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

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Building successful CEP revision applications

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Module 7 (Live webinar)

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Summary of the presentation

- Revisions and renewals of CEPs – an overview
- How to build up a successful dossier for revisions of CEPs and avoid deficiencies – Illustrative and practical examples
- Switch to CEP 2.0
- Take home messages

Revisions and renewals of CEPs – an overview

Basic principles for maintaining a CEP

- Any change must be reported to EDQM for approval
- **The dossier must always be kept up-to-date**

Holder to:

- ✓ **inform customers of changes made following each revision**
- ✓ **send revised CEP** to customers as soon as a revised CEP has been issued

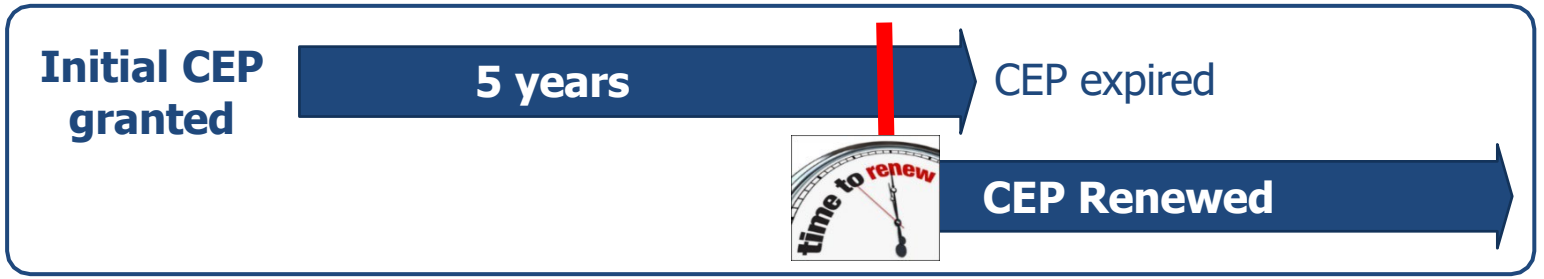
Refer to the EDQM document:

CEP holders responsibilities towards their customers (PA/PH/CEP (21) 57)

Validity of CEP:

- Limited to **5 years** from the first issued date
- **Unlimited <u>after</u>** completion of the **Renewal procedure**

Provided that the dossier is always **kept up-to-date**



Need for revisions of the CEPs

Once a new CEP is granted, the companies can apply for revisions of their certificate in order to:

- be up to date with the most recent legal requirements
- have the changes in the process and in the controls approved
- update the certificate with the administrative changes

Based on EU Regulations on Variations to Marketing Authorisations

- **Specific EDQM guidelines** for revisions of CEPs, available on the EDQM website:
  - **Guideline on Requirements for Revision / Renewal of CEPs**
    - (PA/PH/CEP (04) 2, 7R corr, September 2018)
  - EDQM guidance on **Applications for "Sister Files"**
    - (PA/PH/CEP (09) 141, 2R, November 2018)
  - **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, 3R, November 2021)

Useful guidelines and policy documents

- EDQM policy documents can be found here:

https://www.edqm.eu/en/certification-policy-documents-guidelines

- European Pharmacopoeia (Ph. Eur.) with its supplements (regularly being updated)

- EMA guidelines

- ICH guidelines

How to choose the correct type of revision

EDQM policy document PA/PH/CEP (04) 2

"Guideline on requirements for revision/renewal of CEPs"

(will be revised after the EU Guideline for Classification of Variations is updated)

- lists types of changes, conditions to be fulfilled and necessary documentation required for submission of revisions
- should be used to choose correct type of revision (what types of changes lead to what type of revisions)
- should be consulted before any submission of a revision in order to avoid misclassification of changes which would lead to rejection of the request for revision

EDQM keeps right to reject or reclassify certain revisions if needed.

Types of changes

Changes listed in the EDQM Guideline for revisions/renewals can be of several types:

1. **Administrative changes**
2. **Quality changes: apply to chemical/double and herbal CEPs**
3. **TSE changes**
4. **Use of CEP in an application for another CEP**
5. **Renewal**
6. **Transfer of holdership**

How to make best use of the EDQM Guideline for revisions/renewals

4.II.1.1 Change in the manufacturer of a starting material used in the manufacturing process of the final substance	Conditions	Specific documentation	Type of change
a) The proposed manufacturer of the starting material is part of the same group as the currently approved manufacturer	1, 2	1, 2, 3, 4	IN
b) The proposed manufacturer of the starting material is not part of the same group as the currently approved manufacturer	1,2	1, 2, 3, 4	MIN
c) The proposed manufacturer of the starting material uses a different route of synthesis or manufacturing conditions which impact the specifications of the starting material		1, 3, 4	MIN
d) The proposed manufacturer of the starting material uses a different route of synthesis or manufacturing conditions which impact the specifications of the final substance			MAJ (*)
e) The proposed manufacturer of the starting material is used in the manufacturing process of a biological substance		1, 3, 5	MAJ

Conditions	
1.	The specifications of the starting material are identical to those already approved.
2.	The final substance is not a biological substance or a sterile substance.
Documentation	
1.	A declaration from the Certificate holder that the specifications of the final substance are the same as those already approved.
2.	A declaration from the Certificate holder that the specifications and the quality control procedures of the starting material are the same as those already approved. If a different route of synthesis is retained for the new supplier, the synthetic flowchart of how the starting material is obtained should be provided.

