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

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European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

How to submit a CEP revision application and gain rapid acceptance of proposed changes

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Certification of Substances Department

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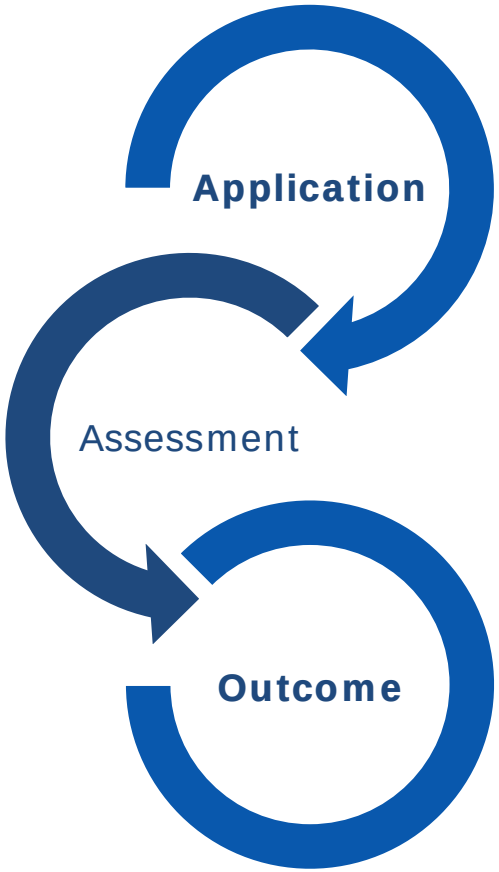
Aim of the webinar

- Draw attention on **best practices** for submissions
- Highlight key points to **prepare optimised submissions**



- Complete **application form**
- Clear and complete **comparative table**
- Appropriate **supportive data**

- More rapid assessment
- Limited request for additional information/clarifications

- Faster approval
- **Gain of time**
- Limitation of costs

By:

- Submitting **clear requests**
- Providing **complete** and **consistent documentation**

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Overview

- **How to apply for revisions**
- **Application form**
- **Classification of changes** in line with the EDQM guideline
- **How to improve your comparative table:**

  Typical changes and examples

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How to apply for revisions

For Notifications, Revisions or Renewals:

- Submission via the **CESP Platform**
- Electronic **baseline** Module 3 required since January 2022
- Format: **eCTD**

Exceptions: - For substances for veterinary use: vNees remain accepted

- For TSE dossiers: PDF format remain accepted

Build your CEP application

New applications

Notifications, Revisions, Renewals and Sister Files

Submission format and electronic submission

Certification policy documents and Guidelines

Technical Advice & One-to-One Meetings

Submission format and electronic submission

- **User guide**: Instructions for submitting electronic documents using the CESP platform (PA/PH/CEP (13) 67, 2R, April 2016)
- **Guidance** for electronic submissions for Certificates of Suitability (CEP) applications (PA/PH/CEP (09) 108, 6R, July 2021)
- **EDQM DCEP sharing tool:** Instructions for using the EDQM DCEP sharing tool (PA/PH/CEP (21) 62, 1R, September 2022)

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How to apply for revisions

Module 1

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

Module 2: Not required but may be submitted

Module 3

- Update of **<u>all</u> 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)2,7R corr)

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Application form

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 box only)*

- ☐ Notification *(may include several changes)*
- ☐ Minor revision *(may include several changes including notifications)*
- ☐ Major revision (*may include notifications and minor changes)*
- ☐ Renewal *(notifications and minor changes may be included)*
- ☐ Transfer of holdership
- ☐ Grouped revision *(several dossiers affected by the same change[s])*

Since April 2022

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 you apply for
- by taking into account all the changes declared in line with the EDQM Guideline for Revision (PA/PH/CEP(04)2,7R corr)

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Application form

*Since **April 2022***

Section 2: to be completed for parts that have changed only

2. Companies details – names and addresses

2.1 Certificate holder:	
NAME OF THE COMPANY*	**CAPITAL LETTERS**
Recommended: **ORG_ID**[1]	
Recommended: **LOC_ID**[1]	
Address*[2]	
City/Town*	
Postcode*	
State/Province	
Country*	
Telephone*	
E-mail*[3]	

Fields marked * are mandatory

[1] see SPOR - Organisation Management Services (OMS) on the EMA website

[2] no PO box, only physical address

[3] please provide one email address. Shared mailboxes are strongly preferred.

For more details, consult the EDQM On-demand webinar:

How to communicate efficiently with the EDQM on CEP applications

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Types of applications

- Notifications (IN or AN)
- Minor revisions (incl. minor by default)
- Major revisions

Do & Tell

Tell & Do

The EDQM timelines depend on the type of revision

A 3-Round policy is applied

➢ Other types of applications

- Possibility to group revisions i.e. the same changes affecting several dossiers
- Transfer of holdership
- Renewal (after 5 years)

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How to classify the changes?

- By referring to the EDQM guideline for the classification of changes:

GUIDELINE ON REQUIREMENTS FOR REVISION/RENEWAL OF CERTIFICATES OF SUITABILITY TO THE EUROPEAN PHARMACOPOEIA MONOGRAPHS

PA/PH/CEP (04) 2, 7R corr

Divided in several parts :

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

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How to make best use of the EDQM Guideline for Revisions

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 notification (**AN**)
- Minor change (**MIN**)
- Major change (**MAJ**)

Non-classified changes are:

Minor changes by default

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Notifications

☒ Notification *(may include several changes)*

- It should be formally confirmed that **<u>all</u> the conditions listed in the guideline are met**
- **The corresponding documentation listed in the guideline should be provided** (for instance declarations or 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.

