European Directorate for the Quality of Medicines & HealthCare

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Module 8

Control of impurities : CEP approach

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Thursday 11 December 2025 (10:00 – 11h30)

Impurities & Control strategy in Active Substances

- ★ Related Substances (Organic impurities)
- ★ Mutagenic impurities
- ★ Nitrosamine impurities
- ★ Residual solvents
- ★ Elemental impurities
- ★ Reagents and Inorganic impurities

What is the impact of a certain impurity in the impurity profile of the API?

How to set specifications accordingly?

NB: Excipients are out of scope of this presentation.

Impurities & Control strategy in Active Substances

Directive 2001/83/EC, as amended

Where a specification contained in a Ph. Eur. monograph might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorisation holder

For veterinary products:

REGULATION (EU) 2019/6 applies (repealing Directive 2001/82/EC)

Which key guidance? *A brief recap…*

ICH Q6A Specifications Test procedures and acceptance criteria for new chemical substances	**PA/PH/CEP (04) 1, 7R** Content of the dossier for chemical purity and microbiological quality

ICH Q3A ← Related substances → **Ph. Eur. 5.10, Ph. Eur. GM 2034**

Antibiotics only: Guideline on setting specifications for related impurities in antibiotics (EMA/CHMP/CVMP/QWP/199250/2009

ICH M7 and its Q&A document ← Mutagenic impurities

EMA Q&A on nitrosamines EMA/409815/2020 ← Nitroso impurities → **Ph. Eur. 2.5.42**

ICH Q3D ← Elemental impurities → **Ph. Eur. 5.20**
PA/PH/CEP (16) 23

ICH Q3C ← Residual solvents → **Ph. Eur. 5.4**

CPMP/QWP/450/03 -Rev.1 (Annex I)

ICH Q2 (R2) ← Analytical procedures → **Ph. Eur. 2.2.46** (*for Pharmacopoeial analytical procedures*)

Informative chapter Ph. Eur. 5.27 – Comparability of alternative analytical procedures

ICH / EMA

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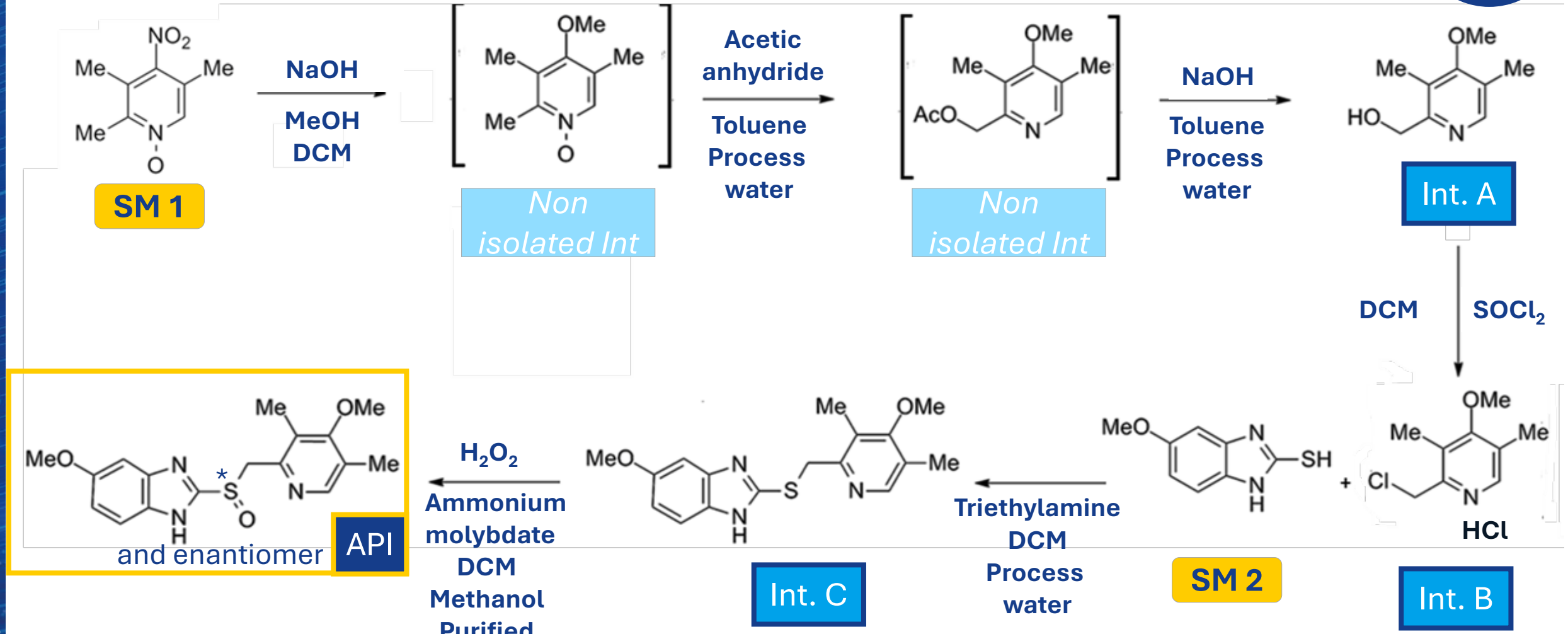
What are the expectations ?

Impurity profile of the material should be **known** in detail

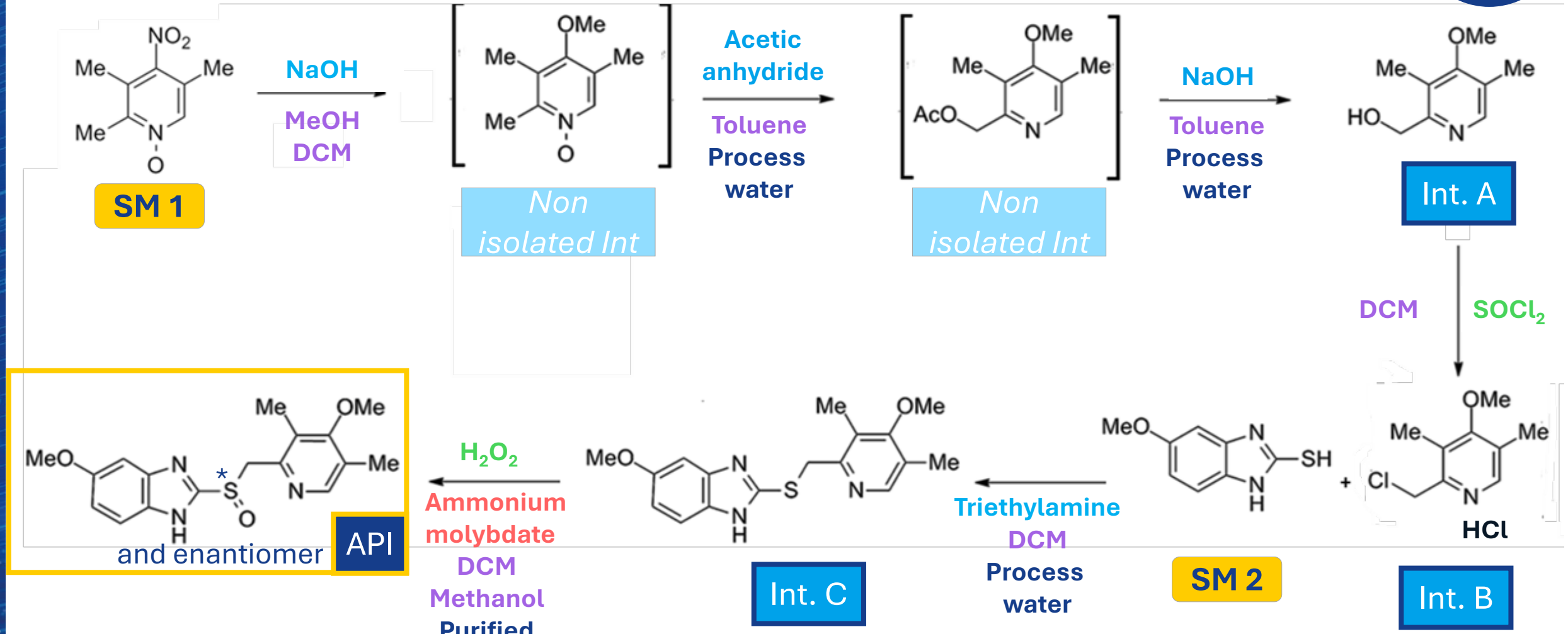
Analytical specifications should **control** the impurity profile and be **representative** of the process adopted