List of changes classified as:

- Notification:
  - Immediate (**IN**)
  - Annual (**AN**)
- Minor change (**MIN**)
- Major change (**MAJ**)

Non-classified changes are:

Minor changes by default

Types of revisions

Depending on classification of changes, revisions are:

- Notification: may contain immediate (IN), annual (AN) or group notifications
- Minor revision: may contain notifications and minor changes
- Major revision: may contain notifications, minor and major changes
- Sister file: specific type of revision procedure where the company applies for a new certificate which would cover a similar process to the parent file (more on the following slides)

Other types of revisions:

- Transfer of holdership
- Renewal (specific revision 5 years after the CEP was initially granted)
- Dossier update following a revision of the Ph. Eur. monograph (may be submitted as part of minor or major revision or renewal if applicable)

Classification of changes – Types of application

Do & Tell	Tell & Do	
Notification (IN / AN)	**Minor changes (MIN)**	**Major changes (MAJ)**
Possible only if: ➢ **<u>All</u> the conditions** listed in the guideline **are met** ➢ Changes **without any impact** on the quality of the final substance ➢ Cover all **administrative changes**	➢ **Minor changes** listed in the guideline ➢ **Minor changes by default** (e.g. non-classified changes)	➢ **Potential impact** on the quality of the final substance ➢ In some cases, the need for a separate application should be considered *(Sister file procedure)*

Types of revision and corresponding types of changes

Examples of changes when conditions of the EDQM guideline PA/PH/CEP(04)2 are met:

Notifications:

- Change of the name of an approved intermediate manufacturer
- Tightening of specification limits for a starting material/intermediate
- Minor change in an analytical procedure for the final substance

Minor revision:

- Addition of a new starting material manufacturer when there is no impact on the final substance specification
- Introduction of an intermediate manufacturer using a different solvent in the process, when this solvent is already used elsewhere in the process and is still demonstrated absent in the final substance
- Revised discussions on impurities (elemental, nitrosamines, mutagenic)
- Addition/extension of a re-test period

Major revision:

- Introduction of a new solvent in the penultimate step of the process, when this solvent has been demonstrated absent in the final substance

Sister file:

- Introduction of a new solvent in the last step of the process
- New substantially different route of synthesis for the same substance

Outcome of the assessment of a CEP revision

Update **CEP 2.0**

When are CEPs revised?

- After any change which **impacts the content of the CEP or its annexes**, resulting from a notification, revision or renewal

- In the other cases, an **approval letter** is issued by EDQM:

APPROVAL OF REQUEST
CEP REMAINS VALID

What to do with a revised CEP ? → Mandatory step

- Holder to provide a copy to their customers
- MAH to update relevant Marketing Authorisation Applications (variation)

What to do when a change is approved but CEP is not revised ? → Mandatory step

- Holder to inform customers, but there is no variation of Marketing Authorisation Application

Refer to the EDQM document:

CEP holders responsibilities towards their customers (PA/PH/CEP (21) 57, January 2022)

How to apply for revisions

Module 1

- **Cover letter**
- Complete **application form**, including:
  - **Comparative table** of the changes
    Refer to: Annex 7 of the application form
  - Updated declarations if needed
    Annexes 3 to 6 of the application form

Module 2: Not required but may be submitted and **should be in line with Module 3**

Module 3

- Update of **all impacted section(s)** of the CTD dossier

Data supporting the request for revision

Applicants should use and refer to the:
EDQM **Guideline on requirements for revisions and renewal** (PA/PH/CEP(04)2)

How to apply for revisions: Application form

since June 2023

Application Form

REQUEST FOR REVISION OR RENEWAL OF A CERTIFICATE OF SUITABILITY

(to be completed for each request for revision or renewal of a Certificate of Suitability to the monographs of the European Pharmacopoeia, in accordance with Resolution AP-CSP (07) 1)

1.2 **Type of application** *(please tick one application box only)*

☐ Notification *(may include several changes)*

☐ Minor revision *(may include several changes including notifications)*

☐ Major revision (*may include notifications and minor changes)*

☐ Renewal

☐ *without changes* ☐ *with changes (notifications and/or minor changes – no major change)*

☐ Transfer of holdership

☐ Grouped revision *(several dossiers affected by the same change[s])*

Please list the dossier numbers and substances below:

NB: if needed, an annex with list of all affected dossiers may be provided

CEP	[Substance name]

Always use the **latest version**

(application form, declarations, Holder's commitment)

It is the **CEP holder's responsibility** to:

- carefully **choose the type of revision**
- by **taking into account all the changes** declared, in line with the EDQM Guideline for Revision (PA/PH/CEP(04)2)

How to present the documentation: Comparative table

- Key element for the **declaration of changes**
- For any request for revision (including notifications, renewals with changes and sister files)

Changes must be **individually classified and declared** in the comparative table

IF NOT, change(s) considered as: not declared = not assessed = **not approved**

4. COMPARATIVE TABLE

The comparative table should highlight the differences between the approved and proposed text of module 3, together with the correct classification of each change according to the EDQM Guideline for revisions.
The justification for the changes should be fully developed in the cover letter.

Annexes	Yes	N/A
7) Comparative table	☐	

Comparative table

- Key element for the **declaration of changes**
- For any request for revision (including Notification or Renewal with changes)

Changes must be **individually classified and declared** in the comparative table

IF NOT, change(s) considered as: not declared = not assessed = **not approved**

- Format of the comparative table available as **Annex 7 of the application form:**

CTD section reference	Approved text of the dossier[1]	Proposed text of the dossier[2,3]	Classification[4] of the change(s) and brief justification

[1, 2] specify the precise approved and proposed wording of the CTD section

[3] underline or highlight the changes in the text

[4] classification according to current version of EDQM Guideline for revisions/renewals PA/PH/CEP (04) 2, including a brief description and justification of the changes, if necessary a complete justification should be provided in the cover letter

Comparative table: expectations

Changes should be:

- **easily identifiable**

- **highlighted** (*e.g.* in bold)

Copy **as much information as needed**

to ensure:

- an **easy overview of the change**

- while remaining in a **legible format**

(e.g. Route of synthesis / Flowcharts copied in the table)

CTD section reference	Approved text of the dossier	Proposed text of the dossier	Classification of the change(s) and brief justification.
3.2.S.2.1	-	No change	-
3.2.S.2.2	**Step 1:** In a clean reactor charge solvent **toluene** (**100 L**), SM 2 (50 kg), acid (**1 L**). Heat and maintain the reaction mass at **80 to 85°C** for **40** hours. Cool reaction mixture and stir for **2 to 3 hours** at 0-5°C. Filter the reaction mass through a Nutsche Filter. Wash the cake with **10L** chilled solvent 1. …	**Step 1:** In a clean reactor charge solvent **methanol** (**910 L**), SM 2 (50 kg), acid (**1.3L**). Heat and maintain the reaction mass at **85 to 90°C** for **25** hours. Cool reaction mixture and stir for **2 hours** at 0-5°C. Filter the reaction mass through a Nutsche Filter. Wash the cake with **8L** chilled solvent 1. …	**Major change:** replacement of solvent toluene by methanol and optimisation of the manufacturing process. Refer to module 1 pages xx and xx for discussion on impact of the change and discussion on carry-over , along with analytical data
3.2.S.2.3	**Process water** Description : clear colourless liquid pH: 5.00 to 7.00 Conductivity : NMT 1,30µS/cm (at 25°C) Total organic carbon: NMT 500 ppb Nitrates: **NMT 0.2 ppm**	**Process water** Description : clear colourless liquid pH: 5.00 to 7.00 Conductivity : NMT 1,30µS/cm (at 25°C) Total organic carbon: NMT 500 ppb Nitrates: **NMT 0.1 ppm**	**Notification :** tightening of specification for nitrates in process water

