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

CEP 2.0: Fresh feedback from stakeholders

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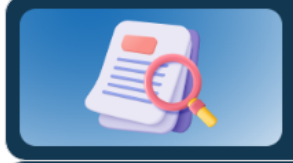
What is the CEP 2.0?

- Project initiated to reshape the CEP and its content
  - Meet the current needs of stakeholders
  - Ease the registration activities linked to the use of CEPs;
  - Increase the acceptance of CEPs.
  - Offer enhanced user-friendliness and greater transparency of information without, increasing regulatory burden related to revisions of CEPs.

➢Resulted in a "new look" CEP called CEP 2.0 implemented beginning of September 2023

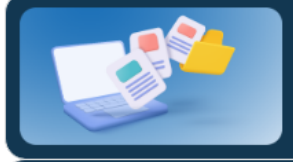
What has changed?

Area 1: CEPs and information reported



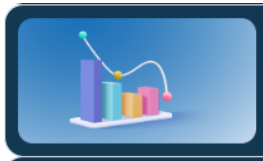
Area 2: Changes regarding assessment of CEP applications

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

Download the document explaining the changes

CEP 2.0

- Focus on chemical CEPs, but same principles apply also for herbal and TSE CEPs as far as they are impacted
- The CEP is a « document », with a layout similar to the previous one.
- Electronic format (pdf) with a digital signature, more details available here.
- No more declaration of access box in the CEP, replaced by a template available on the EDQM website here.
- Revision of "legal" sentences.
- Numbering of the CEP changed

  2-block code
  CEP 20XX-XXX-Rev 00

- No more expiry date (although the renewal process remains mandatory)

Changes to information reported on CEPs

- Quality of the water used in the last steps of the process specified on the CEP
- Technical information appended to the CEP
  - Specification (section 3.2.S.4.1) applied by the CEP holder/applicant and as approved by the EDQM
  - Additional methods (Part of section 3.2.S.4.2) needed to control the quality of the substance.

Details of companies

- Name and address for the CEP holder and manufacturing sites completed by SPOR/OMS ORG_ID and LOC_ID
- No change of policy on the level of details regarding the manufacturing sites mentioned on the CEP:
  - The sites are listed with their role: Site(s) of production of intermediate(s), Site(s) of production of the substance, Site(s) of physical treatment, Site(s) of micronisation and Site(s) of sterilisation
  - Details on which step is performed in each site (if several) and testing sites are available in the CEP Assessment Reports in the Authorities database.
  - No details on exact role of manufacturing sites or on testing sites in the CEP.
  - No details on manufacturing sites in the public Certification database.

Figures of implementation

- Between 01/09 and 31/03, out of 1076 granted CEPs
  - 402 are in CEP 2.0 format (183 new, 115 following renewal)
  - 674 are in hybrid CEP format
- 17 major revision applications out of 59 have been finalised with the outcome "CEP remains valid" (i.e. no revised CEP issued).
  - Following change of policy
    - the CEP is not revised if its content is not impacted by the changes proposed to the dossier
    - no more systematic revision of CEPs in case of major revisions.

Co-existence of “old”, “hybrid” and “CEP 2.0”

- A number of CEP holders submitted a revision to switch to the CEP 2.0.
- No fixed timeline or obligation to switch to the CEP 2.0.
  - Technically not possible to update all existing CEPs to the “new look”, neither for Industry nor for EDQM.
  - Balance needed between updating existing CEPs to the “new look” and the burden generated for holders, EDQM and other users.
- The uptake is monitored and if needed, enhancing the switches to CEP 2.0 will be considered.

Implementation issues

- Increased workload for EDQM and also CEP applicants/holders.
- Many on-going applications at the time of implementation, which triggered additional questions to CEP applicants/holders to fulfill the latest requirements to deliver CEPs, mainly concerning the specification to be appended to the CEP.
- Many questions from CEP applicants/holders and CEP users (mainly FP manufacturers).
- Learning process for CEP applicants/holders, CEP users and EDQM.
- At the time of implementation, many files with missing SPOR/OMS ORG_ID and LOC_ID. Most of them have it now.