Discussion showing **understanding** of the impurity profile.
Origin, fate and carry-over of impurities as basis for justification to the proposed specifications.

Case study (fictitious): Omeprazole



Case study (fictitious): Omeprazole



- **Related Substances (Organic impurities)**
- Mutagenic impurities
- Nitrosamine impurities
- Residual solvents
- Elemental impurities
- Inorganic impurities

Organic impurities

ICH Q3A

Ph. Eur. GM 2034 Substances for Pharmaceutical Use

Ph. Eur. 5.10 Control of Impurities in Substances for Pharmaceutical Use

Individual substance Ph. Eur. monograph

Table 2034.-1. – *Reporting, identification and qualification of organic impurities in active substances*

Use	Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
Human use or human and veterinary use	≤ 2 g/day	> 0.05 per cent	> 0.10 per cent or a daily intake of > 1.0 mg (whichever is the lower)	> 0.15 per cent or a daily intake of > 1.0 mg (whichever is the lower)
Human use or human and veterinary use	> 2 g/day	> 0.03 per cent	> 0.05 per cent	> 0.05 per cent
Veterinary use only	Not applicable	> 0.10 per cent	> 0.20 per cent	> 0.50 per cent

Table 2034.-2. – *Reporting, identification and qualification of organic impurities in peptides obtained by chemical synthesis*

Reporting threshold	Identification threshold	Qualification threshold
> 0.1 per cent	> 0.5 per cent	> 1.0 per cent

A short guide…

Understand risks for the **quality of the API**

Acceptance criteria for impurities to be justified based on their **fate and carryover** up to the final substance, meaning, the ability of the process to purge them

Limit major/recurrent impurities as **specified impurities**

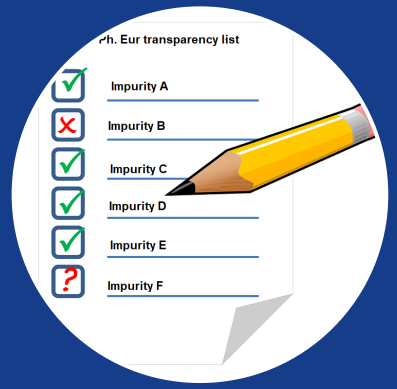
Understand the risk for **uncontrolled impurities** up to the API to ensure compliance

Special attention to be given to:

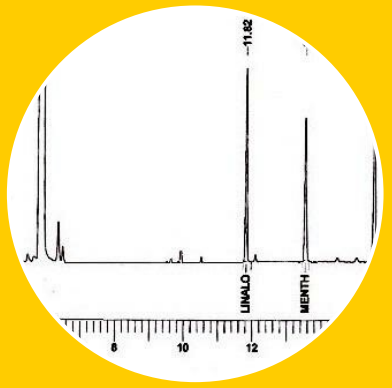
- ★ **Late intermediates,** including the crude API
- ★ Related substances controlled upstream by an analytical procedure **different** from the one used at release
- ★ **API-like impurities**

Certification of suitability to Ph. Eur. monographs

Terminology referring to the Ph. Eur. or traceable to it



Cross-check with transparency list of the monograph



For in-house impurities present or limited above the disregard limit:

Suitability of the monograph and set a control in the specification

Chemical structure and INN/Chemical names given as far as possible

Certification of suitability to Ph. Eur. monographs

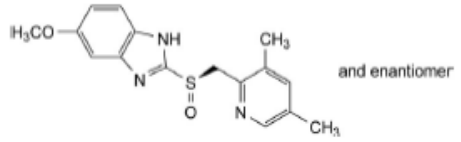
IMPURITIES

Specified impurities: *D, E, F, G.*
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. *Control of impurities in substances for pharmaceutical use*): *A, B, C, H, I.*

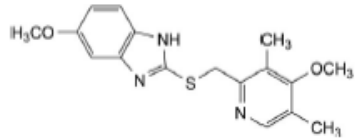
Specified impurities from the transparency list are controlled at a limit reported in the monograph (in this case, impurities F and G are controlled by a UV specific test)

Other detectable impurities **may not** be present in all processes. They are listed in the transparancy list and are **detectable** by the Ph. Eur. Monograph analytical procedure.

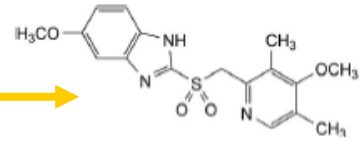
A. 5-methoxy-1*H*-benzimidazole-2-thiol,



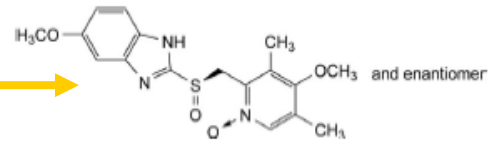
B. 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole,



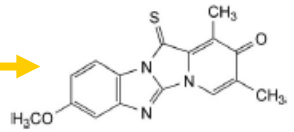
C. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfanyl]-1*H*-benzimidazole (ufiprazole),



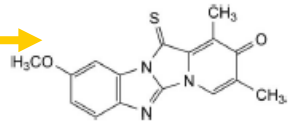
D. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1*H*-benzimidazole (omeprazole sulfone),



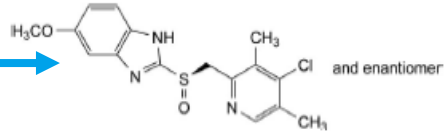
E. 4-methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulfinyl]methyl]-3,5-dimethylpyridine 1-oxide,



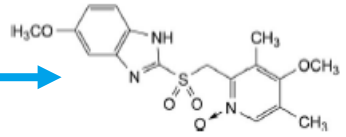
F. 8-methoxy-1,3-dimethyl-12-thioxopyrido[1′,2′:3,4]-imidazo[1,2-*a*]benzimidazol-2(12*H*)-one,



G. 9-methoxy-1,3-dimethyl-12-thioxopyrido[1′,2′:3,4]-imidazo[1,2-*a*]benzimidazol-2(12*H*)-one,



H. 2-[(*RS*)-[(4-chloro-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole,

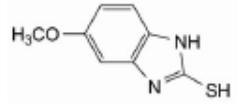


I. 4-methoxy-2-[[(5-methoxy-1*H*-benzimidazol-2-yl)sulfonyl]methyl]-3,5-dimethylpyridine 1-oxide.

Other detectable impurities from the transparency list are controlled at NMT 0.10% as unspecified impurities

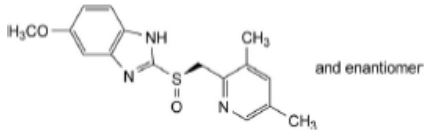
Case study (fictitious): Omeprazole

Are all the impurities from the transparency list possible by the the RoS used?