The **last column of the table** is dedicated to the **classification and justification of the change**:

- Provide a brief description of the change and explain the context
- Classification justified in line with the EDQM Guideline for Requirements for Revision/Renewal (PA/PH/CEP (04) 2)
- If applicable, describe where corresponding **supporting information** is available (for instance: Module 1, page *x/x*)

Revisions and their timelines

EDQM policy document PA/PH/CEP (13) 110 (will be revised soon)

"Management of applications for new Certificates of Suitability, Requests for Revision or Renewal of Certificates of Suitability and applications using the 'sister files' procedure"

Describes timelines for each type of revision:

- After receipt of the documentation by the applicants, the EDQM reviews it within 23 to 69 working days (1-3 months) depending on type of revision
- If estimated necessary, the EDQM may send a request for additional information / clarification / dossier update and the applicant has approx. 1 month (30 calendar days) to reply
- EDQM then has approx. 1 month (23 working days) to evaluate the additional information
- Revised CEP is issued only if the information on the CEP needs to be updated

Quality of submission impacts the revisions timelines

Information provided in the dossier is insufficient or not fully appropriate

↓

Assessors have to ask additional questions and clarifications

↓

This generates additional rounds of assessment

↓

The revision timeline is prolonged

↓

The certificate or the request approval is issued few months later

Revision following an update of the Ph. Eur. monograph

CEP holder responsibility:

(EU Directive 2001/83/EC)

To ensure compliance to the current version of the Ph. Eur. monograph

When a revised Ph. Eur. monograph is published:

- CEP Holder is informed by the EDQM via a letter about the classification:

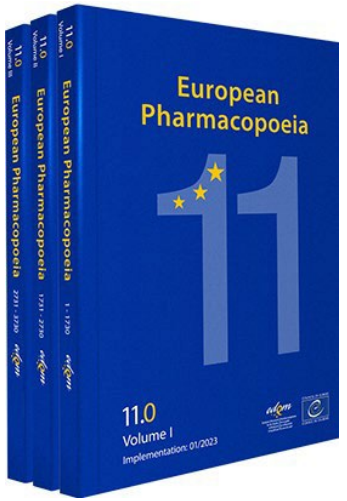
Case A

The changes (e.g. updated specification) should be implemented and should be included in the next request for revision.

Case B

The CEP holder is asked to:

- ✓ provide sufficient 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



Timeline for assessment :

3 months

Notifications

- It should be formally **confirmed** that **<u>all the conditions are met</u>, as listed in the EDQM guideline on Requirements for Revision/Renewal of CEP**
- **The corresponding documentation listed in the EDQM guideline for revisions/renewals should be provided** (for instance declarations, batch analysis data…)

4.II.1.6 Change in test procedure for in-process tests or limits applied during the manufacture of the final substance or specification limits for a starting material /reagent/intermediate	Conditions	Specific documentation	Type of change
a) Tightening of the limits of in-process tests applied during the manufacture of the final substance or specification limits for a starting material /intermediate / reagent used in manufacture	1, 2, 3	1	AN

Conditions	
1	The change does not result from unexpected events arising during manufacture.
2	Any change should be within the range of currently approved limits.
3.	The test procedure remains the same (e.g. a change in column length or temperature, but not a different type of column or method), or changes in the test procedure are minor.

Documentation	
1.	Comparative table of approved and proposed in-process tests or limit in starting material/intermediate/reagent.

Notifications – examples

Type of change	Type of notification	Examples
Administrative	Immediate notification (IN)	Change of the name of an approved intermediate manufacturer (administrative change without change of the physical location)
Quality change	Annual notification (AN)	Tightening of specification limits for a starting material or an intermediate
Quality change	Annual notification (AN)	Deletion of a non-significant specification parameter for a starting material or an intermediate
Quality change	Annual notification (AN)	Minor changes to an analytical procedure for the final substance
Quality change	Immediate notification (IN)	Change in the composition of the immediate packaging of the final substance (if not sterile and if not liquid) regardless of the re-test period being mentioned or not on the CEP

Minor and major revisions

- Confirmation that the conditions for the changes are met is not enough. Appropriate justification has to be provided for introduction of the change
- Justification: Reason why the change is proposed + supporting analysis (risk analysis, theoretical considerations, experimental studies)
- For example: replacement of one starting material with another one which uses different route of synthesis of the starting material

Justification to be mentioned in the comparative table (and in detail in the supportive documentation if necessary or module 3 sections):

- the previous manufacturer stopped production/business reasons/to increase market demands…
- we assessed quality risks in line with ICH Q3D / ICH M7 (as applicable), performed spike/purge studies, concluded that the quality of the intermediates and final substance is unchanged…

Organisation of the submitted information

All minor and major changes require supporting documentation to be submitted (for example, risk estimation, details about spike/purge studies, explanation of the experimental studies design, interpretation and discussion of results, theoretical discussions…). Few tips:

- Number of pages submitted (for example, is there a need to submit long explanations on dozens of pages if you are only adding a micronized grade? And to repeat this information in detail in the cover letter, in the comparative table, in a supporting annex and in the concerned section?)
- Submit only parts of the CTD dossier which have changed. There is no need to submit all sections of the dossier if you are making changes only in section 3.2.S.2.3 for example

Quality of information submitted

- Introduction of recovery of solvents: exact points of recovery and re-introduction of the recovered solvents should be indicated in the process flow-chart and in the description of the process. Recovery procedures have to be described.
- Introduction of reprocessing of materials: triggers for reprocessing have to be stated and reprocessing procedures have to be described (reworking is not allowed)
- Spike/purge studies: spiked batches (batch No.) → result in intermediate batches (batch No.) → resulting in final substance batches (batch No.) – link between the spiked, analysed and produced batches has to be highlighted
- Starting materials: routes of synthesis, manufacturers (not suppliers!) full addresses, discussion about impurities, any changes in specification or analytical procedures to be highlighted as well as its impact on the subsequent intermediates and final substance quality
- Introduction of a Risk Management Summary (RMS) for elemental impurities: route of administration has to be stated, definition of "absent" has to be stated (e. g. < 30% of ICH Q3D option 1; if option 2a: MDD used for calculation should be stated). If you submit an RMS, it will automatically be appended to the certificate

