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How to build a good new CEP application?

Module 6, Building successful CEP dossiers

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2025 EDQM Virtual Training Programme

9 December 2025

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

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How to build a good new CEP application?

CEP process overview

How to build a successful Dossier and avoid deficiencies?

Examples

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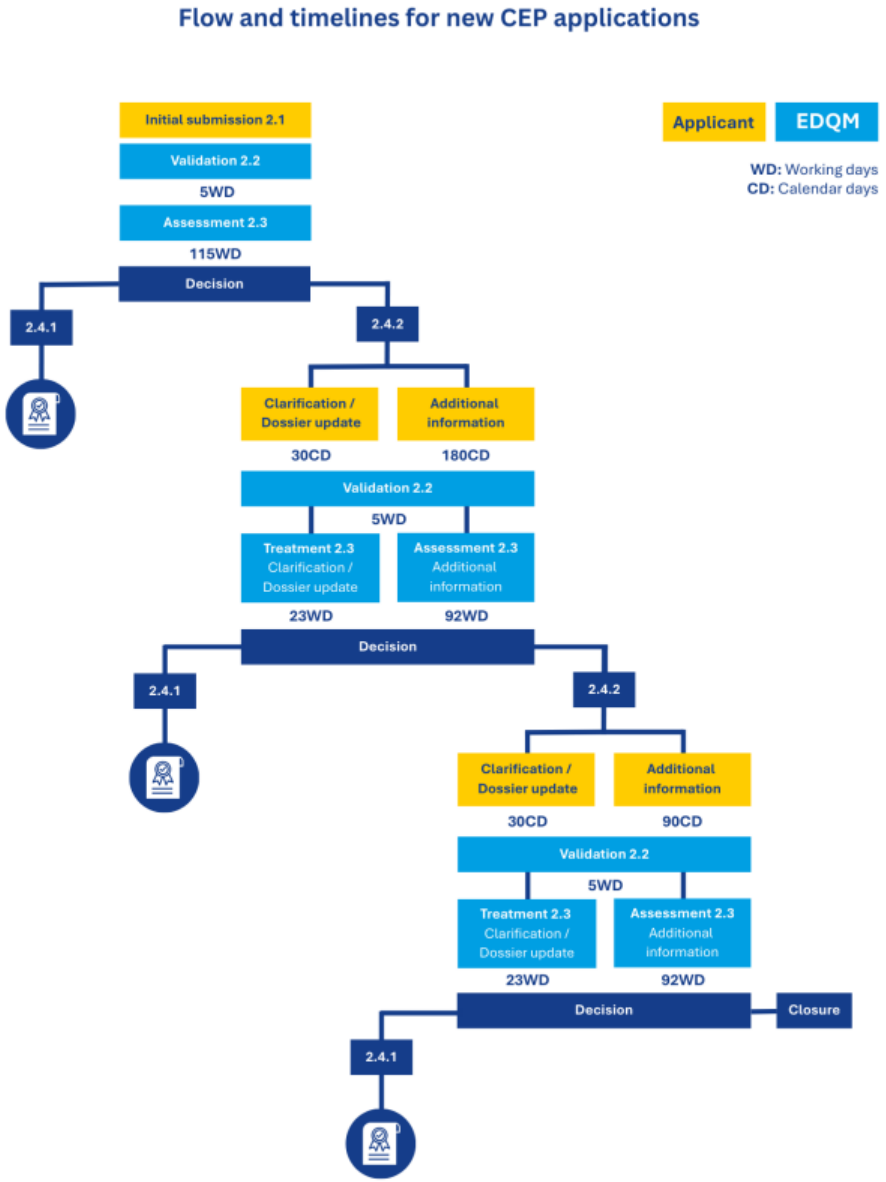
CEP Process Overview

Stepwise process to get a CEP/having a change approved, PA/PH/CEP (24) 51

New

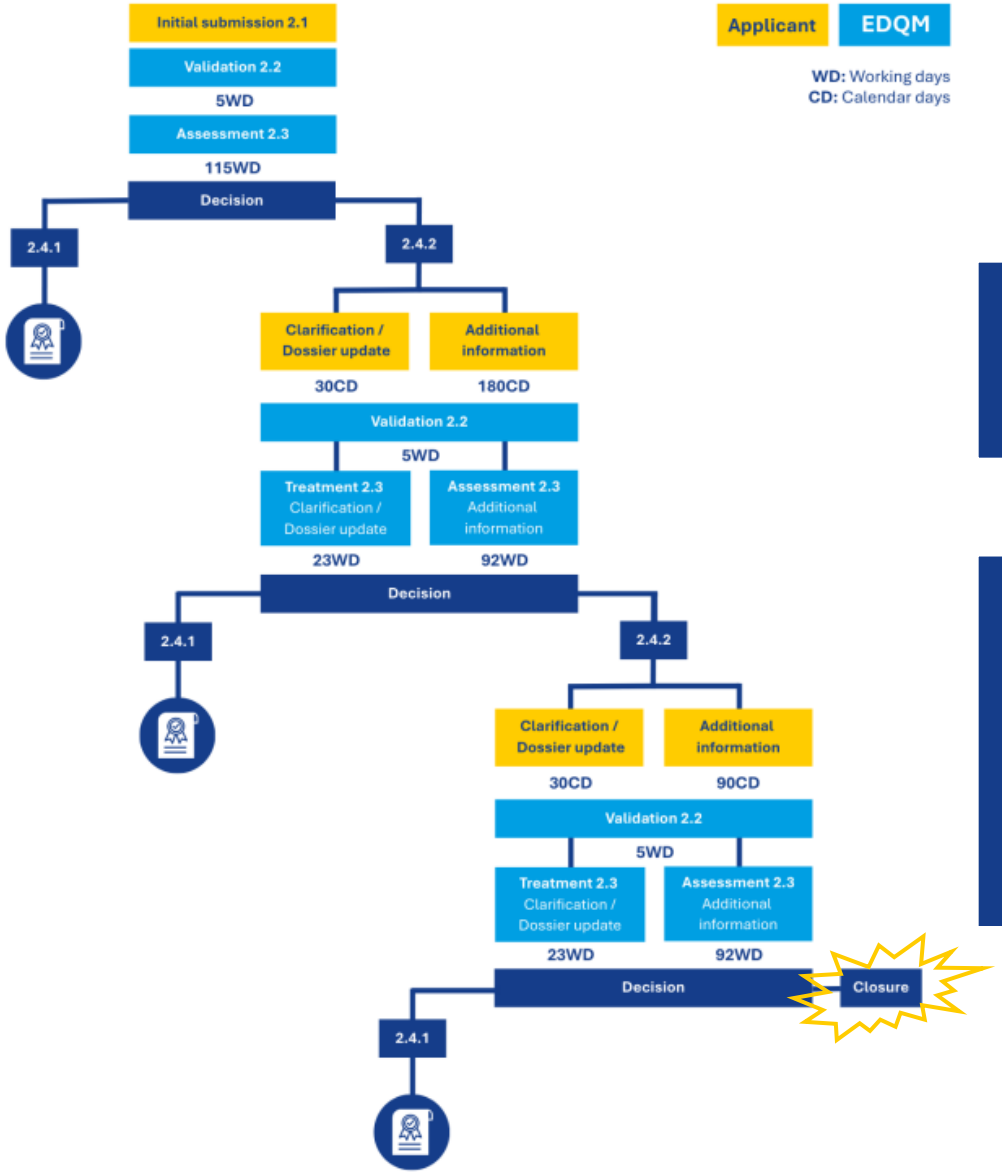
Supersedes “Management of applications for new Certificates of Suitability, Requests for Revision or Renewal of Certificates of Suitability and applications using the ‘sister files’ procedure”, PA/PH/CEP (13) 110, 3 R

- Process and steps to obtain a CEP
  - → Submission
  - → Validation: Format and Content
  - → Assessment
  - → Communication of decision
- Timelines
- Interactions between evaluation and GMP inspection activities of the CEP procedure



No change but
CLARIFICATION of the procedure

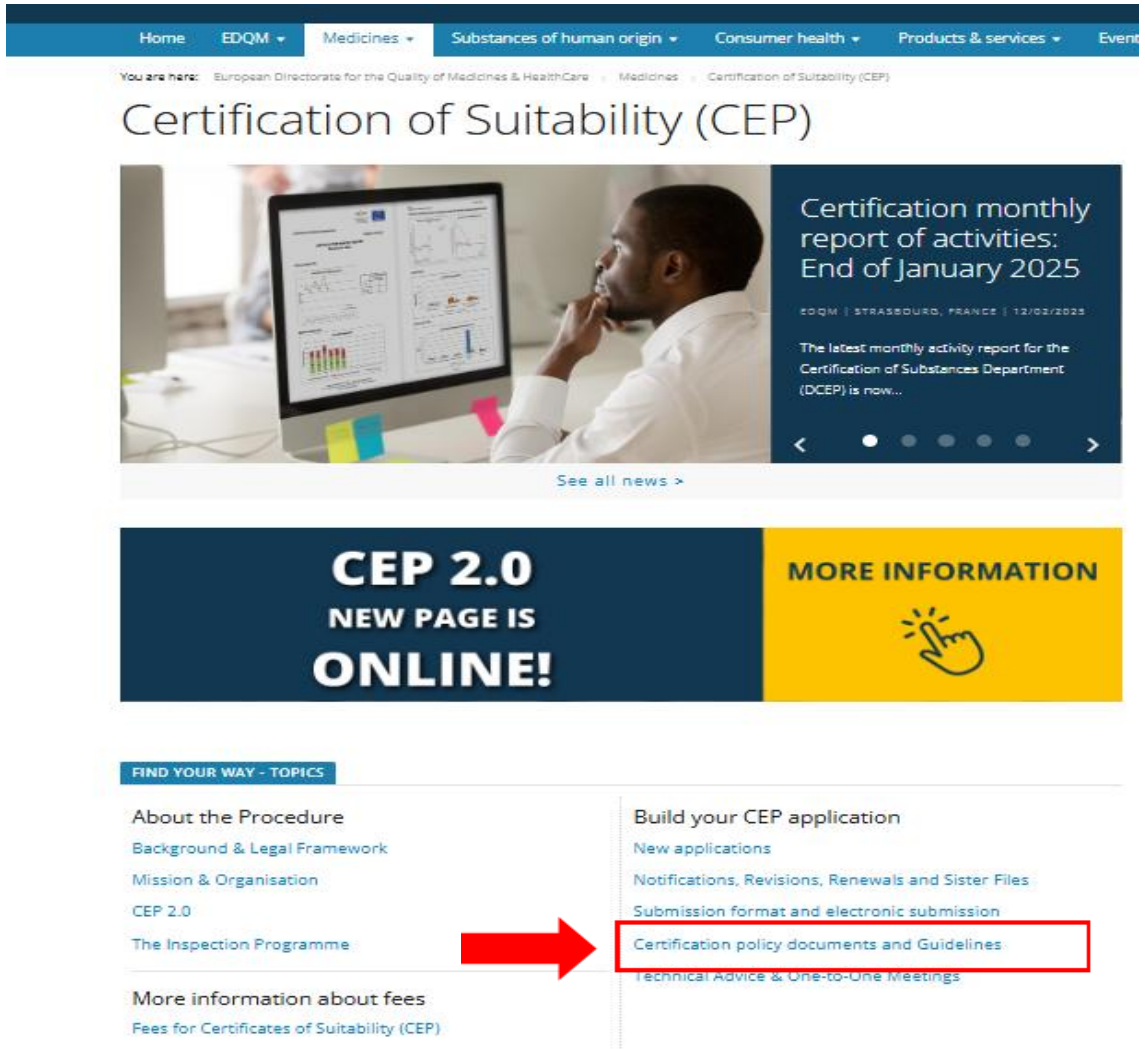
CEP Process Overview



To ensure efficient treatment of a CEP application, maximum 2 requests for information in a procedure.

