAV dossier (in addition to full dossier and ASMF)
- The CEP certifies that the respective active substance complies with the European Pharmacopoeia (Ph. Eur.) and that the Ph. Eur. monograph is able to adequately control its quality
- The inclusion of a CEP in an MAA simplifies the assessment procedure for Authorities and the submission procedures for pharmaceutical industry (DS manufacturers and MA applicants) – Centralized assessment at EDQM in Strasbourg

→ After 25 years of successful use, a survey to stakeholders (industry and NCAs) was launched by EDQM in 2020, to see what could be further improved (**CEP of the future**)

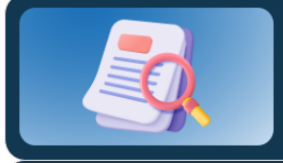
Outcome of the CEP of the Future Survey

It would be good if…:

- Include more details on all sites involved in manufacturing in order to understand the supply chain and roles of each site
- Increased transparency regarding the specifications of the substance covered by the CEP
- Include statements on the CEP with regard to risk assessment of nitrosamine and mutagenic impurities and also on the maximum daily dose and route of administration considered during assessment
- Mandatory inclusion of a re-test period on the CEP, with the possibility of covering more climatic zones, together with statements on the need and absence of need for specific storage conditions
- Electronic CEP (e-CEP) rather than a paper document
- Reduce revisions of CEPs

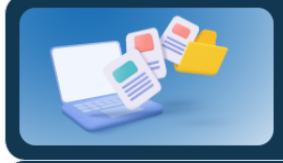
Result: CEP 2.0!

Area 1: CEPs and information reported

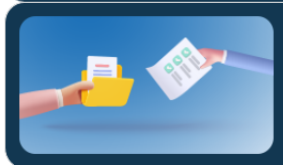


Area 2: Changes regarding assessment of CEP applications

Area 3: On-line public certification database



Area 4: Authorities Database



Area 5: Fostering information sharing between CEP holders & MAH

Area 6: Reduction of revisions of CEPs

Area 7: Impact of changes and their implementation

Area 8: Trainings for assessors, CEP holders and CEP users

Area 9: Revising documents available on the website

Common Ground

Irrespective of the “look” of the CEP (old, hybrid or 2.0)

- The CEP procedure greatly simplifies submission of information on drug substances
- Valuable tool for saving of resources at NCA – time and expertise
  - Initial marketing authorisation (MAA)
  - Product life-cycle (variations)

→ Agencies are in great favor of CEPs

→ Based on gained experience over the years, some aspects of MAH responsibilities need further clarification

Clarification Needed

- In parallel to the “CEP of the future” project, two separate guidance documents were drafted
- Aimed at all users of CEP during life-cycle of a medicinal product
  - Drug substance manufacturers
  - Drug product manufacturers / Applicants
  - National Competent Authorities

→ How to read a CEP (PA/PH/CEP (15) 31, 1R)

→ How to use a CEP in the context of a MAA / MAV (EMA/CHMP/CVMP/QWP/5/2024)

Where CEPs are Accepted

CEPs are accepted by:

- 40 Members of the CoE (non-EU with conditions)
- International partners (some with conditions)*
  - Australia
  - Brazil
  - Canada
  - Israel
  - New Zealand
  - Singapore
  - South Africa

* List not exhaustive

Q&A Document (EMA)

3 January 2024
EMA/CHMP/CVMP/QWP/5/2024
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary use (CVMP)

QWP Questions and Answers (Q&A): how to use a CEP in the context of a Marketing Authorisation Application (MAA) or a Marketing Authorisation Variation (MAV)

➡ Q&As only applicable for MAAs/MAVs in EU/EEA

Collection of 18 Q&As

- ***General Cases***
  - QP Declaration
  - Which information to include in S-Part of Applicant
- ***Specific Cases***
  - Intermediate covered by CEP
  - CEPs for sterile substances
  - API mix
  - TSE CEPs
  - And others…

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Document Structure

- ***Question***

  If a CEP is referred to a sterile substance, is there any additional data to be submitted in MAA or MAV?

- ***Answer***

  Sterilisation and aseptic processing of active substances are considered to be the first steps of the manufacture of the finished product. In case of sterile substances, the MA dossier should include full information on the sterilisation process and aseptic processing as well as results of any tests applied and validation data of the sterilisation process, even when the CEP states the substance is sterile. More information is found in section 4.2.1 of EU guideline on the sterilisation of the medicinal product, active substance, excipient and primary container19 and the relevant Q&A20.

- ***Reference***

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[19] Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container, EMA/CHMP/CVMP/QWP/850374/2015

[20] https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/qa-quality/quality-medicines-questions-answers-part-1#active-substance---good-manufacturing-practice-compliance-for-sterilisation-of-an-active-substance-section

3. Information To Be Included In The MAA Dossier

3.2.R

- A copy of the most recent version of the CEP should be included
- Current version can be verified at www.edqm.eu (section Certification of Suitability)

3.2.S

S.2.1 Manufacturers

- All manufacturing sites involved in the manufacturing process should be provided, including sites for quality control/testing
- The MAH should be aware of which steps of the process are performed at which site

Information in the S-Part (I)

S.3.2 Impurities

- EDQM reviews limits for impurities not specified in the Ph. Eur. monograph based on the known routes of administration and maximum daily dose (MDD) of already approved medicinal products in which the active substance is used.
- In case a product with different indication, posology (e.g. higher MDD, longer duration of treatment) or route of administration is applied for, MAHs/applicants referring to a CEP should determine whether the specified impurity limits and control strategy are still appropriate for their product.
- Information on any impurity containing vulnerable amines such as secondary or tertiary amines that may trigger formation of nitrosamine impurities should be available to the MAHs/applicants in order to perform a risk assessment.