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Minor changes

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

- Typical changes are listed in the guideline

(e.g. addition of a new starting material manufacturer when there is no impact on the final substance specifications, introduction of a RMS or a retest period etc.)

- **All changes that are neither listed as a notification nor as a major are « minor by default »**

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Major changes

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

- Any substantial change to the process or to the specifications of the final substance/intermediate that **may potentially** impact the quality of the final substance.

Remember

Type of submission depends on the **potential impact** on the quality of the final substance, and not necessarily on the final result

- It is CRUCIAL to discuss the impact of the change on the quality and control strategy for the final substance. Science-based argumentation and relevant analytical data are expected.

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Reminders on the type of revision

Classification of changes depends on the **potential impact** on the quality of the final substance, and **not only** on the final result

Each change should be **individually classified**

Most common types of revision :

- ☐ Notification *(may include several changes)*
- ☐ Minor revision *(may include several changes including notifications)*
- ☐ Major revision (*may include notifications and minor changes)*

Appropriate type of revision according to the proposed changes:

Type of change:	Type of Revision:		
	Notification	**Minor** revision	**Major** revision
Notification (**AN** or **IN**)	✖	✖	✖
Minor change (**MIN**)	⊘	✖	✖
Major change (**MAJ**)	⊘	⊘	✖

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Reminders on the type of revision

Classification of changes depends on the **potential impact** on the quality of the final substance, and **not only** on the final result

Each change should be **individually classified**

Most common types of revision :

- ☐ Notification *(may include several changes)*
- ☐ Minor revision *(may include several changes including notifications)*
- ☐ Major revision (*may include notifications and minor changes)*

Appropriate type of revision according to the proposed changes:

Type of change:	Type of Revision:		
	Notification	Minor revision	Major revision
Notification (**AN** or **IN**)	✖	✖	✖
Minor change (**MIN**)	⊘	✖	✖
Major change (**MAJ**)	⊘	⊘	✖

Technical Advice Meeting possible in case of doubt for questions:

REQUEST FOR TECHNICAL ADVICE MEETING FOR CERTIFICATION OF SUITABILITY

to be filled in for each request for a Technical Advice meeting related to the procedure for Certificate of Suitability to the monographs of the European Pharmacopoeia AP-CSP (07) 1

- of technical nature, on matters concerning the content of an application
- or related to the requirements for the submission of revision / renewal with **complex or multiple changes**

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Why should the type of revision be carefully selected ?

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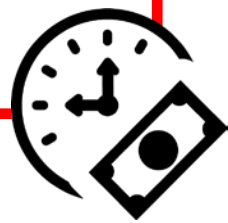
Why should the type of revision be carefully selected ?

Misclassifications of revisions / notifications:

- lead to the **rejection** of **all submitted changes** at any stage of the process
- increase the total **time and costs** of your revision application



Selecting the **right type of revision** facilitates the whole approval process ...

... together with:

- a detailed **comparative table**
- and appropriate **supportive data**

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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**

3. 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	☒	

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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 <u>and</u> 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

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Comparative table: expectations

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

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Comparative table: expectations

Changes should be:

- **easily identifiable**

- and **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

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Comparative table: expectations

Changes should be:

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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 comparative table should always **mention which update has been made**, but sometimes, the complete comparison of the approved/proposed texts of the dossier is not relevant:

Examples: certificates of analysis, method validation reports, detailed description of an analytical method when the method is completely replaced, stability data

Editorial changes generally do not need to be reported in the table

Examples: periodic updates of the format of specifications of raw materials/ updates of the internal codes for specifications

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Comparative table: expectations

Changes should be:

- **easily identifiable**

- and **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**

CTD section reference	Approved text of the dossier	Proposed text of the dossier	Classification of the change(s) and brief justification.
3.2.S.3.2		Introduction of a risk management summary on elemental impurities	**Minor change by default**
3.2.S.4.2	**Related substances HPLC:** Chromatographic conditions: Column **25 cm x 4.6 mm packed with BDS, C-18, (5µm)** Wavelength: 286 nm Injection volume: **20 µl** Run time: **45minutes**	**Related substances HPLC:** Chromatographic conditions: Column: **15 cm x 4.6 mm, C-8, (3µm)** Wavelength: 286 nm Injection volume: **10 µl** Run time: **35minutes**	**Minor change:** replaced in-house HPLC method with *change in type of column* and adapted parameters. No change is made in the specifications of the final substance. Refer to page xx of module 1/ module 3 for complete description of the method/ validation data/ cross validation data with EP method/analytical data
3.2.S.7	No re-test period on certificate	Re-test period of 48 months to be included to the certificate	**Minor change:** addition of a re-test period of 48 months for the final substance. Stability data provided in 3.2.S.7.3

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 some context
- The change should be summarised, its classification justified in line with the EDQM Guideline for Revision (PA/PH/CEP (04) 2)
- If applicable, describe where corresponding **supportive information** is available (for instance: Module 1, page x/x)

Reminder for Notifications:

it should be **formally confirmed** that all the conditions listed in the EDQM Guideline for Revision are fulfilled.

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Comparative table: expectations

	Approved process	Proposed process
Step 1	Dichloromethane **Cyclohexane** Methanol Purified Water Sodium hydroxide	Dichloromethane **-** Methanol Purified Water Sodium hydroxide **Toluene** **Acetic acid**
Step 2	Purified water Ethyl acetate Raney nickel **Chloroform** **Ethyl acetate**	Purified water Ethyl acetate Raney nickel **-** **-**
Step 3	No change	No change

For **changes to the materials** used in the process:

Example: addition/deletion of solvents/reagents/catalysts

→ In addition to the Route of synthesis, include also a **comparative list of the materials** used in approved and proposed process steps

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 some context
- The change should be summarised, its classification justified in line with the EDQM Guideline for Revision (PA/PH/CEP (04) 2)
- If applicable, describe where corresponding **supportive information** is available (for instance: Module 1, page x/x)

Reminder for Notifications:

it should be **formally confirmed** that all the conditions listed in the EDQM Guideline for Revision are fulfilled.