Minor changes – examples

Type of change	Type of a minor change	Examples
Quality	Typical minor	Introduction of recovery procedures
Quality	Typical minor	Addition of a solvent in a synthesis step which is not the final purification and when this solvent is already used elsewhere in the approved process
Quality	Typical minor	Changes to the process resulting in a new grade of the substance including micronisation
Quality	Typical minor	Introduction or revision (non-editorial changes) of a RMS (Risk management summary) regarding elemental impurities
Quality	Typical minor	Change of a limit for a mutagenic impurity in a starting material/intermediate/reagent according to the principles and limits of the ICH M7 guideline
Quality	Minor by default	Addition of risk assessment for nitrosamines
-	Minor by default	Switch to CEP 2.0 format (more on the following slides)

Major changes – examples

Type of change	Examples
Quality	The proposed manufacturer of the intermediate replaces the previously approved intermediate manufacturers and uses a substantially different route of synthesis or manufacturing conditions which are likely to change the specifications (qualitative and/or quantitative impurity profile) of the final substance (e.g. change in synthetic strategy, new reagents, solvents, materials are introduced into the synthesis)
Quality	Widening of in-process test limits applied during the manufacture of the final substance or specification parameter for a starting material / intermediate / reagent which may have a significant effect on the overall quality of the final substance
Quality	Addition of a new in-process test and limit regarding a critical parameter
Quality	Deletion of in-process test limits applied during the manufacture of the final substance, which may have a significant effect on the overall quality of the final substance

Rejection of a request for revision

Type of revision (e. g. notification, minor, major) is not appropriate

↓

EDQM rejects the request for revision

↓

The company has to submit the revision again

(this time appropriately classified)

and pay the fees again for the new revision

↓

At least 1-2 months are lost + additional costs for the company

Examples

We are submitting several AN, one IN and a risk assessment for nitrosamines. What revision should we apply for?

→ Minor revision

Submission of risk assessment for nitrosamines is a minor change by default. Therefore, a minor revision should be submitted

Examples

We have optimised the penultimate stage of the process where crude final substance is obtained.

We noticed that increased levels of impurity XYZ are formed with the new process in the crude final substance. This impurity was previously controlled as unknown at NMT 0.15% in the crude final substance.

Now, with the optimised process, we have added a limit NMT 0.20% for impurity XYZ in crude final substance. The limit for unknown impurities in the crude final substance stays unchanged.

Same analytical procedure is used for analysis of impurities in the crude final substance and in the final substance.

We have analysed purge of the impurity XYZ in the optimised process from crude substance to final substance and we have found its levels within the limit for unspecified impurity (NMT 0.10%) in new final substance batches.

We understood this as widening of a limit for an impurity and we wish to submit a major revision.

→ Acceptable

Although there is no impact on the final substance specification, its quality is potentially impacted by the introduced change in the process. Major revision is appropriate.

Examples

We wish to add an alternative intermediate manufacturer which uses a substantially different route of synthesis for the intermediate (different reagents, solvents and starting materials are used and different early intermediates are involved). We are applying for a major revision.

→ Rejected

We should either replace the old intermediate process with the new one and submit a major revision, either submit a separate sister file application with the new intermediate process (change 4.II.1.2 c in the EDQM guideline)

Examples

We have changed the process:
New solvent has been introduced in
an earlier or penultimate step

↓

There is a potential impact
on the final substance quality

↓

Do relevant batch results confirm impact on the final substance?

May the information reported on the CEP be modified?

No → For example, solvent demonstrated absent
in the final substance
(<10% of its ICH Q3C limit)

MAJOR REVISION

Yes → Solvent <u>not</u> demonstrated absent
in the final substance
(>10% of its ICH Q3C limit)

SISTER FILE

We have changed the process:
New solvent has been introduced in
the last step

↓

SISTER FILE

Sister file procedure

In certain cases, it may not be possible to apply for a revision of the initial CEP, and a new application should be requested via the 'Sister file' procedure

The 'Sister file' procedure has the same timeline as for a major revision

EDQM policy document PA/PH/CEP (09) 141

"Guidance on applications for sister files"

https://www.edqm.eu/en/certification-policy-documents-guidelines

- **To apply:**

➢ A **specific application form**

➢ The **comparative table** to indicate the differences between the existing CEP (Parent file) and the new application proposed via the Sister file procedure

➢ a **complete dossier** in eCTD format

Sister file procedure

- ✓Facilitates the treatment of **similar production processes**
- ✓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** and a **comparative table** should be given

Sister file procedure

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
- The **solvents used in final purification steps** have been changed
- A new solvent is introduced that **cannot be demonstrated absent**
- **Substantially different route of synthesis**?
  - Different starting materials
  - Different intermediates
  - Use of different catalysts/reagent

This applies even when the impurity profile of the final substance is unchanged

Sister file procedure

Documentation needed:

- **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)
  - ✓ **Comparative table:**
    - as included in the application form, is a **key document for acceptability of sister file**
    - **should include all sections** and be **sufficiently detailed** to easily understand the differences between the "Parent" and the "Sister" dossiers
- **Module 2**
  - ✓ Quality overall summary (QOS), which **should be coherent with Module 3**
- **Module 3**
  - ✓ Full technical documentation according to current procedures (as for standard new CEP application)

→ **Complete dossier should be given,** not substituted by references to the parent file

Renewal procedure

Upcoming **update CEP 2.0**

Initial CEP granted → **5 years** → CEP expired

6 months before the expiry date of the CEP

CEP Renewal procedure

Renewal is a specific procedure of review of the dossier after the experience with the process has been gained. Renewal assessment focuses on compliance with:

- Ph. Eur. general monograph 2034
- key regulatory changes – recent European quality guidelines (e. g. nitrosamine risk assessment)

Documentation:

- **Updated declarations for each manufacturing site** (Annex 3a and Annex 4 of the application form)
- **Recent** batch data (≤18 months)

How to apply for renewal of your certificate

GUIDELINE ON REQUIREMENTS FOR REVISION/RENEWAL OF CERTIFICATES OF SUITABILITY TO THE EUROPEAN PHARMACOPOEIA MONOGRAPHS
PA/PH/CEP (04) 2, 7R corr, current version

5. Renewal of the certificate of suitability	Conditions	Specific documentation	Type of change
a) No change has been made since the last CEP was granted or last revision approved	1	1, 2, 3	Renewal
b) Changes are included in the request for renewal	1	2, 3, 4, 5, 6	Renewal

Conditions
1. No major changes to the content of the CEP application are introduced.