✓

Ph. Eur. Imp A: unreacted SM2 carried over in the API



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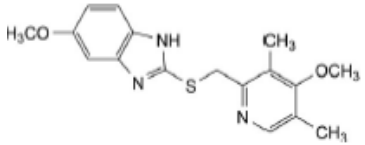
Ph. Eur. Imp B: unreacted first non isolated intermediate carried over and transformed in the downstream process



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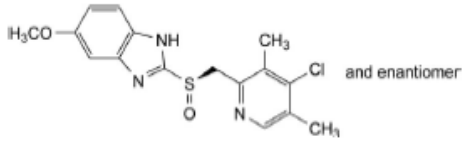
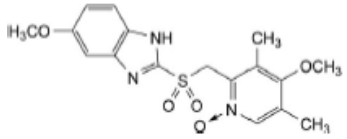
Ph. Eur. Imp C: unreacted intermediate D carried over in final API



X

Ph. Eur. Imp H: **unlikely from the RoS.**



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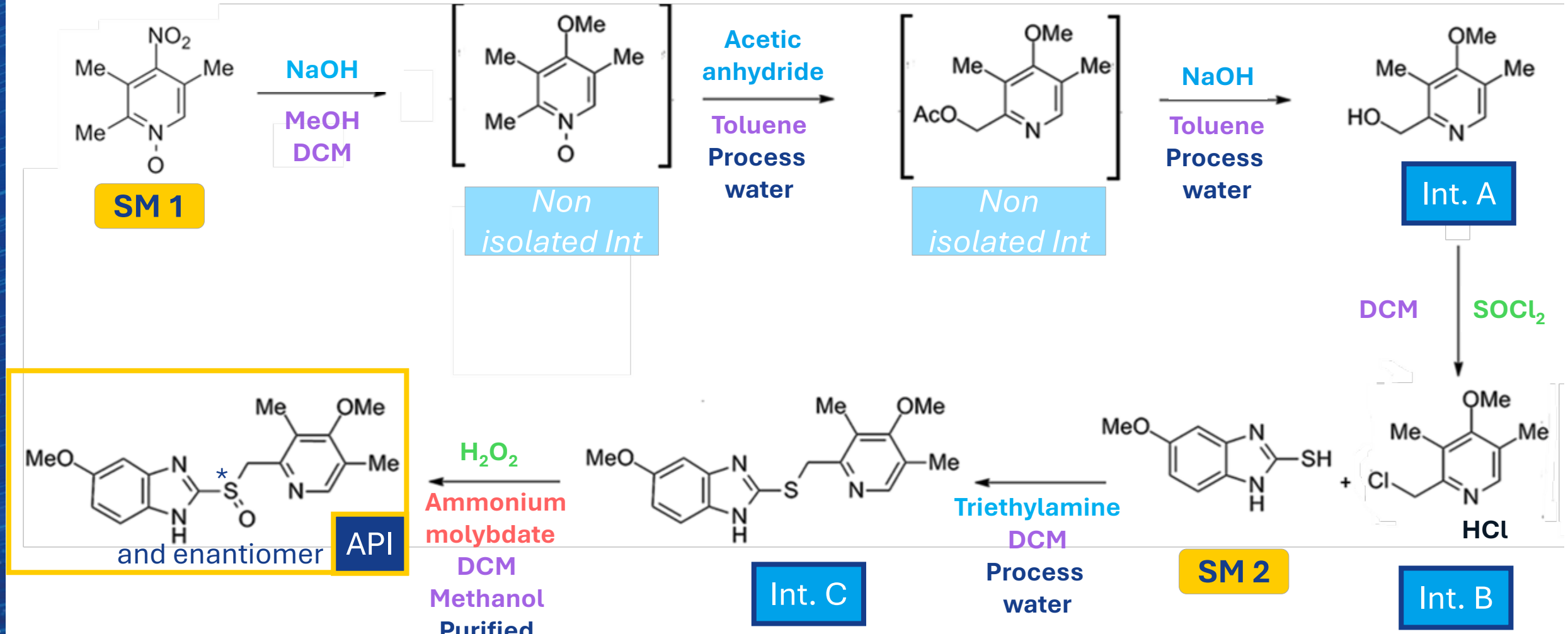
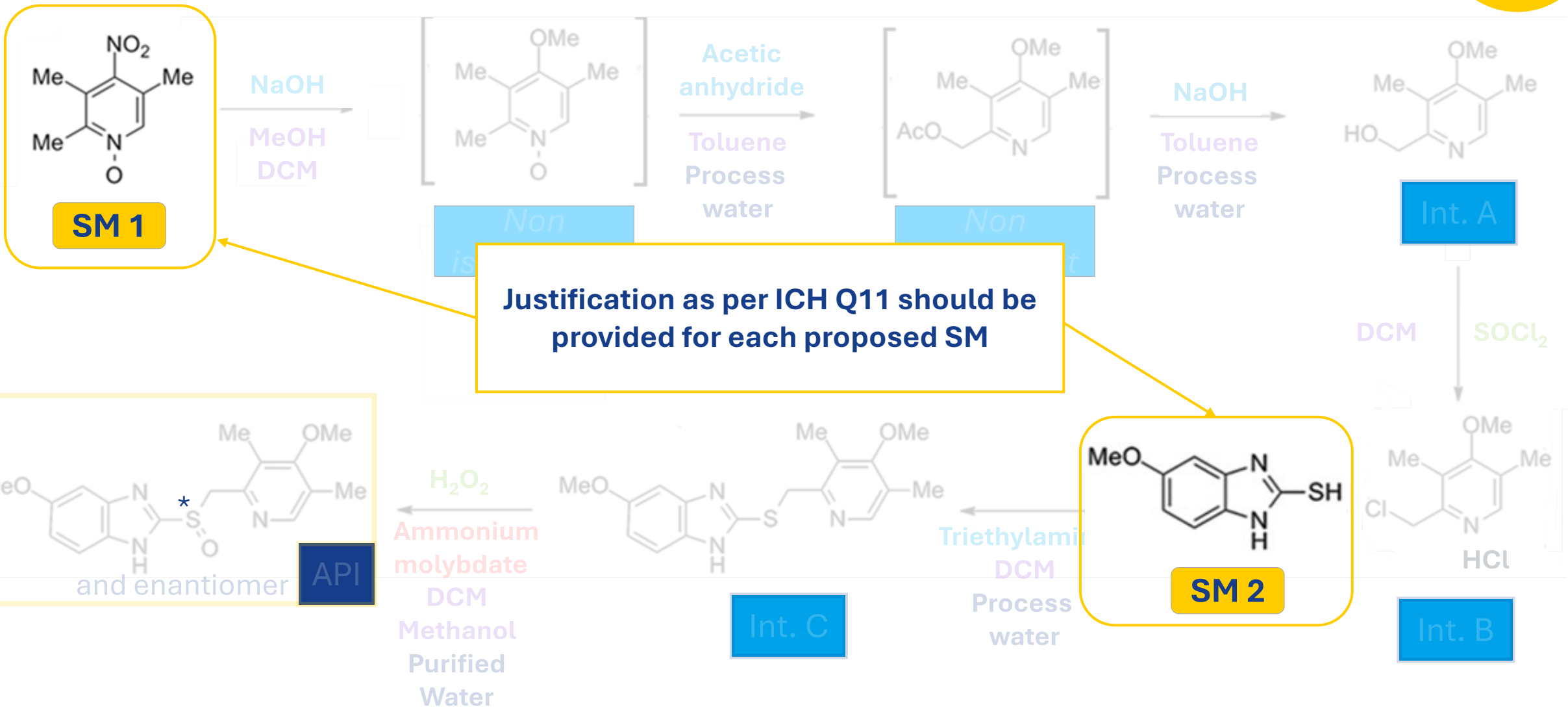
Ph. Eur. Imp I: potentially formed by oxidation of Ph. Eur. Imp. D