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Comparative table: expectations

	Approved process	Proposed process
Step 1	Dichloromethane **Cyclohexane** Methanol Purified Water Sodium hydroxide	Dichloromethane **-** Methanol Purified Water Sodium hydroxide **Toluene** **Acetic acid**
Step 2	Purified water Ethyl acetate Raney nickel **Chloroform** **Ethyl acetate**	Purified water Ethyl acetate Raney nickel **-** **-**
Step 3	No change	No change

For **changes to the materials** used in the process:

Example: addition/deletion of solvents/reagents/catalysts

→ In addition to the Route of synthesis, include also a **comparative list of the materials** used in approved and proposed process steps

For **changes to specifications**:

Example: tightening/widening of specification limits

→ **always** provide a comparison of the approved and proposed specifications and **include the details of the specifications limits**

CTD section	Approved text of the dossier		Proposed text of the dossier	
3.2.S.2.3	**Specification limits of Starting material I**		**Specification limits of Starting material I**	
	Any unspecified impurities	NMT 0.20%	Any unspecified impurities	**NMT 0.10%**
	Total impurities	NMT 1.00%	Total impurities	NMT 1.00%
	Assay	NLT 99.00%	Assay	NLT 99.00%

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Comparative table: what not to do…

… If you aim for a successful comparative table:

DO NOT use general comments:

- such as “update” , “to improve control” (…) to **justify** the proposed change
- without reporting **enough context** to **identify** the change

CTD section	Approved text of the dossier	Proposed text of the dossier	Classification of the change(s) and brief justification.
3.2.S.2.2	Page 22/ sub-section 1 : NaOH 10L Page 23 : isopropanol 200L Page 25 : 20°C page26 : yield 12kg	Page 22/ sub-section 1 : NaOH 20L Page 23 : 300L Page 25 : 25-26°C Page 26 : yield 12-13kg	For process update
3.2.S.2.3	**Existing** specifications and test methods for methanol n° 02	**Proposed version** of specifications and test methods for methanol n° 03	Update of section 3.2.S.2.3
3.2.S.2.3	Specifications for starting material A	New version	For better control
3.2.S.2.4	Specifications for Intermediate I	Updated specification	Annual update of SOP
3.2.S.4.1	Update of the microbiological control test , see dossier p. 254		Annual notification

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Comparative table

Annex 7 of the application form

- **Clearly identify changes**
- Report short sequences of text to **highlight the change(s)**
- Include **enough details** to clearly identify change(s)
- Always ensure **readability**, for instance when Route of synthesis / Flowcharts are copied in the table

- Use of general terms or comments (such as « To update the documentation »)
- Report only very short sequences of text without enough context
- Misclassify changes (e.g. by omitting the potential impact on the final substance)

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Supportive information

Supportive documentation depends on the classification of the change...

- For **notifications**: a **short justification** in the comparative table may be sufficient
- For **minor / major changes**: the comparative table **may not be sufficient**.

The change should be justified and supportive information is needed regarding the **quality and control of the final substance** and should cover:

Need for the change and associated risks:

- why are you making the change and what are the critical points of the change to be considered ?
- what are the risks associated with the change ?
- what impact can this have on the quality of the final substance ?

&

Impact on the control strategy :

- how does the control strategy ensure that the quality of the final substance is maintained ?
- what science based discussion and/or supporting data is provided which helps to justify the change ?

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Reminders on the content of the dossier

Dossier in line with the EDQM Guideline 'Content of the dossier' (PA/PH/CEP (04) 1, 6R):

EDQM
Certification of Substances Department

PA/PH/CEP (04) 1 6R

CONTENT OF THE DOSSIER FOR A SUBSTANCE FOR CHEMICAL PURITY AND MICROBIOLOGICAL QUALITY EVALUATION

1 This document is intended for applicants as a guide for compiling a dossier that is suitable for
2 evaluation for a Certificate of Suitability (CEP).

For each updated section: ensure that your dossier is in accordance with the EDQM guideline **'Content of the dossier'** (PA/PH/CEP (04) 1, 6R) **before to submit** your revision application

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Reminders on the content of the dossier

Dossier in line with the EDQM Guideline ‘Content of the dossier’ (PA/PH/CEP (04) 1, 6R):

CONTENT OF THE DOSSIER FOR A SUBSTANCE FOR CHEMICAL PURITY AND MICROBIOLOGICAL QUALITY EVALUATION

Example: 3.2.S.2.1 **Intermediate and final substance manufacturers**

147 Manufacturer(s) (3.2.S.2.1):

148 Names and addresses of each manufacturer involved in the manufacturing process from the
149 introduction of starting material(s) to the final substance should be listed in the application and
150 their role explained.

Example: 3.2.S.2.3 **Starting material manufacturers**

215 The name and address of the manufacturer(s) of the starting materials(s) should be declared and
216 where more than one supplier is used then batch analyses results from the final substance
217 manufactured from the different sources of starting material should be given.

Example: 3.2.S.2.4 **Intermediate specifications**

242 Controls of critical steps and intermediates (3.2.S.2.4):

243 Any critical steps should be identified. Tests and acceptance criteria performed at the critical
244 steps should be provided. In-process controls should be described.

