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

edqm

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

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Module 6: Building successful CEP dossiers (Live Webinar)

How to build a good new CEP application?

Rita Almeida
EDQM, Certification of Substances Department
10 December 2024

Summary

- CEP process overview
- How to build a **successful dossier** and **avoid deficiencies**?
- Examples

CEP Process Overview

EDQM

Applicant

Validation
- Administrative
- Technical

180 CD

1st round — 115 WD
- **CEP granted** or
- Additional information requested

90/30 CD

2nd round — 92 WD
- **CEP granted** or
- Additional information requested

3rd round — 92/23 WD
- **CEP granted** or
- Application closed without the CEP being granted

3 rounds

CEP

At which round a successful application would get approval?

Full information in PA/PH/CEP (13) 110

CEP Process Overview

EDQM

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3 rounds

1st Round

180 CD

90/30 CD

CEP

Full information in PA/PH/CEP (13) 110

How to build a successful dossier and avoid deficiencies?

Reference documents

Content of the dossier

- Content of the dossier for chemical purity and microbiological quality (PA/PH/CEP (04) 1 7R, May 2024) New
- Requirements for the content of the CEP dossier according to the CEP 2.0 (PA/PH/CEP (23) 21 1R, October 2023)

Technical

- Top ten deficiencies in New Applications for Certificates of Suitability for chemical purity (PA/PH/CEP (24) 10, Feb. 2024) New

Submission format

- *Guidance for electronic submissions for Certificates of Suitability (CEP) applications (PA/PH/CEP (09) 108, 6R, July 2021)*

How to build a successful dossier and avoid deficiencies?

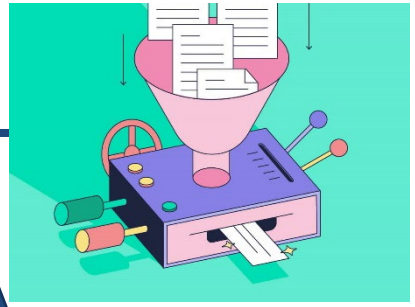
- All documents are publicly available on the EDQM website
- Describe what we expect to see in the dossier

How to build a successful dossier and avoid deficiencies?

Keep 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 1R, January 2024)

New version

- 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

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

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 consistent/exactly 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)

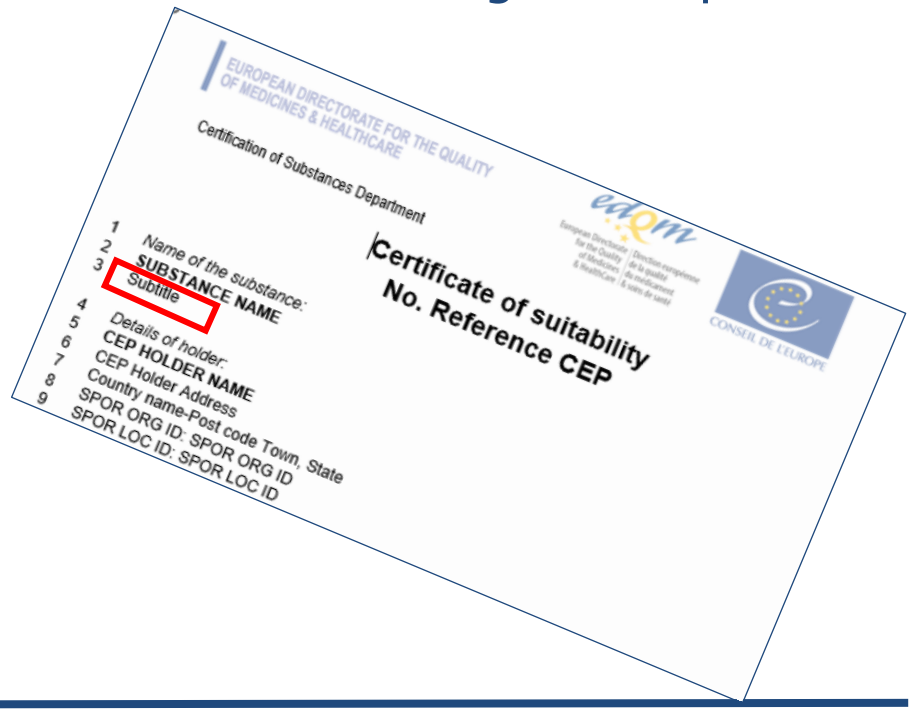
Grade (optional) → Subtitle on CEP

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

CEP 2.0

- 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)



General properties (3.2.S.1.3)