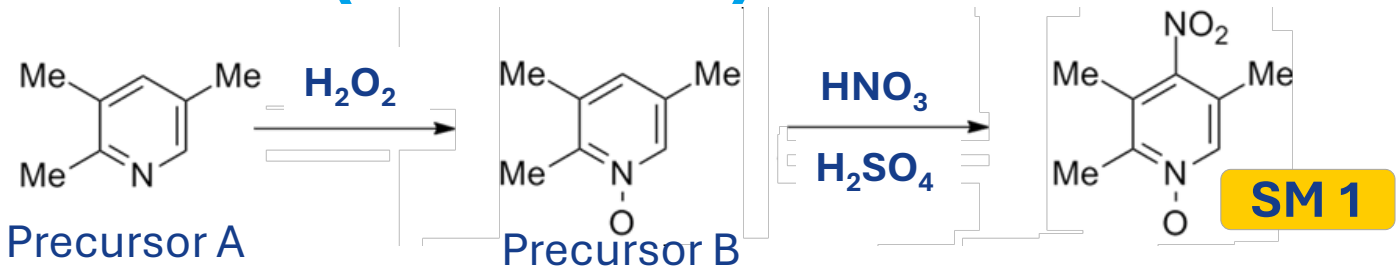
Case study (fictitious): Omeprazole



Case study (fictitious): Omeprazole



Starting materials (3.2.S.2.3)



Precursor A

Precursor B

Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
Precursor A	Raw material, eliminated during crystallisation	0.26%	Controlled as specified impurity in the SM at NMT 0.50%
Precursor B	Precursor. Eliminated during crystallisation in mother liquor.	0.08%	Controlled as specified impurity in the SM at NMT 0.15%.
3,5-lutidine	Positional isomer carryover. Not reactive in the downstream process	0.24%	Controlled as specified impurity at NMT 0.50%

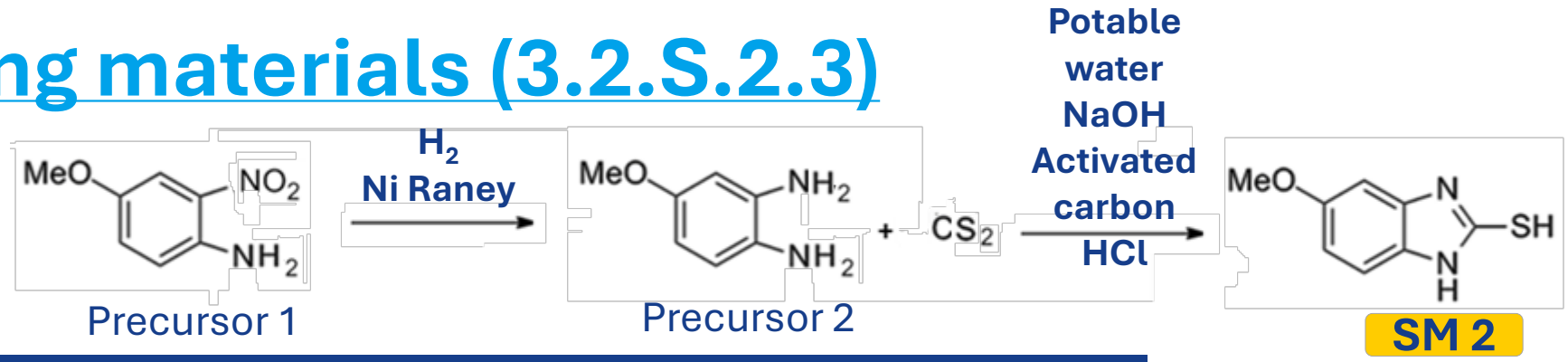
Fate: potential by-products, side-reactions should be considered as well!

Which specification ?

Impurity	Limit
Precursor A	NMT 0.50%
Precursor B	NMT 0.15%
3,5-lutidine	NMT 0.50%
Unspecified imp.	NMT 0.20%
Total	NMT 1.5%

Any limit for unspecified impurities should be justified

Starting materials (3.2.S.2.3)



Precursor 1 Precursor 2 **SM 2**

Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
Precursor 1	Raw material. Found <0.05% in INT-C. Alerting structure (see **mutagenic impurities**).	0.13%	Controlled as specified impurity in the SM at NMT 0.30%
Precursor 2	Alerting structure (see **mutagenic impurities**). Found <0.05% in INT-C.	0.06%	Controlled as specified impurity in the SM at NMT 0.10%
CS_2	Hydrolyzed in water to H_2S.	ND	No control is needed.

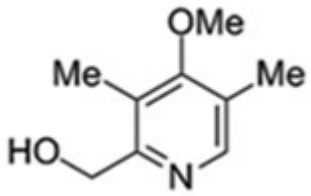
Fate: potential by-products, side-reactions should be considered as well!

Which specification ?

Impurity	Limit
Precursor 1	NMT 0.30%
Precursor 2	NMT 0.10%
Unspecified imp.	NMT 0.15%
Total	NMT 0.8%

Intermediates (3.2.S.2.4)

Intermediate A



Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
SM1	**Mutagenic impurity**. Tested ND in API (see mutagenic impurities).	11 ppm	Controlled as specified impurity at NMT 30ppm
4-methoxy derivative	In-situ intermediate, unreactive in the dowstream process. Alerting structure (see **mutagenic impurities**).	0.15%	Controlled as specified impurity at NMT 0.25%
Acetyl derivative	Non-isolated intermediate. Carryover in Int-B (0.15%).	0.53%	Controlled as specified impurity at NMT 1.0%
4-chloro impurity	Impurity by substitution of nitro derivative	0.18%	Controlled as specified impurity at NMT 0.25%

Fate: potential by-products, side-reactions should be considered as well!

