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

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How to build a good new CEP application

Rita Almeida
EDQM, Certification of Substances Department

Module 6: Building successful CEP dossiers (Live Webinar)
04 July 2023

Summary

- CEP process overview
- How to build up a successful Dossier and avoid deficiencies?
- Examples

CEP Process Overview

Validation
- Administrative
- Technical

EDQM

Evaluation 1
- CEP granted or
- Additional information requested

115 WD

Applicant

1st Round:
5% CEP
95% AI

180 CD

Evaluation 2
- CEP granted or
- Additional information requested

92 WD

90/30 CD

Evaluation 3
- CEP granted or
- Application closed without the CEP being granted

92/23 WD

CEP

Deficient application delays the CEP!

Deficiencies: How to avoid them ?

Reference documents

PA/PH/CEP (04) 1 6R (December 2018)
"Content of the dossier for chemical purity and microbiological quality"

PA/PH/CEP (23) 21 (April 2023) New
"Requirements for the content of the CEP dossier according to the CEP 2.0"

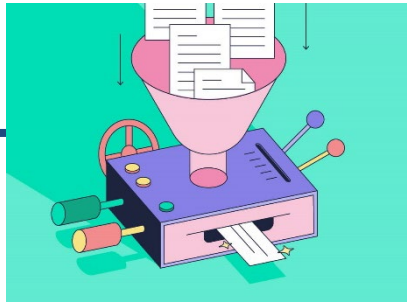
- Publicly available on the EDQM website
- Describe what we expect to see in the dossier

Deficiencies: How to avoid them ?

To be kept in mind…

- The scheme is Certification of suitability to the monographs of the EUROPEAN Pharmacopoeia.
- References, terminology, etc. should be to the Ph. Eur. or at least traceable to it
- There is a requirement to show that the monograph is suitable to control the actual quality of your substance.

Module 2 Quality Overall Summary



Template for Quality Overall Summary to be submitted for Certification applications (PA/PH/CEP (15) 26, September 2015)

- Important working tool
- Provides a clear and concise insight on the information and discussions expected to be developed in Module 3
- Reflects guidance provided in "Content of the dossier for chemical purity and microbiological quality"

Manufacturer(s) (3.2.S.2.1) & Application form

NEW: MANDATORY FROM 1 JUNE 2023 - Application form "Request for new Certificate of Suitability"

Holders and manufacturers information

- EMA SPOR/OMS ORG and LOC_ID mandatory and reflected on the CEP
- **SPOR requests to be handled via the SPOR (EMA) website**
- Information fully coherent/exatly the same across application form and sections 2.3.S.2.1 and 3.2.S.2.1

Reminder: EU market status

→ Impact on Qualification (limits) of impurities and applicability of guidelines

→ Potential use of ASMF assessment reports to facilitate evaluation and harmonise decisions

General properties (3.2.S.1.3) / Application form (box 1.5)

- **Grade (optional)**

  Specific physico-chemical characteristics for a substance (e.g. polymorphic form or particle size distribution), sterility.

  - If claimed, each section of the CEP dossier should be consistent with the grade requested.
  - If not claimed, information **not to be included**

- **Maximum Daily Dose (MDD), treatment duration and route of administration** considered in the development of control strategy
  - Based on EU Human medicine European public assessment report (EPAR), summary of product characteristics (SmPCs), or agreed literature such as Martindale
  - Will be checked (and challenged if needed) during assessment.

Description of the manufacturing process and process controls

- Detailed **narrative** process description (not batch records)
- Starts with the introduction of starting materials
- Complete information on:
  - ➢ chemicals used and their quantities
  - ➢ operations conducted with conditions adopted (e.g. temperature, time, use of vaccum, etc)
  - ➢ these requirements apply equally for outsourced intermediates
- Maximum batch size which should correspond to batches referred in the dossier

- Information corresponding to a grade

→ **only** if a grade is claimed

New CEP 2.0

Description of the manufacturing process and process controls

- Recovery
  - description of recovery procedure(s) in place and where recovered material(s) is re-introduced in the process
  - specification for recovered material(s) to be provided in the appropriate section and differences against fresh material justified
- Reprocessing
  - routine reprocessing should be identified and justified;
  - reprocessing method should be clearly described, as well as criteria for deciding when reprocessing will be performed

EU Guideline on the chemistry of active substance (EMA/454576/2016)

Control of materials - Starting materials

- Identification and justification of the proposed starting material
- Names and addresses of manufacturers (not vendors or suppliers)
- Brief description of the process/synthesis of the starting material
- Specification and analytical procedures
- Detailed discussion about the impurity profile of the starting material justifying the proposed specification

Definition of starting materials

- For synthetic processes the production of an active substance starts with the introduction of the starting materials (ICH Q7)
- The approved starting materials are the starting point for GMP and variations and must be representative of the overall synthetic process.

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging

Definition of starting materials

Reference documents: **ICH Q11 and its Q&A document**

Annex 1 to ICH Q11 Q&A-Decision tree

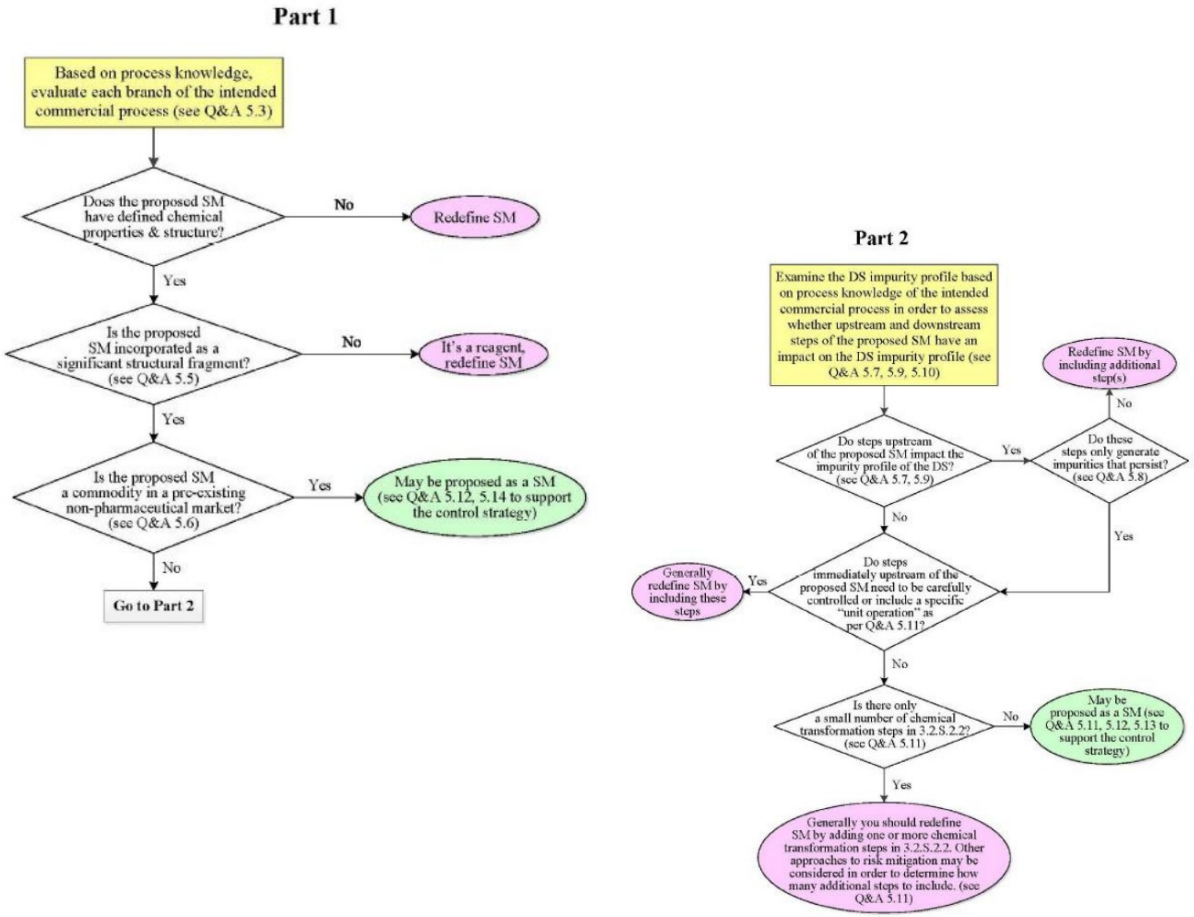
Relationship between risk for the quality of the final substance and number of synthetic steps