Documentation
1. A statement that no changes that may affect the quality, safety or efficacy of the final substance have been made.
2. Certificates of analysis from at least two recent production batches.
3. Updated declarations as annexes to the application form.
4. An updated dossier in CTD format and/or updated sections affected by the changes.
5. List of changes introduced in the format of a comparative table (i.e. approved text vs proposed text).
6. Relevant data supporting each change as described in this guideline.

Condition:

- No Major change

Documentation depending on:

- Renewal without changes (**5a**)
- Renewal with changes (**5b**)

Renewal

Request for renewal:

- should be submitted about 6 months before the expiry date of the CEP
- should not contain any major change
- can include notifications, minor changes and updates of dossier following a revision of the Ph. Eur. Monograph (if applicable)
- should include risk assessment for nitrosamines (if not previously submitted)
- should have sections 3.2.S.4.1 and 3.2.S.4.2 updated in line with CEP 2.0 requirements if applicable (more about this later in the presentation)
- should include recent batch data (batches produced within last 18 months) or if such data are not available at time of renewal, a commitment should be given to provide batch data to EDQM once they are available

How to apply for revisions: Renewal application

*Updated application form since **June 2023***

Application Form
REQUEST FOR REVISION OR RENEWAL OF A CERTIFICATE OF SUITABILITY

(to be completed for each request for revision or renewal of a Certificate of Suitability to the monographs of the European Pharmacopoeia, in accordance with Resolution AP-CSP (07) 1)

1.2 **Type of application** *(please tick one application box only)*

☐ Notification *(may include several changes)*

☐ Minor revision *(may include several changes including notifications)*

☐ Major revision (*may include notifications and minor changes)*

☐ Renewal
☐ *without changes* ☐ *with changes (notifications and/or minor changes – no major change)*

☐ Transfer of holdership

☐ Grouped revision *(several dossiers affected by the same change[s])*
Please list the dossier numbers and substances below:
NB: if needed, an annex with list of all affected dossiers may be provided

CEP	[Substance name]

Attention:
Even if your renewal is without changes, you should still submit:

- recent batch data (or a commitment to provide it once available if not available at time of renewal)
- risk assessment for nitrosamines (if not previously provided)

Examples of revisions

We wish to add a new starting material manufacturer in addition to an already approved starting material manufacturer.

The new starting material manufacturer uses a different synthetic route for the same starting material, which in this example can be a trigger for application of ICH M7 guideline.

We have assessed the potential impact on the quality of the final substance taking into account ICH Q3D and ICH M7 guidelines and performed an update to our risk assessment for nitrosamines.

- Does this change impact the starting material specification?
- No impact on the intermediates and final substance quality:

  → minor revision
- Impact on the intermediates, but not on the final substance quality:

  → major revision or sister file
- Impact on the final substance quality: → sister file

Revisions and potentially mutagenic impurities: example

We wish to change the control strategy for a potentially mutagenic impurity XYZ controlled regularly in final substance from ICH M7 option 1 to option 4.

Justification: We have demonstrated that the impurity levels in final substance are below 30% of TTC.

→ Not accepted

- ICH M7 guideline does not associate levels below 30% of TTC with option 4 control strategy
- ICH M7 guideline (sections 8.1 and 8.2) states that process parameters that impact the residual impurity levels should be understood, including fate and purge knowledge. No fate of the impurity has been discussed, no purge experiments have been performed. → Not acceptable
- ICH M7 Q&A 8.1, 8.2, 8.3, 8.5 and 8.6 give clarifications related to option 4 control strategy. Critical levels are 1% of TTC and 10% of TTC
- Important: ICH M7 Q&A 8.1 highlights: case by case assessment for option 4

Revisions and potentially mutagenic impurities: example

We are replacing the approved process for an intermediate with a new process which results in increased levels of a potentially mutagenic impurity XYZ in final substance.

Control of the impurity XYZ at TTC level in final substance is proposed to be added (ICH M7 option 1 control strategy). We have submited a major change in line with change 4.II.1.2 c) from the EDQM guideline PA/PH/CEP (04) 2 for revisions.

→ Rejected

Although the approved process is replaced with the new one, the resulting quality of the final substance from the new process is not equivalent with the final substance from the approved process.

→ Sister file application is needed

(Same approach should be used for a non-mutagenic impurity too)

Revisions and potentially mutagenic impurities: example

Spike/purge studies

For a sister file application (which has a slightly different route of synthesis than in the approved parent file), we are proposing an ICH M7 option 3 control strategy for impurity XYZ which is controlled at NMT 0.05% in starting material.

TTC = 20 ppm

Among other supportive information, we have performed spike studies: we have spiked starting material with 0.04% of the impurity XYZ and found that the corresponding final substance batches contain impurity XYZ at levels below 20 ppm.