Information in the S-Part (II)

S.4.1 Specification

- The MAH/ applicant/finished product manufacturer's specification for control of the active substance should include all relevant test attributes of the respective Ph. Eur. monograph and all additional test parameters mentioned on the CEP.
- Some additional attributes of the active substance might need to be considered and included in the MAH/applicant/finished product manufacturer's active substance specification in order to ensure that the active substance is of suitable quality for use in a given specific medicinal product, e.g.:
  - Particle size distribution
  - Polymorphic form
  - Bacterial endotoxins

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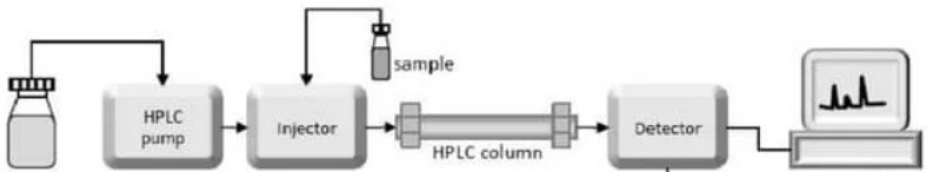
Information in the S-Part (III)

S.4.2/3 Analytical Procedures/Validation

- In cases where the MAH/applicant/finished product manufacturer uses **the same analytical methods as those annexed to the CEP**, then these methods should be referenced in the MA dossier and validation data is not required.
- Where an **alternative method** of the CEP dossier **is not annexed to the CEP** (as the method been considered equivalent to that of the Ph. Eur. monograph of the active substance by EDQM), it should be described in the MA dossier together with a declaration that the method is the same as assessed and approved by EDQM and validation data is not required.
- In case where the MAH/applicant/finished product manufacturer uses their **own in-house analytical methods**, description and validation data should be submitted in the MAA/MAV dossier supporting the suitability of the methods.



Information in the S-Part (IV)

S.4.4 Batch analyses

- API batch results from by the finished product manufacturer should be provided demonstrating compliance with the Ph. Eur. monograph, the CEP requirements and any additional tests on critical quality attributes.

S.4.5 Justification of specification

- In particular for those quality attributes established in relation to the finished product (e.g. PSD, polymorphic form or BET), a justification of the MAH/applicant/finished for the proposed control limits is expected.

S.5 Reference standards and materials

- Information on the reference standards of the active substance and impurities used in analytical procedures applied by the finished product manufacturer/MAH/applicant to control the active substance should be included.

Information in the S-Part (V)

S.6 Container closure system

- CEPs issued prior to September 2011 may not include information on the CCS.
- In this case, the following information needs to be included:
  - Description of primary packaging material, including specifications and confirmation of compliance with European food regulations/Ph.Eur. requirements
  - Description of secondary packaging material, including specifications

S.7 Stability

- Where no retest period is mentioned on the CEP, stability data may be separately included in the MA dossier for assessment by the Competent Authority to support a retest period.

Use of API batches covered by a superseded CEP

- Batches of API manufactured and supplied to the MAH in accordance with a superseded version of the CEP may still be used for manufacture of the finished product, provided there are no quality, GMP and/or safety concerns that have led to the revision of the CEP
- Additionally, these batches should be:
  - Still compliant with the Ph. Eur. Monograph in force at the point of use
  - Tested in compliance with the new specifications of the revised CEP

- Use of AS batches covered by a superseded version of a CEP should be documented in the PQS of the medicinal product manufacturer and carried out under the responsibility of the qualified person.

What should be considered in case of CEP revisions?

- When a CEP has been revised, a new version is issued which supersedes the previous certificate
- The CEP holder is responsible for promptly communicating this to the MA holder providing a signed copy of the latest CEP, highlighting any changes.
- MA holders should be informed by CEP holders of all changes to the CEP and the API covered by it regardless of whether it leads to a revision of the CEP to evaluate the impact and, if needed, to update the MA information

→ Any MA holder having received a copy of a revised CEP should immediately consider the implications of such changes and as appropriate update any impacted sections of its MA dossier via a MAV application

Summary

- CEPs are one of three possibilities to present information on the quality of the active substance in a MAA dossier (in addition to full dossier and ASMF)
- In many cases, CEPs can be used “as is”, no additional assessment from NCA is needed

  → Significant saving of resources for NCA (time and expertise)
- After 25 years of successful use, a survey to stakeholders (industry and NCAs) was launched by EDQM, in order to see what could be further improved (CEP of the future)
- Improvements requested in “CEP of the future” lead to CEP 2.0
- In parallel to the “CEP of the future” project, separate guidance documents were drafted in order to aid users of CEPs

  → How to read a CEP (PA/PH/CEP (15) 31, 1R)

  → How to use a CEP in the context of a MAA / MAV procedure (EMA/CHMP/CVMP/QWP/5/2024)

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Thank you!

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