Length of the synthesis

and

Control strategy

both have to be taken into account



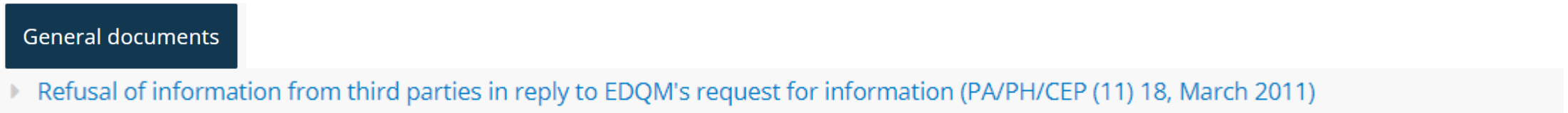
Redefinition of starting materials - consequences

The definition of starting materials is expected to be justified by the applicant.
If not acceptable, a redefinition is required.

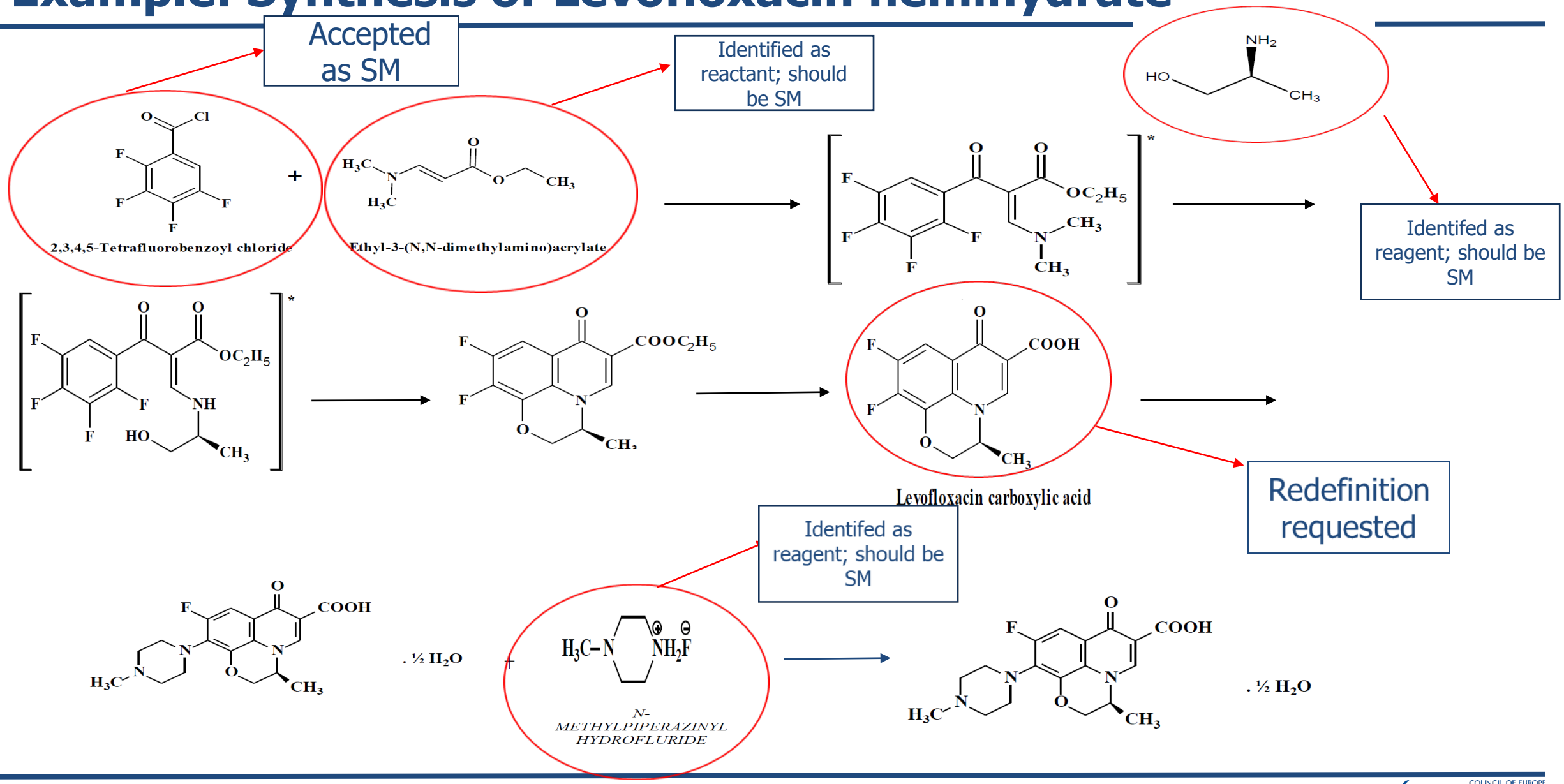
What are the consequences?

Manufacturers of non-acceptable starting materials
become manufacturers of intermediates and:

- GMP and willingness to be inspected declarations are necessary
- Section 3.2.S.2.1 and the application form need to be updated as well as other impacted Module 3 sections
- Information submitted from third parties is not acceptable. The API manufacturer must be fully aware of the information supplied.



Example: Synthesis of Levofloxacin hemihydrate



Quality of starting materials - Fate and carryover of impurities

What do we expect?

1. The impurity profile of the starting material should be adequately characterised

2. Analytical specifications with justified acceptance criteria should be proposed to control the impurity profile of starting materials. Analytical specification should be representative of the process adopted.

3. Discussion on fate and carry-over of impurities.

Quality of starting materials - Fate and carryover of impurities

Example of non-acceptable analytical specification

Chromatographic purity (By GC) Purity	Not less than 98.00 %
Impurity X	
Unknown single impurity	Not more than 0.50%
Total impurities	Not more than 1.00% Not more than 2.00%

It is not clear what the major impurity is → risks of having uncontrolled impurities → risks for the quality of final substance

It is understandable and acceptable that there may be limitations in characterizing the impurity profile of a starting material but these limitations should not prevent the manufacturer from demonstrating that the level of characterization reached does not pose risks for the quality of the final substance.

Quality of starting materials - Fate and carryover of impurities

Acceptance criteria in place to control impurities in starting materials should be justified by the manufacturer, taking into account fate and carryover of impurities from starting materials to the final substance (ability of the process to purge unreacted impurities and potential by-products).

Exemplary batch data not mandatory

Absence of carryover of an impurity into intermediate/final substance should be supported by batch data, unless otherwise justified.

Assurance should be given on the risk of having uncontrolled impurities later in the process.