Maximum Daily Dose (MDD), treatment duration and route of administration

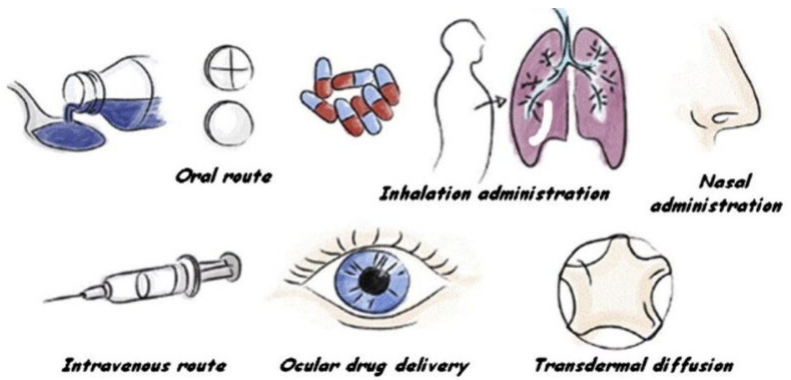
CEP 2.0

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.

20 mg,
> 10 years to lifetime

100 mg,
> 1- 12 months



8 mg,
> 1- 10 years

1 g,
< 1 months

Description of the manufacturing process and process controls

3.2.S.2.2

- 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

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).

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

Description of the manufacturing process and process controls

- Detailed **narrative** process description (not batch records)
  - **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 intermediates or the final substance

    → clear that it is performed in accordance with ICH Q7 and batches are fully tested prior to blending as per relevant specification

Description of the manufacturing process and process controls

The reprocessing and recovery of raw materials are inadequately addressed.

- **Reprocessing** of intermediates and/or final substance
  - Steps where 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

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

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

↓

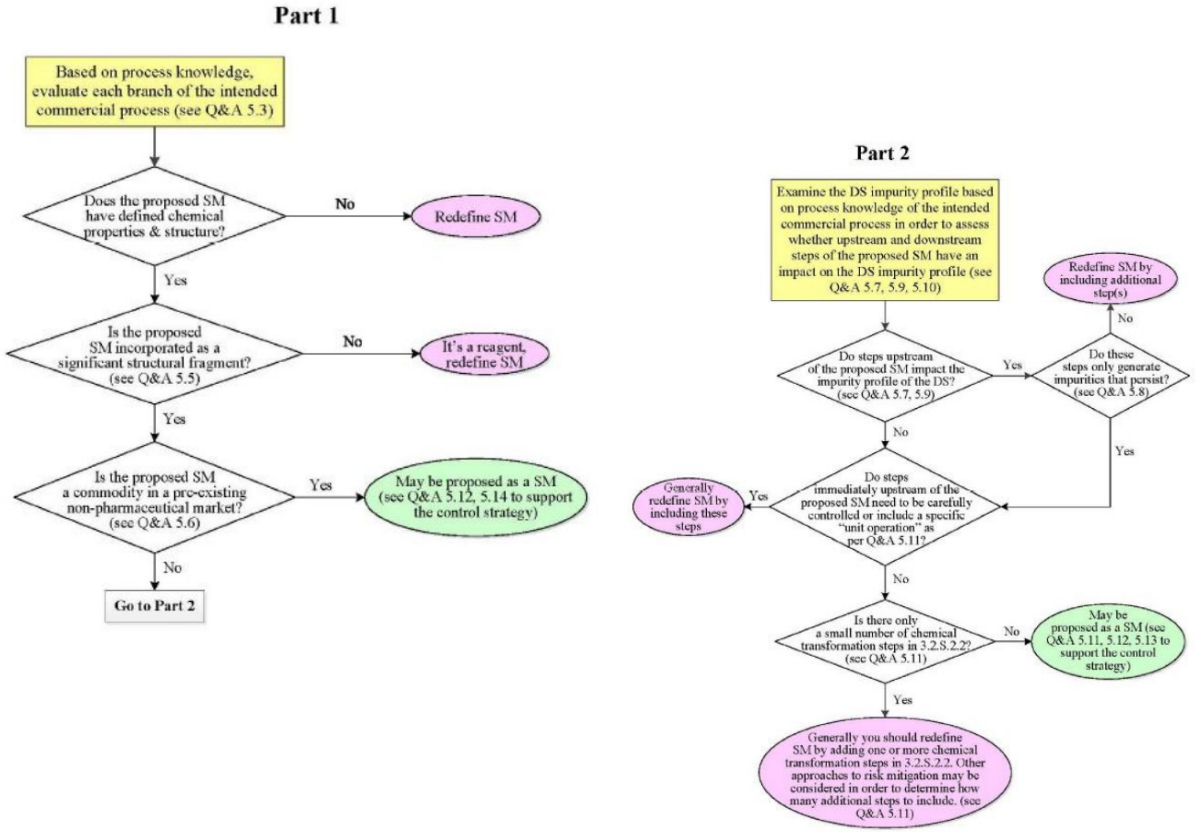
Relation between the risk to the quality of the final substance considering