→ Not acceptable

- If the proposed limit for impurity XYZ in starting material is 0.05%, then the spiked material has to have the impurity XYZ at levels same or higher than the proposed limit.
- Demonstrating that the final substance resulting from the spiked sample has levels of the impurity XYZ below TTC is not enough. ICH M7 clearly mentions the limit 30% of TTC for this purpose

Revisions and nitrosamines

It is the company's responsibility to follow updates of the

EMA Q&A document EMA/409815/2020 and its appendix 1 with acceptable intakes for nitrosamines (EMA/393815/2024)

Updates in risk assessment for nitrosamines and changes in control strategy in line with the above mentioned guideline:

Minor change by default

Switch to CEP 2.0

Switch to CEP 2.0 format

- CEP 2.0 is a more user-friendly and more transparent format of the certificate
- Switch to CEP 2.0 format for revisions is not automatic
- Switch to CEP 2.0 format is a minor by default
- If you wish to have your certificate in CEP 2.0 format, you have to explicitly request it in both:
    - cover letter
    - annex 7 of the application form (comparative table)

Old, hybrid and CEP 2.0 certificates

- This is only a tip how you can quickly screen whether the CEP you are looking at is old, hybrid or in CEP 2.0 format:

Old CEP	Hybrid CEP	CEP 2.0
CEP number begins with “R”	CEP number begins with “CEP”	CEP number begins with “CEP”
No SPOR ID numbers	SPOR ID numbers are indicated for the CEP holder and all manufacturing sites	SPOR ID numbers are indicated for the CEP holder and all manufacturing sites
Quality of water used in the last steps is **not** indicated *)	Quality of water used in the last steps is **not** indicated *)	Quality of water used in the last steps is indicated *)
Specification is **not** appended	Specification is **not** appended	Specification is appended
Can have annexes	Can have annexes	Has production sites, specification, test procedures and miscellaneous information (as applicable) appended

*) If water is used in the last steps

This table does not describe all differences in old, hybrid and CEP 2.0 in detail. For details, see webpage: https://www.edqm.eu/en/what-is-the-cep-2.0

Revision of CEPs

We currently have an old or hybrid CEP and the changes submitted will lead to revision of the CEP. There are two possibilities:

- If we do not explicitly request switch to CEP 2.0 format, certificate will be automatically revised into hybrid format.
- If we explicitly request switch to CEP 2.0 format (in cover letter and comparative table), we will get the revised certificate in CEP 2.0 format.

We currently have CEP 2.0 and the revised CEP will also be in CEP 2.0 format.

Renewal of CEPs

We currently have an old CEP → at renewal, the CEP will be revised into CEP 2.0

We currently have a hybrid CEP → there are several possibilities:

- The changes submitted within the request for renewal lead to revision of the CEP:
  → if we request switch to CEP 2.0, we will get the revised certificate in CEP 2.0 format
  → if we do not request switch to CEP 2.0 explicitly in the cover letter, the EDQM will issue a hybrid CEP
- The changes submitted within the request for renewal **do not** lead to revision of the CEP
  → we will get a letter stating the CEP remains valid

We currently have a CEP 2.0 → there are two possibilities:

- The changes submitted within the request for renewal lead to revision of the CEP
  → renewed certificate will be in CEP 2.0 format
- The changes submitted within the request for renewal **do not** lead to revision of the CEP
  → we will get a letter stating the CEP remains valid

Update of dossier in line with CEP 2.0 requirements

- CEP 2.0 requirements have been included in the EDQM policy document PA/PH/CEP (04) 1 « Content of the dossier for CEP applications for chemical purity and microbiological quality of substances for pharmaceutical use »
- In next few slides, only key points are highlighted and illustrative and practical examples are given to facilitate the companies to apply for switch to CEP 2.0 format
- Sections 3.2.S.4.1 and 3.2.S.4.2: submission of scanned documents should be avoided, electronic format is preferred
- Section 3.2.S.4.1: for in-house impurities which are controlled in final substance and are not listed in the Ph. Eur. monograph, full chemical names should be stated (mentioning in-house names only, for example « Acid impurity » without a chemical name is not acceptable). However, for Ph. Eur. impurities chemical names should not be given.

Update of dossier in line with CEP 2.0: key points

Section 3.2.S.1.3 should contain:

- MDD, intended route of administration and duration of treatment

Section 3.2.S.4.1 should contain three columns:

- Names of the quality attributes (specification parameters) tested
- Acceptance criteria
- References of the associated analytical procedures (« Ph. Eur. current edition » or « in-house »)

Section 3.2.S.4.2 should contain two subsections:

- Subsection 1: analytical procedures alternative (equivalent) to Ph. Eur.
- Subsection 2: analytical procedures additional to Ph. Eur.

(Procedures from Ph. Eur. monograph for specific substance should not be reproduced. Procedures from Ph. Eur. general chapters which need to be adapted should be described with corresponding adaptations)

MDD, route of administration and treatment duration

CEP 2.0 requires that section 3.2.S.1.3 contains following information:

MDD: a reference should be given (for example Martindale, SmPC…)

If the substance is in a salt or hydrate form, the counterion and water have to be taken into account for calculation of MDD. Be careful whether the data from literature references take this into account or not.

Route of administration: oral, parenteral, inhalation, topical

Treatment duration should be given in a following format:

- Less than 1 month
- 1-12 months
- 1-10 years
- lifetime

Quality of water mentioned on the CEP 2.0 certificate

If water is used in the last steps of the process, its quality has to be clearly stated in section 3.2.S.2.3. Following wordings are possible on the CEP:

- Potable water: should meet directive 98/83/EC or WHO requirements for potable water
- Purified water: should meet requirements of the Ph. Eur. monograph 0008 for purified water
- Water for injections: should meet requirements of the Ph. Eur. monograph 0169 for water for injections

Following formulations are not encouraged as EDQM will report the lower Ph. Eur. quality on the CEP: process water, reverse-osmosis water, demineralized water…

Examples:

- We submitted a notification containing few IN and AN and request to switch to CEP 2.0 certificate

  → Rejected (switch to CEP 2.0 is a minor by default and not a notification)

- We submitted a request for minor change containing for example several AN (which would normally not lead to a revision of the CEP by themselves) and update of sections 3.2.S.4.1 and 3.2.S.4.2 in line with CEP 2.0 requirements. Our section 3.2.S.1.3 already contains information on MDD, intended route of administration and duration of treatment. We explicitly stated in cover letter and in the comparative table that we wish to switch to CEP 2.0 format.

  → Accepted

- We state in the comparative table that we updated 3.2.S.4.1 in line with CEP 2.0 requirements, but we also explicitly state that we **do not** want to switch to CEP 2.0 certificate.

  → Acceptable

Example: CEP 2.0 and polymorphic form

We hold a certificate in old format.

Section 3.2.S.4.1 contains an XRPD test for polymorphism, however, no subtitle is mentioned on the CEP (which means that the polymorphic form has not been claimed).

We wish to switch to CEP 2.0 format.

