Revisions of CEPs

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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 CEPs and applications for revision/renewal of CEPs* (PA/PH/CEP (13) 110 1R)
  - *Guideline on requirements on revision / renewal of CEPs* (PA/PH/CEP (04) 2, 6R)

Guideline under revision and webinar to be organised ➔ EDQM website to be checked for public announcement during Summer 2018

- Webinar on "how to get acceptance of CEP revisions quickly" (2017)-training material available on EDQM website

A revision application includes

- 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.
- Update of all impacted sections of Module 3
- Fee to be paid at receipt of the invoice

How long does it take?

- 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
- The performances are published monthly

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)
- Update following revision of the monograph or following regulatory changes
- 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 the 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 company (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 the 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

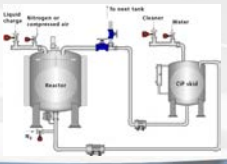
- Annual Notification

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.

Change in the manufacturing process of final substance (cont)

- Examples:
  - Introduction of inert process aids (e.g. activated charcoal, cellulose,...).
  - Addition of a reprocessing step which is the exact repetition of an existing step.
  - Repetition of washing/purification operations within the same step.
  - 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, typical examples:
  - Introduction of recovery procedures (e.g. solvents, intermediates).
  - Addition of a solvent in a synthesis step (excluding final purification) when that solvent is already used elsewhere in the approved process.
  - Introduction of alternative inorganic salts in order to control process parameters (e.g. sodium hydroxide instead of ammonium hydroxide for pH adjustment).
  - Changes to the process resulting in a new grade of the substance to be covered by the CEP (e.g. addition of a micronisation step).

Change in the manufacturing process of final substance

Substantial change to the manufacturing process: Change of catalyst, change to synthetic route

- MAJOR change

Need for more supportive data justifying the quality of the final substance

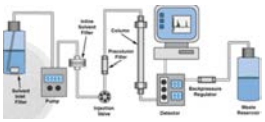
If there is a change in the impurity profile of the final substance, the new process has to replace the old one in the dossier, or a new application has to be submitted (not possible to have 2 different impurity profiles in the same application)

Change in the manufacturer of Intermediate

- The type of revision 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, impact on the control strategy (intermediate specification, IPC, carry-over of impurities) should be described

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.)

  ➔ Immediate Notification

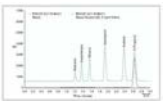
- Widening of approved limits, but within the limits of the Ph. Eur. / ICH-VICH guidelines (e.g. widening limits within the range of ICH requirements for an ICH Class 2 or Class 3 residual solvent)

  ➔ 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.

Changes related to stability

Re-test period/ storage conditions

- Addition / extension of a re-test period for the final substance
  - ➢ Minor change
- Removal of a re-test period for the final substance
  - ➢ Immediate notification
- Change in the storage conditions for the final substance
  - ➢ More restrictive: Immediate notification
  - ➢ Less restrictive: Minor change
- If minor/major changes are made, the impact on the re-test period should be discussed (cf. EU guideline Stability testing for applications for variations to marketing authorisation)

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.

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
- 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 ?

- **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

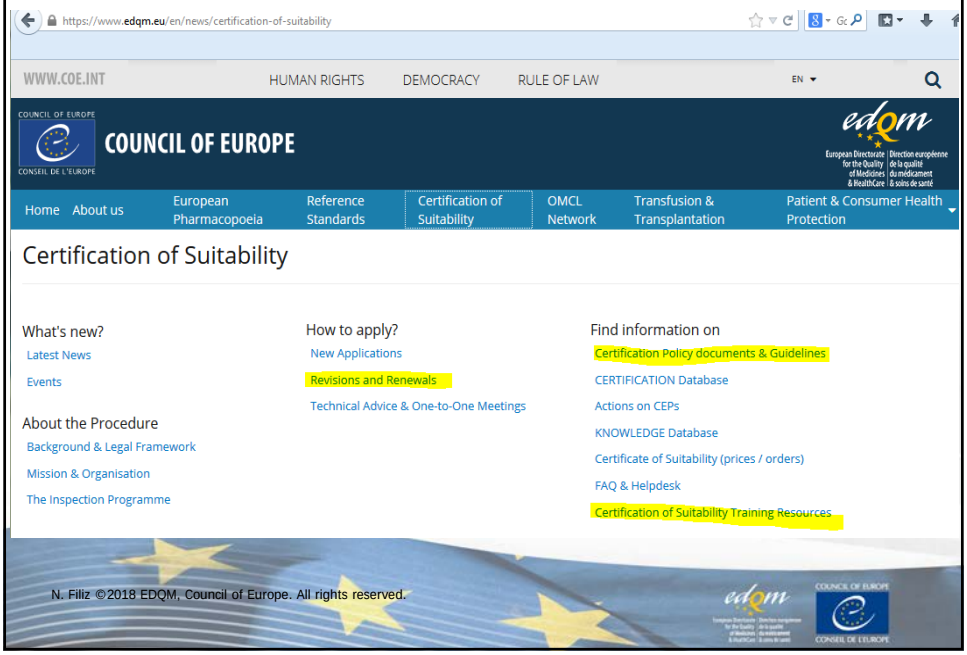
Sister files

- Facilitates the treatment of similar dossiers
- Fast track procedure (3 months)
- Applicable to chemical applications only
- Substance is the same as for parent file for which the CEP is valid
- Holder & manufacturer are in the same group
- Differences with parent file could be classified as a revision

Sister files

- Scope, conditions and typical examples are given in EDQM Guidance on applications for « sister files » PA/PH/CEP (09) 141,1R
  - ➢ Alternative process (different purification procedures)
  - ➢ Alternative site

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