245 A suitable and detailed specification is expected for each isolated intermediate, along with
246 analytical methods descriptions. The specification should generally be justified and information on
247 the impurities found in isolated intermediates during manufacture should be included (e.g.
248 specified, unspecified or total impurities) as necessary.

Ensure that your dossier is **complete** and in accordance with the EDQM guideline **‘Content of the dossier’** (PA/PH/CEP (04) 1, 6R) **before to submit** your revision application

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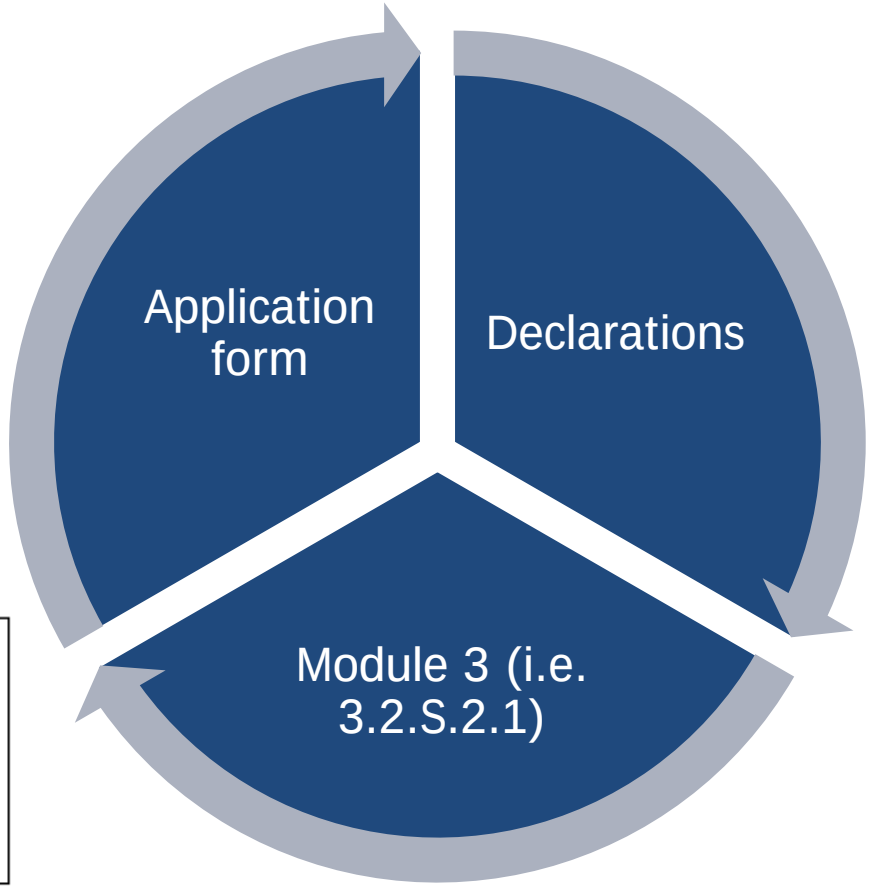
3.2.S.2.1 **Manufacturers:** Administrative changes (Notifications)

- Changes in name or address of CEP holder, manufacturing site of intermediate/final substance when the location is unchanged, deletion of sites, etc.

Details of **all sites should be consistent** in submitted documentation



2.3 Manufacturing site(s): detailed name and address of all sites° involved in the manufacture of this substance

° All sites involved in the manufacture of the substance after the introduction of starting material(s), including quality control / in process testing sites, intermediate manufacturers, milling, micronisation and sterilisation sites should be listed in separate boxes and their role should be specified.

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3.2.S.2.2 Manufacturing process - Typical changes

- **Notification**: minor updates to the process that do not have any impact on the quality of the final substance (adjustments to operating conditions, changes in equipment, deletion of the use of recovered solvents or of a reprocessing step, etc.) → specification of the final substance and intermediates are unchanged and the ROS remains the same; a clear statement is expected.

- **Minor revision**: introduction of recovery procedures, addition of a solvent in one step excluding final purification and when this solvent is already used elsewhere in the approved process, etc. The change should not impact the quality and specification of the final substance and the ROS should remain the same.

- **Major revision**: introduction of a telescoped process or new technology such as flow chemistry, introduction of a new solvent in the manufacturing process excluding the last step and when this solvent is demonstrated absent in the final substance.