→ We can choose one of the following two options:

a) We wish to claim a polymorphic form: we have to propose a subtitle (e. g. « Form I »), to make sure that appropriate validation data for XRPD method are present in 3.2.S.4.3 and that XRPD method is selective for the claimed form (can also be supported with literature). If a re-test period is indicated on the CEP, we have to demonstrate that Form I is stable throughout the whole re-test period.

b) We do not wish to claim a polymorphic form: we remove the XRPD test from 3.2.S.4.1/4.2 and highlight this in the comparative table.

Example: CEP 2.0 and micronisation/sieving grades

We have described micronisation (and/or sieving) of the substance in section 3.2.S.2.2.

We wish to claim « Micronised » grade (or « Sieved », or « Micronised, sieved » or « Micronised grade, sieved grade ») of the substance.

We have to make sure that:

- We have indicated micronisation and sieving sites in the application form and in section 3.2.S.2.1 of the dossier (+ GMP declarations)
- There are suitable limits/ranges for particle size/bulk density (tapped/untapped) in 3.2.S.4.1 and corresponding analytical procedures in 3.2.S.4.2 and suitable validation in 3.2.S.4.3
- We have proposed a suitable subtitle
- If there is a re-test period indicated on the certificate, we have to demonstrate that the particle size/bulk density is unchanged throughout the whole re-test period

Example: CEP 2.0 and micronisation/sieving grades

- Micronisation and sieving sites will be indicated separately on the certificate in CEP 2.0 and hybrid format (difference from old format) even if they are the same as final substance production site

- If a company does not wish to claim a micronised grade of the substance, section 3.2.S.2.2 can mention micronisation, however it should also be clearly stated that it is optional/according to customer requirements and « Micronised grade is not claimed ». In this case, micronisation should be addressed within the marketing autorisation application

How to organise a specification with several grades

Substance XYZ has subtitle "Semi-micro powder, fine powder" on the certificate Specification in 3.2.S.4.1 can for example be presented in two pages:

Semi-micro powder grade of (*substance name*)

Parameters	Acceptance criteria	Reference
Characters	White or almost white, crystalline powder	Ph. Eur. current edition
Solubility	Practically insoluble in water, slightly soluble in anhydrous ethanol and DCM	Ph. Eur. current edition
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%	
Impurity D	≤ 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	≤ 5000 ppm	
N,N-dimethylformamide	≤ 880 ppm	
N-Nitrosodimethylamine (NDMA) (by GC-MS)	≤ 3.0 ppm	In-house
Sieve test (cumulative % retained)	60 mesh (250 µm): minimum 5% 140 mesh (106 µm): min. 75%	In-house

Specification parameters not necessary to satisfy European regional requirements		
Heavy metals	≤ 10 ppm	Ph. Eur. 2.4.8

Fine powder grade of (*substance name*)

Parameters	Acceptance criteria	Reference
Characters	White or almost white, crystalline powder	Ph. Eur. current edition
Solubility	Practically insoluble in water, slightly soluble in anhydrous ethanol and DCM	Ph. Eur. current edition
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%	
Impurity D	≤ 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	≤ 5000 ppm	
N,N-dimethylformamide	≤ 880 ppm	
N-Nitrosodimethylamine (NDMA) (by GC-MS)	≤ 3.0 ppm	In-house
Sieve test (cumulative % retained)	140 mesh (106 µm): maximum 5% 270 mesh (53 µm): minimum 60%	In-house

Specification parameters not necessary to satisfy European regional requirements		
Heavy metals	≤ 10 ppm	Ph. Eur. 2.4.8

How to organise a specification with several grades

Another possible solution is to have a single page specification in 3.2.S.4.1:

Specification of (*substance name*)

Parameters common for all grades	**Acceptance criteria**	**Reference**
Characters	White or almost white, crystalline powder	Ph. Eur. current edition
Solubility	Practically insoluble in water, slightly soluble in anhydrous ethanol and DCM	Ph. Eur. current edition
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%	
Impurity D	≤ 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	≤ 5000 ppm	
N,N-dimethylformamide	≤ 880 ppm	
N-Nitrosodimethylamine (NDMA) (by GC-MS)	≤ 3.0 ppm	In-house

Semi-micro powder		
Sieve test (cumulative % retained)	60 mesh (250 µm): minimum 5% 140 mesh (106 µm): min. 75%	In-house

Fine powder		
Sieve test (cumulative % retained)	140 mesh (106 µm): maximum 5% 270 mesh (53 µm): minimum 60%	In-house

Specification parameters not necessary to satisfy European regional requirements		
Heavy metals	≤ 10 ppm	Ph. Eur. 2.4.8

Tests not necessary to satisfy European requirements

We wish to switch our certificate from old to CEP 2.0 format.

In section 3.2.S.4.1, we can leave some tests additional to those described in the Ph. Eur. monograph for a specific substance which are not necessary to satisfy European requirements.

We should indicate them separately in the specification (see an example how to do it on the previous slide).

These tests can be (non-exhaustive list):

- heavy metal tests
- water content / loss on drying
- assay by HPLC

However, note that the associated analytical procedures will not be appended to the CEP.

Tests not necessary to satisfy European requirements

However:

- We do not wish to claim a polymorphic form, but we wish to leave XRPD test for Form II as test « not necessary to satisfy European regional requirements ».

→ Not accepted.

We should either claim a form and leave the test in the main body of the specification, or remove the test (as described in one of the previous slides)

Section 3.2.S.4.2, subsection 1

- Anaytical procedures from Ph. Eur. monograph for a specific substance used as such should not be reproduced in subsection 1
- Analytical procedures from Ph. Eur. monograph for a specific substance adapted within ranges described in Ph. Eur. chapter 2.2.46 should not be reproduced in subsection 1 either
- Analytical procedures alternative (equivalent) to Ph. Eur. should be fully described in subsection 1, for example:

- in-house method for related substances which has been suitably validated and cross-validated with the Ph. Eur. method and it was found that the in-house method is equivalent to the Ph. Eur.
- in-house method for assay (HPLC) which has been suitably validated and cross-validated with the Ph. Eur. titration method for assay and it was found that the in-house method is equivalent to the Ph. Eur.