Length of the synthesis (number of steps)

&

Control strategy

Annex 1 to ICH Q11 Q&A - Decision tree



Top 10

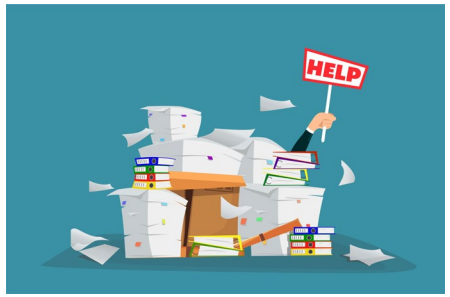
Failure to suitably identify starting materials

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:

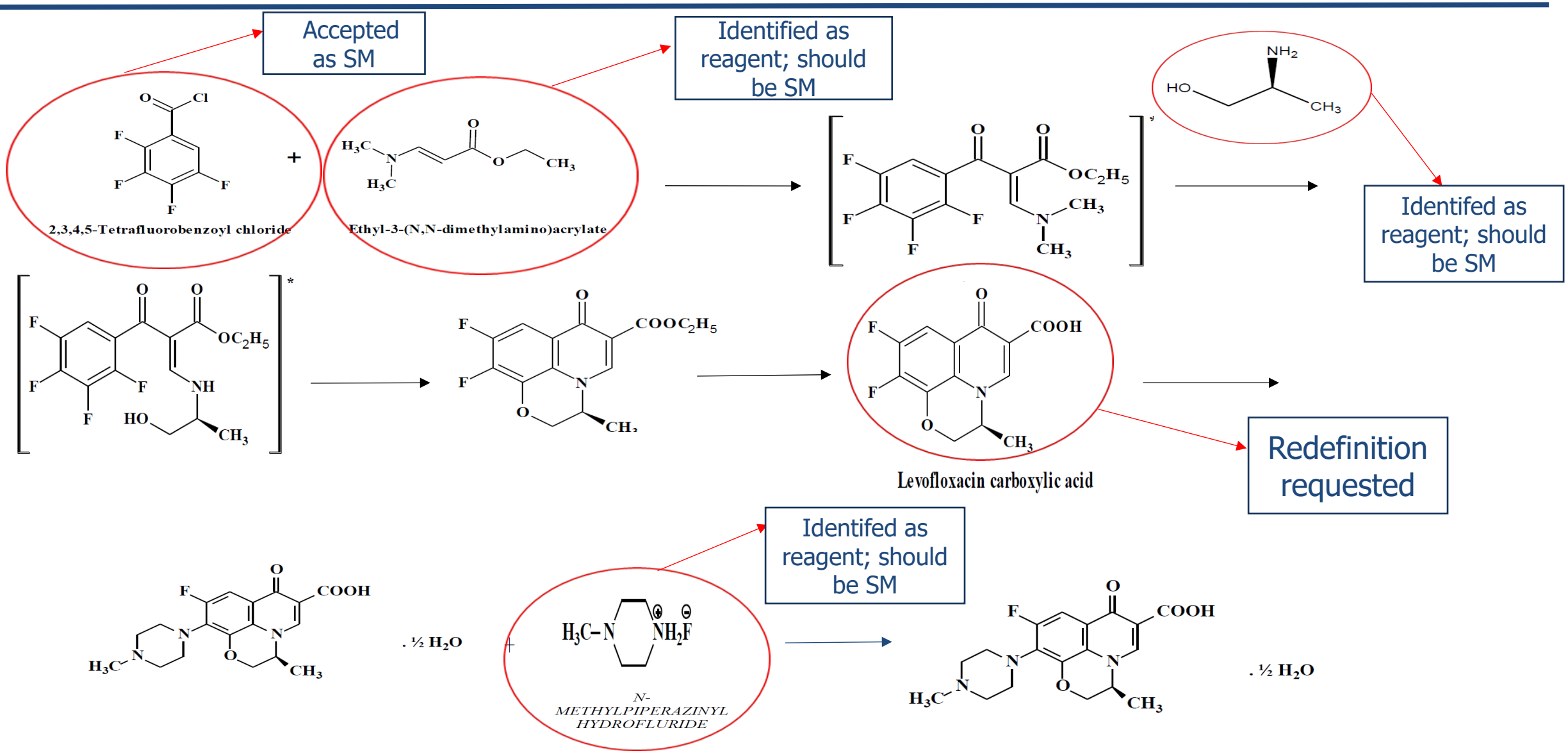


- GMP and willingness to be inspected declarations are necessary
- Section 3.2.S.2.1 and the application form need to be updated as well as other impacted Module 3 sections
- Information submitted from third parties is not acceptable. The API manufacturer must be fully aware of the information supplied.