Major change *vs* Sister file

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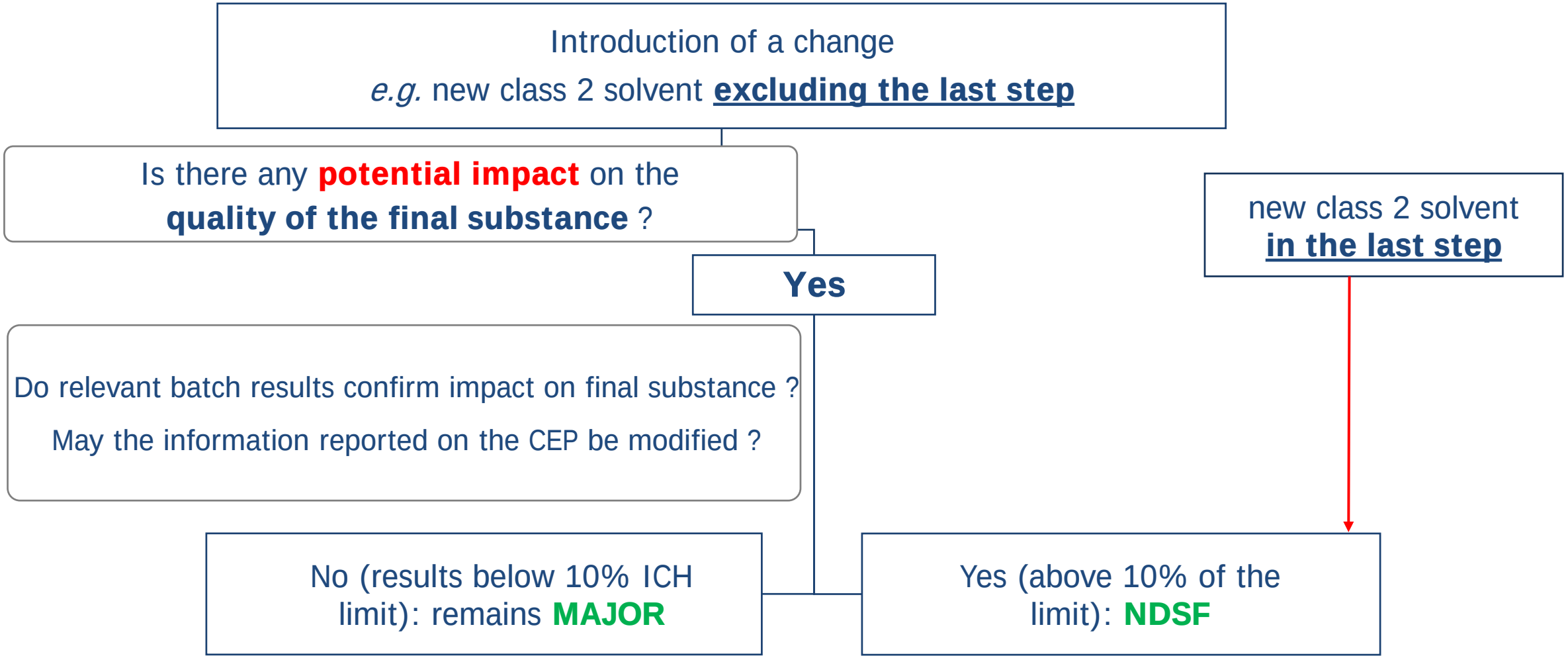
Classification of changes

Depending on the change, a ‘sister file’ (NDSF) submission might be needed instead:



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Cases where a separate CEP application is needed (NDSF)

- 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

- 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

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CEP via the ‘Sister file’ Procedure (NDSF)

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 is a **fast track procedure**: same timeline as for a Major revision

Consult the EDQM guidance on applications for “Sister Files” (PA/PH/CEP (09) 141 2R)

To apply:

- The **specific application form**
- A **comparative table** of the differences between the existing CEP and the new application via the sister file procedure
- a **complete dossier** in eCTD format

Application Form
REQUEST FOR
A CERTIFICATE OF SUITABILITY
VIA THE ‘SISTER FILES’ PROCEDURE

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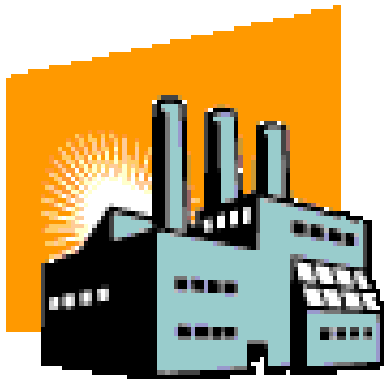
3.2.S.2.3 Starting material manufacturers - Typical changes

- The type of application (notification / minor / major) mainly depends on the specification of the SM and final substance:
  - If specification of the starting material is unchanged: IN/MIN depending on whether the manufacturer of SM is part of the same group
  - If specification and/or RoS of the starting material are changed: MIN
  - If specification of the final substance are potentially impacted: MAJ

- A comparative description listing the approved and proposed:
  - **Manufacturers**

Approved	Proposed
Manufacturer A	Manufacturer A
Manufacturer B	-
Manufacturer C	Manufacturer C
	Manufacturer D

  - If different to approved, the **synthetic flow chart**
  - If different to approved, the **specifications**



- Supportive data may be provided (e.g carry-over studies of solvents, justification for impurities)
- Provide **batch analysis data** (in a comparative tabular format) of the final substance obtained using SM from the approved and proposed manufacturer

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3.2.S.2.1 / 3.2.S.2.4 Intermediate manufacturers - Typical changes

- The type of application depends on changes made to the synthesis (notif / minor / major NDSF)

CTD section	Approved text of the dossier	Proposed text of the dossier	Classification of the change(s) and brief justification.
3.2.S.2.2	Information related to intermediate and drug substance manufacturer provided	**Updated Information** related to intermediate and drug substance manufacturer provided	Information from new manufacturer incorporated

- The relevant declarations should be provided (i.e. for GMP compliance)
- Provide a full and comparative description of the approved and proposed:
  - Manufacturers
  - Route of synthesis
  - Specifications of intermediates

- Include information on the starting material(s) suppliers used by proposed manufacturer(s) of intermediate.
- Discuss the impact on the control strategy (specification, IPC, carryover of impurities) when the route of synthesis is changed.

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3.2.S.2.3 / 3.2.S.2.4 / 3.2.S.4.1 Specifications - Typical changes

Change to the **specifications** of:

- starting material(s)
- intermediate(s)
- in-process controls
- final substance

What is the **potential** impact on the quality of the final substance?

- **Notification**
- Minor change (by default)
- **Major change**

Notification if:

- All conditions of the EDQM Guideline are met
- and that: the change does not result from unexpected events during manufacturing.

Example: - tightening of limits for impurities
- deletions of non-significant tests (e.g. a test for odour.)

Related substances are not considered as non-significant parameters.