Failure to respond within the timelines or to provide sufficient information will result in the closure of the application … No CEP granted

How to build a good new CEP application ?



All guidance documents are publicly available on the EDQM website

Describe what we expect to see in the dossier

Submission & Format validation

Electronic submissions

These documents describe the tools and format to be used for electronic submissions for CEP applications.

Reference documents

★ Guidance for electronic submissions for Certificates of Suitability (CEP) applications, PA/PH/CEP (09) 108, 6R)

★ Use of CESP to submit electronic documents to EDQM (PA/PH/CEP (13) 67 3R)

Certification procedure → **100% digital CEP**

Applicants advised to **reduce** or **eliminate** scanned documents

Future starts now....

Changes to e-submission requirements for CEP applications

EDQM | 17/10/2025 | STRASBOURG, FRANCE

The EDQM will soon be introducing automation to improve its process for receiving CEP submissions. As of 1 November 2025, applicants will have to comply with the following requirements: The eCTD validation report must be provided as part of eCTD submissions: Submissions with eCTD sections must be...

e-submission requirements for CEP applications

★ Electronic submission via **CESP platform**
(register for a CESP account on the Heads of Medicines Agencies website)

★ As of 1st of November 2025, new requirements should be fulfilled :

- **eCTD validation report must be provided for eCTD submissions**
  - Must be validated against the currently applicable EU region validation criteria using an appropriate eCTD validation tool.
  - Location, name and file format as follows:

eCTD Validation report	eCTD Validation report location	eCTD Validation report name	eCTD Validation report format
Required for eCTD submissions.	Must be included as part of the submission (zipped folder) and in the top-level folder (outside the sequence folder). Example: Name 0001 validation report 0001.pdf	Must include 'validationreport', 'eVreport' or 'validation report' Not case sensitive	PDF, RTF, HTML or MHTML

Failure to comply with these new requirements will **delay** validation or may lead to the application being **blocked** on receipt

- **Use of the CESP:** Mandatory fields include "Substance name" (corresponding to monograph, no additional text), "Regulatory activity", CEP dossier number (if there is one).

Content validation

Application is checked…

- ✓ suitable for assessment, i.e., includes **ALL** relevant information
- ✓ within the scope of the Certification procedure

Applications are **blocked!**
(≈ 20%)

The clock does not start until suitable information is given

An incomplete application delays the CEP!

Content validation

Applications are blocked when…

- Reference is made to an old version of the Ph. Eur. monograph
- Non-compliance with the definition or production section of the monograph
- Unsuitable information on the impurity profile of the substance
  - Absence of discussion on mutagenic impurities, nitrosamines, related substances, residual solvents, elemental impurities
- Alternative routes of synthesis (significantly different??)
- Absence of a suitable flow or synthetic flow diagram for the final substance
- Provision of batch production records instead of a detailed process description
- Use of Class I solvents without justification and control
- Absence of quantitative method to replace a non-specific TLC test of the monograph

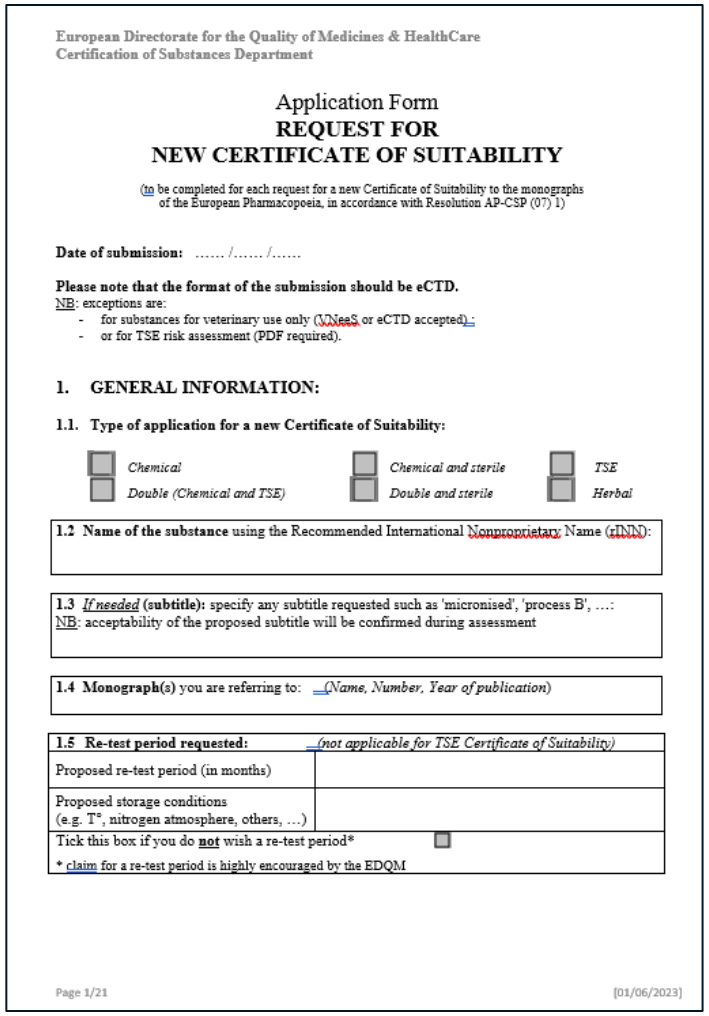
Content validation

Applications are also blocked when…

- ★ If different manufacturing sites for the final substance are listed which are not part of the same group
- ★ Failure to provide the name and address of the manufacturer(s) of the starting material (SM) (exception: SM is a strain or cell bank)
- ★ Absence of the QOS and declarations (annexes to the application form)
- ★ Possibility that the New Dossier application could be a Sister File
- ★ Failure to provide a copy of a CEP referenced in an application (if not the same holder)
- ★ Sterile substances: absence of validation data on the sterilisation

Application form

Application form "Request for new Certificate of Suitability"



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Certification of Substances Department

Application Form
REQUEST FOR
NEW CERTIFICATE OF SUITABILITY

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

Date of submission: ...../...../.....

Please note that the format of the submission should be eCTD.
NB: exceptions are:
- for substances for veterinary use only (VNeeS or eCTD accepted);
- or for TSE risk assessment (PDF required).

1. GENERAL INFORMATION:

1.1. Type of application for a new Certificate of Suitability:

☐ *Chemical* ☐ *Chemical and sterile* ☐ *TSE*
☐ *Double (Chemical and TSE)* ☐ *Double and sterile* ☐ *Herbal*

1.2 Name of the substance using the Recommended International Nonproprietary Name (rINN):

1.3 *If needed* **(subtitle):** specify any subtitle requested such as 'micronised', 'process B', ...:
NB: acceptability of the proposed subtitle will be confirmed during assessment

1.4 Monograph(s) you are referring to: *(Name, Number, Year of publication)*

1.5 Re-test period requested: *(not applicable for TSE Certificate of Suitability)*

Proposed re-test period (in months)	
Proposed storage conditions (e.g. T°, nitrogen atmosphere, others, ...)	
Tick this box if you do **not** wish a re-test period* ☐	

* claim for a re-test period is highly encouraged by the EDQM

Page 1/21 [01/06/2023]

- ★ Used version of Ph. Eur. monograph
- ★ 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 consistent/exactly the same in application form and section 3.2.S.2.1
- ★ Request for
  - ★ Grade/subtitle (1.3)
  - ★ Re-test period (1.5)
- ★ History of the substance
- ★ Annex declarations

History of the substance

Marketing and approval status

- ★ Summarise the API commercial history: make clear if and on which medicinal product(s) THIS source of API is on the EUROPEAN market
- ★ Information on ASMF submitted for the same substance
- ★ Give as much information as possible (companies, products names, countries, registration dates, marketing dates)

- Impact on Qualification (limits) of impurities and applicability of guidelines
- Potential use of ASMF assessment reports to facilitate evaluation and harmonise decisions **(Reliance)**

Fast-Track and Reliance procedure

To facilitate access to quality medicines for patients

Fast-Track:
expedited assessment for some applications

e.g. (EU) Union List of critical medicines

Reliance:
increased use of assessments of trusted authorities

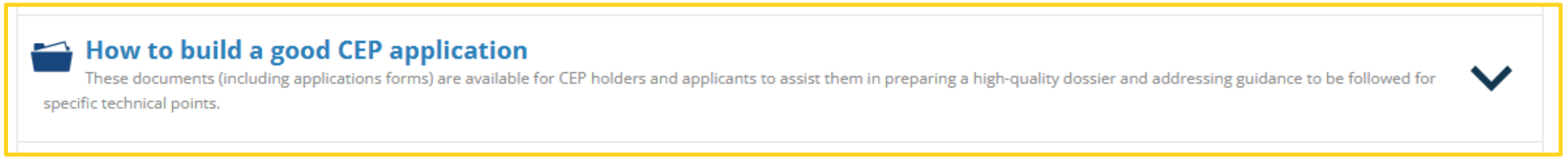
Regulatory Reliance and Fast track assessment in the CEP procedure

EDQM | 09/10/2025 | STRASBOURG, FRANCE

According to the World Health Organization (WHO), "Good reliance practices are anchored in overall good regulatory practices (GRP), which provide a means for establishing sound, affordable, effective regulation of medical products as an important part of health system strengthening. If...

Official procedures for fast tracked applications will be published in 2026

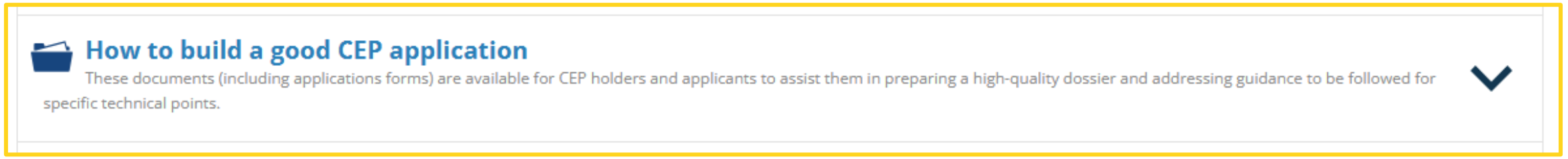
How to build a successful dossier and avoid deficiencies?



Reference documents – Chemical application

- ★Content of the dossier for chemical purity and microbiological quality (PA/PH/CEP (04) 1 7R, May 2024)
- ★Requirements for the content of the CEP dossier according to the CEP 2.0 (PA/PH/CEP (23) 21 1R, October 2023)
- ★Top ten deficiencies in New Applications for Certificates of Suitability for chemical purity (PA/PH/CEP (24) 10, Feb. 2024)

How to build a successful dossier and avoid deficiencies?



