THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

Everything you've always wanted to know about the certification (CEP) procedure.

Andrew McMath / Andrea Melloni / Pascale Poukens
Scientific officers

Summary

- Frequent questions from previous webinars on CEP 2.0

- Questions raised following the advertisement of this webinar

- Questions and answers session

From the previous webinars

- CEP 2.0
- SPOR
- Submission of a change not impacting the CEP
- Renewal process
- Specifications
- Analytical procedures
- QOS/MDD

Types of CEPs

What is the trigger for hybrid CEP/ CEP 2.0 ?

- "New look" CEPs = CEP 2.0 format, are systematically issued for any new CEP granted and if needed after renewal procedures. CEP holder can also ask for a revision to switch to CEP 2.0 format.

- The "hybrid look" CEPs are granted after approval of revision/renewal applications and after notifications, for existing CEPs where the content of the CEP is impacted (and is not already in CEP 2.0 format)

SPOR OMS database

- *How to declare a change in ORG_ID and LOC_ID?*
- *What does EDQM expect as match with the SPOR OMS database?*

✓ORG_ID and LOC_ID identifiers are assigned and managed by the European Medicines Agency (EMA), using the SPOR/OMS database.

✓EDQM uses the entries in the SPOR/OMS database as a reference to have more consistency in the data.

✓Change should first be declared and approved in SPOR /OMS database.

✓EDQM uses the legal organisation names as mentioned in SPOR /OMS and not alternative names.

✓Information listed in application form should match with information in SPOR /OMS database.

Maximal Daily Dose (MDD) (1)

Where to find acceptable information and how to calculate it?

- For substances for human use, the information regarding Maximum Daily Dose (MDD), route of administration and treatment duration should be based on human medicine European Public Assessment Report (EPAR), Summary of Product Characteristics (SmPC), or agreed literature such as Martindale.

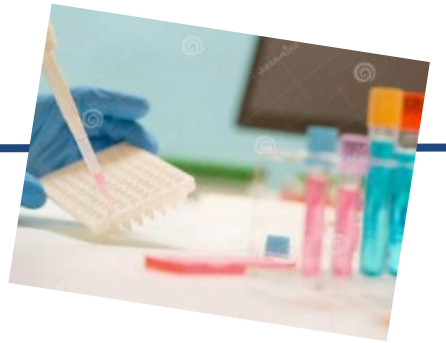
Maximal Daily Dose (MDD) (2)

Where to find acceptable information and how to calculate it?

- EDQM FAQ "CEP 2.0 requires maximum daily dose (MDD), route of administration and treatment duration to be provided in S.1.3. However, these characteristics do not apply to active ingredients. What should I do?

Maximum daily dose, route of administration and treatment duration are the only characteristics used by substance manufacturers to develop and justify the control strategy implemented and described in the CEP dossier. For substances for human use, this information should be based on human medicine European Public Assessment Report (EPAR), Summary of Product Characteristics (SmPC), or agreed literature such as Martindale as explained in the EDQM document New requirements for the content of the CEP dossier for chemical purity and for herbal drugs/herbal drug preparations according to the CEP 2.0 (PA/PH/CEP (23) 21 1R)

Specification: microbiological requirements



Can I include microbiological requirements in the specifications?

- This aspect is generally not covered in the CEP procedure since the final use of substance is not known and this should be assessed in MAA. However, in some cases e.g. when API is known to be for parenteral use only, this quality attribute may be part of the specification appended to the CEP.
- Otherwise microbiological requirements have to be deleted from the section 3.2.S.4.1

Skip testing

Is skip testing acceptable?

- Skip testing is acceptable only when foreseen by EMA or ICH guidelines (mutagenic impurities, nitrosamines, elemental impurities)
- Otherwise EDQM does not take position on skip testing
- EMA is currently working on this topic

Analytical procedures (1)

How to deal with Ph. Eur. analytical procedure adjusted vs GC 2.2.46?

- The analytical procedures described in the monograph may be adjusted according to in Ph. Eur. general chapter 2.2.46 *Chromatographic separation techniques*
- a cross-reference to the current respective Ph. Eur. monograph is considered sufficient

Analytical procedures (2)

How to deal with Ph. Eur. analytical procedure adjusted vs GC 2.2.46?