EMA SPOR/OMS **Org** and **Loc** IDs

- use of the EMA SPOR/OMS Organisation (**Org**) and Location (**Loc**) ID is mandatory for all sites listed in the application form.
- Administrative changes related to the address or the name of the entity should be handled via EMA SPOR/OMS database **before** applying for a CEP application or a revision.
- EDQM considers information reported on EMA SPOR/OMS database as the official one to be taken into consideration.

Specification (3.2.S.4.1)

- The specification required to control the substance should be presented in tabular format.
- Parameters, acceptance criteria and reference of the method should be clearly reported in the table (e.g. Ph. Eur., in-house).
- In case of in-house impurities controlled in the substance, an unequivocal chemical name of the compound should be used (in-house code may be added if relevant).

How to present specification in section 3.2.S.4.1

Example 1

Parameters	Acceptance criteria	Reference
Identification Test A (IR) Test B (HPLC)	 Complies to reference Positive	Ph. Eur. current edition
Specific optical rotation (o.d.b.)	+158° to + 167°	Ph. Eur. current edition
Loss on drying	≤ 0.5%	Ph. Eur. current edition
Related substances		Ph. Eur. current edition
Impurity A	≤ 0.5%	
Impurity B	≤ 0.3%	
Impurity C	≤ 0.15%	
Unspecified impurities	≤ 0.10%	
Total	≤ 1.5%	
Assay (o.d.b.)	97.0% to 102.0%	Ph. Eur. current edition
Residual solvents (by GC)		In-house
Ethanol	≤ 5000ppm	
N,N-dimethylformamide	≤ 880ppm	
N-Nitrosodimethylamine (NDMA) (by GC-MS)	≤ 3.0 ppm	In-house

How to present specification in section 3.2.S.4.1

Example 2

Parameters	Acceptance criteria	Reference
Identification Test A (IR) Test B (HPLC)	 Complies to reference Positive	Ph. Eur. current edition
Specific optical rotation (o.d.b.)	+158° to + 167°	Ph. Eur. current edition
Loss on drying	≤ 0.5%	Ph. Eur. current edition
Related substances		In-house
Impurity A	≤ 0.5%	
Impurity B	≤ 0.3%	
Impurity C	≤ 0.15%	
Unspecified impurities	≤ 0.10%	
Total	≤ 1.5%	
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How to present specification in section 3.2.S.4.1

- **Example 1 – Two <u>additional</u> in-house analytical test procedures to those of the Ph. Eur. monograph** are required to control the quality of the substance. Those additional methods are methods, which are either not detailed in the Ph. Eur. monograph for the substance or which are applied when the Ph. Eur. monograph methods are not suitable to control impurities or which are used to control additional parameters.

- RESULT ⟹ **Two** methods appended to the CEP.

- **Example 2 - Two additional in-house analytical test procedures and one <u>alternative</u>** which following validation and cross validation with the method of the Ph. Eur. monograph, has been determined to be equivalent.

- RESULT ⟹ **Two** methods appended to the CEP.

How to present specification in section 3.2.S.4.1

If a CEP holder decides to include a parameter in their specification, that is present only to satisfy a regulatory requirement in another region (i.e. non-European requirement), it is strongly encouraged to separate them from the other parameters and to clearly identify them as such (e.g. as "applied but not necessary to satisfy European regional requirements").

Specification parameters not necessary to satisfy European regional requirements		
Assay by titrimetry (o.d.b.)	99.0% to 101.0%	USP
Heavy metals	≤ 10 ppm	Ph. Eur. 2.4.8
Water content (KF)	≤ 0.5%	JP

The relevant analytical procedures **will not be appended to the CEP**, the related parameters are considered "unnecessary", consequently also the methods.

Specification (3.2.S.4.1)

- EDQM does not take position on **skip testing** unless specifically foreseen in quality guidelines e.g. ICH Q3D for elemental impurities, ICH M7 for mutagenic impurities and EMA/425645/2020 for nitrosamine impurities. Therefore, any other reference to skip testing should not be reported in section 3.2.S.4.1.
- Microbiological parameters are generally **out of scope** of the CEP procedure. They should not be reported in the specification (not even as non-European regional requirement) and should be addressed in the Marketing Application.