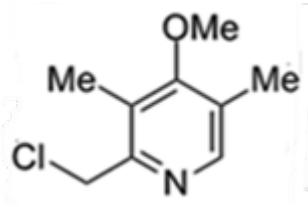
Any limit for unspecified impurities should be justified

Which specification ?

Impurity	Limit
SM 1	NMT 30 ppm
4-MeO derivative	NMT 0.25%
Acetyl derivative	NMT 1.0%
4-Cl derivative	NMT 0.25%
Unspecified imp.	NMT 0.30%
Total	NMT 1.5%

Intermediates (3.2.S.2.4)

Intermediate B



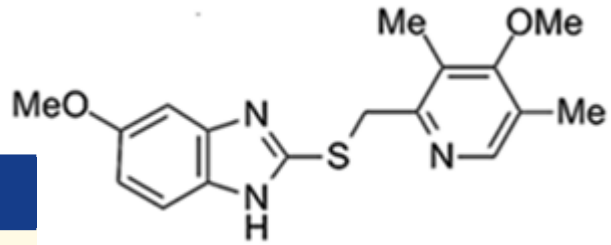
Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
Acetyl derivative	Non-isolated intermediate. Carryover in Int-B (0.18%).	0.18%	Controlled as specified impurity at NMT 0.25%
INT-A	Unreacted intermediate carried over. Eliminated during crystallisation of INT-C. When spiked at 1.2%, found ND in INT-C	0.38%	Controlled as specified impurity at NMT 1.0% in INT-B
Unknown impurity	Present in all batches	0.14%	Controlled as unspecified impurity at NMT 0.20%

Which specification ?

Impurity	Limit
Int-A	NMT 1.0%
Acetyl derivative	NMT 0.25%
Unspecified imp.	NMT 0.20%
Total	NMT 1.5%

Intermediates (3.2.S.2.4)

Intermediate C



Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
Ph. Eur. Imp A (SM2)	SM2 carryover. Removed during crystallisation stage.	0.38%	Controlled as specified impurity at NMT 0.50% in INT-C and at NMT 0.10% in API
INT-B	Unreacted intermediate. Removed workup. Found <0.05% in API.	0.17%	Controlled as specified impurity at NMT 0.40% in INT-C and as unspecified impurity in the API
Impurity RRT 1.10	Unidentified impurity. Found <0.05 – 0.06% in API.	0.13%	Controlled as specified impurity at NMT 0.20% in INT-C and in the API as unspecified impurity

Assuming Ph. Eur. Monograph analytical procedure for Related Substances is used to control the last intermediate

Which specification ?

Impurity	Limit
Ph. Eur. Imp A	NMT 0.50%
INT-B	NMT 0.40%
Impurity RRT 1.10	NMT 0.20%
Unspecified imp.	NMT 0.10%
Total	NMT 1.0%

Case study: Omeprazole

Related substances. Liquid chromatography (*2.2.29*).

Limits:
- *impurities D, E*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
- *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Omeprazole specification:

Impurity	Limit	Batch data	analytical procedure
Ph. Eur. Impurity D	NMT 0.15 %	0.05-0.08%	Ph. Eur. Current edition
Ph. Eur. Impurity E	NMT 0.15 %	<0.05-0.11%	
Unspecified impurity	NMT 0.10%	<0.05 – 0.06%	
Total impurities	NMT 0.5%	0.14-0.20%	

All related substances can be controlled by the analytical procedure of the monograph

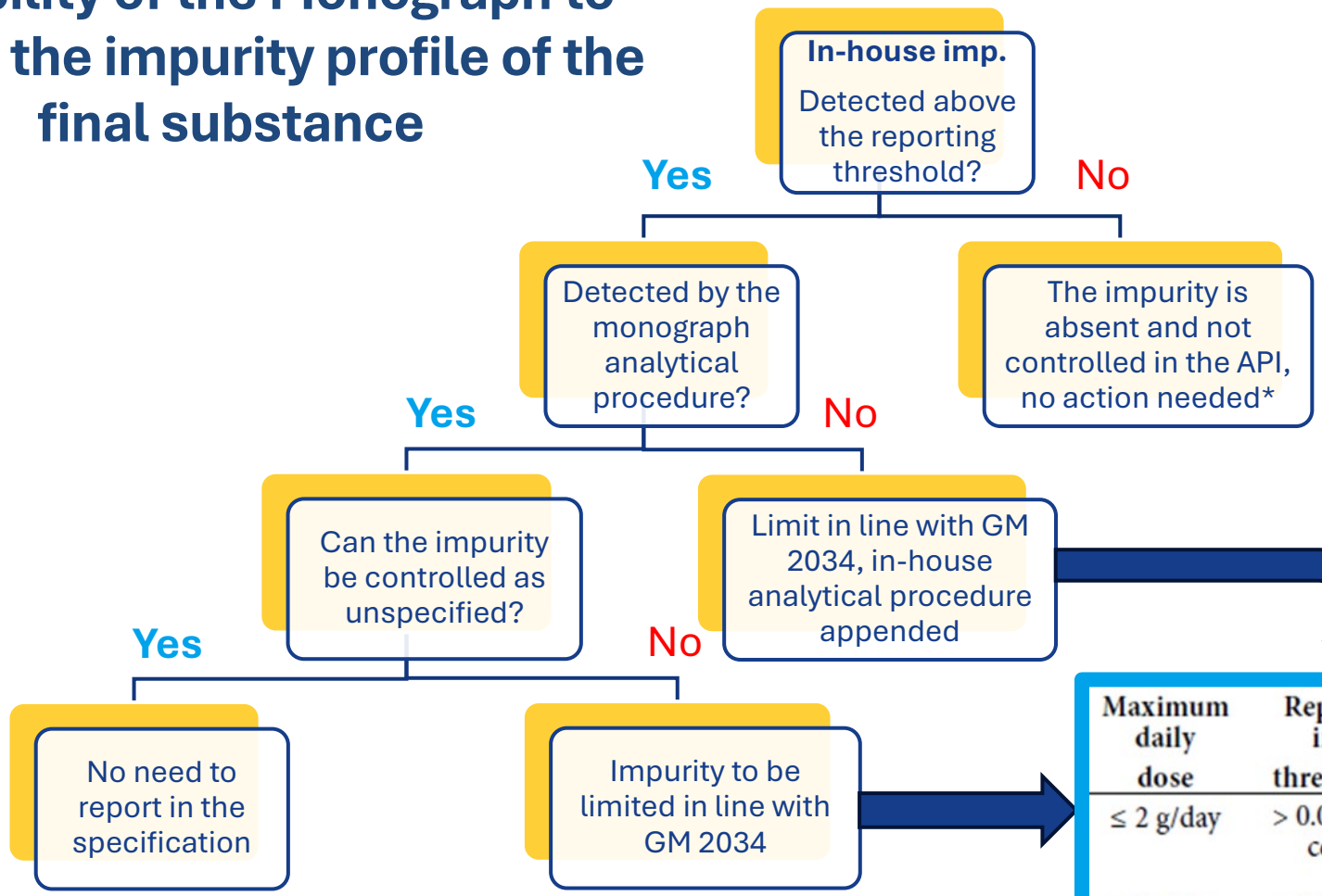
→ **No in-house impurity present in the API**

Different situations...