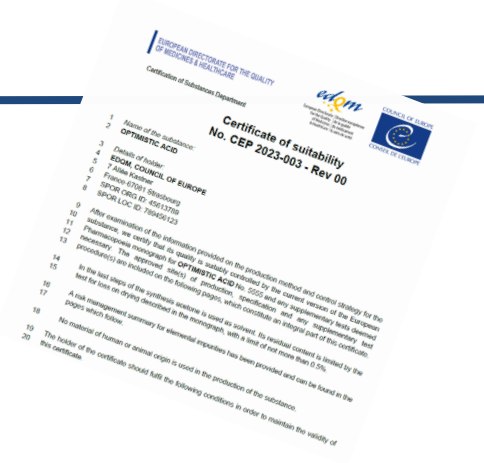
- Analytical procedures adjusted within the limits prescribed in GC 2.2.46 *Chromatographic separation techniques* are considered to be the pharmacopeial analytical procedures:

Quality of medicines questions and answers: Part 1 | European Medicines Agency (EMA)

Questions and answers for biological medicinal products | European Medicines Agency (EMA)

CEP

How to read a CEP ?


Certificate of suitability
No. CEP 2023-003 - Rev 00

- The EDQM document « How to read a CEP » is under revision. The document is being updated to reflect the changes introduced with CEP 2.0.
- The revised document will be available soon and will be announced on the EDQM website.

Submission of change

Do I need to submit a change not impacting the CEP and do I need to inform my customers?

- Yes, any change has to be submitted regardless of whether it leads to a revision of the CEP. In addition, the MAH needs to be informed of any change introduced by the API manufacturer/CEP holder to evaluate its impact, and to update the marketing authorisation information. It is of utmost importance that the CEP holder provides the necessary information to their customers.

CEP database

How to interpret the history table from the CEP database?

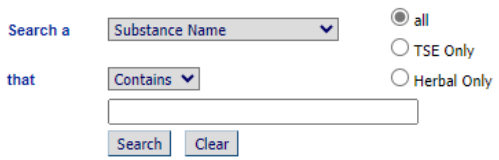
- You can search the certification database by:

  - Substance Name
  - Monograph Number
  - Holder Name
  - SPOR IDs
  - Type of CEP
  - CEP Number
  - Issue date of CEP
  - Status of CEP
  - Renewal due date for CEP
  - End date of CEP
  - Closure date of last Procedure

Certification Online Database User Guide

- The substance name is equal to the monograph name for "Chemical", "Herbal" and "Chemical and TSE" (= double) certificates and is the substance name for "TSE" certificates.

If you are interested in all types of certificates , please select the button beside "all". If you are only interested in TSE or herbal certificates, please select the button beside your required choice and only TSE or herbal certificates will be displayed as a result of your choice.



When there is a history of procedures available for the CEP, there is a hyperlink on the CEP number and if clicked on

Monograph Number	Substance	Type CEP	Certificate (CEP) Holder	Holder SPOR ORG-ID SPOR LOC-ID	Certificate (CEP) Number	Issue Date CEP	Status CEP	Renewal due	End date CEP	Closure Date of last Procedure
568	Propranolol hydrochloride	Chemical	IPCA Laboratories Limited Mumbai IN	100011685 100018680	R1-CEP 2002-026 - Rev 05	03/08/2023	Valid			03/08/2023

Procedure Type	Outcome	Closure Date of Procedure
Notification	CEP granted	03/08/2023
Minor revision	CEP granted	22/05/2023
Minor revision	Accepted - CEP remains valid	15/07/2022
Minor revision	CEP granted	21/09/2021
Minor revision	Accepted - CEP remains valid	01/04/2021
Minor revision	Accepted - CEP remains valid	13/03/2020

Renewal

Do I need to apply for renewal and when?

- Renewal process is necessary and applies only once. This should be initiated 6 months before the expiry date mentioned on the CEP or the Renewal due date mentioned in the public Certification database.
- CEP still mentioning an expiry date have to be revised after renewal.
- CEP without expiry date may remain unchanged and renewal process will be traced via the history of procedure table from the Certification database.
- CEP holders SHOULD ASK (cover letter) if they want a CEP 2.0 when a CEP hybrid has already been issued

From the registration form

Specification (1)

The solvents that are stated on the old CEP are those likely to be present in the substance, i.e. solvents used in the final manufacturing steps and solvents whose levels in the substance are above 10% of the concentration (option 1) limit established by ICH Q3C.

In the new CEP 2.0 the CEP holder include all the solvents used in the synthesis in the specification of the CEP. Should finished product manufacturers also include all the solvents in their specification?