Purity by HPLC		
a) Impurity at RRT 0.14	Not more than 2.5 % w/w	1.54 %
b) Single max unknown impurity	Not more than 1.0 % w/w	0.21 %
c) Total impurities	Not more than 3.0 % w/w	2.27 %

Batch data on their own DO NOT justify limits!

Analytical specifications for reagents and solvents and their carry-over

- Specifications of reagents and solvents used to manufacture the substance from the introduction of the starting materials is needed. Purity should be defined and a reasonable mass balance should be observed;
- Specifications of recycled material before being re-introduced in the process should be given and justified;
- Particular attention should be paid to the quality of solvents (both fresh and recovered) used in the last steps;
- Carryover to the final substance of reagents and solvents should be discussed, as applicable.

Water

Quality of the water used within a manufacturing process shall be in line with the EMA "Guideline on the quality of water for pharmaceutical use (EMA/CHMP/CVMP/QWP/496873/2018)"

- **Quality** of the water used in the **last** manufacturing steps (as a solvent or during isolation and/or purification) will be reported on the CEP

- Quality of the water used within the manufacturing process :
  - should be specified in Section 3.2.S.2.3
  - should be defined referring to the Ph. Eur.
  - where potable water is used: compliance with EU Directive 98/83/EC or WHO requirements for water for human consumption is expected

Quality of intermediates
Fate and carryover of impurities

The proposed control strategy is evaluated keeping in mind the risk of having uncontrolled impurities in the final substance above acceptable limits.

The impurity profile of isolated intermediates should be characterised and this becomes particularly important in case of:

- Intermediates which are isolated late in the process;
- Intermediates showing low purity;
- Related substances in the crude substance are controlled by a method which is different comparing to the one adopted at release.

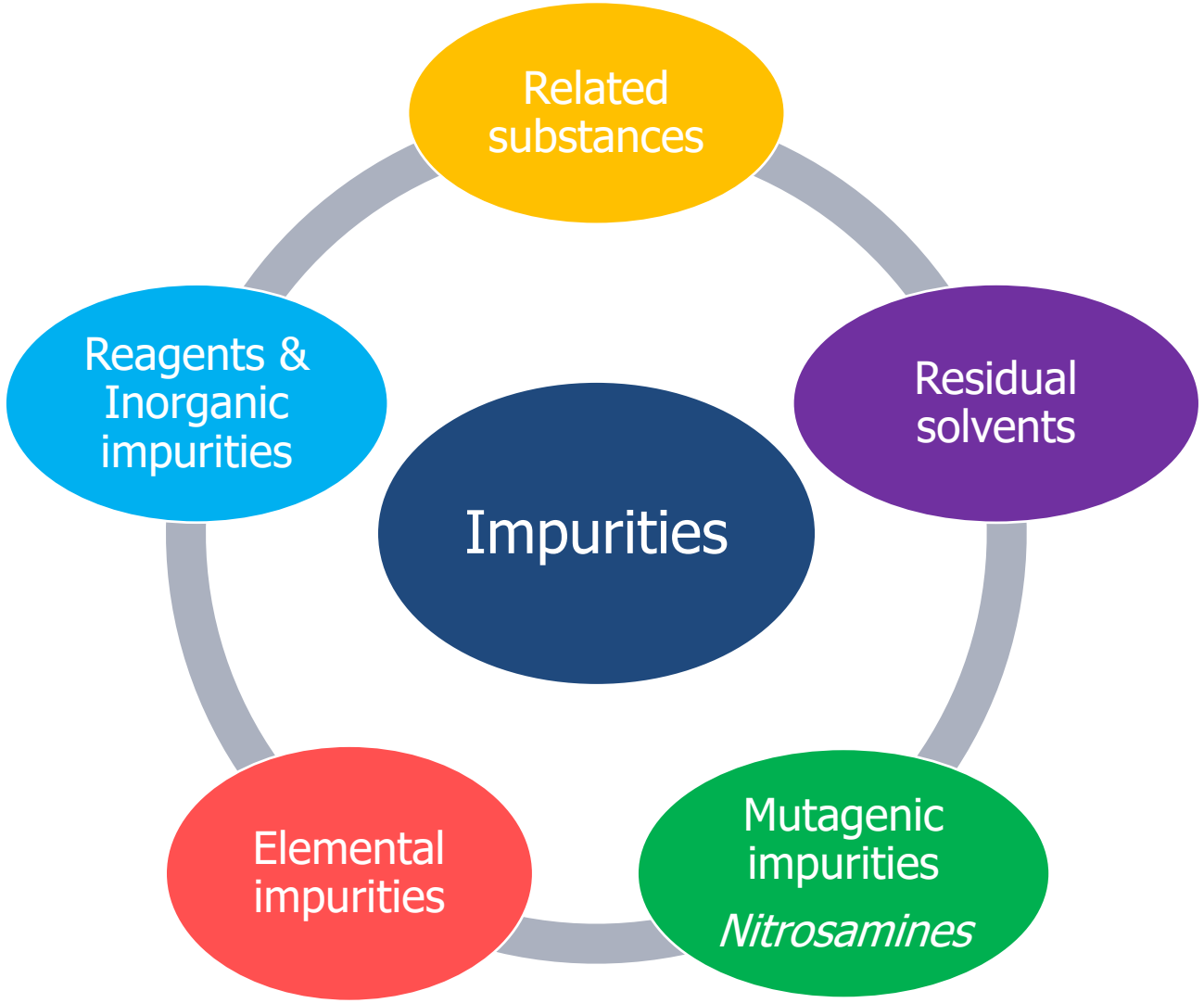
Quality of intermediates
Fate and carryover of impurities

Isolated intermediates are potentially contaminated by related substances that can lead to API-like impurities.

Information should be given on the impact the quality of isolated intermediates can have on the quality of the final API. Hence:

- Fate and carryover of impurities from intermediates to the final substance should be discussed;
- Absence of residues of intermediates (isolated and non-) in the final substance should be demonstrated by batch data, unless otherwise justified;
- The suitability of the monograph to control the quality of the final substance coming from the presented synthesis should be discussed.

Control of impurities



Module 7:

Control of impurities: CEP approach

6 July 2023

Mutagenic impurities

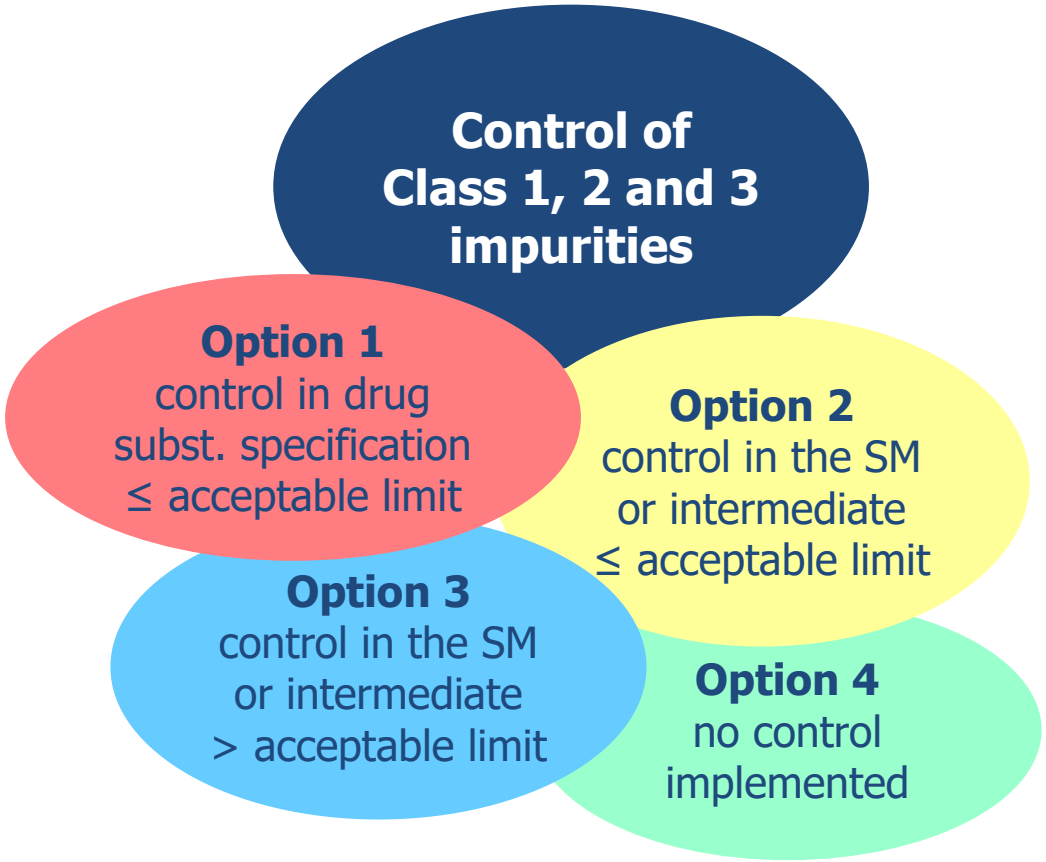
Reference documents

ICH M7 (R1) and its Q & A document

"Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk"

Complete discussion on mutagenic impurities is expected in the dossier (section 3.2.S.3.2)

- Hazard assessment in order to classify actual and potential impurities (class from 1 to 5);
- For impurities characterized as Class 1, 2, and 3 the principles of **risk characterization** (as in ICH M7) should be used to derive acceptable intakes;
- For Classes 1,2 and 3 impurities **Control strategy** according to one of the options as per ICH M7 should be developed



Guideline on assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products (EMA/CVMP/SWP/377245/2016) (from 01/07/2020)

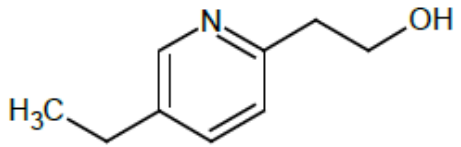
How to develop a control strategy

Pioglitazone, antidiabetic. MDD= 45 mg

- Acceptable limit NMT 33 ppm

Methanesulphonyl chloride

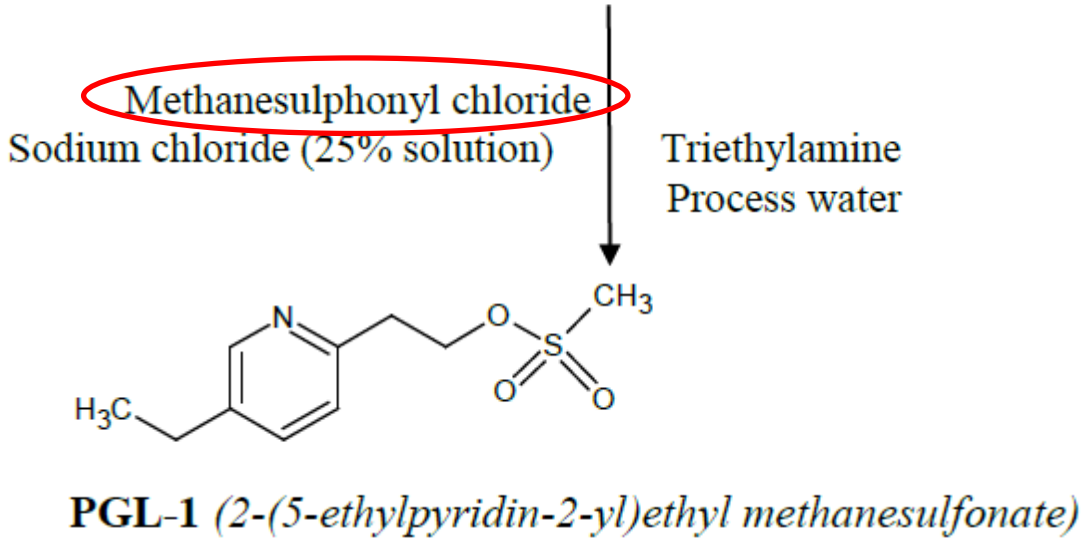
- Washing step with water?



HEEP *(2-(5-Ethyl-pyridin-2-yl)-ethanol)*

Theoretical impurity

Option 4



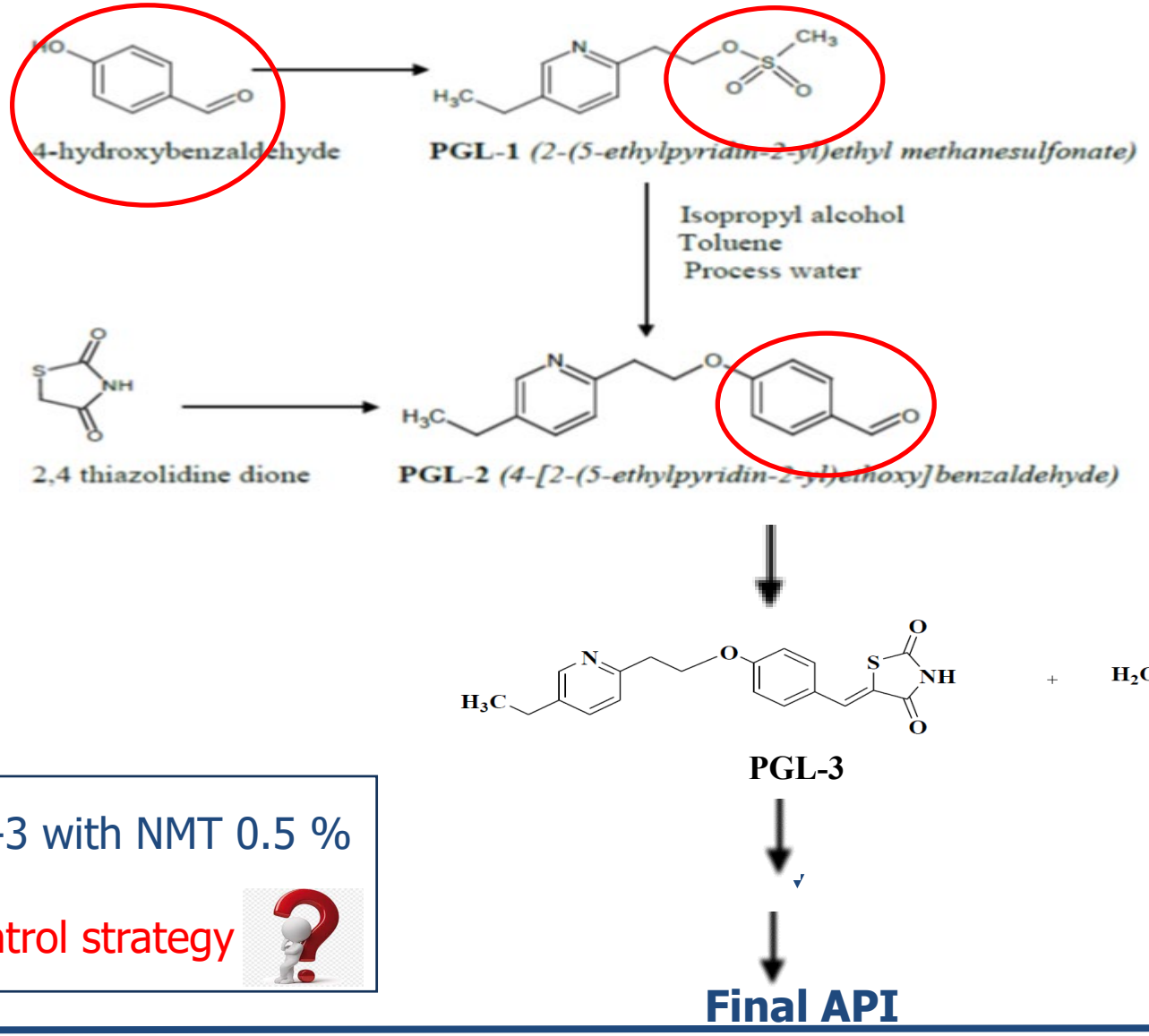
PGL-1 *(2-(5-ethylpyridin-2-yl)ethyl methanesulfonate)*