- ★ If in-house impurities are present?
- ★ If you are using an in-house analytical procedure?
- ★ How to handle the situation?
- ★ Which impurity to include in the specification?

In-house impurities

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



CEP 2.0

*If a control is implemented although not needed:

- Suitability of Ph. Eur. procedure to be demonstrated
- If not suitable, in-house analytical procedure to be appended

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

Do not forget …

Suitability (or unsuitability) of the analytical procedure of the monograph to control all the related substances present/limited above the disregard limit should be demonstrated

Alternative analytical procedure

- When: Ph. Eur. analytical procedure **is suitable** to control in-house impurities, but in-house procedures may be used
- Equivalent results comparing to the corresponding Ph. Eur. procedure(s): cross-validation data on the same batches, using spiked solutions if necessary
- Validation in line with ICH Q2(R2)

Additional analytical procedure

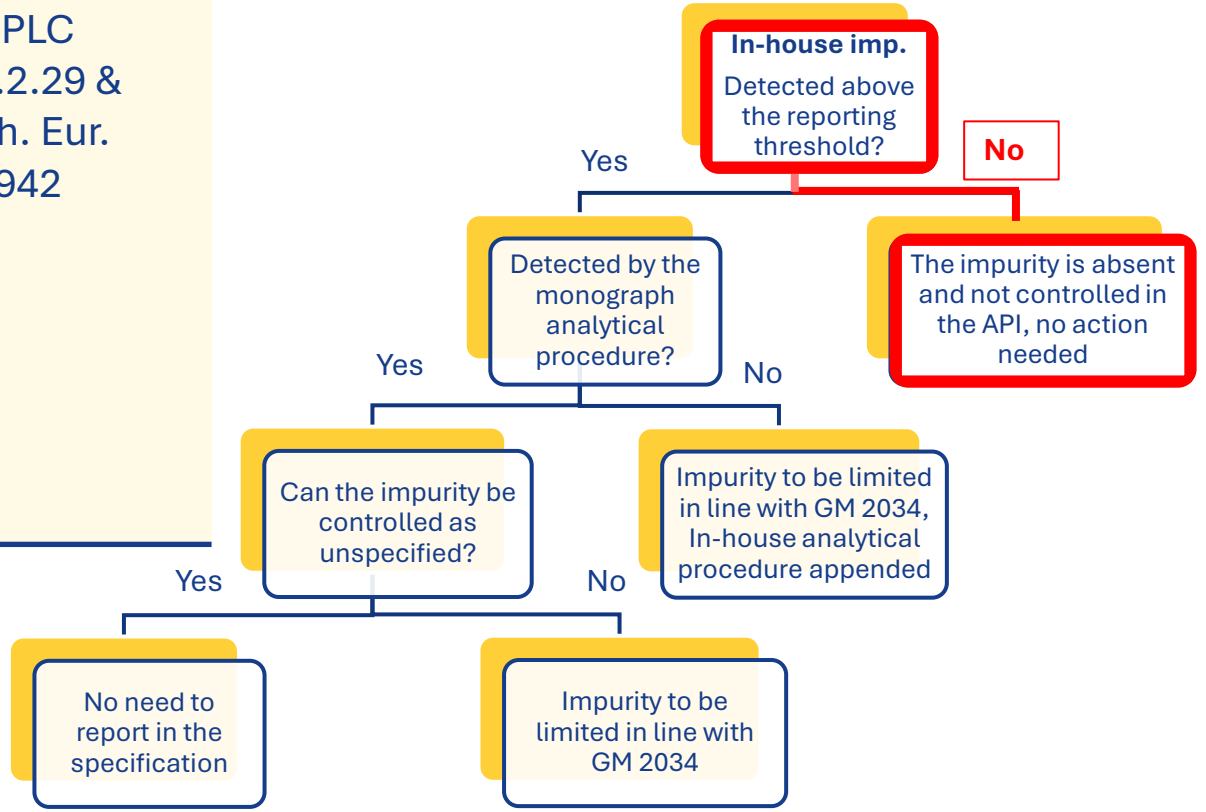
- When : Ph. Eur. analytical procedure **is not suitable** to control in-house impurities
- To supplement monograph procedure(s)
- Unless absence of corresponding impurities is demonstrated, it will be reported on the CEP
- Validation in line with ICH Q2(R2)

Case study: Omeprazole

Other situations : specifications for in-house impurities 1, 2 and 3 ?

Impurity	Limit	Batch data	analytical procedure
Ph. Eur. Impurity D	NMT 0.15%	0.05-0.08%	HPLC 2.2.29 & Ph. Eur. 0942
Ph. Eur. Impurity E	NMT 0.15%	0.05-0.11%	
In-house impurity 1	**?**	**0.001-0.02%**	
In-house impurity 2		0.04-0.06%	
In-house impurity 3		0.08-0.12%	
Unspecified impurity	NMT 0.10%	0.01-0.06%	
Total impurities	NMT 0.5%	0.19-0.31%	

Reporting threshold: 0.05%



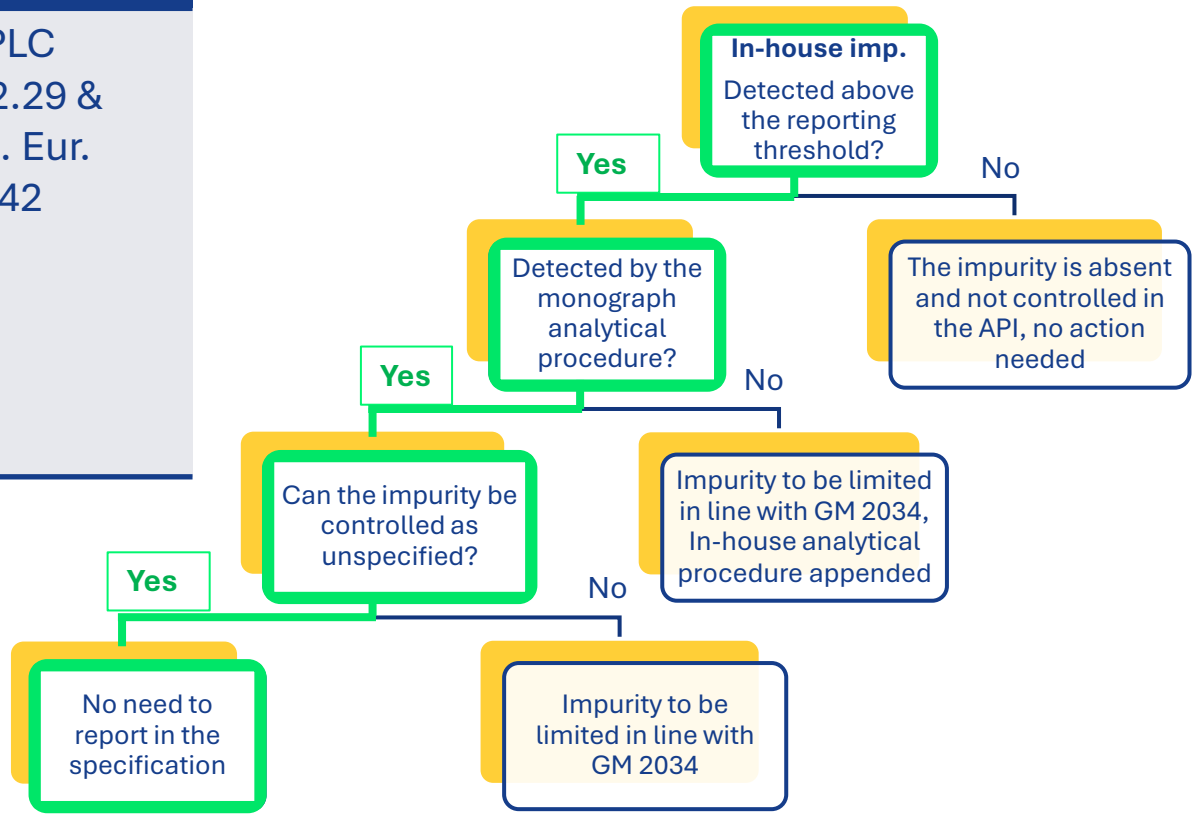
Impurity always found below the reporting threshold, can be considered absent.

