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

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Revisions and renewals of CEPs: Principles, frequent changes and sister files

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Basic principles for maintaining a CEP

- Any change must be reported to EDQM for approval
- Original CEP is valid 5 years
- Holder needs to apply for renewal in time
- After renewal, CEP valid for an unlimited period, provided the dossier is kept up-to-date

- Revised CEP to be sent to customers
- Holder to inform customers of changes made

Revisions of CEPs: Background

- Based on EU Regulations on Variations to Marketing Authorisations
- Specific EDQM guideline for revisions of CEPs:
  - Management of applications for new Certificates of Suitability, Requests for Revision or Renewal of Certificates of Suitability and applications using the 'sister files' procedure (PA/PH/CEP (13) 110, 2R)
  - Guideline on requirements on revision / renewal of CEPs (PA/PH/CEP (04) 2, 7R corr)

A revision application (contents)

- **Module 1:**
  - Application form for Revisions (www.edqm.eu)
  - Comparative table (Annex 7 of application form) highlighting approved and proposed content, important to review easily the changes made
  - Discussion of the changes made & supportive data, as described in the EDQM guideline for Revisions.

- **Module 3:**
  - Update of all impacted sections

€ Fee to be paid at receipt of the invoice **€**

Timelines

- The EDQM timelines depend on the type of revision
  - 1 month (notifications) to 3 months (renewal, update following monograph revision)

Type of application	EDQM Timelines for assessment of initial application	Applicant Timeline to reply to first request for additional information	EDQM Timelines for assessment of reply to request for information	Applicant Timeline to reply to second request for additional information	EDQM Timelines for assessment of reply to request for information	CEP revised if application accepted ?
New	5 months	6 months*	4 months*	3 months*	4 months*	New CEP issued
		1 month #	1 month #	1 month #	1 month #	
Sister file	2 months	1 month	1 month	1 month	1 month	New CEP issued
Minor revision(s)	1 month	1 month	1 month	1 month	1 month	Revised CEP issued only if information on CEP requires to be changed otherwise a letter accepting the revision is issued
Major revision	2 months	1 month	1 month (TSE or Herbal: 2 months)	1 month	1 month (TSE or Herbal: 2 months)	Revised CEP issued
Monograph revision	3 months	1 month	1 month (TSE or Herbal: 2months)	1 month	1 month (TSE or Herbal: 2 months)	Revised CEP issued only if information on CEP requires to be changed otherwise a letter accepting the revision is issued
Renewal	3 months	1 month	1 month (TSE or Herbal: 2 months)	1 month	1 month (TSE or Herbal: 2 months)	Renewed CEP issued

* if the request from EDQM relates to significant information required to address the issues identified

if the request from EDQM relates to clarification of minor issues or update of the dossier

- 3-Round policy is applied. A request may be rejected if insufficient information is given
- Results/Statistics are published monthly

Cases where a separate CEP application is needed

- Addition of a new manufacturing site of the final substance that does not belong to the same group and **even when a qualified contract manufacturer**
- Changes to the manufacturing process resulting in:
  - Sterile grade of a non-sterile active substance
  - Non-sterile grade of a sterile active substance
  - Addition of raw materials resulting in simultaneous use of material from different origin (e.g. TSE risk material vs non TSE risk material/substance from animal/human origin vs non animal/human origin)
  - Different polymorphic forms
  - Introduction of a new substantially different route of synthesis (even when the impurity profile of the final substance is equivalent)

Types of changes

- Notifications (IN or AN) — Do & tell
- Minor revisions (incl. minor by default) — Tell & do when approved
- Major revisions — Tell & do when approved
- Renewal (after 5 years) — Tell & do when approved

- Update following revision of the monograph or following regulatory changes (initiated EDQM)
- Possibility to group revisions i.e. the same changes affecting several dossiers

The type of revision should be carefully selected

- Selecting the right type of revision facilitates the whole approval process
- Changes must be individually classified and identified in annex 7 of application form (if not, considered as not declared = not assessed = not approved)
- Notifications which do not meet the criteria are rejected by EDQM – need to apply again ➔ delays + costs
- Type of revision depends on the **potential impact on the quality of the final substance,** and not on the final result

The type of revision should be carefully selected (cont.)