Reference documents

- ★ *Content of the dossier for sterile substances (PA/PH/CEP (23) 54)*
- ★ *Content of the Dossier for Herbal Drugs and Herbal Drug Preparation Quality Evaluation (PA/PH/CEP (02) 6 1R)*
- ★ *Use of a CEP to describe a material used in an application for another CEP (PA/PH/CEP (14) 06 1R)*

How to build a successful dossier and avoid deficiencies?

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

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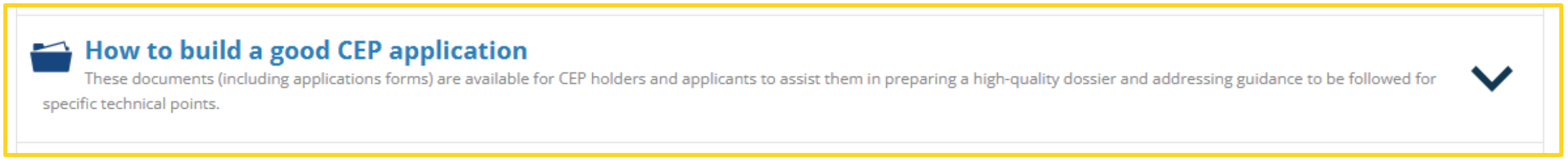
Module 2 Quality Overall Summary



› Template for Quality Overall Summary to be submitted for Certification applications (PA/PH/CEP (15) 26 1R, January 2024)

- ★ 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”
- ★ Available in Word format for better user experience

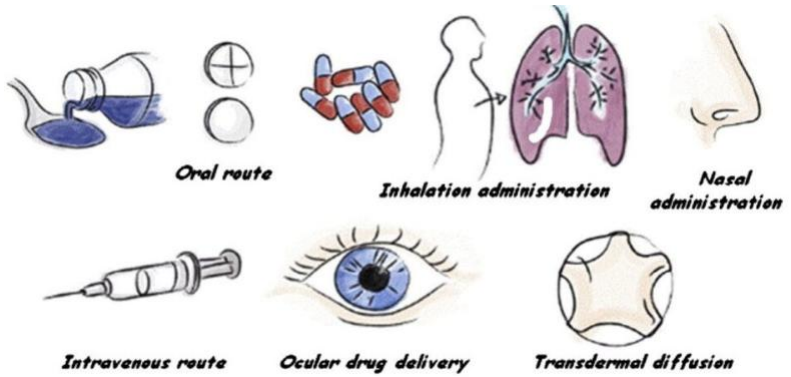
General properties (3.2.S.1.3)

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 may be challenged if needed) during assessment.

20 mg,
> 10 years to lifetime

100 mg,
> 1- 12 months



8 mg,
> 1- 10 years

1 g,
< 1 months

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

Grade (optional) → Subtitle on CEP

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

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

  For each grade, information is expected on:

  - Specification limit (3.2.S.4.1)
  - Analytical procedure (3.2.S.4.2) and corresponding validation data (3.2.S.4.3)
  - Characterisation data (3.2.S.3.1)
  - Batch data (3.2.S.4.4) & if re-test period required, compliance during stability (3.2.S.7)
  - Description of specific manufacturing process steps (3.2.S.2.2, if relevant, e.g. micronisation)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Certification of Substances Department

Certificate of suitability
No. Reference CEP

1 Name of the substance:
2 SUBSTANCE NAME
3 Subtitle

4 Details of holder:
5 CEP HOLDER NAME
6 CEP Holder Address
7 Country name-Post code Town, State
8 SPOR ORG ID: SPOR ORG ID
9 SPOR LOC ID: SPOR LOC ID

Description of the manufacturing process and process controls (3.2.S.2.2):

Top 10 deficiencies in new CEP applications for chemical purity

Top 1 and Top 6

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Description of the manufacturing process and process controls

TOP 1

Lack of details and/or poor description of the manufacturing process of the substance from the introduction of starting materials (including discrepancies with information given in sections S.2.3 and S.2.4).

★ Starts with the introduction of starting materials

★ Synthetic flow diagram

- ✓ structural formula of the starting material(s) and all intermediates (if non-isolated, represented within square brackets)
- ✓ all solvents, reagents, catalysts and process-aids used in the process

★ Detailed narrative process description

Information in S.2.2, S.2.3, and S.2.4 **should be consistent**

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Description of the manufacturing process and process controls

Detailed narrative process description (not batch records) should include complete information on:

- ★ all materials used and their quantities;
- ★ operations conducted with conditions adopted (e.g. temperature, time, use of vaccum, etc);
- ★ yield ranges for each isolated intermediate;
- ★ special emphasis should be given to the final steps, including purification procedures;
- ★ these requirements apply equally for outsourced intermediates;
- ★ information corresponding to a grade → only if a grade is claimed;

- ★ Maximum batch size should correspond to batches referred in the dossier

- ★ Blending of the final substance → clear that it is performed in accordance with ICH Q7 and batches are fully tested prior to blending as per specification

Description of the manufacturing process and process controls

Top 6

The reprocessing and recovery of raw materials are inadequately addressed

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

Reprocessing of intermediates and/or final substance:

- ★ Steps where routine reprocessing may be carried out should be identified and justified (supportive batch data)
- ★ Detailed narrative description of reprocessing step
- ★ Triggering criteria

Recovery of mother liquors or filtrates, reactants, solvents, intermediates or final substance:

- ★ Where materials are recovered from and re-introduced into the process
- ★ Detailed narrative description of recovery procedure
- ★ Specification for recovered material(s) to be provided in the appropriate section and differences against fresh material justified

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Top 10 deficiencies in new CEP applications for chemical purity

Control of materials (3.2.S.2.3)

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

Top 2

Top 4

Top 5

Top 10

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Definition of starting materials (3.2.S.2.3)

★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 (3.2.S.2.3)

Reference documents:

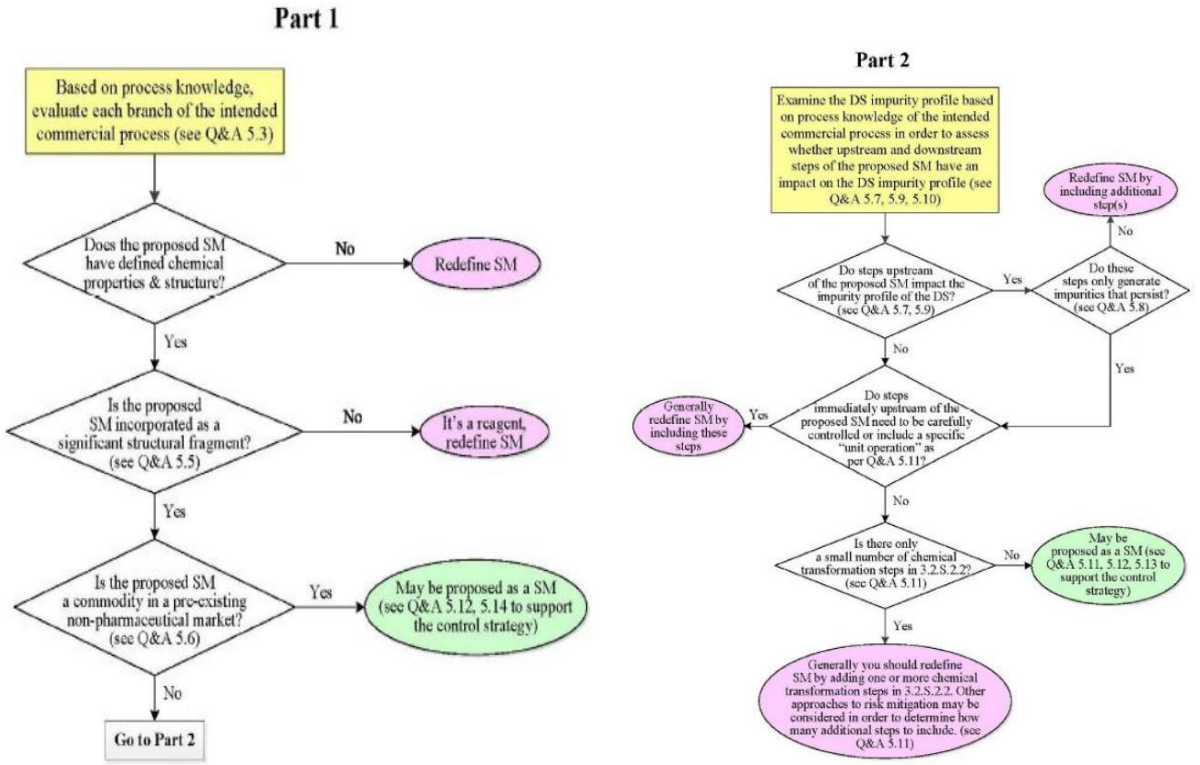
ICH Q11 and its Q&A document

↓

Relation between the
risk to the quality of the final
substance considering

Length of the synthesis
(number of steps)
&
Control strategy

Annex 1 to ICH Q11 Q&A - Decision tree



Top 10

Failure to suitably identify starting materials

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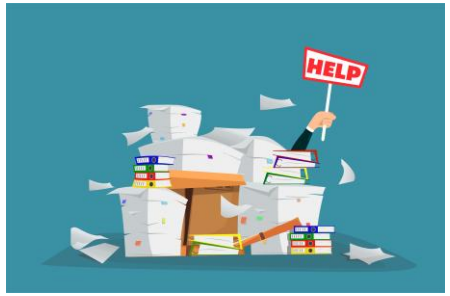
Redefinition of starting materials - consequences

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.

Governance documents

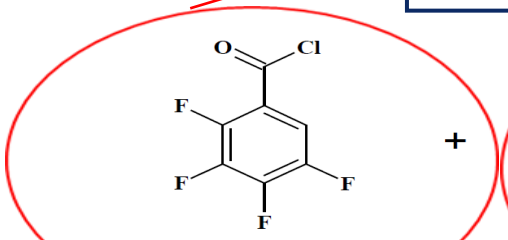
These documents describe the background and the legal framework of the Certification Procedure. They clarify its mission and organisation.