Minor revision (by default) if: the request is neither a notification nor a major revision

Example: Widening of approved limits within the limits of the Ph.Eur./ICH-VICH

Major revision if: the limits of a critical specification parameter are widened

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Specifications – Example of misclassification

Example: Widening of specification limits for an intermediate (Major change)

CTD section	Approved text of the dossier	Proposed text of the dossier	Classification of the change(s) and brief justification.
3.2.S.2.4	**Specifications of Intermediate B** Description: white powder Identification by IR: complies -: - Any unspecified impurities: NMT 0.20% Total impurities: NMT 1.00% Assay: NLT 99.00%	**Specifications of Intermediate B** Description: white powder Identification by IR: complies **Impurity A: NMT 0.30%** Any unspecified impurities: **NMT 0.10%** Total impurities: NMT 1.00% Assay: NLT 99.00%	**4.II1.6.e) MAJOR: 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**

CTD section	Approved text of the dossier	Proposed text of the dossier	Classification of the change(s) and brief justification.
3.2.S.2.4	Intermediate specification and testing procedure of intermediate B is available	**Updated** Intermediate specification and testing procedure of intermediate B are provided	Information from new manufacturer incorporated
3.2.S.3.2	Discussion on impurities	Updated discussion on impurities	To have **better control**

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3.2.S.3.2 **Impurities** - Typical changes

- Revised discussions on impurities should be submitted as **minor revisions**.
- Please mention **explicitly**:
  - The new impurity(ies) identified
  - Provide **supportive discussion as appropriate**:
    - Discussing the impurity's origin, fate & carry over, spiking purge studies
    - For mutagenic impurities, the proposed ICH M7 control strategy i.e. option 1/2/3/4

CTD section	Approved text of the dossier	Proposed text of the dossier	Classification of the change(s) and brief justification.
3.2.S.3.2	Discussion on impurities	Updated discussion on mutagenic impurities	**Minor 4.II.1.6.h :** Compound X is newly identified mutagenic impurity controlled as per ICH M7 option 3, see 3.2.S.3.2 p. 20-22 for the supportive discussion

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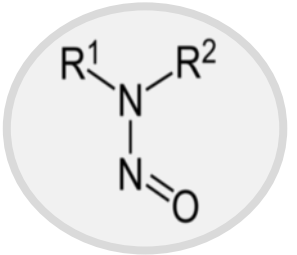
3.2.S.3.2 - Risk assessment for N-nitrosamine impurities

The risk assessment for N-nitrosamine impurities should:

- Be submitted as a **Minor change**
- Be updated when the **proposed changes** modify the current risk
- Be included for any **Sister file** application and for **Renewal** application



It is the **responsibility of the CEP holder** to complete the procedure described for all impacted CEPs:

STEP 2

Confirmatory testing

DEADLINE: **26 September 2022**

If a **risk of presence of nitrosamines was identified during the risk assessment**, confirmatory testing should have been carried out using appropriately validated and sensitive methods.

STEP 3

Revision to the CEP

DEADLINE: **1 October 2023**

If nitrosamine impurities have been detected, CEP holders should **apply for a revision** to their application(s) in a timely manner to introduce any required changes (e.g. amendment of the manufacturing process, changes to specifications and introduction of controls.)

Refer to the **EMA Q&A document for N-nitrosamine impurities**

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3.2.S.3.2 - Risk assessment for Elemental impurities

Example: Introduction of a RMS for Elemental impurities (Minor change)

CTD section	Approved text of the dossier	Proposed text of the dossier	Classification of the change(s) and brief justification.
3.2.S.3.2		Introduction of a risk management summary on elemental impurities	**4.II.2.1.h. Minor change:** Introduction of a **RMS** (Risk management summary) regarding elemental impurities

The introduction of the **RMS on elemental impurities** is optional:

- should be **clearly declared** in the comparative table
- The **RMS table** should be in line with the requirements of the EDQM documentation **PA/PH/CEP (16) 23, 2R:**
  - ✓ **Route of administration** indicated
  - ✓ Elemental impurities used **after** the introduction of the starting material reported as '**Intentionally added**'
  - ✓ Control strategy clearly mentioned: No risk identified; Specified limit; Absent with its definition (e.g. less than 30% of the ICH Q3D option 1 limit)

Risk management summary

Intended route of administration: Oral

Element	Class	Intentionally added ?	Considered in risk management?	Conclusion
Cd	1	No	Yes	*Absent
Pb	1	No	Yes	*Absent
As	1	No	Yes	*Absent
Hg	1	No	Yes	*Absent
Co	2A	No	Yes	*Absent
V	2A	No	Yes	*Absent
Ni	2A	No	Yes	*Absent
Tl	2B	No	No	No risk identified
Au	2B	No	No	No risk identified
Pd	2B	Yes	Yes	Controlled in API with limit of NMT 5 ppm
Ir	2B	No	No	No risk identified
Os	2B	No	No	No risk identified
Rh	2B	No	No	No risk identified
Ru	2B	No	No	No risk identified
Se	2B	No	No	No risk identified
Ag	2B	No	No	No risk identified
Pt	2B	No	No	No risk identified
Li	3	No	Yes	*Absent
Sb	3	No	No	No risk identified
Ba	3	No	No	No risk identified
Mo	3	No	No	No risk identified
Cu	3	No	Yes	*Absent
Sn	3	No	No	No risk identified
Cr	3	No	No	No risk identified

*: Absent means less than 30% of ICH Q3D option 1 limit)