How to develop a control strategy

4-HB: aromatic aldehyde

PGL-1: mesilate

PGL-2: aromatic aldehyde



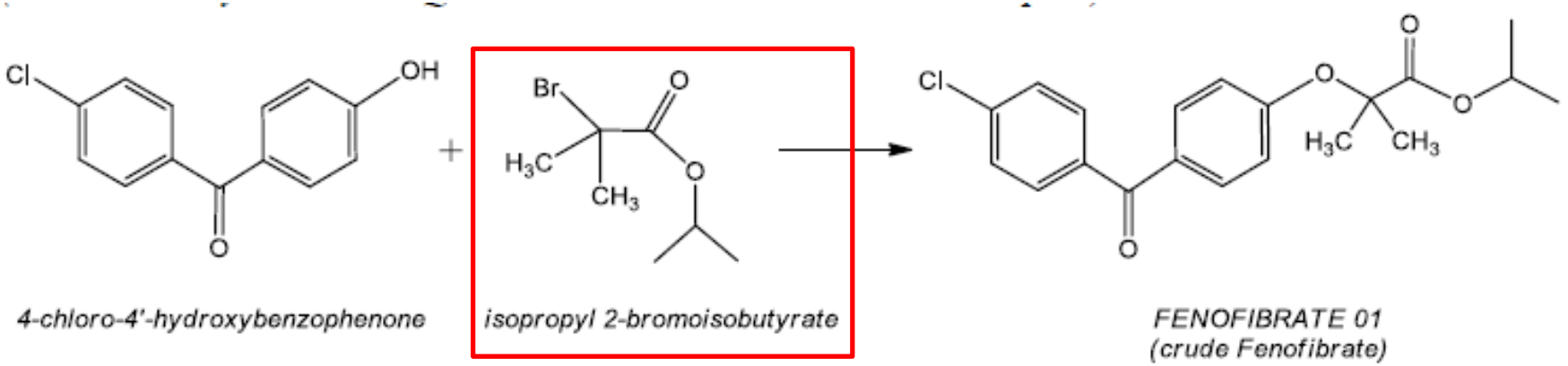
Options 2 or 3

Option 3: PGL-1 is controlled in PGL-3 with NMT 0.5 %

Justification of option 3 of control strategy

How to develop a control strategy

- **Fenofibrate**, lipid regulation drug.



4-chloro-4'-hydroxybenzophenone + *isopropyl 2-bromoisobutyrate* → *FENOFIBRATE 01 (crude Fenofibrate)*

According to ECHA website: mutagenic compound both in vivo and in vitro

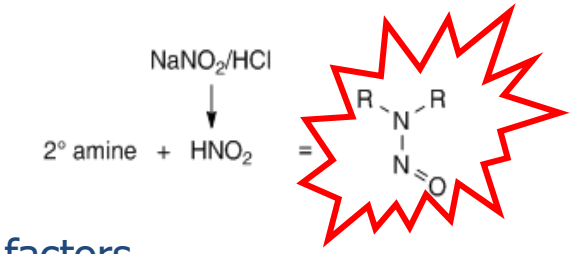
Introduced in the last synthetic step → **Option 1** (control in the final API)

28

Nitrosamine impurities

Reference document
EMA Q & A (EMA/409815/2020)

Concomitant presence of a secondary/tertiary amine and a nitrosating agent under acidic conditions:



- Step 1: Comprehensive risk assessment.
  All risk factors to be considered.
  Quote the risk (high, medium, low, negligible)
- Step 2: If a risk is identified → Confirmatory testing
- Step 3: Presence of nitrosamines confirmed
  - Risk mitigating measures
    and/or
  - Suitable control strategy

Other factors
- Reaction conditions (reagents, solvents, their quality, degradation of materials)
- Cross-contaminations between processes (running on same line)
- Recovery of solvents (incl. contamination at 3rd party)

Summary and outcome of Risk Assessment to be provided in section 3.2.S.3.2

Elemental impurities

Reference documents

- **ICH Q3D**
- **PA/PH/CEP (16) 23, 2R** published in April 2021

Specific discussion on elemental impurities is expected in the dossier (section 3.2.S.3.2)

Two different scenarios in CEP dossier:

- The substance manufacturer can submit a risk management summary (RMS) for elemental impurities (component approach). This helps the Drug Product manufacturer's risk assessment and it is evaluated by assessors

- No RMS given by the substance manufacturer.

The EDQM encourages the submission of a RMS in the CEP Dossier.

Elemental impurities

How to define control strategy for both scenario?

EI intentionally introduced in last synthetic step:
- Specification in the final substance is normally expected unless levels below 30% of ICH Q3D option 1 limit (or alternatively and if justified, based on option 2a)

EI intentionally introduced prior to the last step:
- Specification in the final substance if proposed by the applicant ➔ will be mentioned on CEP (irrespective of presence/absence of the elemental impurities);
- No specification proposed by applicant ➔ no control required

Method description with validation data according to ICH Q2 to be provided

In both scenarios: the EI used are reported on the CEP

Specification (3.2.S.4.1) and Analytical procedures (3.2.S.4.2)

Specification applied by the CEP holder/applicant (section 3.2.S.4.1) will be appended to the CEP

as well as the **additional methods** to the Ph. Eur. monograph for control of the substance (already appended, no policy change)

- Tabular format
- Parameters, acceptance criteria and reference to used method (e.g. Ph. Eur., in-house)
- Unequivocal chemical name for in-house additional impurities
- Only specification parameters corresponding to the quality claimed
- Validation expected in section 3.2.S.4.3 for all non Ph. Eur. methods
  - Summary table
  - Results expressed with regard to sample (not analytical concentration)

Stability

Re-test period highly recommended

- Stability data, even if limited (e.g. 3 or 6 months), can be provided in the initial application and a longer re-test period (with additional data) may be proposed during the assessment phase when replying to a request for additional information

- Re-test period is requested: application form (box 1.5) and in section 3.2.S.7.1
- Re-test period not requested: no data

- Climatic zones as per
  - EU guideline on Stability testing of existing active substances and related finished products (CPMP/QWP/122/02 and EMEA/CVMP/846/99)
  - WHO Technical Report Series, No. 1010, 2018 (optional)
- Use of restrictive storage conditions should be explained

Conclusions: how to avoid deficiencies?

CEP 2.0 & New requirements for the content of the dossier

- All sections of the dossier should be consistent within the dossier itself and with the CEP when granted
- CEP dossier (modules 2 and 3) ssment performed and the approved specification
- The process description and the s contain **only the information** corresponding
- Any other data **should not be** included in the dossier if **no corresponding** specific **grade** is requested

Full details

The CEP 2.0 – Webinar for CEP holders and CEP users

EDQM website

Conclusions: how to avoid deficiencies?