› Refusal of information from third parties in reply to EDQM's request for information (PA/PH/CEP (11) 18)

Example: Synthesis of Levofloxacin hemihydrate

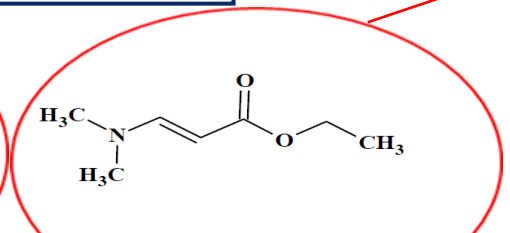
Accepted as SM

Identified as reagent; should be SM

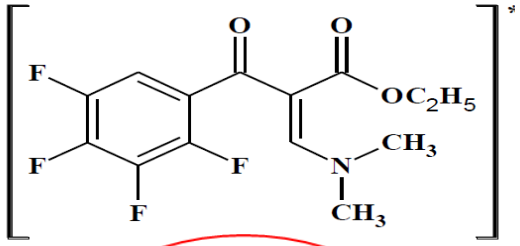


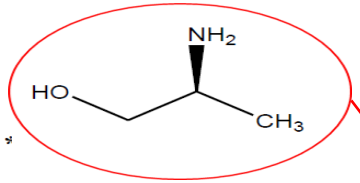
2,3,4,5-Tetrafluorobenzoyl chloride

+

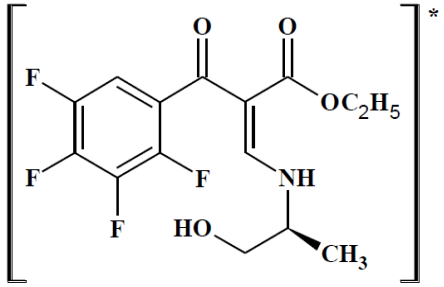


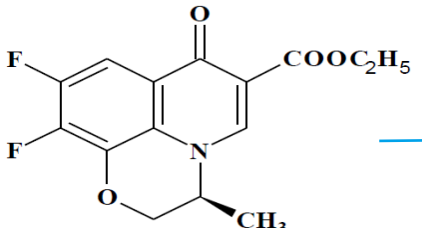
Ethyl-3-(N,N-dimethylamino)acrylate

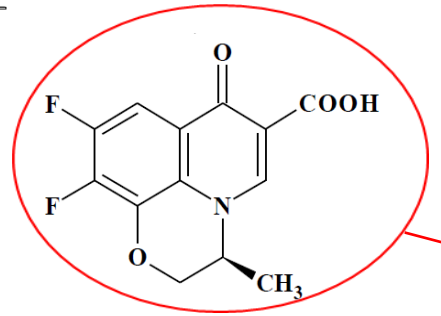




Identified as reagent; should be SM

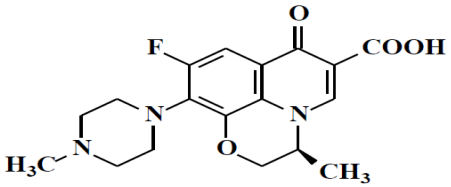






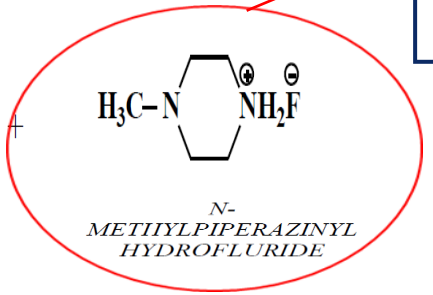
Levofloxacin carboxylic acid

Redefinition requested



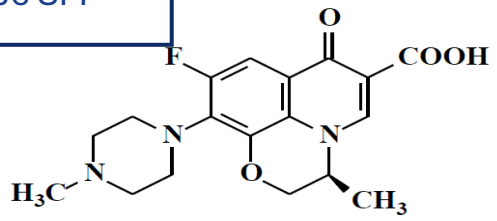
. ½ H_2O

+



N-METIIYLPIPERAZINYL HYDROFLURIDE

Identifed as reagent; should be SM



. ½ H_2O

Which information should be included for each starting material?

- ★ Identification and justification of the proposed starting material (each branch when synthesis is convergent)
  - ⚠ Identification of a substance that contributes with a significant structural fragment to the final substance as a reagent is not acceptable.
- ★ Names and addresses of manufacturers (not vendors or suppliers)
- ★ Brief description of the process/synthesis of the starting material (except for commodities)
- ★ Specification and analytical procedures
- ★ Detailed discussion about the impurity profile of the starting material justifying the proposed specification

Top 2
Top 4

Non-adequate or poorly justified specifications proposed to control the quality of **isolated intermediates** (S.2.4) and **starting materials** (S.2.3)

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Control strategy of starting materials and intermediates

Expectations on the specifications proposed to control the quality of isolated intermediates (S.2.4) and starting materials (S.2.3)

Specification
SM & isolated intermediates

Should reflect **knowledge** of the impurity profile and **understanding** of the manufacturing process

- Specified impurities → Any **major** and **recurrent** impurities:
  a) identified and/or characterised
  b) specified individually at justified acceptance criteria
- Unspecified impurities → If wider than those proposed for specified impurities, this should be well justified
- Total impurities → Mass balance (sum of assay and total impurities as well as water or solvents, if relevant) is expected, otherwise should be justified

Control strategy of starting materials and intermediates

What does it mean that specification limits should be **justified**?

A specification should mitigate any potential risk to the quality of the final substance

RISK = Uncontrolled impurities in final substance above acceptable limits

⚠ **All** acceptance criteria should be justified based on a discussion on the **fate** and the **carryover** of the impurity/ies (including spiking studies, if necessary)

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Justification of specification of starting materials

Top 4

Item	Specifications	Batch results
Appearance	Light gray or off-white crystalline powder	Conform
Loss on drying	≤0.5%	0.23 – 0.28%
Related substance	Individual impurity ≤ 1.5%	0.63 – 0.68%
	Total impurity ≤ 4.0%	1.30 – 1.43%
Purity（HPLC）	≥96.0%	98.5 – 98.7%

No information on the major impurities actually present in the SM

→ risks of having uncontrolled impurities

→ risks for the quality of final substance

Not acceptable

Batch data on their own DO NOT justify limits!

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 of the final substance or an intermediate, unless otherwise justified.
- Assurance should be given on the risk of having uncontrolled impurities later in the process.

Justification of specification of starting materials

Related Substances (HPLC)	
- *Valga 1 + Valga 2*	≤ 4.0%
- *Diacetylganciclovir*	≤ 0.5%
- *Monoacetylganciclovir*	≤ 0.5%
- *Any other impurity*	≤ 0.2%
- *Total impurities*	≤ 5.0%

Acceptable?

- ★ Major recurring impurities have been specified
- ★ Limit for unspecified impurities tighter than that for specified impurities
- ★ Mass balance

Not yet…

- ★ Fate and carryover of impurities has to be also considered and discussed

Control strategy – Additional considerations on intermediates

Top 2

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

⚠ Special attention expected for:

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

In practice…

Justification of specification based on a discussion on the impact of the quality of the isolated intermediate(s) on the quality of the final API

- ✓ Fate and carryover of impurities from intermediates to the final substance;
- ✓ 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.**

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Raw materials (3.2.S.2.3)

Raw materials…

… Fresh or Recovered…

- ★solvents, including water
- ★reagents
- ★catalysts
- ★processing aids

Top 5

Absence or inadequate acceptance criteria (and/or analytical methods) for raw materials (incl. recovered materials) used in the manufacture of the final substance

What to provide?

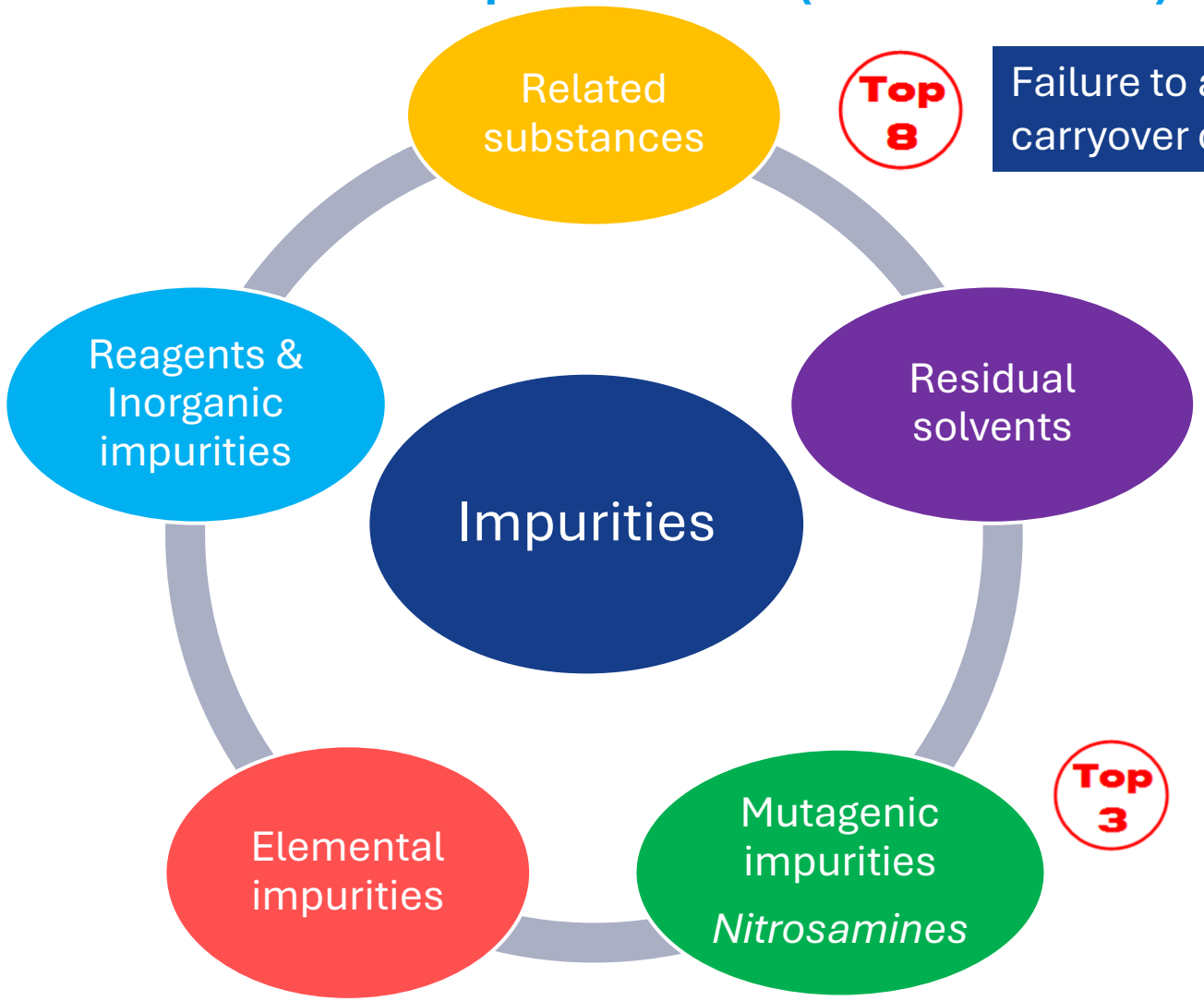
- Specifications for **all** raw materials (fresh & recovered) used from the introduction of starting materials
  - Purity should be defined and a reasonable mass balance should be observed
  - If used in the last steps: wide limits should be justified based on their impact on the impurity profile of the final substance
  - Recovered materials: justification of differences against fresh materials
- Carryover to the final substance of raw materials 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. (e.g. purified water, water for injections, water for preparation of extracts etc), other terms should be avoided
  - ✓ where potable water is used: compliance with EU Directive 98/83/EC or WHO requirements for water for human consumption is expected

Control of impurities (3.2.S.3.2)



Top 8

Failure to adequately address the origin, fate, and carryover of related substances into the final substance