General documents

Refusal of information from third parties in reply to EDQM's request for information (PA/PH/CEP (11) 18, March 2011)

Example: Synthesis of Levofloxacin hemihydrate



Which information shall I include 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)

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 my 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)

Justification of specification of starting materials

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 to be also considered

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 strategy of intermediates

Top 2

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

Specification

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 – Additional considerations on intermediates

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

⚠ Special attention expected for:

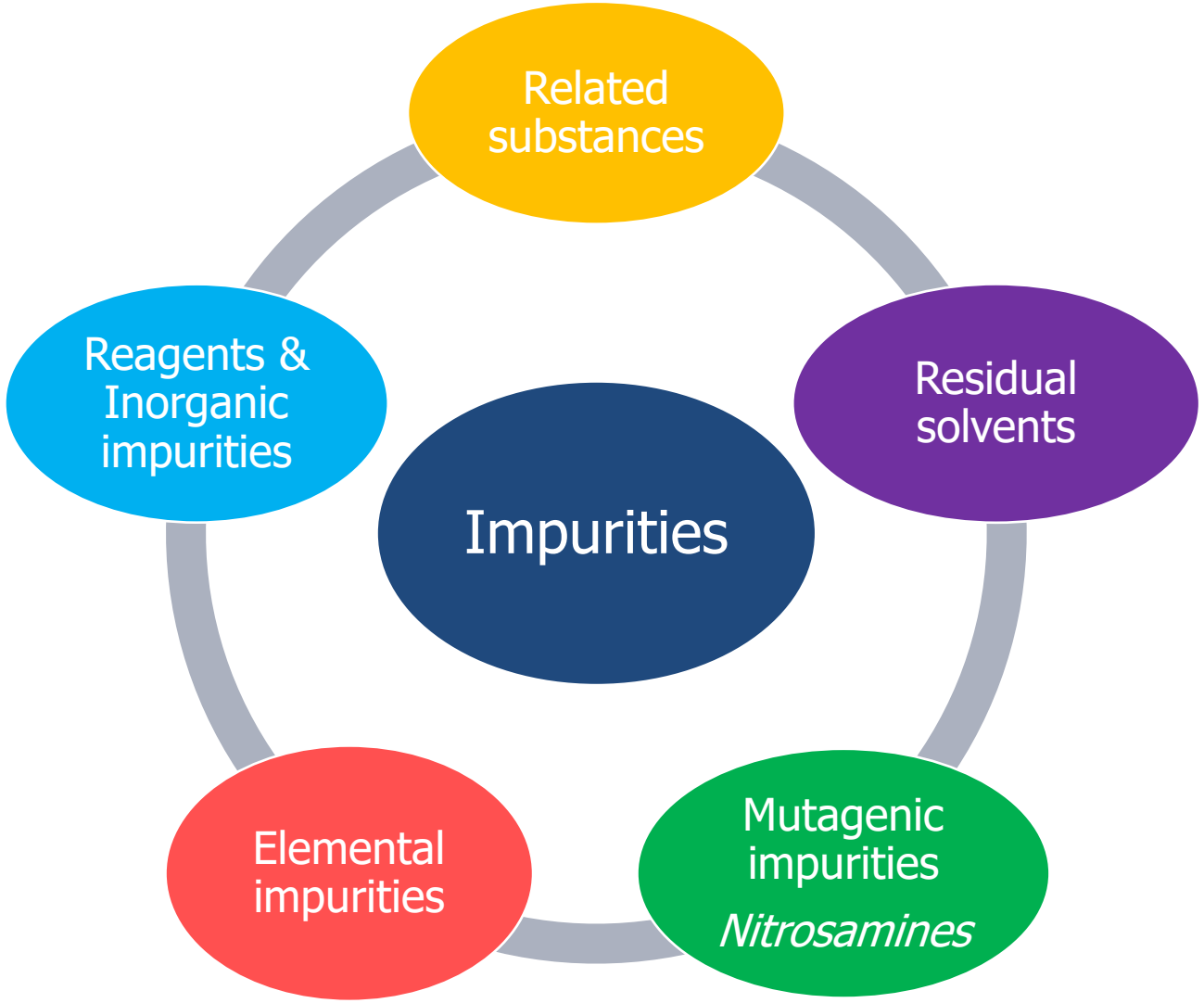
- Intermediates isolated late in the process;
- Intermediates showing low purity;
- When related substances in the crude substance are controlled by a method which is different comparing to the one adopted at release.