Case study: Omeprazole

Other situations : specifications for in-house impurities 1, 2 and 3 ?

Impurity	Limit	Batch data	analytical procedure
Ph. Eur. Impurity D	NMT 0.15%	0.05-0.08%	HPLC 2.2.29 & Ph. Eur. 0942
Ph. Eur. Impurity E	NMT 0.15%	0.05-0.11%	
In-house impurity 2	**?**	**0.04-0.06%**	
In-house impurity 3		0.08-0.12%	
Unspecified impurity	NMT 0.10%	0.01-0.06%	
Total impurities	NMT 0.5%	0.19-0.31%	

Reporting threshold: 0.05%



Include the impurity in the specification is not required as it can be controlled as any unspecified impurity.

Case study: Omeprazole

Other situations : specifications for in-house impurities 1, 2 and 3 ?

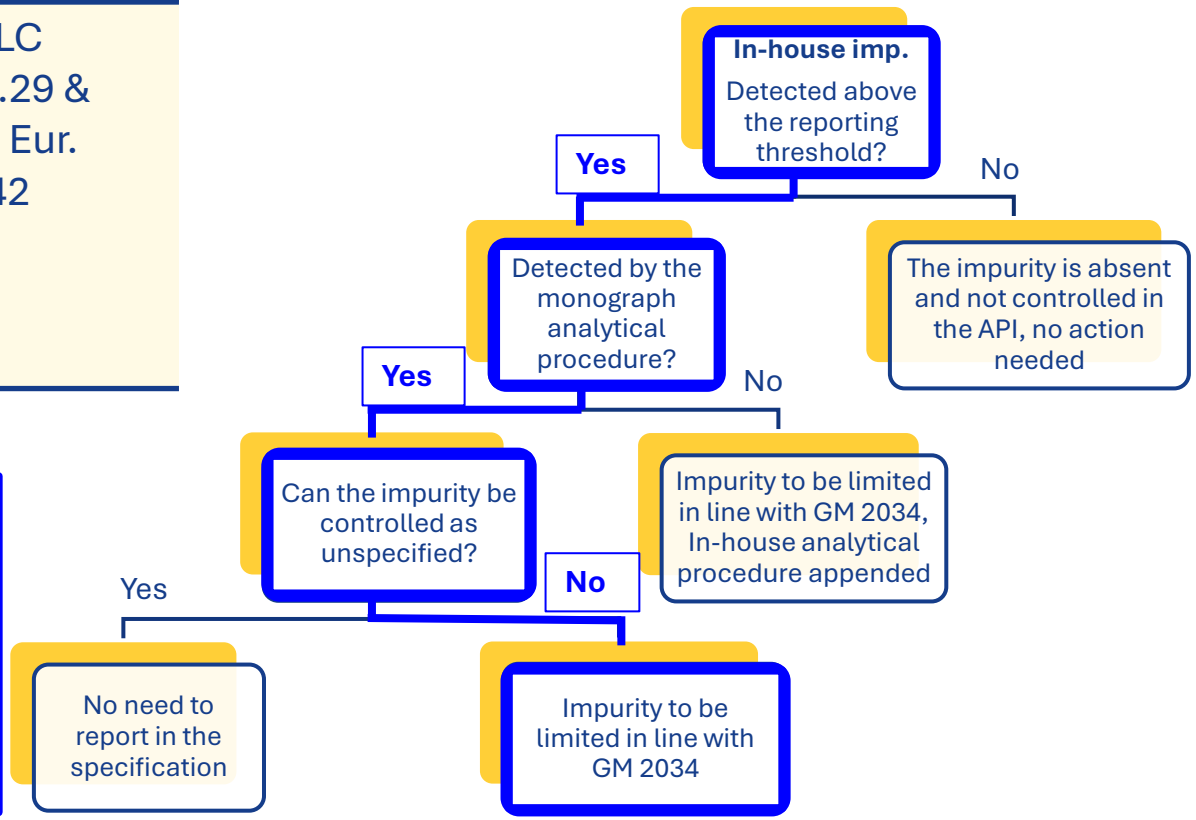
Impurity	Limit	Batch data	analytical procedure
Ph. Eur. Impurity D	NMT 0.15%	0.05-0.08%	HPLC 2.2.29 & Ph. Eur. 0942
Ph. Eur. Impurity E	NMT 0.15%	0.05-0.11%	
In-house impurity 3	**?**	**0.08-0.12%**	
Unspecified impurity	NMT 0.10%	0.01-0.06%	
Total impurities	NMT 0.5%	0.19-0.31%	

Reporting threshold: 0.05%

The in-house impurity should be individually specified in the specification with a limit set according to GM 2034:

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

If above 0.15%, the impurity should be qualified at its level



Case study: Omeprazole

Other situations : specifications for in-house impurities 1, 2 and 3 ?