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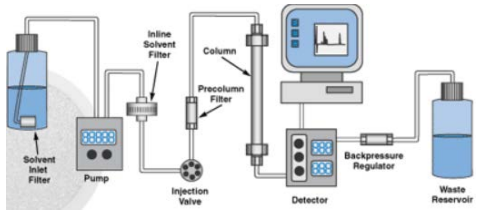
3.2.S.4.2 / 3.2.S.4.3 Analytical procedures - Typical changes

A change to a **test procedure** can be declared as:



- **Notification**, if **all the conditions of the EDQM Guideline are met**.
  - The method should remain essentially the same
  - Changes should be within the ranges allowed by Ph. Eur. general chapter for Chromatographic separation techniques (2.2.46).
- **Minor change** if not a notification and appropriate supportive data should be provided :
  - For a method used to control the final substance, **validation** data is needed
  - If an **in-house method** is used (instead of the Ph. Eur. monograph method): **cross validation results** against the Ph. Eur. monograph should be provided
  - For proposals to disregard peaks in a chromatographic method: a **rationale** discussing the origin of the peak + its identification + levels of found

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3.2.S.4.2 Analytical procedures - Typical changes

Editorial changes to an Analytical procedure appended to the CEP (Notification)

- A revised CEP will be issued with the updated description of the method ...
- **...in a format to be appended to the certificate of suitability.**
- Useful to clarify in the comparative table whether you do not wish a revised CEP before the next revision

4.II.2.2 Change in test procedure for the final substance	Conditions	Specific documentation	Type of change
a) Minor changes to a test procedure for the final substance. Editorial changes to a method description annexed to a certificate of suitability	1, 2, 3, 4	1, 2, 3	IN

Conditions	Documentation
1. **Appropriate validation studies** have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. 2. There have been **no changes of the total impurity limits**; no new unqualified impurities are detected. 3. The method of analysis should remain the same (...) 4. The test method is not a biological method (...)	1. Description of the analytical method and revised specifications. 2. **Comparative validation results**, or if justified comparative analysis results showing that the approved test and the proposed one are equivalent 3. Updated description of the method **in a format to be appended to the certificate of suitability**.

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3.2.S.4.4 Batch Analyses

Recent batches: manufactured within the last **18 months**

For **Renewal** application:

CoA from **at least two recent production batches** should be provided

Whenever batch data are required, they should:

- be in accordance with the specification of the current Ph. Eur. monograph and when relevant with the additional requirements of the CEP
- specify:
  - the manufacturing site
  - the manufacturing date
  - the size of the batch(es)
- present **quantitative results numerically** and with the appropriate number of decimal places (general terms such as “complies” should be avoided)

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3.2.S.6 Container closure system

- The **packaging description** is mentioned on the CEP (immediate and outer packaging)

Example: The substance is packed in double polyethylene bags (outer black), placed in a polyethylene drum.

The substance is packed in Inner layer packaging (*Mandatory*), in Middle layer packaging (*Optional*), placed in Last layer packaging (*Mandatory*)

- **If requested and accepted**, the re-test period is also specified.

Example: The re-test period of the substance is 60 months if stored in double polyethylene bags, placed in a polyethylene drum.

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3.2.S.7 Stability - Reminders

Re-test period on the CEP: Optional (but highly recommended)

- The CEP statement reflects the fact that the substance is stable in long-term conditions:

  25°± 2°C/40% RH°± 5% or 30°C °± 2°C/35% RH°± 5% RH

- If applicable, **specific storage conditions should be properly justified**.

Reminders:

- Precautionary storage conditions are not accepted
- Storage conditions of the Ph. Eur. Monographs are not binding

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3.2.S.7 Stability - Typical changes

Example: Stability studies provided as supportive data

4.II.4 Stability

4.II.4.1 Change in the re-test period or storage conditions of the final substance	Conditions	Specific documentation	Type of change
a) Removal or reduction of an approved re-test period	1	1	IN
b) Addition of a re-test period for the final substance and/or change in the storage conditions for the final substance		2, 3	MIN
c) Extension of the re-test period of the final substance and/or change in the storage conditions for the final substance		4	MIN

Documentation	
1	Justification of the removal/reduction of the re-test period or of more restrictive storage conditions.
2.	Results of long-term and accelerated stability studies for at least two pilot or production scale batches.
3.	Appropriate data on the packaging material including a confirmation that the material complies with relevant pharmacopoeial requirements or EU legislation on plastic materials and objects in contact with foodstuffs.
4.	Updated results of stability studies for at least two pilot or production scale batches.

- **Addition of the re-test period** on the CEP
- **Extension** of the current re-test period

MINOR revisions:
- Change **4.II.4.1.b)**
- Change **4.II.4.1.C)**

If the appropriate “Minor change” is not mentioned in the comparative table:

→ Stability data will not be assessed as a minor revision

→ No addition / extension of the re-test period on the CEP

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3.2.S.7 Stability - Typical changes

Example: Addition of a re-test period of 48 months on the CEP (Minor change)

CTD section reference	Approved text of the dossier	Proposed text of the dossier	Classification of the change(s) and brief justification.
3.2.S.7	Stability data provided up to 24 months	Updated stability data up to 36 months	Updated stability data provided in 3.2.S.7.3

In the comparative table, the request for **addition / extension** of a re-test period should:

- Be clearly declared as a **Minor change**
- Specify the **length** of the proposed re-test period in the comparative 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.7	No re-test period on the certificate	**Re-test period of 48 months** to be included to the certificate	**Minor change (4.II.4.1.b):** addition of a re-test period of **48 months** for the final substance. Stability data provided for accelerated and long-term studies up to 36 months