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.**

Control of impurities (3.2.S.3.2)

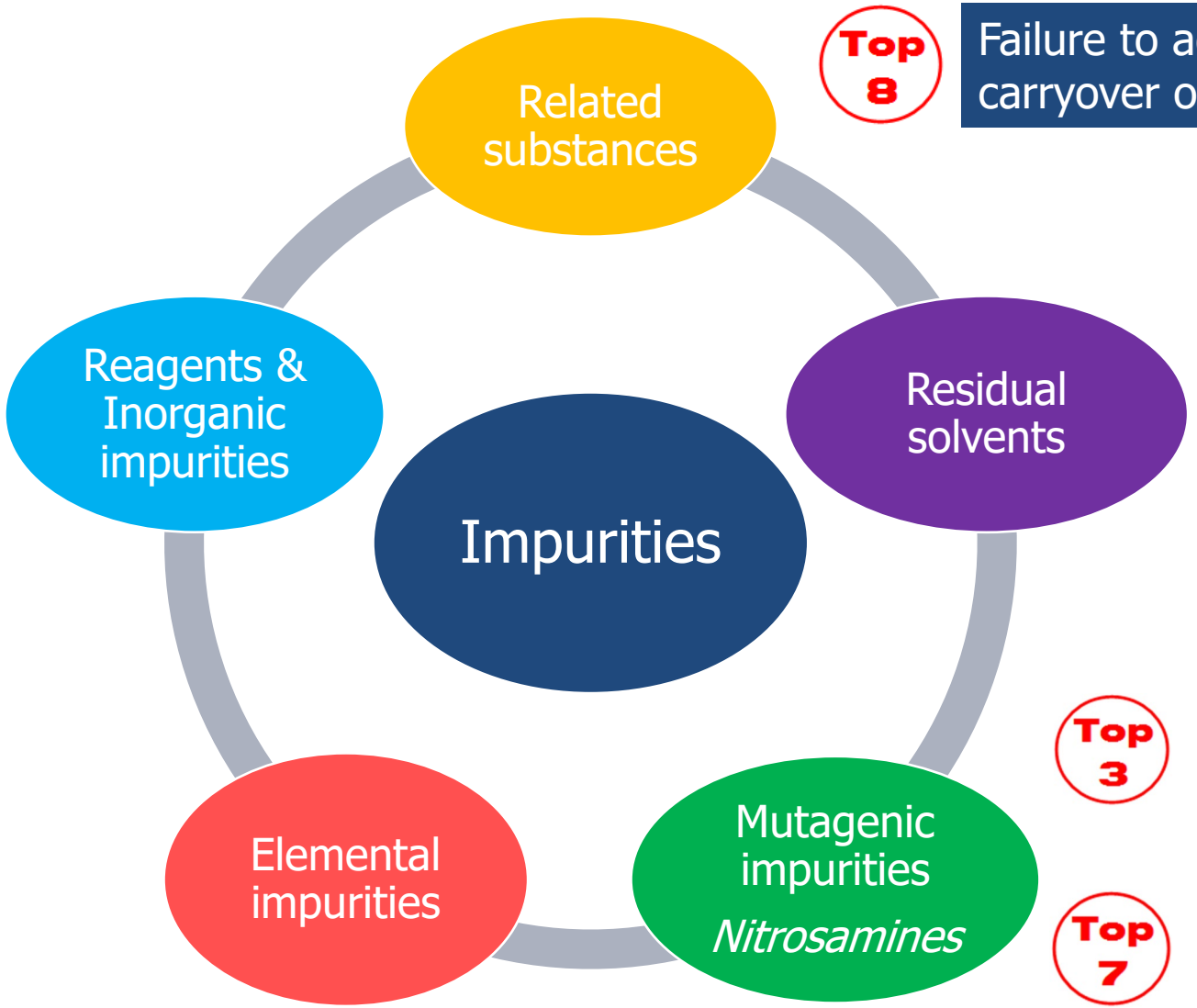


Module 8:

Control of impurities: CEP approach

12 December 2024

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

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*

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
- Class 1 solvents as potential contaminants of used solvents