- To classify a change as notification, all conditions listed in the EDQM Guideline on Revision/ Renewal of Certificates of Suitability to the European Pharmacopoeia Monographs should be met, and all supporting documentation should be provided.
- Any change not classified as a notification or as a major change should be classified as a **minor change by default**.
- Common examples are given for minor changes, but the list is not exhaustive.

Administrative changes

- Change in name and/or address of CEP Holder:

  ⚠ Same legal entity (except sold/merger)

- Change in name and/or address of:
  - Manufacturing site
  - Manufacturer of intermediate
  - Manufacturer of starting material

  ⚠ The location remains the same

Quality changes related to manufacture

Change in the manufacturing process of final substance

- The type of the revision depends on the type of changes made
  - ➢Slight modifications to operating conditions?
  - ➢Substantial changes to the process?

Change in the manufacturing process of final substance

➢Annual Notification

Minor changes only

Specification of the final substance and intermediates are unchanged and there is no adverse change in impurity profile AND the ROS remains the same

➢Examples:

- Adjustments to operating conditions (e.g. in temperatures, stirring/reaction times, pH range, loading order of materials within a same step).
- Changes/upgrades in equipment (e.g. new reaction vessels, driers, filters…), except for sterile substances.
- Introduction of inert process aids (e.g. activated charcoal, cellulose,...).
- Deletion of the use of recovered materials in the process.
- Deletion of an optional reprocessing step.

Change in the manufacturing process of final substance (cont.)

➢Minor by default:

- Any change not classified as a notification or a major change (or if all conditions of a change are not respected) should be classified as a **minor change by default.**

E.g. Introduction of alternative inorganic salts in order to control process parameters (e.g. sodium hydroxide instead of ammonium hydroxide for pH adjustment).

Change in the manufacturing process of final substance

➢MAJOR change

⚠ The introduction of substantially different route of synthesis (even when the impurity profile of the final substance is equivalent) should be requested as part of a **separate CEP application.**

If in doubt on the appropriate classification, please contact us via the EDQM helpdesk.

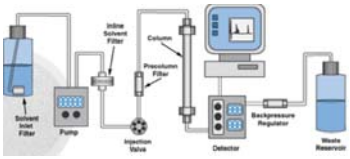
Change in the manufacturer of Intermediate

- The type of application depends on changes made to the synthesis (notification / minor / major)
- GMP compliance should be declared
- Information on sources of SM for the new supplier is needed
- If major changes are done in the synthesis – **Separate CEP application**

Quality changes related to the control of the final substance

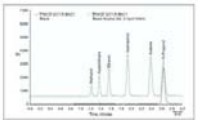
Change in specification for the final substance

- Tightening of limits for impurities, or deletions of non-significant tests (e.g. a test for odour.)
  - ➔ Annual Notification
- Widening of approved limits, but within the limits of the Ph. Eur. / ICH-VICH guidelines (e.g. widening limits within the range of ICH requirements for an ICH Class 2 or Class 3 residual solvent)
  - ➔ Minor change
- Widening limit for a specified (non Ph. Eur.) impurity
  - ➔ Major change



Change in specification for the final substance (cont.)

- A change to a **test procedure** is to be declared as:
  - ➢a **notification**, provided that all the conditions of the EDQM Guideline are met. The method should remain essentially the same: typically changes should be within the ranges allowed by Ph. Eur. general chapter 2.2.46 Chromatographic separation techniques.
  - ➢if not a notification → a **minor revision**.
    - ✓for a method used to control the final substance a summary of **validation** data may be needed.
- *Editorial changes* to a method description for control of the final substance should be submitted as a notification *only if appended to the CEP* since the CEP would need to be revised.



Renewal

- Holder to apply about 6 months before expiry
- 2 options:
  - ✓ Declaration that no changes occurred since the last revision
  - ✓ Minor revisions and notifications can be submitted at the time of the renewal **BUT NOT MAJOR REVISIONS**
  - → In both cases, include recent batch data for final substance
- Assessment will focus on compliance with
  - ✓ GM 2034
  - ✓ Recent Eur. Qual. gdls: e.g. impurities, Q3D, solvents
  - ✓ Nitrosamines risk

Update after monograph's revision

- Ensures that all CEPs refer to the current version of a Ph. Eur. Monograph
- When a revised Ph. Eur. monograph is published and an update is needed, a letter is sent to the CEP Holder* by EDQM asking to
  - ✓ provide data to demonstrate suitability of the monograph
  - ✓ clarify whether all related substances are controlled by the method of the revised monograph
  - ✓ Whether the final substance contains additional impurities
- Reply is mandatory – For monograph revisions classified as case B*
- Assessment takes 3 months
- If applicable a revised CEP is issued

When are CEPs revised?