Top 9

Deficient discussion on residual solvents

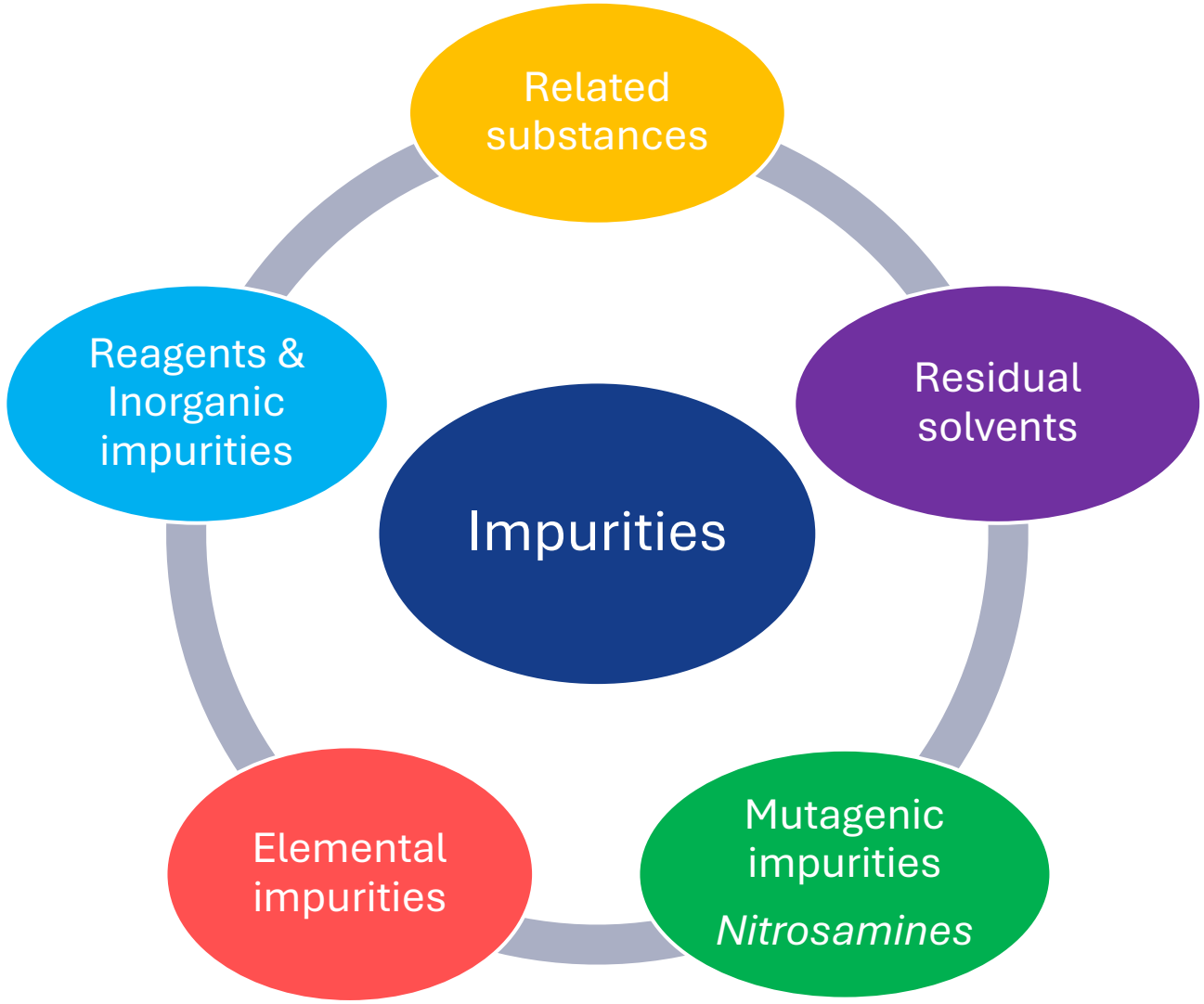
Top 3

Absence or deficient discussion on the risk of having potential mutagenic impurities in the final substance

Top 7

Absent or deficient risk assessment related to Nitrosamines

Control of impurities (3.2.S.3.2)



Module 8:

Control of impurities: CEP approach

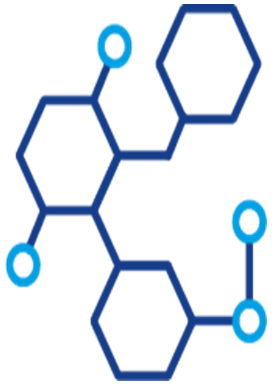
11 December 2025

Related substances (3.2.S.3.2)

Top 8

Failure to adequately address the origin, fate, and carryover of related substances into the final substance

- ★All Ph. Eur. impurities in the transparency list of the monograph
  - ★they are SMs, intermediates, by-products?
  - ★cannot be formed: why?
- ★In-house impurities specific from the adopted route of synthesis



Use EDQM QOS template to support you !!

(I) Related substances

Identify all the potential and actual impurities, their origin and fate in the process, and briefly justify the specification applied or the absence of control.

Impurity*	Origin	Company acceptance criteria	Ph. Eur. acceptance criteria	Test results **		Analytical method****
				at release	in stability studies, as available***	
Impurity X						
Unspecified impurities						
Total	-					

** Refer to the Ph. Eur. name when one exists, otherwise chemical /in-house name*

*** typical levels in the final substance or any other appropriate intermediate stage*

**** in case a re-test period is requested*

***** indicate whether the Ph. Eur. method is used or an in-house method*

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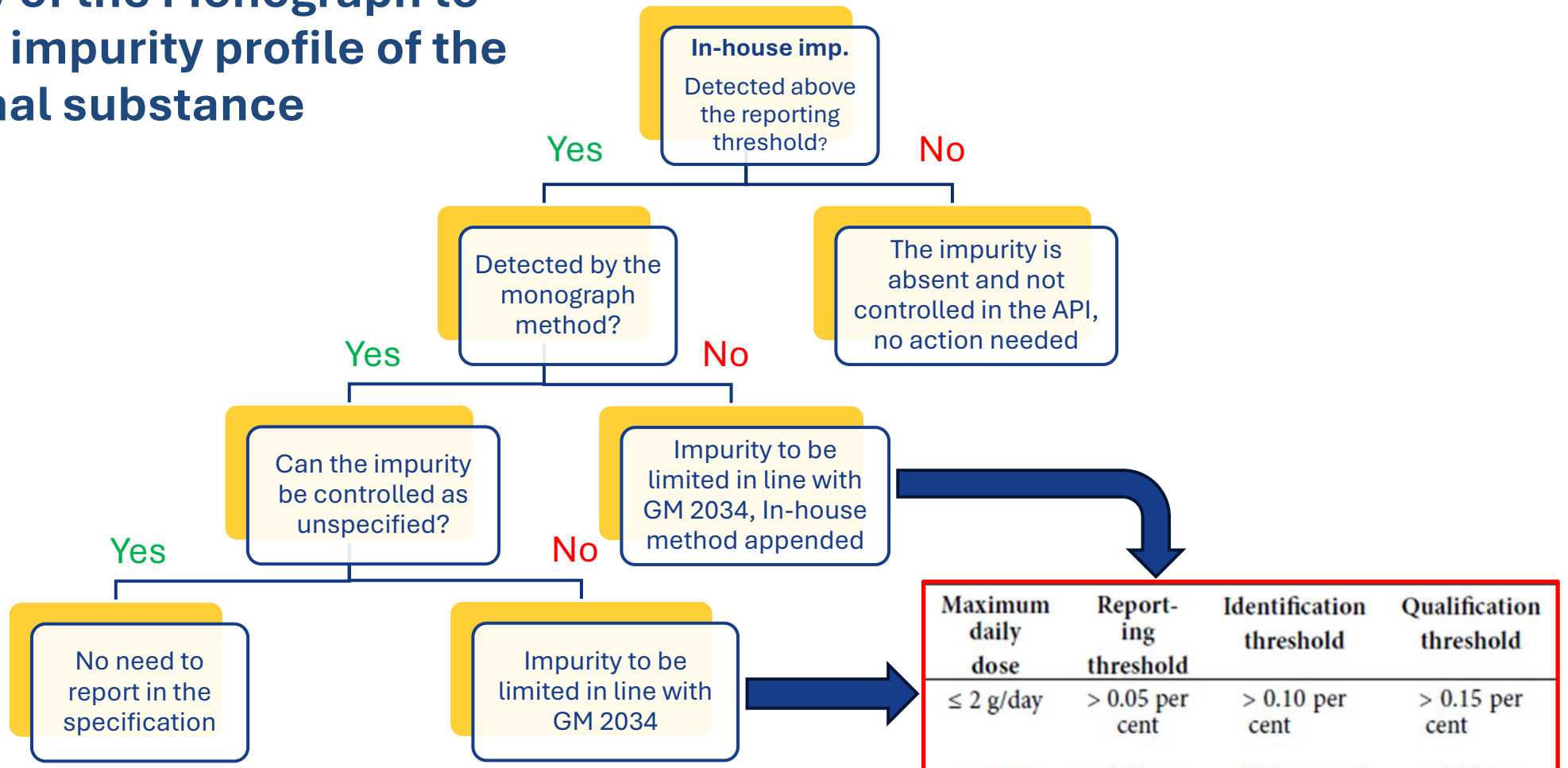
Related substances (3.2.S.3.2)

Suitability (or unsuitability) of the method(s) of the monograph to control all the additional in-house impurities for which control in the final substance is proposed or required (found above reporting threshold) should be demonstrated

If the Ph. Eur method is not suitable to control in-house impurities then it has to be supplemented with an additional (validated) analytical procedure

In-house impurities

Suitability of the Monograph to control the impurity profile of the final substance



Maximum daily dose	Report-ing threshold	Identification threshold	Qualification threshold
≤ 2 g/day	> 0.05 per cent	> 0.10 per cent	> 0.15 per cent
> 2 g/day	> 0.03 per cent	> 0.05 per cent	> 0.05 per cent

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Mutagenic impurities (3.2.S.3.2)

Top 3

Absence or deficient discussion on the risk of having potential mutagenic impurities in the final substance

Reference documents

ICH M7 (R1) and its Q&A document

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

⚠ **Complete but summary discussion on mutagenic impurities is expected in the dossier**

Mutagenic impurities (3.2.S.3.2)

Discussion in 3.2.S.3.2 section reflecting the outcome of:

- **Hazard assessment** in order to classify actual and potential impurities (class from 1 to 5)

For Class 1, 2, and 3 impurities:

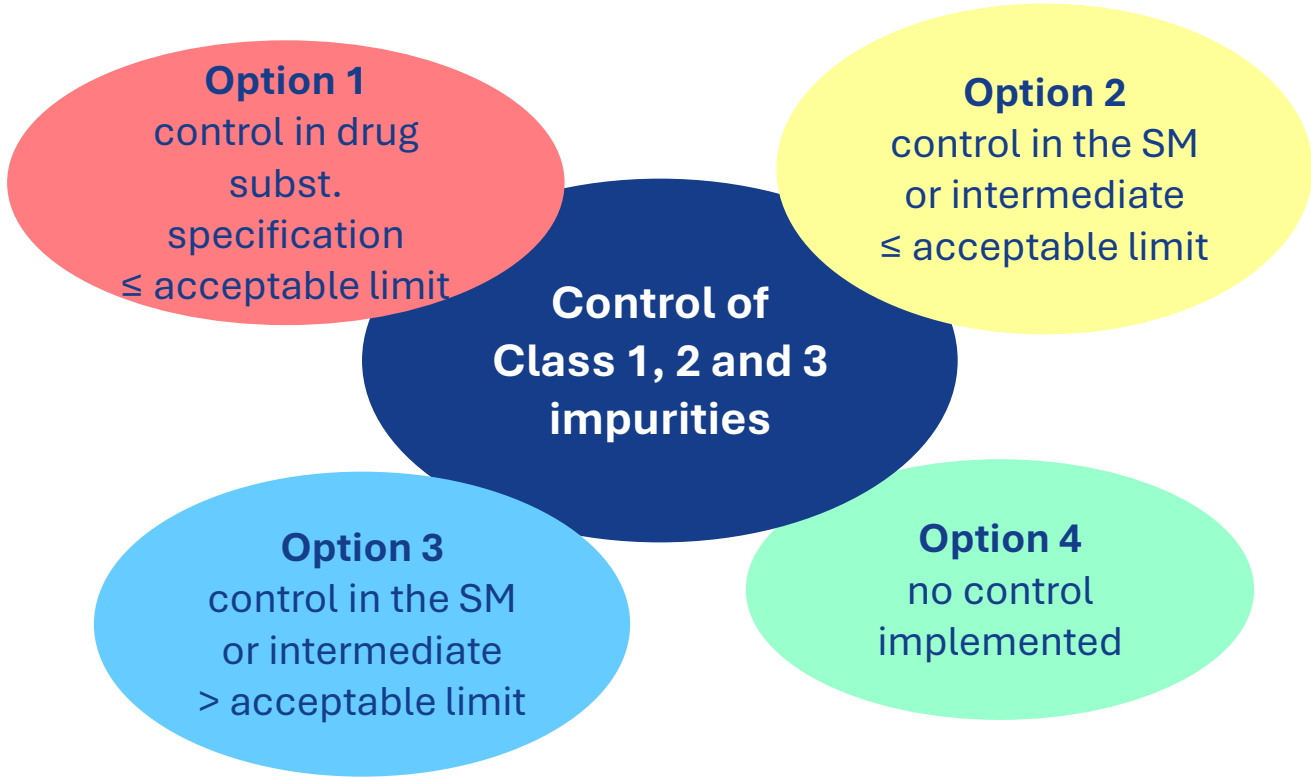
- Principles of **risk characterization** (as in ICH M7) should be used to derive acceptable intakes;
- **Control strategy** according to one of the options as per ICH M7 should be developed
- Correct **acceptable limit** (TTC limit) should be used for the control strategy

For Class 4 and 5 impurities presenting mutagenicity alerting structures: supportive toxicological data expected (e.g. (Q)SAR, literature, AMES test, etc.)

Class	Definition	Proposed action for control (details in Section 7 and 8)
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (appropriate TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

How to develop a control strategy?

$$Acceptable\ limit = \frac{PDE\ (\frac{\mu g}{day})}{MDD\ (\frac{g}{day})}$$



Impurity *	Origin	Class	Control option justification, acceptance criteria

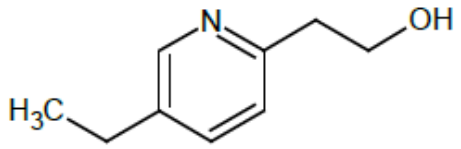
* presenting relevant structural alert or known mutagen

Use EDQM QOS template to support you !!

How to develop a control strategy?

$$Acceptable\ limit = \frac{PDE\ (\frac{\mu g}{day})}{MDD\ (\frac{g}{day})}$$

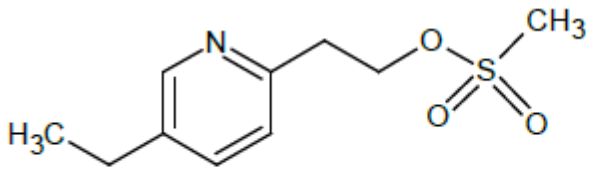
Pioglitazone, antidiabetic. MDD= 45 mg
Acceptable limit NMT 33 ppm



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

Methanesulphonyl chloride
- Washing step with water?

Methanesulphonyl chloride
Sodium chloride (25% solution)
Triethylamine
Process water



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

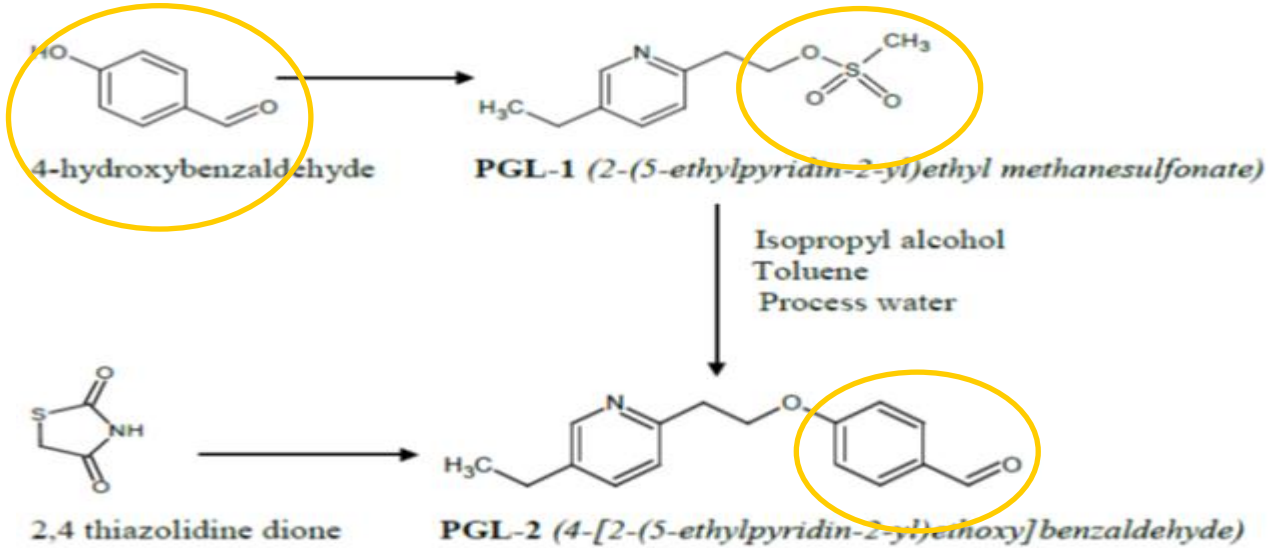
Theoretical impurity
Option 4

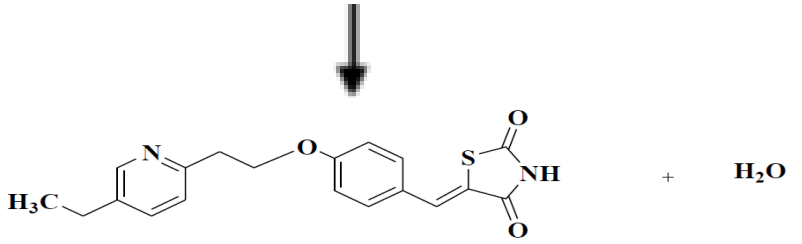
How to develop a control strategy

4-HB: aromatic aldehyde

PGL-1: mesilate

PGL-2: aromatic aldehyde



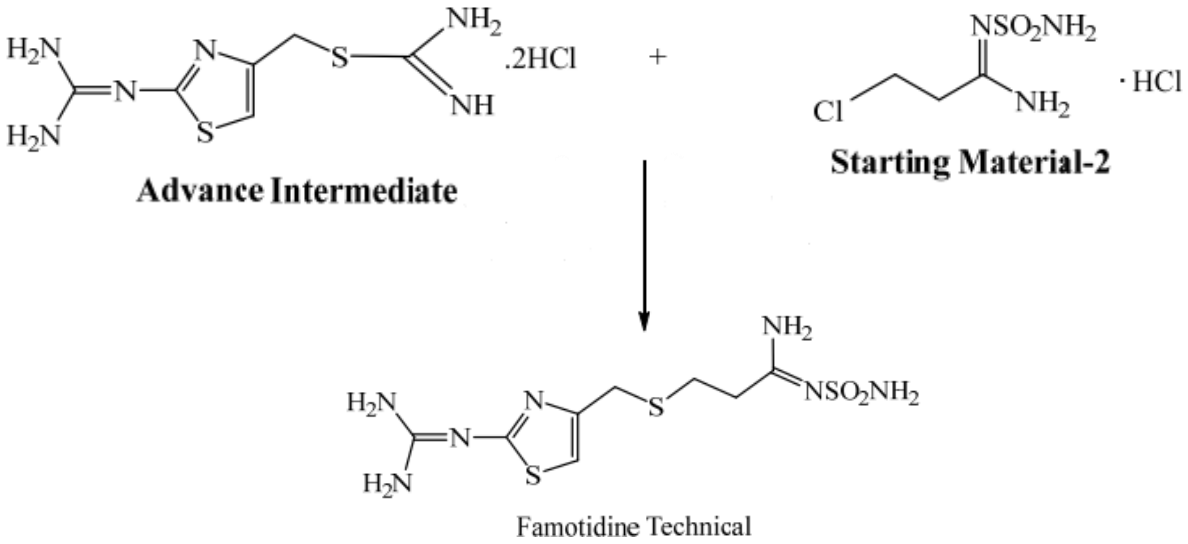


Options 2 or 3

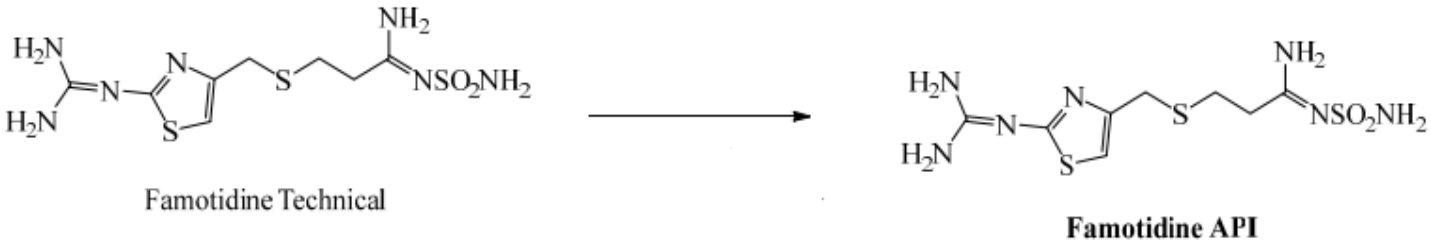
Final API

How to develop control strategy?

Stage N-1



Stage N Purification



Famotidine, histamine H_2-antagonist

★ Acceptable limit NMT 37.5 ppm

★ Starting material 2 (SM2), ICH M7 Class 2.
As per ECHA database, *in vitro gene* mutation study in bacteria shows positive results for mutagenicity.

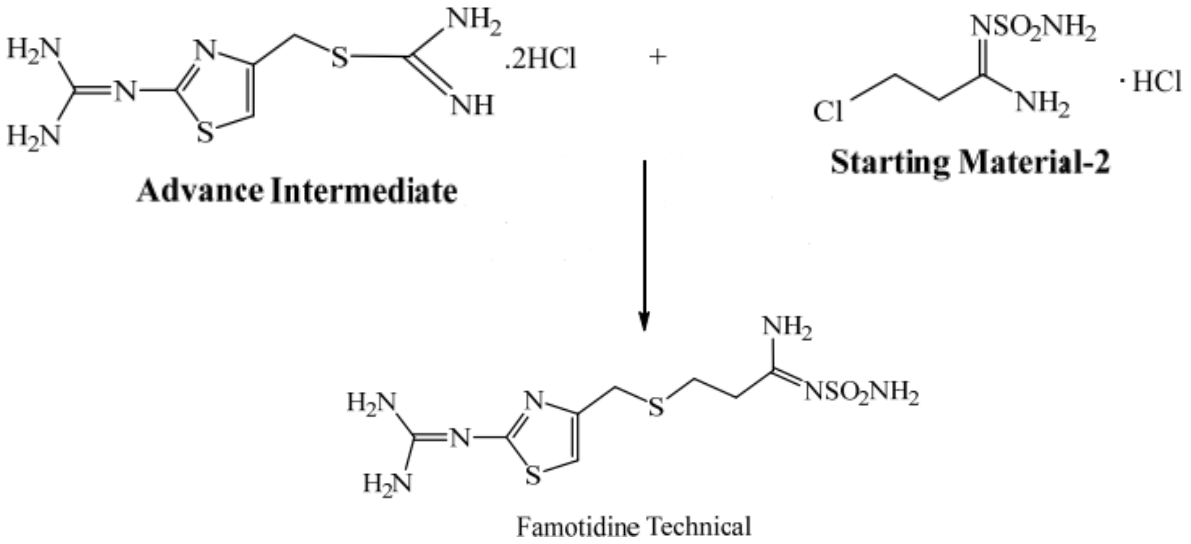
★ Introduced in the last synthetic step

How to set a control?