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*

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

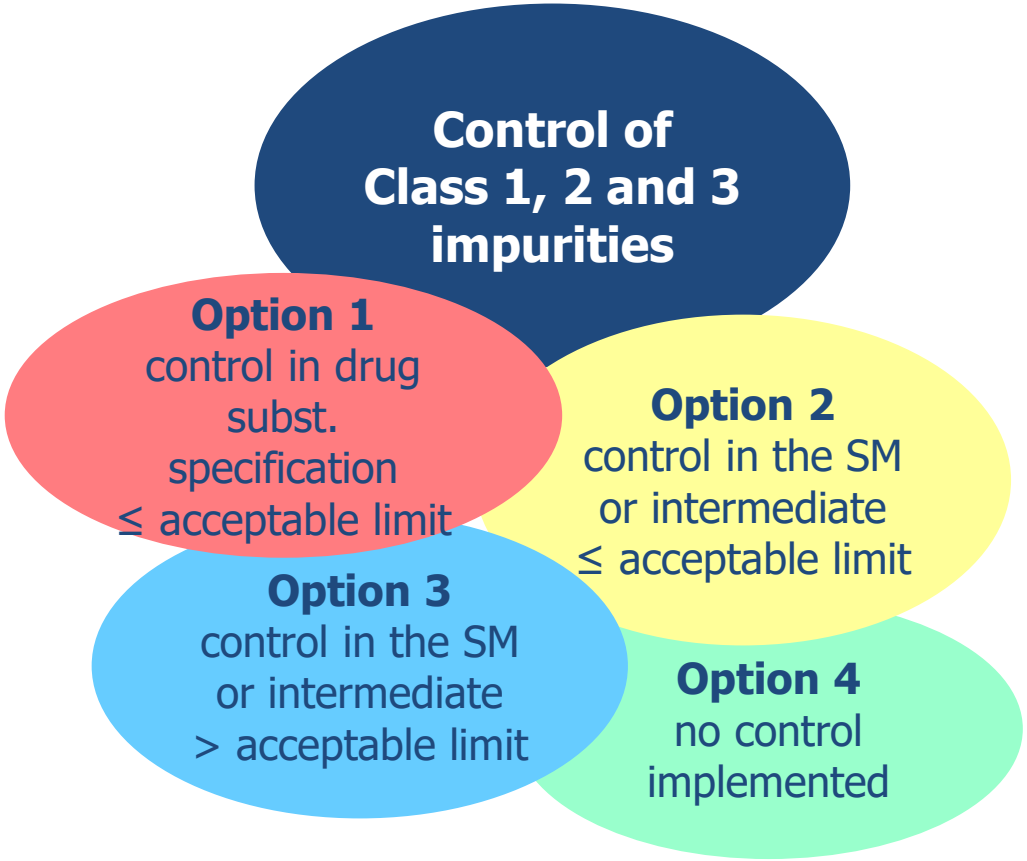
Guideline on assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products (EMA/CVMP/SWP/377245/2016) (from 01/07/2020)

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

Mutagenic impurities (3.2.S.3.2)

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



Impurity *	Origin	Class	Control option justification, acceptance criteria

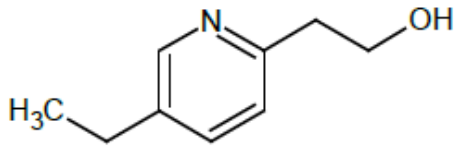
* presenting relevant structural alert or known mutagen

Use EDQM QOS template to support you !!

How to develop a control strategy

Pioglitazone, antidiabetic. MDD= 45 mg

- Acceptable limit NMT 33 ppm



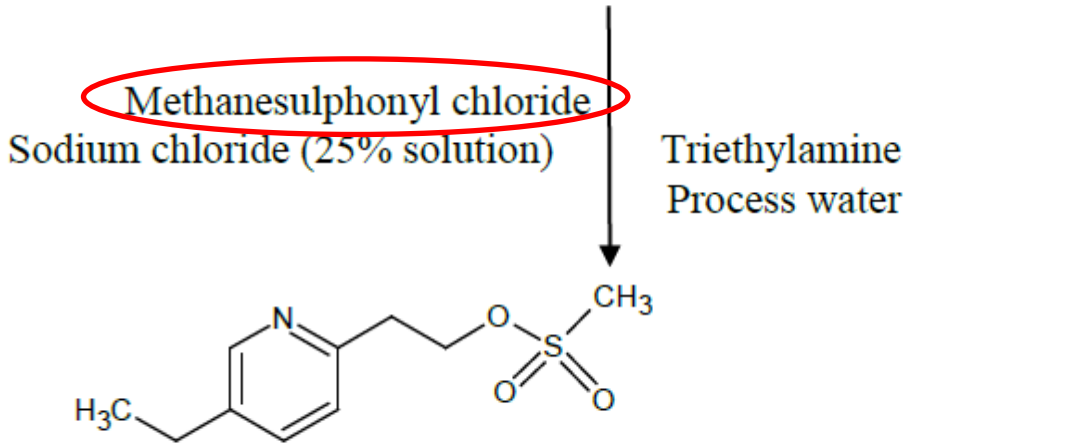
HEEP *(2-(5-Ethyl-pyridin-2-yl)-ethanol)*

Methanesulphonyl chloride

- Washing step with water?