- After any notification/minor revisions, update following implementation of a revised monograph, impacting the content of CEP
- After any major revision
- After renewal (renewed CEP)

In the other cases, an approval letter is sent by EDQM

What to do after approval of a request for revision/renewal ?

- **What to do with a revised CEP ?**
  - ➢Holder to provide a copy to their customers
  - ➢MAH to update relevant Marketing Authorisation Applications (variation)

  → Mandatory

- **What to do when a change is approved but CEP is not revised ?**
  - ➢Holder to inform customers, but there is no variation

  → Mandatory

Sister files

- Facilitates the treatment of similar dossiers
- Fast track procedure – a new application treated as a revision (2 months)
- Applicable to chemical/herbal applications only

- Substance is the same as for parent file for which the CEP is valid
- Holder is the same (or belongs to the same group) in both applications
- Differences with parent file could be classified as a revision

Sister file - Documentation

Module 1

✓Application form (for sister files)

✓Cover letter – Number of parent file indicated and overview of differences between parent/sister file (and subtitle to be included)

- The comparative table included in the application form is a **key document for acceptability of sister file**

- The comparative table should include all sections and should be sufficiently detailed to easily understand the differences between files.

Module 2

✓Quality overall summary (QOS)

Module 3

✓ Full technical documentation according to current procedures (as for standard new CEP application) → Complete dossier given not substituted by references to parent file

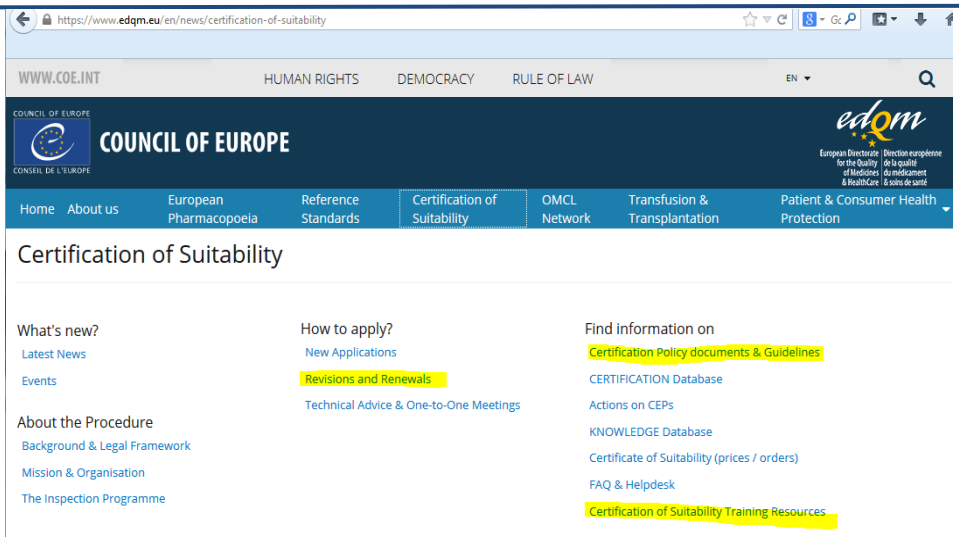
Sister files – more information

For more information on sister files relating to:

- Compliance to guidelines or policies
- Technical content of the dossier (M3)
- Lifecycle of the dossier
- Conditions for sister file acceptability

Please consult the EDQM document Guidance on Applications for "Sister Files" (PA/PH/CEP (09) 141 2R, November 2018)

Consult EDQM website…



- Any question, doubts on classification?

➔ Consult EDQM website for supportive guidance documents

- The Certification Department provides support through the EDQM helpdesk for general questions, or on the account communicated by EDQM for specific dossiers
- Technical advice meetings are also possible (fees)
- One-to-one meetings during conferences/CPHIs

Thank you for your attention

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