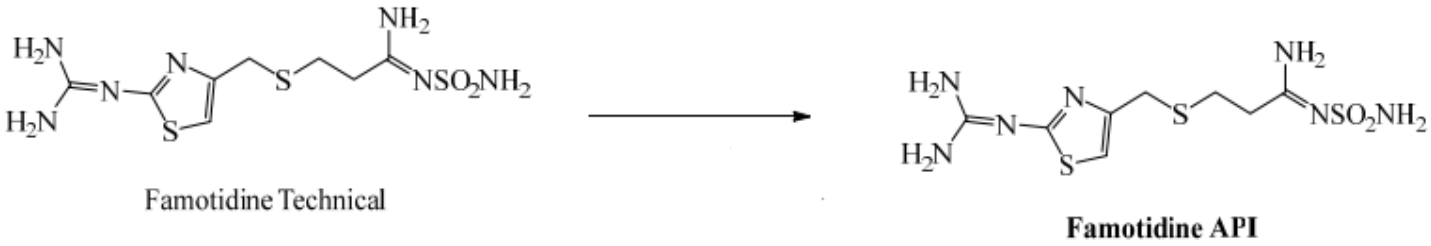
ICH M7 Q&A 8.3

How to develop control strategy?

Stage N-1



Stage N Purification



ICH M7 Q&A 8.3

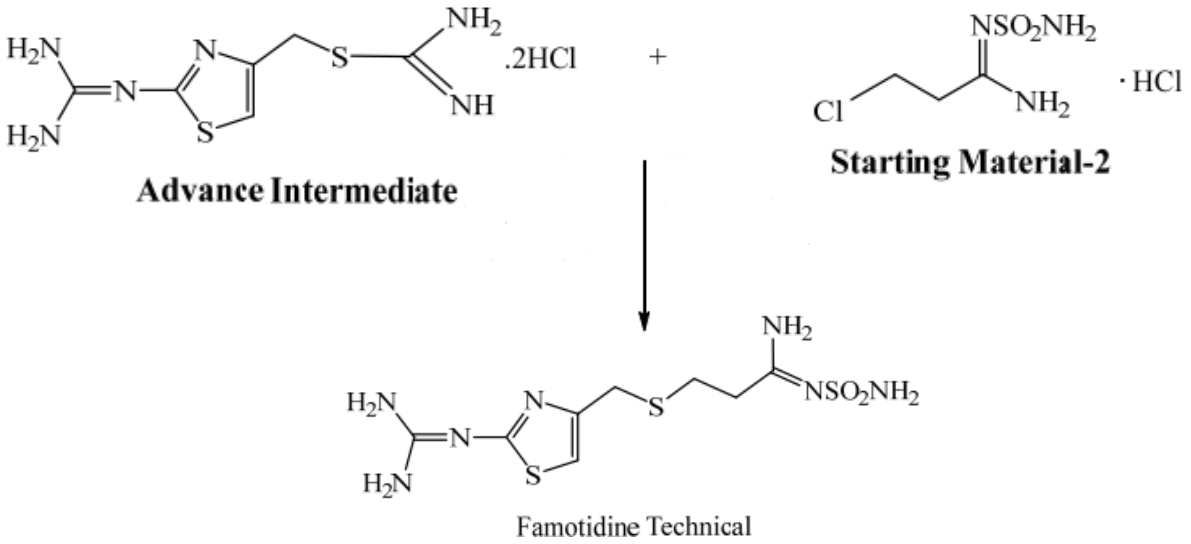
Impurities introduced in the last synthetic step

→ **Option 1** (i.e. control in the final API) is **preferred**

→ **Option 2 and 3 control** (i.e. IPC or limit in isolated crude/technical API) approaches may be possible when appropriately justified

How to develop control strategy?

Stage N-1



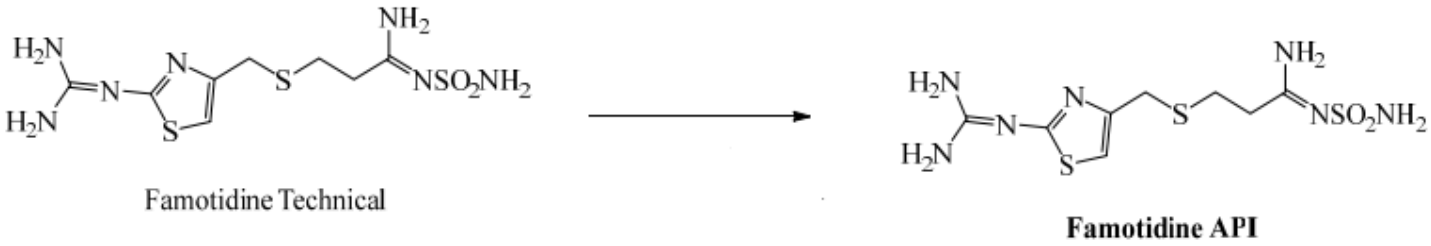
Example: How to justify a control in line with Option 3?

Limit for SM2 at NMT 0.05% in Famotidine Tech

- **Spike-purge study**:
When SM2 is **spiked** in Tech API at 0.10% (i.e. **above proposed limit**), SM2 is reported **absent in final substance**

- **Absence** in at least 3 routine batches of final substance

Stage N Purification



Absent as per ICH M7

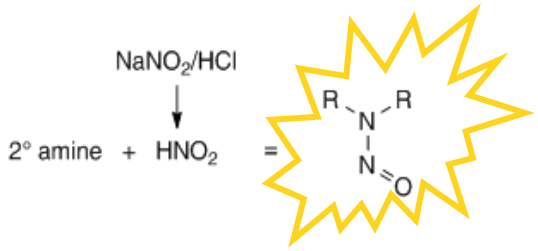
i.e. <30% acceptable limit

Nitrosamine impurities (3.2.S.3.2)

Top 7

Absent or deficient risk assessment related to Nitrosamines

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



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)

Risk assessments to be **systematically** included by CEP applicants in new dossiers, renewals, and revisions where a risk of nitrosamine formation may be introduced (i.e. changes to the manufacturing process, change of suppliers of starting materials or intermediates, etc.) since **1 October 2020**

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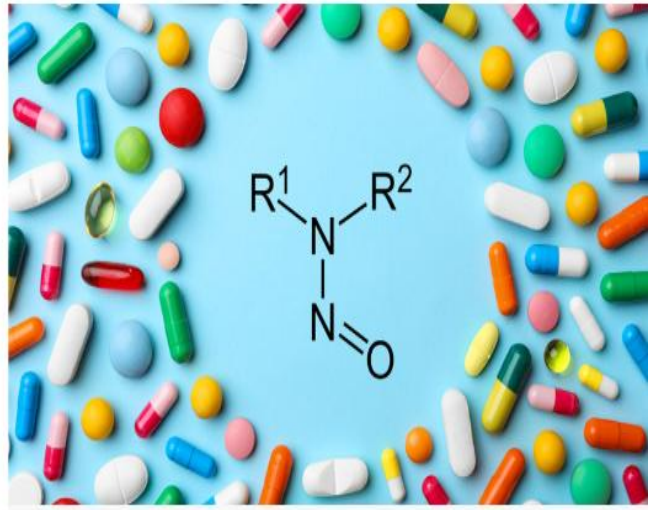
Nitrosamine impurities (3.2.S.3.2)

Reference document

EMA Q & A (EMA/409815/2020)

Frequent revision of the Q&A and its corresponding appendices



- 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

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

Residual solvents (3.2.S.3.2)

Top 9

Deficient discussion on residual solvents

- Used in the manufacturing process from the introduction of the starting materials (origin should be clarified)
- Class 1 solvents as potential contaminants of used solvents should be discussed
- Statements such as “not detected” or “less than limit of quantification” be supported by provision of the LOD / LOQ for the associated method.

Use EDQM QOS template to support you !!

Solvent	Used in step x/y	ICH solvent classification and limit*	Proposed limit	Test results**	LOD /LOQ of the method (ppm)

** when not limited in the Ph. Eur. general chapter 5.4 shortly indicate the basis for setting the acceptance criteria*

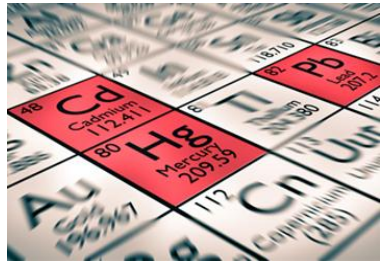
*** typical levels in the final substance or any other appropriate intermediate stage*

Reference documents

ICH Q3C / Ph.Eur. General Chapter 5.4

CPMP/QWP/450/03 “Annex 1: specifications for class 1 and class 2 residual solvents in active substances”

Elemental impurities (3.2.S.3.2)