- Build up your Dossier taking into account applicable policies and addressing the requirements discussed in this workshop.
- With your Dossier you should give assurance on the ability of the process to remove impurities and to reduce the risk of having uncontrolled impurities above acceptable limits. Hence:
  - do not build up your Dossier on your purest batches of starting materials, intermediates and final substance. This would just lead to questions
  - include in the Dossier any relevant (recent and non-) analytical results and studies in support, even though performed during development phase
- Suitability of the specific monograph to control the quality of your substance should be demonstrated
- Deficient Dossier delays the granting of the CEP and might lead to the closure of the application without the CEP being granted.

Thank you for your attention

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Introduction to preparing a revision application

Clara VAN HOEY
EDQM, Certification of Substances Department

EDQM training 2023
4 July 2023

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

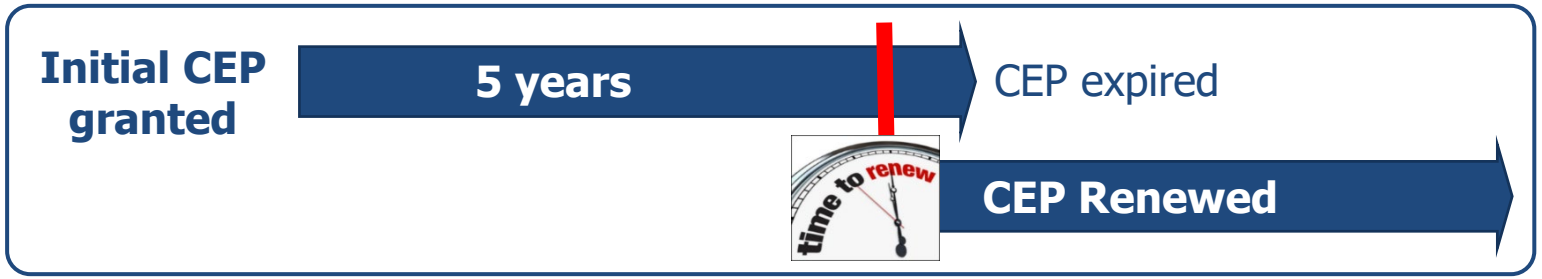
Refer to the EDQM document:

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

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**



Overview of the types of Revision applications

- **Revisions depending on the classification of changes:**
  - Notifications (IN or AN) and the possibility of grouped revisions
  - Minor revisions (incl. minor by default)
  - Major revisions
  - Sister file application

- **Other types of applications**
  - Transfer of holdership
  - Renewal (to be completed before the initial CEP expiry date)
  - Following a revision of Ph. Eur monograph

Revisions of CEPs: Background

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)

Timelines for revision applications

Refer to the EDQM document:

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)

Type of application	EDQM Timelines for assessment of initial application	Applicant Timeline to reply to first request for additional information	EDQM Timelines for assessment of reply to request for information	Applicant Timeline to reply to second request for additional information	EDQM Timelines for assessment of reply to request for information
New	115 WD °	180 CD* 30 CD #	92 WD* 23 WD #	90 CD * 30 CD #	92 WD * 23 WD #
Sister file	46 WD	30 CD +	23 WD	30 CD	23 WD
Minor revision(s)	23 WD	30 CD	23 WD	30 CD	23 WD
Major revision	46 WD	30 CD	23 WD (TSE or Herbal:46 WD)	30 CD	23 WD (TSE or Herbal:46 WD)
Monograph revision	69 WD	30 CD	23 WD (TSE or Herbal:46 WD)	30 CD	23 WD (TSE or Herbal:46 WD)
Renewal	69 WD	30 CD	23 WD (TSE or Herbal: 46 WD)	30 CD	23 WD (TSE or Herbal:46 WD)

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

EDQM Timeline for the assessment of the initial application	
• **Notification** • **Minor Revision**	23 Working Days
• **Major Revision** • **Sister file application**	46 Working Days
Renewal procedure	69 Working Days

The EDQM timelines depend on the type of revision

Fees for CEPs

Outcome of the assessment of a CEP revision

Update **CEP 2.0**

When are CEPs revised?

- After any change which **impact the content of the CEP or its annexes**, resulting of a Notification, Revision or Renewal

- In the other cases, an **approval letter** is sent 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)

Overview of the types of Revision applications

- **Revisions depending on the classification of changes:**
  - Notifications (IN or AN) and the possibility of grouped revisions
  - Minor revisions (incl. minor by default)
  - Major revisions
  - Sister file application

- **Other types of applications**
  - Transfer of holdership
  - Renewal (to be completed before the initial CEP expiry date)
  - **Following a revision of Ph. Eur monograph**

CEP and Revision of the Ph. Eur. monograph

CEP holder responsibility:

(EU Directive 2001/83/EC)

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:

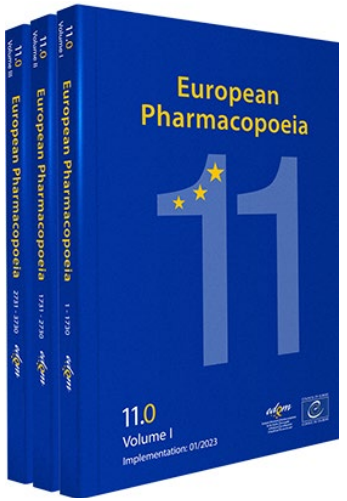
Case A

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

How to apply for revision: different types of revision

- **Revisions depending on the classification of changes:**
  - **Notifications (IN or AN)** and the possibility of grouped revisions
  - **Minor revisions (incl. minor by default)**
  - **Major revisions**
  - **Sister file application**

- **Other types of applications**
  - Transfer of holdership
  - **Renewal** (to be completed before the initial CEP expiry date)
  - Following a revision of Ph. Eur monograph

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)2,7R corr)

How to apply for revisions: the 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)2,7R corr)

How to apply for revisions: the Comparative table

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

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

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

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

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
- Classification justified in line with the EDQM Guideline for Requirements for Revision/Renewal (PA/PH/CEP (04) 2)
- If applicable, describe where corresponding **supportive information** is available (for instance: Module 1, page x/x)

How to apply for revisions: the classification of 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**

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

How to apply for revisions: Example of the **Renewal application**

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**)

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

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]

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

Renewal procedure

Upcoming **update CEP 2.0**

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

6 months before

the expiry date of the CEP

CEP Renewed

Specific procedure to obtain the <u>Renewed</u> CEP:

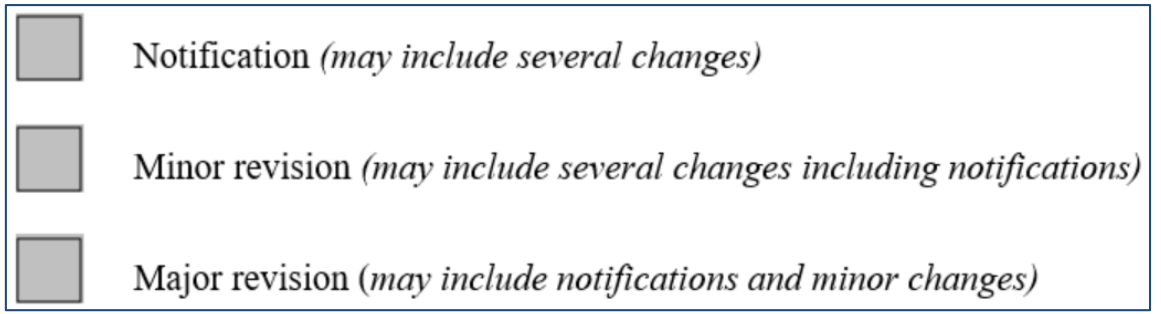
- **A initially granted CEP is valid 5 years**
- Renewal assessment focuses on compliance with: Ph. Eur. GM 2034, recent European quality guidelines (e.g. **Nitrosamines risk assessment**)

Documentation:

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

Overview of the types of Revision applications

- **Revisions depending on the classification of changes:**
  - **Notifications (IN or AN)** and the possibility of grouped revisions
  - **Minor revisions** (including minor changes by default)
  - **Major revisions**
  - **Sister file application**



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)*

Notifications

☒ Notification *(may include several changes)*

- It should be formally **confirmed** that **all the conditions are met, as listed in the EDQM guideline on Requirements for Revision/Renewal of CEP**
- **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.