The finished product manufacturer's specification for control of the active substance should include all relevant parameters. It is CEP holder's responsibility to provide to its client sufficient information in order to settle adequate specification parameters.

Specification (2)

Manufacturers can use alternative methods to those described in the Ph. Eur. monographs provided these methods are at least equivalent to the Ph. Eur. methods; if the in-house methods are considered equivalent, they not annexed to the CEP.

If CEP 2.0 specification includes both the Ph. Eur. and the in-house method can MAH choose which method to be included in its specification?

The use of two methods to control the same parameter is discouraged in the CEP procedure. In any case, when in-house methods are used and are considered equivalent to the methods of the monograph, these are not appended to the CEP since the monograph is considered capable to control the substance.

Specification (3)

CEP 2.0 can show stricter limits for certain specified impurities or for unspecified/total impurities compared to those prescribed by the monograph. Should the finished product manufacturer apply also the stricter limits?

CEP Holders may decide to apply stricter limits, however, in the vast majority of the cases, the limits of the monograph and complementary regulations (e.g. GM 2034) remain the reference.

Specification (4)

Additional (to Ph. Eur.) specification is no more clearly mentioned on the CEP, how can we identify such specifications in CEP 2.0?

Additional specification parameters are those not foreseen by the monograph. These may be needed to cover a specific grade (e.g. polymorph or micronised) or due to the specific manufacturing process and controls (e.g. mutagenic impurities, elemental impurities etc.).

Specification (5)

Should parameters for appearance and solubility be included in the specification table to be appended to the CEP Certificate, or is it OK to omit this information?

The statements in the Characters section do not constitute Ph. Eur. requirements and are given for information only.

Different sentences on CEP

Is it possible to see how a CEP 2.0 will be presented especially when there are several grades with different water quality and/or with different retest period?

The use of different water qualities in the last step is strongly discouraged, it is therefore not possible to have two different sentences on the quality of water used in the same CEP.

The re-test period of the substance is 24 months if stored in double polyethylene bags (outer black), placed in a polyethylene drum and 36 months if stored in an amber glass bottle with a polyethylene screw cap.

Letter of Access

Could you please show an example of an issued LoA?

The CEP holder commits to share information which is not on the CEP and to provide necessary information concerning CEP Revisions to their customers. Is this after request of customer?

The EDQM's template for the Letter of Access can be filled with the relevant information requested by the specific MoH/NCA.

The CEP holder should proactively inform the CEP users of the relevant changes. The correct information sharing may be verified during GMP inspections.

Alternative routes of synthesis

For an API with two intermediates with two manufacturers each who use different routes of synthesis, can this be provided within one CEP with a sufficient impurities assessment, if the API itself has always the same specification?

If this is done later as a variation, is a sister file necessary (if so, how many), or can it be included into one documentation?

Different routes of synthesis to obtain an intermediate implies different starting materials, different intermediates, would generally lead to a consideration that this is 'substantially different' and hence they could not be described in the same file, EVEN IF THE IMPURITY PROFILE IS EQUIVALENT

Reference to another CEP

If I refer to an old CEP (not CEP2.0) in a new application (as intermediate), will this trigger a change to CEP 2.0 for the old CEP?

Cross-reference to another CEP will generally never lead to a change to the referenced CEP initiated by the EDQM.

Need for an updated QoS

In which cases is a QOS to be revised? Only when the information on quality of the substance and the scientific reasoning / rationale which are meaningful for taking decision on the control strategy are changed?

This situation may occur during the initial evaluation when the documentation has been significantly revised i.e. following redefinition of the starting material(s), changes to an ICH M7 control strategy or indeed on the occasion of a major revision dealing with similar situations. Generally, it is good practice that the QOS follows the lifecycle of Module 3.

Extrapolation of stability data

If I could claim 60 months retest date extrapolating from submitting 48 months, how do I classify the addition of the 60 months data to the documentation?

Accelerated stability studies are performed at a time T. If the monograph evolves, accelerated stability studies are not repeated. Are the results of the accelerated stability study usable to claim a retest period?

If the updated stability data confirms the retest period the inclusion of the updated stability data can be provided on the occasion of the next revision that needs to be declared, and it should also be confirmed that the current retest period remains valid. However, if the retest period is not valid either an immediate notification or a minor revision should be declared depending upon the exact situation.

The use of stability data from other methods, including a previous monograph could well be quite acceptable. A scientific justification should be provided why this would be the case should be provided.