Section 3.2.S.4.2, subsection 2

Contains analytical procedures additional to Ph. Eur. such as:

- Suitably validated in-house analytical procedures for residual solvents, in-house impurities, potential mutagenic impurities, elemental impurity, nitrosamines, XRPD for polymorphic form, particle size, sieving tests, bulk density …

- Analytical procedures from Ph. Eur. general chapters which need to be adapted should be fully described with corresponding adaptations: for example, you should not reference « Ph. Eur. 2.2.23 » for elemental impurity by AAS. Instead, « in-house » should be referenced in 3.2.S.4.1 and full method description provided in 3.2.S.4.2, subsection 2

Container-closure system - reminder

Should be clearly described in section 3.2.S.6 so that it can be understood what is primary, secondary and tertiary (if applicable) packaging. Example:

Substance is packed in:

- Primary packaging: clear LDPE bag

placed in

a black LDPE bag (with silica gel bag between two PE bags)

placed in

- Secondary packaging: triple layered PET/Al/PE bag

placed in

- Tertiary packaging: carton box or aluminium container

Addition of a re-test period: minimum requirements

EMA guideline CPMP/QWP/122/02

- Stability data should cover minimum 6 months long-term and accelerated studies at time of submission
- Number of batches on stability studies: three pilot scale or two production scale batches should be tested at least
- Extrapolation: decision tree at the end of the EMA guideline
- If there is an increasing trend of an impurity over time, simple extrapolation might not be possible

- It is possible to have several re-test periods on the same CEP for different grades and container systems
- Stay vigilant and check the guidelines regularly as EDQM policies about re-test period may evolve in future

Where to provide information

Addition of a re-test period should be highlighted in three places:

- Application form:

If applicable: **introduction or modification of a re-test period on the certificate:** *(not applicable for TSE Certificate of Suitability)*	
Proposed re-test period (in months)	Proposed retest period is 60 months
Proposed storage conditions (e.g. T°, nitrogen atmosphere, others, …)	---

- Comparative table (annex 7 of the application form)
- Section 3.2.S.7.1 of the dossier

Section 3.2.S.7.1 should also contain:

- Exact description of the packaging used for stability studies
- Batch numbers, sizes and manufacturing dates for batches placed on stability studies + mention if batches are pilot or commercial scale
- Explanation of need for any restrictive conditions (if applicable)

Re-test period: few tips

- Check whether appearance of solution is a mandatory test as per Ph. Eur. monograph for a specific substance – this parameter should be included in stability studies if it is present in the Ph. Eur. Monograph
- If a polymorphic grade is claimed, test for polymorphism should be included in the stability studies
- If a micronized/sieved grade is claimed, test for particle size/bulk density should be included in the stability studies
- EDQM encourages the applicants to apply for a re-test period. For example, 3 months accelerated and long-term studies can be provided (which is less than a required minimum), and additional stability data can be submitted in the next round(s) supporting a re-test period of 6 months or more, as suitable.

Re-test period: example (1)

We state in section 3.2.S.6 that the packaging used for the substance is double PE bag (outer black) with silica gel bag in between, placed in a triple layered PET/Al/PE bag.

We performed stability studies for substance XYZ in double polyethylene bag, placed in triple layered PET/Al/PE bag. We provided following stability data in section 3.2.S.7.3 for three pilot scale batches:

- 3 months accelerated data at 40°C (no significant variability observed),
- 3 months long-term data at 25°C (no significant variability observed).

We request a re-test period 6 months for the substance packed in container described in 3.2.S.6.

→ Cannot be approved. Minimum period covered with stability studies should be 6 months and there are inconsistencies between packaging description in 3.2.S.6 and packaging used for stability studies.

Re-test period: example (2)

We state in section 3.2.S.6 that the substance is packed under nitrogen in double PE bag (outer black), placed in a triple layered PET/Al/PE bag.

We performed stability studies for substance XYZ in double PE bag (outer black), placed in a triple layered PET/Al/PE bag.

We provided following stability data in section 3.2.S.7.3 for three pilot scale batches:

- 3 months data at 40°C (OOS results observed),
- 6 months accelerated data at 25°C (no significant variability observed),
- 6 months long-term data at 5°C (no significant variability observed).

We request a re-test period 12 months for the substance stored at 5°C in container described in 3.2.S.6.

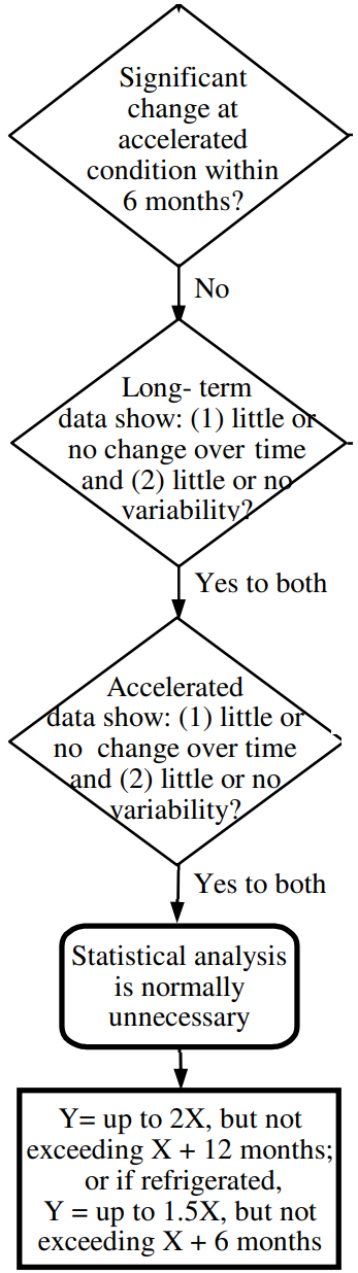
Re-test period: example (2)

- 6 months accelerated data at 25°C (no significant variability observed),
- X = 6 months long-term data at 5°C (no significant variability observed).

Proposed re-test period is Y = 12 months for the substance stored at 5°C in container described in 3.2.S.6.

In this case, Y = 2X. According to the decision tree, if refrigerated, Y can be up to 1.5X. The applicant's request therefore cannot be approved.

Moreover, there are inconsistencies between packaging described in 3.2.S.6 and used for stability studies ("under nitrogen" is not indicated).



Take home messages

- For your submission of Revision / Renewal, make sure to:

➢ **Classify changes in line with the EDQM guideline** on requirements for Revision/renewal (PA/PH/CEP (04) 2)

➢ Submit a **consolidated comparative table**

➢ Facilitate a **quick and clear understanding of the changes**

- The **need for the change and the associated risks** as well as the impact of the change on the control strategy for the manufacturing process should always be **properly justified**

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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