Specification for special grades

- Specification attached to the CEP are considered approved by EDQM.
- Specification for grades (e.g. particle size, identification of polymorphic forms, etc.) should be included only if the applicant requests a related grade.
- Acceptance criteria such as "for information only" or "as per customer requirements" are **never acceptable**.
- Tests for identification of polymorphic forms and other physical properties (e.g. PSD, bulk and tapped density, etc.) **cannot** be included in the specification as "applied but not necessary to satisfy European regional requirements").

Approved CEP specification, how this is applied in the MAA?

- The CEP holder may apply stricter limits compared to the acceptable requirements (Ph Eur and/or EU/ICH requirements).
- The MAH is responsible to propose appropriate tests and limits for the API, that are appropriate for the drug product. These will be assessed during the marketing authorization application (or variation).

Parameters	Acceptance criteria	Reference
Related substances		Ph. Eur. current edition
Impurity A	≤ 0.5%	
Impurity B	≤ 0.3%	
Unspecified impurities	≤ 0.10%	
Total	≤ 1.0%	
Residual solvents (by GC)		In-house
Ethanol	≤ 3000ppm	
N,N-dimethylformamide	≤ 880ppm	

Ph Eur Monograph

Limits:

- *impurity A*: maximum 1.0 per cent;
- *impurity B*: for each epimer, maximum 0.3 per cent;
- *unspecified impurities*: for each impurity, maximum 0.10 per cent;
- *total*: maximum 1.5 per cent;

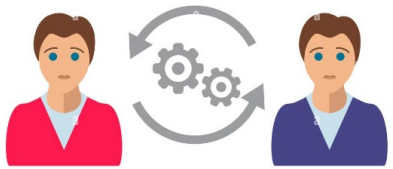
Information sharing between CEP holders & MAH

- Reminder to CEP holders in 2022 with the document "CEP holders responsibilities towards their customers" on the EDQM website (here)
- CEP holder shall provide information to their customers in addition to the CEP
- Reinforcement of this responsibility with the CEP 2.0

A commitment as part of the application form for a CEP

Effective sharing of information is checked during EDQM GMP inspections.

A specific sentence on this obligation in the CEP document



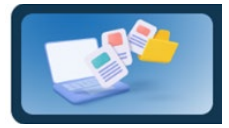
A specific sentence on this obligation in the CEP letter of access

Publication of history of procedures in the public Certification database, so users are aware of changes and can ask details from the CEP holders

On-line Certification database

- New features in addition to current ones:
  - EMA SPOR OMS ORG_ID and LOC_ID for holder
  - **Renewal date for the CEP (where not yet renewed)**
  - Access to short history of finalised procedures (which can be downloaded as pdf) with:
    - ✓ type of procedure (e.g. minor revision, notification, major revision, renewal, monograph revision)
    - ✓ closure date of the last procedure, outcome (i.e. CEP revised, CEP remains valid etc)
    - ✓ corresponding CEP number if any
- History available only for procedures opened as of 1 January 2020 (due to change of IT technology)
- More details can be found here.

Authorities database



- Restricted access for Ph. Eur. regulatory authorities, as well as other regulatory authorities accepting CEPs under suitable confidentiality agreements and MoU.
  - Publication on the EDQM website of the list of authorities having access to assessment and/or inspection reports.
  - Updated holder's declarations as part of the CEP application form to cover this aspect.
- Access to details of CEP applications, history of procedures, access to assessment reports for CEP applications and access to the corresponding CEP document for each procedure, if any.

Ressources on EDQM website

CEP 2.0 NEW PAGE IS ONLINE! MORE INFORMATION

- Webpage dedicated to the CEP 2.0 and FAQ section available on the EDQM website here, **updated regularly**.
- In case of doubt or question, contact the EDQM via the helpdesk (choosing the topic "CEP 2.0").
- Recording of webinars organised in May 2023 available here as training material together with the slides, explaining the changes and new requirements for the CEP dossier.

STAY UP-TO-DATE

Online training

The CEP 2.0 – Webinar for CEP holders and CEP users

Target audience

This webinar is of interest to CEP applicants, holders and users, including manufacturers and competent authorities.

WATCH NOW (Duration: 1 hours, 57 minutes)

Download the presentations

- The CEP 2.0 Webinar for CEP holders and CEP users presented by the EDQM
- Introduction to Organisation Management Service (OMS) presented by EMA

The Floor is Yours

FEEDBACK

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