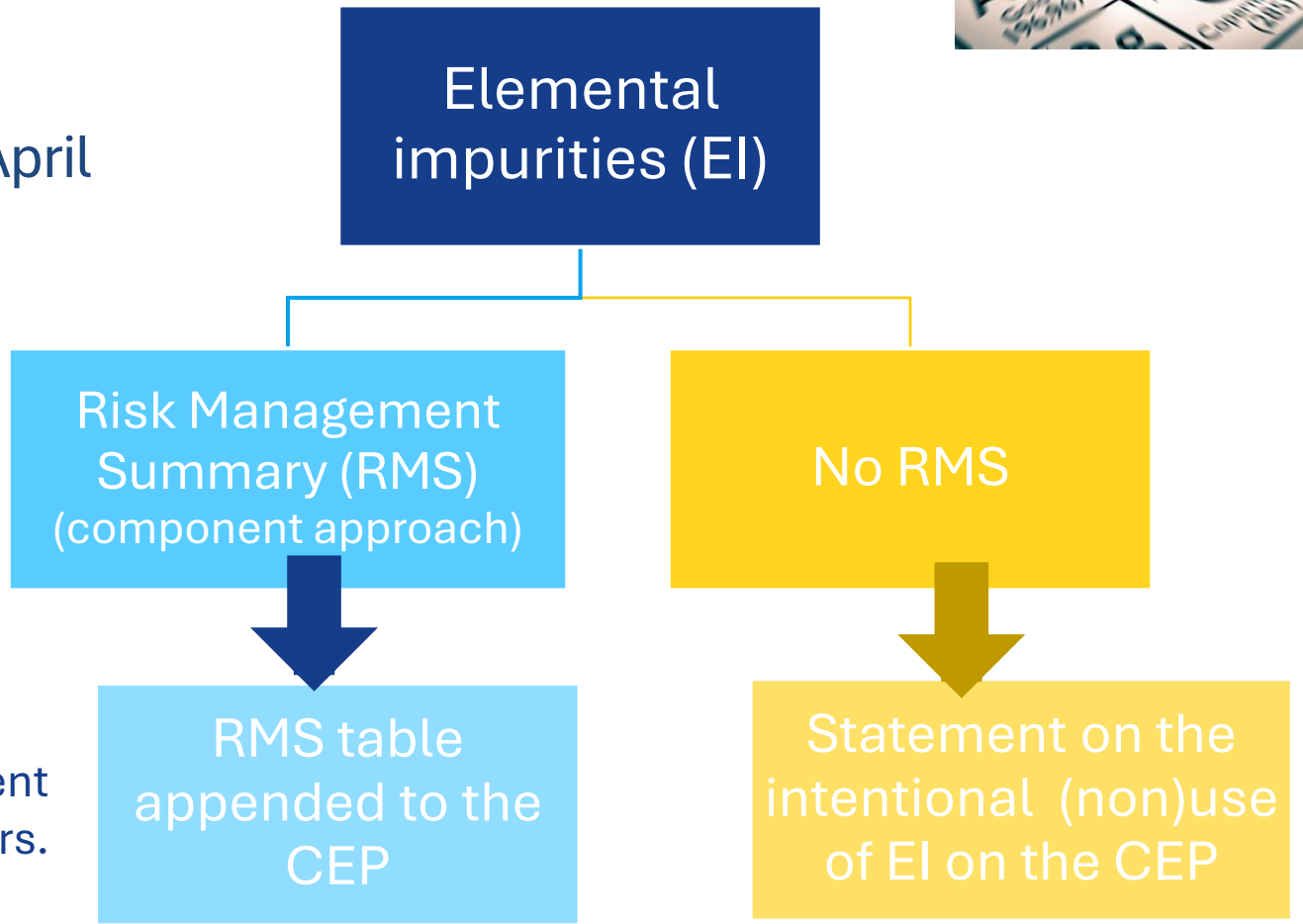


Reference documents

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)



This helps the Drug Product manufacturer's risk assessment and it is evaluated by assessors.

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

Elemental impurities (3.2.S.3.2)

How to define control strategy regardless of the 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

Analytical procedure description with validation data according to ICH Q2 to be provided

Control of the substance (3.2.S.4)

Specification (3.2.S.4.1)

Specification applied by the CEP holder/applicant is appended to the CEP

CEP 2.0

Analytical procedures (3.2.S.4.2)

Alternative and additional in-house analytical procedures to the Ph. Eur. monograph for control of the substance

⚠ Only additional methods appended to CEP, no policy change

Validation of analytical procedures (3.2.S.4.3)

Validation expected for **all non-Ph. Eur. analytical procedures**

- Summary table
- Results expressed with regard to sample (not analytical concentration)

Batch analyses (3.2.S.4.4)

- Summary table
- Results expressed in appropriate units and with appropriate number of decimals

Specification (3.2.S.4.1)

Parameters	Acceptance criteria	Reference
Characters	White or almost white, crystalline powder	Ph. Eur. current edition
Solubility	Practically insoluble in water, slightly soluble in anhydrous ethanol and in methylene chloride.	Ph. Eur. current edition
Identification Test A (IR) Test B (HPLC)	 Complies to reference Positive	Ph. Eur. current edition
Specific optical rotation (o.d.b.)	+158° to + 167°	Ph. Eur. current edition
Loss on drying	≤ 0.5%	Ph. Eur. current edition
Related substances		Ph. Eur. current edition
Impurity A	≤ 0.5%	
Impurity B	≤ 0.3%	
Impurity C	≤ 0.15%	
Impurity D	≤ 0.15%	
Unspecified impurities	≤ 0.10%	
Total	≤ 1.5%	
Assay (o.d.b.)	97.0% to 102.0%	Ph. Eur. current edition
Residual solvents (by GC)		In-house
Ethanol	≤ 5000 ppm	
N,N-dimethylformamide	≤ 880 ppm	
N-Nitrosodimethylamine (NDMA) (by GC-MS)	≤ 3.0 ppm	In-house

Specification parameters not necessary to satisfy European regional requirements		
Assay by titrimetry (o.d.b.)	99.0% to 101.0%	USP
Heavy metals	≤ 10 ppm	Ph. Eur. 2.4.8
Water content (KF)	≤ 0.5%	JP

- Tabular format
- Parameters, acceptance criteria and reference to used method (e.g. Ph. Eur., in-house)
- Unequivocal chemical name for in-house additional impurities
- Parameters for compliance with pharmacopoeias other than the Ph. Eur. or other non-EU regional requirements

  → strongly encouraged to separate and clearly identify them as such in the specification
- Only specification parameters corresponding to the quality claimed

Grade: Micronised

Grade: Form-A

Specification parameters relating to grades (examples)		
Particle size dimension	x_{10} not less than 0.8 µm x_{50} not less than 3.5 µm x_{90} not less than 15 µm	In-house
Polymorphism	Presents characteristic peaks corresponding to Form-A occurring at 2θ values of 10.55, 15.99, 16.55, 17.93, 20.45 ± 0.2°	In-house

Analytical procedures (3.2.S.4.2)

⚠ Additional procedures are appended to the CEP

- Legible analytical procedure description
- Use of scanned documents to be avoided

Residual Solvents by Gas chromatography

Blank solution.

Test solution. Dissolve *(weight)* g of the substance to be examined into *(solvent)* and dilute to *(volume)* mL with the same solvent.

Reference stock solution. Dissolve *(weight)* g of *(reference)* into *(solvent)* and dilute to *(volume)* mL with the same solvent.

Reference solution. Dilute *(volume)* mL of reference stock solution to *(volume)* mL with *(solvent)*. Pipette *(volume)* mL of this solution into a headspace injection vial to obtain a solution containing about *(concentration)* of reference standard.

Chromatographic conditions:
Column material:
–size:
–stationary phase:
Carrier gas:
Flow rate: Split ratio:
Injection mode:
Temperature:
Injection method:
Headspace equilibrium temperature:
Headspace equilibration time: Loop temperature:

System suitability requirements:

Test method:
Injections order.

Calculation:

N-Nitrosodimethylamine (NDMA) by GC-MS

Chromatographic conditions:
Column material:
–size:
–stationary phase:
Carrier gas:
Flow rate: Split ratio:
Injection mode:
Temperature:
Injection method:

Mass spectrometer conditions:
Electron impact ionisation mode:
Ion source temperature:
Analyser temperature:
Dwell time:
Gain factor:
Detection mode:

Solutions preparation:
Internal standard solution. Dissolve *(weight)* g of standard into *(solvent)* and dilute to *(volume)* mL with the same solvent.

Spiking solution. In a single volumetric flask, dilute *(volume)* µL of each of CRS to *(volume)* mL with *(solvent)*. Dilute *(volume)* µL of this solution to *(volume)* mL with *(solvent)*.

Test solution. Dissolve *(weight)* g of the substance to be examined into *(solvent)* and dilute to *(volume)* mL with the same solvent.

Spiked solution. Dissolve *(weight)* g of the substance to be examined into *(solvent)*, add *(volume)* mL of spiking solution and dilute to *(volume)* mL with the same solvent.

Reference solution. Dilute *(volume)* mL of spiking solution to *(volume)* mL with *(solvent)*. Pipette *(volume)* mL of this solution into an injection vial to obtain a solution containing about *(concentration)* of reference standard.

System suitability requirements:

Test method:
Injections order.

Calculation:

Batch data (3.2.S.4.4)

Use EDQM QOS template to support you !!

		Batch Number *Batch size* *Manufacturing date* *Production site(s)**	*Batch Number* *Batch size* *Manufacturing date* *Production site(s)**	*Batch Number* *Batch size* *Manufacturing date* *Production site(s)**
Test	Acceptance criteria	Results		
Appearance				
Identification				
Related substances				
…				

** in case multiple sites are declared in the dossier for final substance and /or intermediates.*

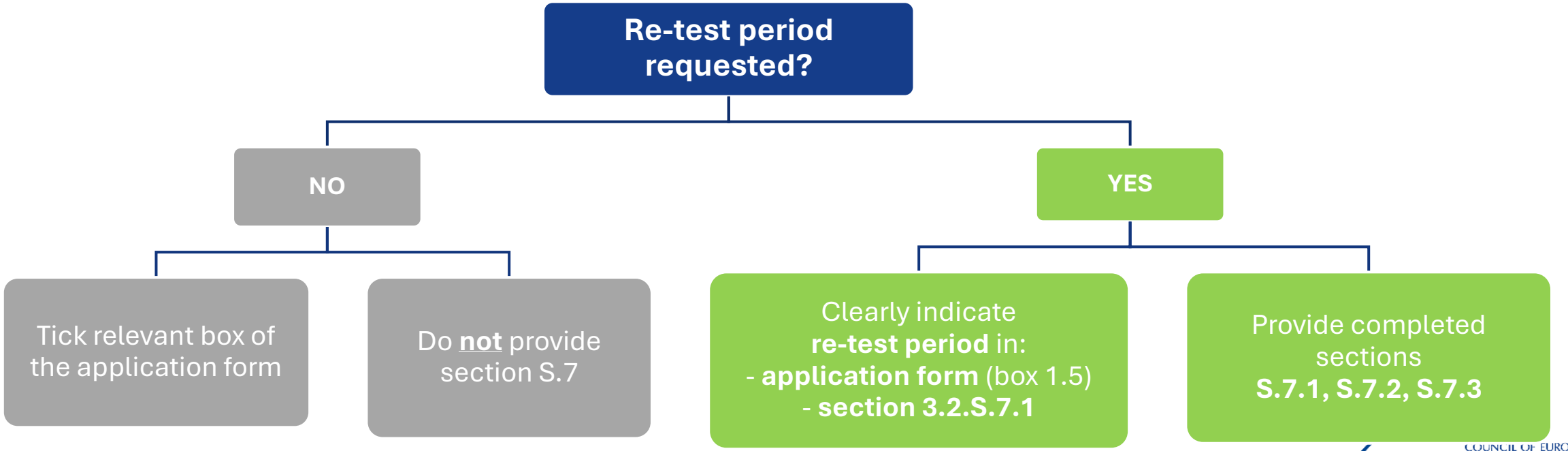
Quick overview of the quality of the final substance!!

Stability (3.2.S.7)

Re-test period highly recommended

CEP 2.0

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



Stability (3.2.S.7)

Stability protocol

Study conditions	Accelerated conditions	Long-term conditions	Intermediate conditions (if any)
	e.g. 40°C±2°C / 75%± 5% RH	*e.g. 25°C± 2°C/ 60%± 5% RH*	…
Data available	*x months, number of batches*	*x months, number of batches*	*x months, number of batches*
Batch size			
Manufacturing date			
Packaging	*Indicate if it is the same as for commercial purpose*		

Use EDQM QOS template to support you !!

If not the same as in 3.2.S.6, justification to be provided

- 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

CEP 2.0

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
- Keep in mind new requirements due to CEP 2.0 (dossier should contain only information corresponding to the quality claimed)

⚠ Deficient Dossier **delays** the granting of the CEP and might lead to the **closure** of the application without the CEP being granted ⚠

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