Theoretical impurity

Option 4



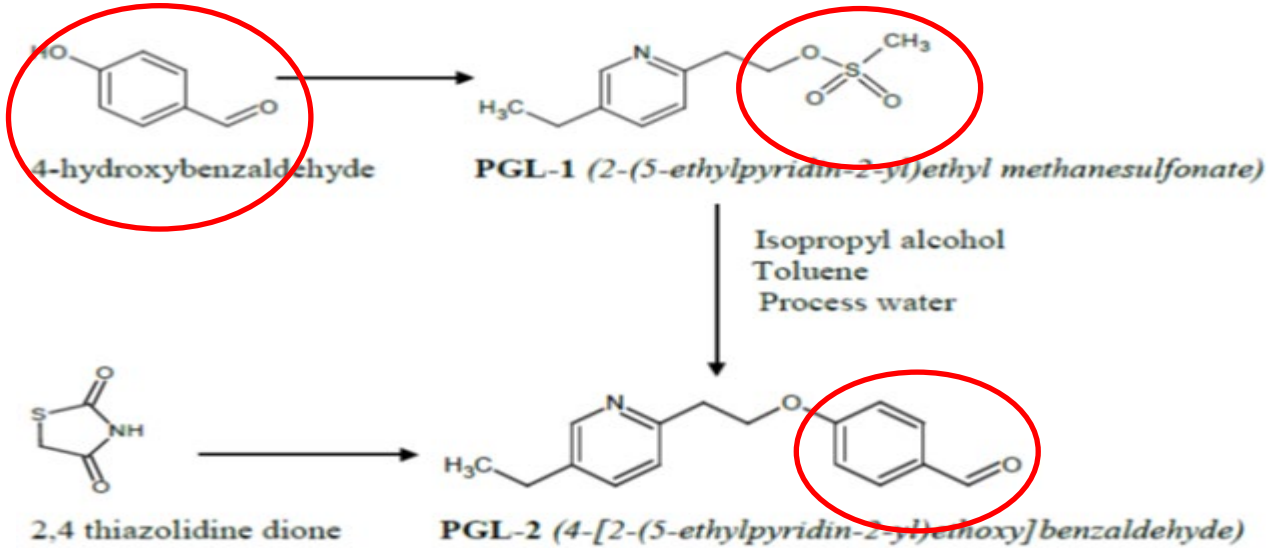
PGL-1 *(2-(5-ethylpyridin-2-yl)ethyl methanesulfonate)*

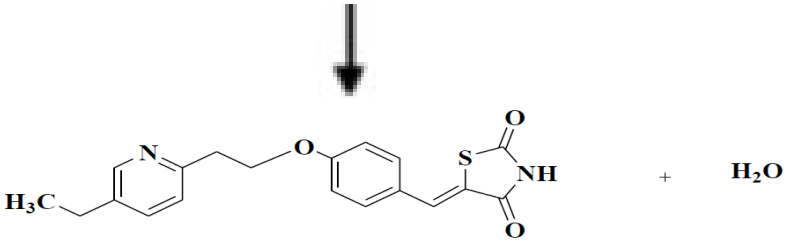
How to develop a control strategy

4-HB: aromatic aldehyde

PGL-1: mesilate

PGL-2: aromatic aldehyde





Options 2 or 3

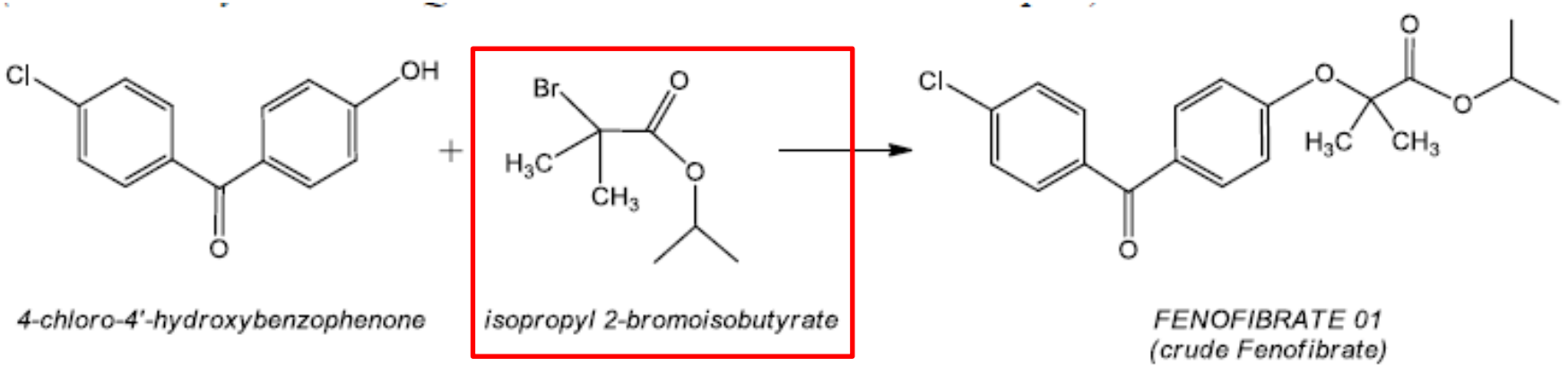
Option 3: PGL-1 is controlled in PGL-3 with NMT 0.5 %