Minor changes

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

- **Typical changes are listed** in the guideline

Examples: addition of a new starting material manufacturer when there is no impact on the final substance specifications, addition/extension of a **re-test period**, …

- Revised discussions on **impurities** should be submitted as **minor revisions**:

Examples: Risk assessment on Elemental impurities, **Nitrosamine impurities**, Mutagenic impurities, …

- **All changes** that are **neither listed as a notification** nor as a **major change** in the guideline **are considered as « minor by default »**

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 **<u>may potentially</u>** impact the quality of the final substance.

The type of submission depends on the **<u>potential impact on the quality</u>** 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 !

Reminders on the type of revision: examples of changes

NOTIFICATION

- Change of the name of an approved intermediate manufacturer
- Tightening of a specification limit (*e.g.* **4.II.1.6.a**)

MINOR revision

- Introduction of an intermediate manufacturer who is **using a different solvent** in the manufucturing process, **when** this solvent is already used elsewhere in the process of the final substance **and** is still demonstrated absent in the final substance (*e.g.* **4.II.1.4.b**)

MAJOR revision

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

Sister file application

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

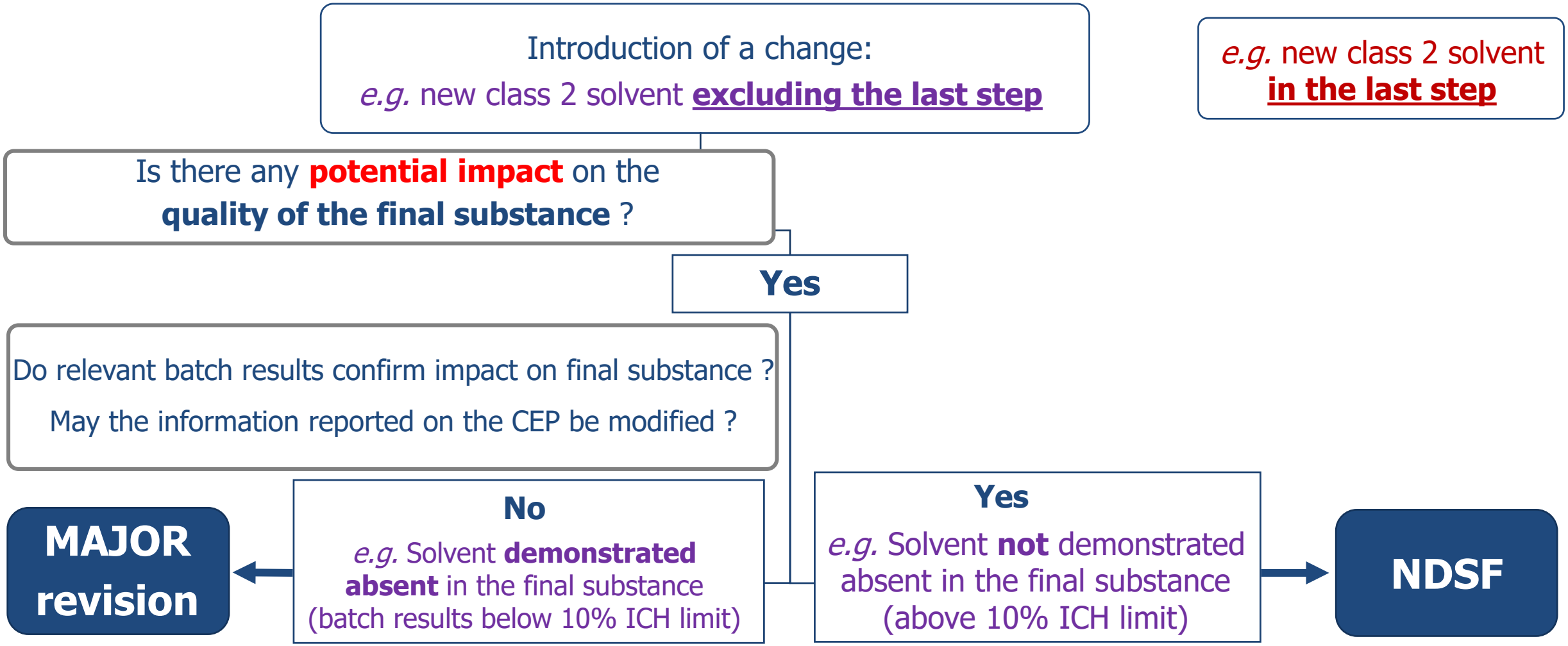
to be filled in for each request for a Technical Advice meeting related to the procedure for Certificate of Suitability to the monographs of the European Pharmacopoeia AP-CSP (07) 1

- 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**

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**

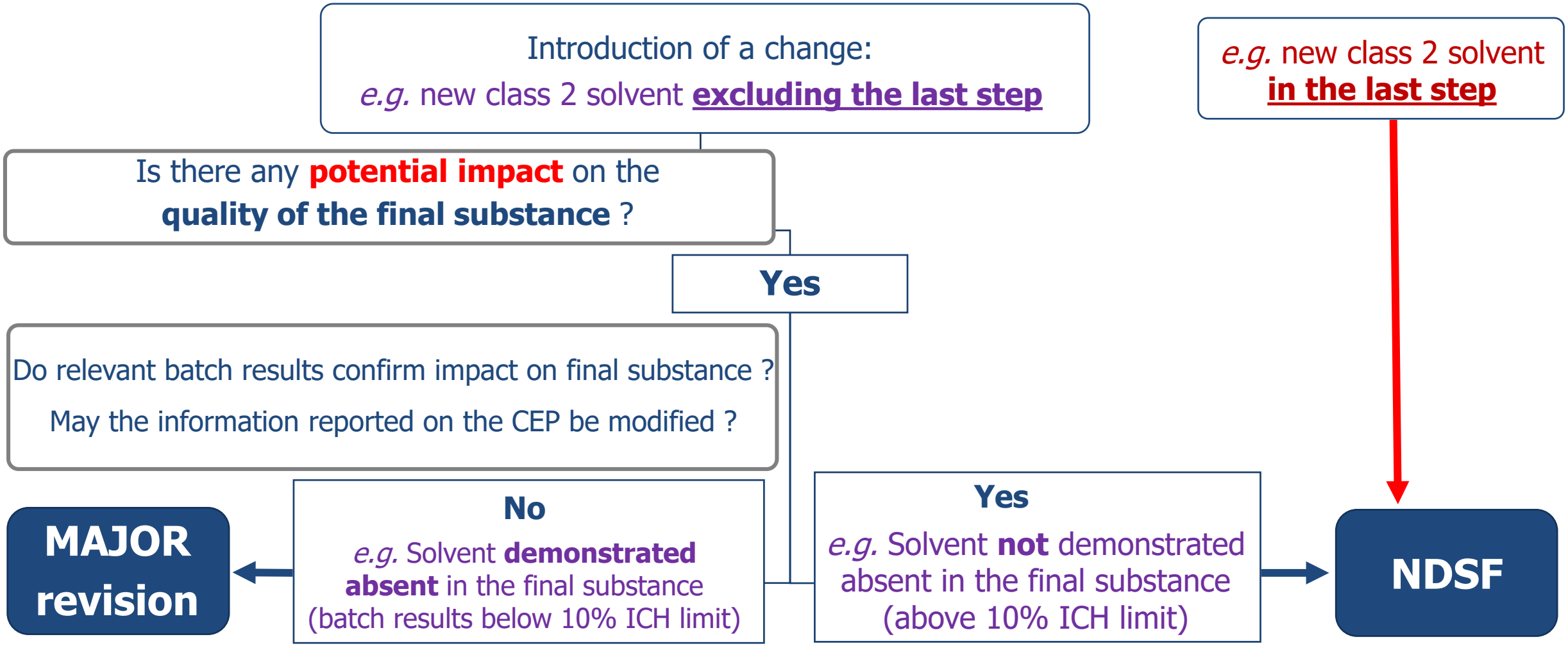
Classification of changes: Major revision vs Sister File (NDSF)