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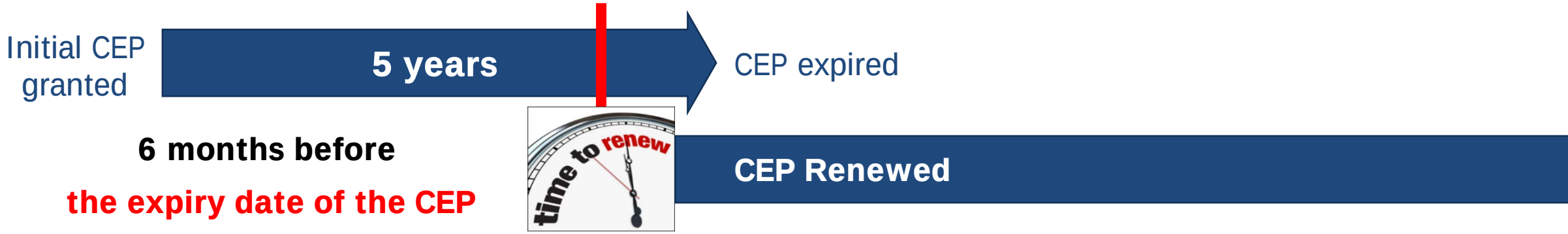
Renewal procedure

☒ Renewal *(notifications and minor changes may be included)*

Specific procedure to obtain the **Renewed** CEP:

- **A initially granted CEP is valid 5 years**
- Renewal assessment focuses on compliance with: Ph. Eur. GM 2034, recent European quality guidelines (e.g. **Nitrosamines risk assessment**)
  - **Updated declarations** (e.g. Annex 3a and Annex 4 of the AF)
  - **Recent** batch data (≤18 months)



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Take home messages

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

- Classify changes in line with the EDQM guideline

- Submit a consolidated comparative table
- Facilitate a **quick and clear understanding of the changes** made

- Justify properly: 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

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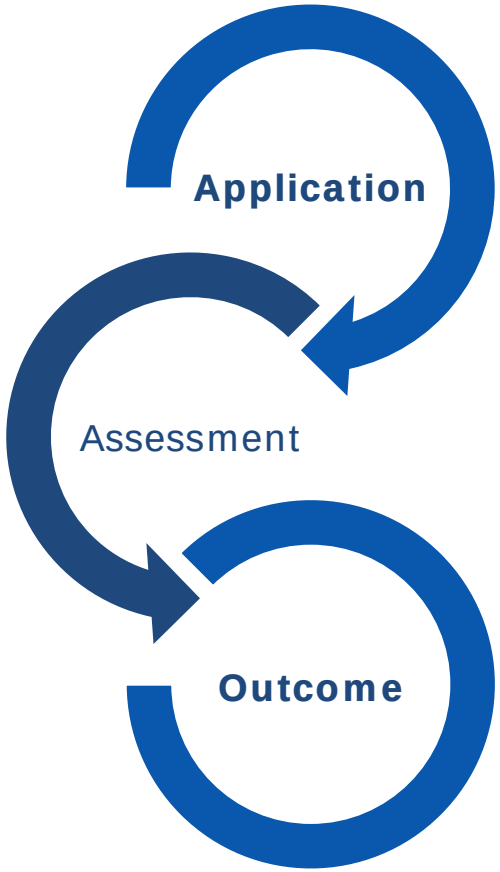
Take home messages

- **Incomplete** application form
- **Deficient** comparative table
- **Lack** of supportive data
- **Misclassification**

- Requests for additional information / clarifications
- Risks of rejections

- Increase of costs and time



- Complete **application form**
- Clear and complete **comparative table**
- Appropriate **supportive data**

- More rapid assessment
- Limited request for additional information / clarifications

- Faster approval
- **Gain of time**
- Limitation of costs

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Certification of Suitability

"CEP of the future": second project update

EDQM | STRASBOURG, FRANCE | 21/10/2022

Since conducting a wide public survey on the Certification of suitability to the European...

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MORE NEWS

EDQM 12/04/2022 STRASBOURG, FRANCE

EDQM sticker no longer to appear on Certificates of suitability

11th Edition at a glance

FIND YOUR WAY - TOPICS

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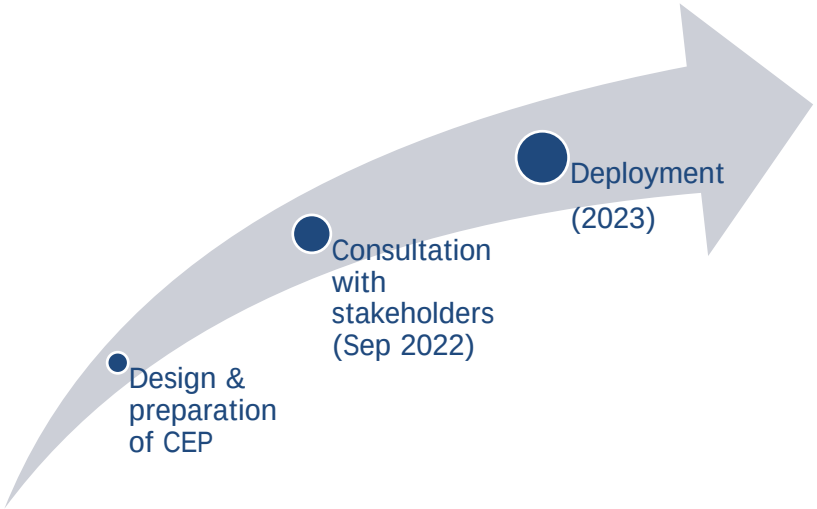
Notifications, Revisions, Renewals and Sister Files

Submission format and electronic submission

Certification policy documents and Guidelines

UPCOMING EVENTS

The Project "CEP of the future"



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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

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