Justification of option 3 of control strategy

Final API

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 is **preferred**)
Option 2 and 3 to be justified as per ICH M7 Q&A 8.3

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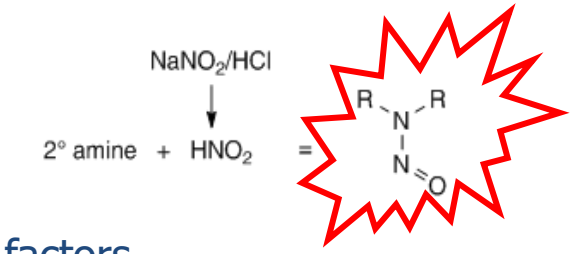
Nitrosamine impurities (3.2.S.3.2)

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 (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)

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 (3.2.S.3.2)

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

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 methods are appended to the CEP

- Legible method 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.*

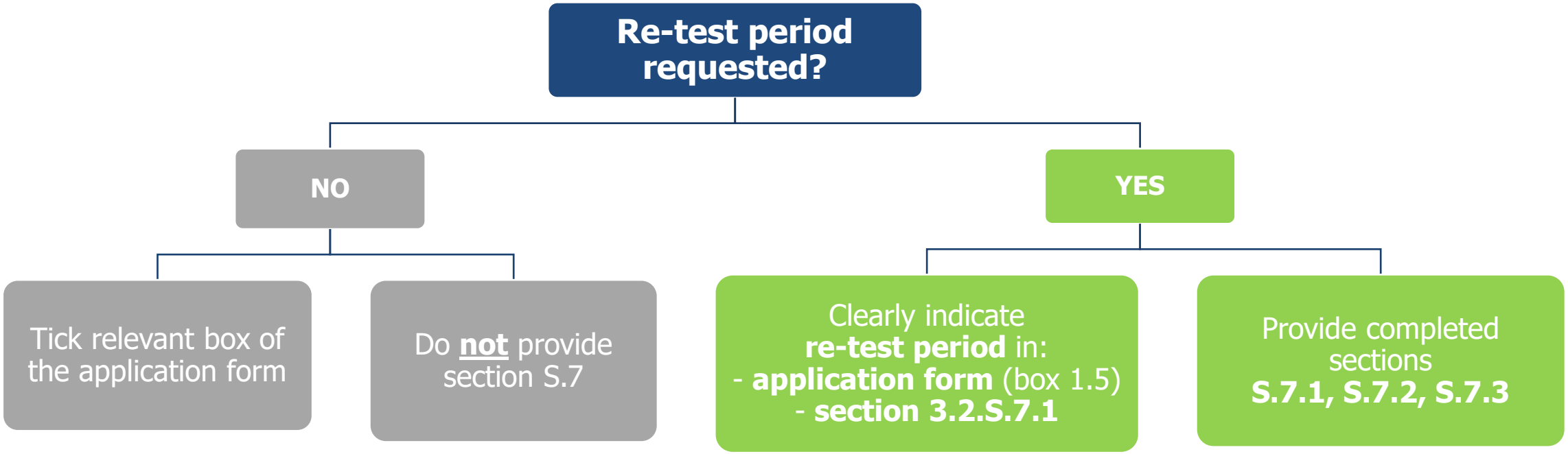
Quick overview of the quality of the final substance!!

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?

CEP 2.0

Keep in mind new requirements due to CEP 2.0!!

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

Conclusions: how to avoid deficiencies?

- Build 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 [illegible]ence:

  - do not build up your Dossier on your purest batche[illegible]diates and final substance. This would just lead to questions

  - include in the Dossier any [illegible]esults and studies in support, even though performed

- Suitability of the sp[illegible] 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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