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)

• 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
- Renewal (after 5 years)
- 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).

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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. gdfs: 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...

Find information on:
- Certification Primary Documents & Guidance
- Certification Database
- Actions on CEPs
- KNOWLEDGE Database
- Certificate of Suitability (prices/orders)
- FAQ & Helpdesk
- Certification of Suitability training resources
• 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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