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



Classification of changes: Major revision vs Sister File (NDSF)

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

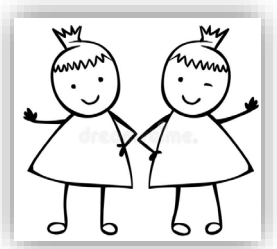


CEP via the 'Sister file' Procedure (NDSF)

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, November2018)



- ✓ **Facilitates the treatment of similar dossiers**
- ✓ **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**

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"
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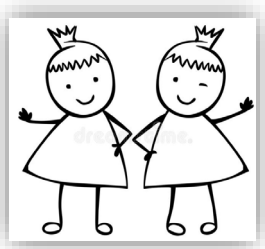


To apply:

- The **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

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

CEP via the 'Sister file' Procedure (NDSF)

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

CEP via the 'Sister file' Procedure (NDSF)

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" CEPs.

Module 2

- ✓ Quality overall summary (QOS), which **should be in line with Module 3**

Module 3

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

More information available regarding:

➢ Revision applications

Refresher on How to submit a revision application and gain rapid acceptance of proposed changes: Reminders and Updates!

CERTIFICATION OF SUITABILITY | ON-DEMAND WEBINAR | 22/11/2022

This webinar is aimed at holders of a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP). Experienced EDQM CEP Assessors explain how to maintain the validity of a CEP once it has been granted, and attendees are advised on what to include in a revision application...

➢ CEP 2.0

Upcoming **updates for CEP 2.0**

The CEP 2.0 – Webinar for CEP holders and CEP users

CERTIFICATION OF SUITABILITY (CEP) | PDF PRESENTATION | 16 MAY 2023

In 2020, the European Directorate for the Quality of Medicines & HealthCare (EDQM) launched the "CEP of the future" project to design a "new-look" CEP to better meet the current needs of stakeholders, offer enhanced user-friendliness and provide greater information transparency. This project is...

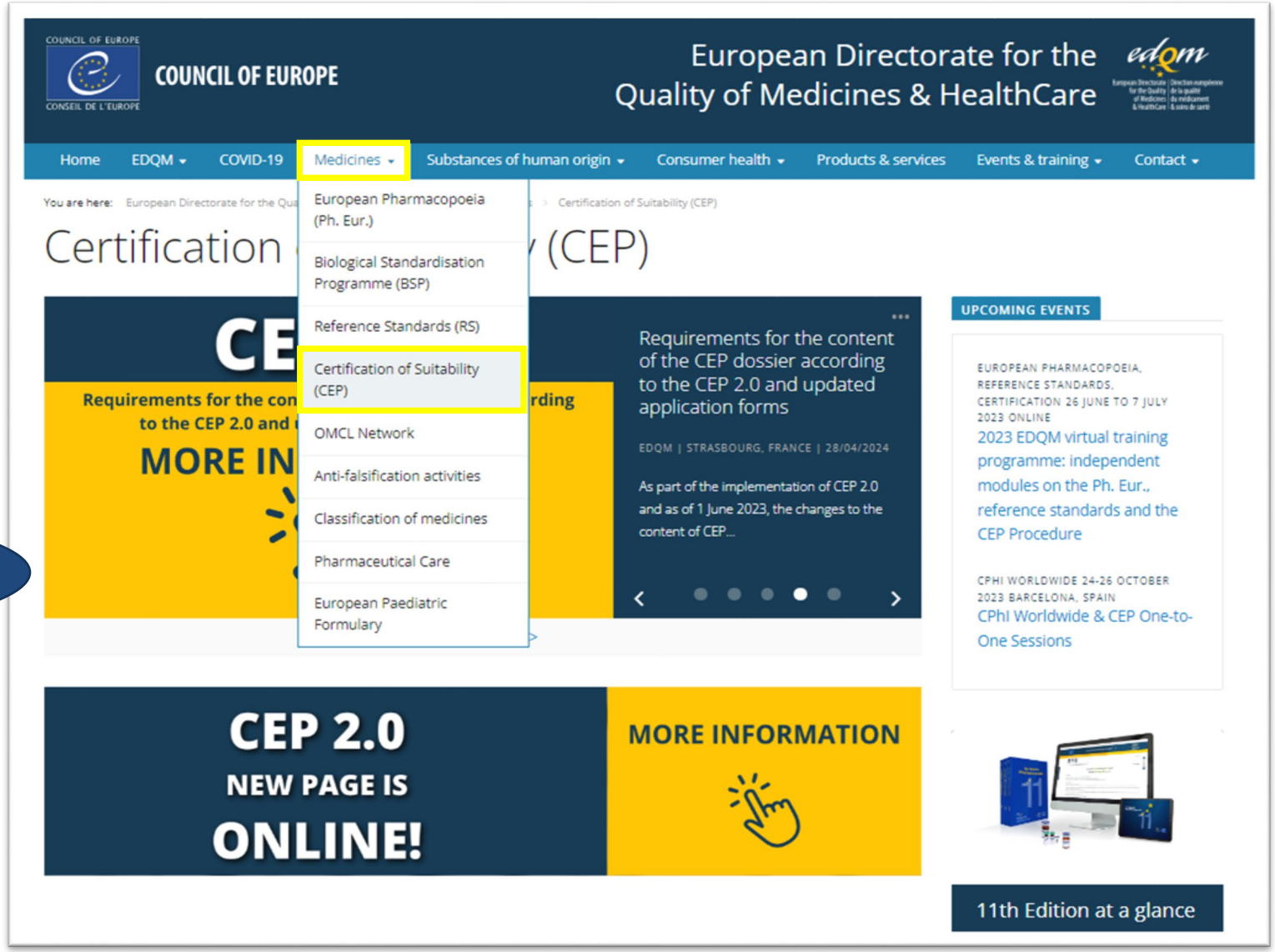
Regularly consult EDQM website !

CEP 2.0

Requirements for the content of the CEP dossier according to the CEP 2.0 and updated application forms

MORE INFORMATION

- 3.2.S.2.1 Manufacturer(s)
- 3.2.S.2.2 Description of Manufacturing Process and Process Controls
- 3.2.S.4.1 Specification
- 3.2.S.4.2 Analytical Procedures
- 3.2.S.7 Stability



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, 7R corr)
- 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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