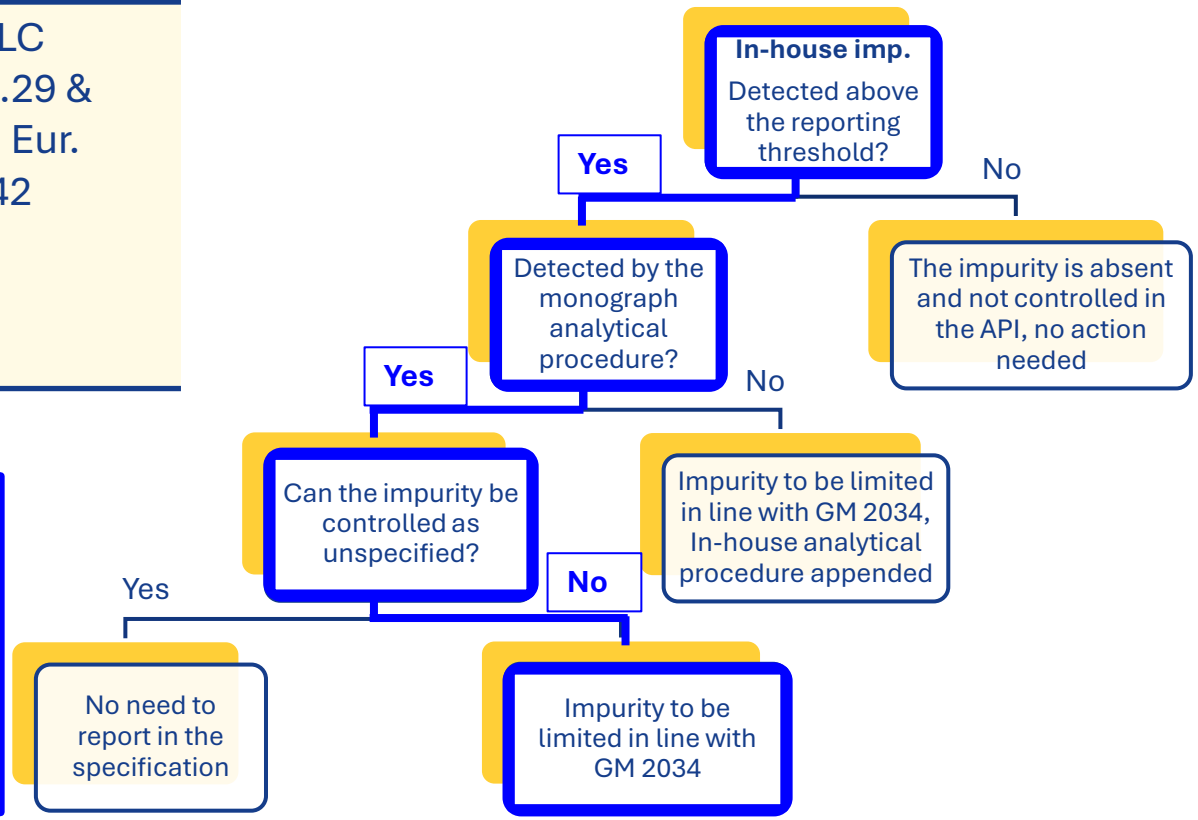
Impurity	Limit	Batch data	analytical procedure
Ph. Eur. Impurity D	NMT 0.15%	0.05-0.08%	HPLC 2.2.29 & Ph. Eur. 0942
Ph. Eur. Impurity E	NMT 0.15%	0.05-0.11%	
In-house impurity 3	**NMT 0.15%**	**0.08-0.12%**	
Unspecified impurity	NMT 0.10%	0.01-0.06%	
Total impurities	NMT 0.5%	0.19-0.31%	

Reporting threshold: 0.05%

The in-house impurity should be individually specified in the specification with a limit set according to GM 2034:

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

If above 0.15%, the impurity should be qualified at its level



Case study: Omeprazole

Specification for related substances:

Impurity	Limit	Batch data	analytical procedure
Ph. Eur. Impurity D	NMT 0.15%	0.05 - 0.08%	Ph. Eur. current edition
Ph. Eur. Impurity E	NMT 0.15%	0.05 - 0.11%	
In-house impurity 3	NMT 0.15%	0.08 - 0.12%	
Unspecified impurity	NMT 0.10%	0.01 - 0.06%	
Total impurities	NMT 0.5%	0.19 - 0.31%	

CEP 2.0

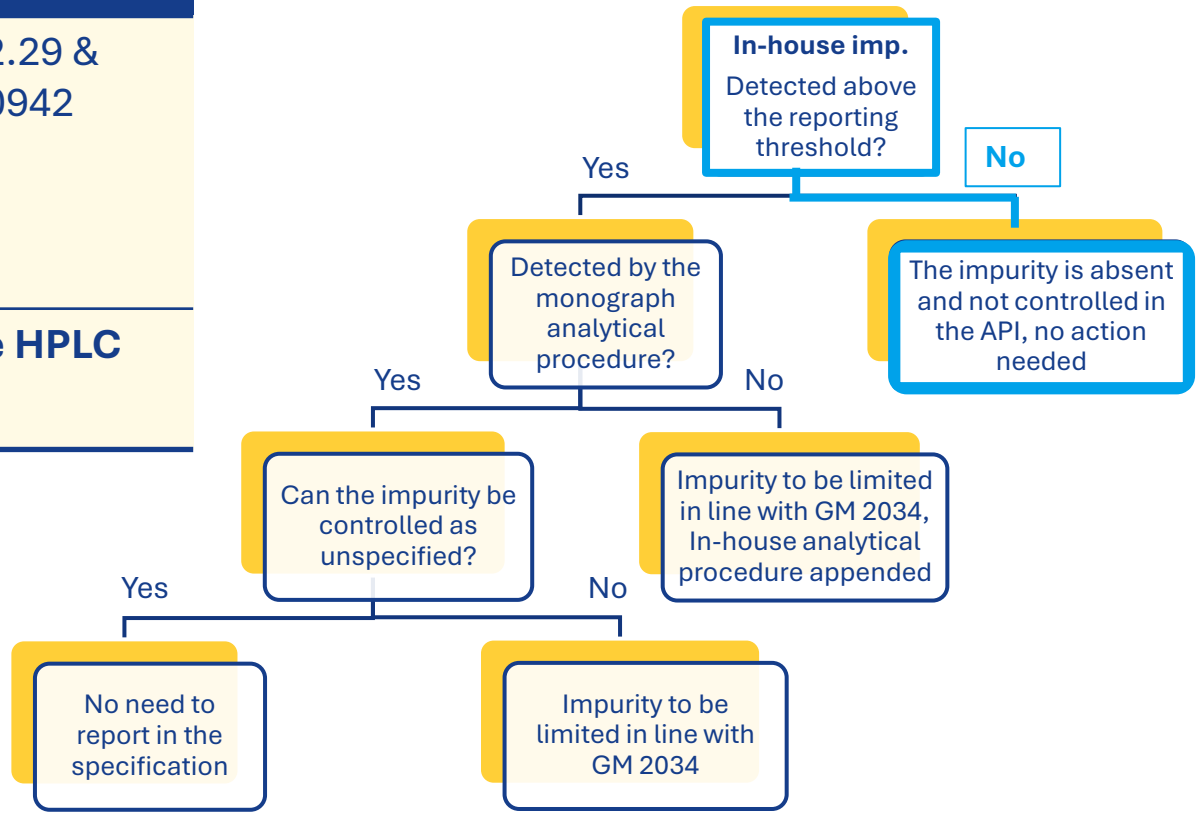
Specification for the final substance in section 3.2.S.4.1 should make reference to the analytical procedures of the monograph.

Case study: Omeprazole

Other situations : specifications for in-house impurities 4 and 5?

Impurity	Limit	Batch data	analytical procedure
Ph. Eur. Impurity D	NMT 0.15%	0.05-0.08%	HPLC 2.2.29 & Ph. Eur. 0942
Ph. Eur. Impurity E	NMT 0.15%	0.05-0.11%	
Unspecified impurity	NMT 0.10%	0.01-0.06%	
Total impurities	NMT 0.5%	0.19-0.31%	
In-house impurity 4	**?**	**0.01-0.03%**	**In-house HPLC**
In-house impurity 5		0.05-0.11%	

Reporting threshold: 0.05%



Impurity always found below the reporting threshold, can be considered absent.

CEP 2.0

If control is implemented although not needed:

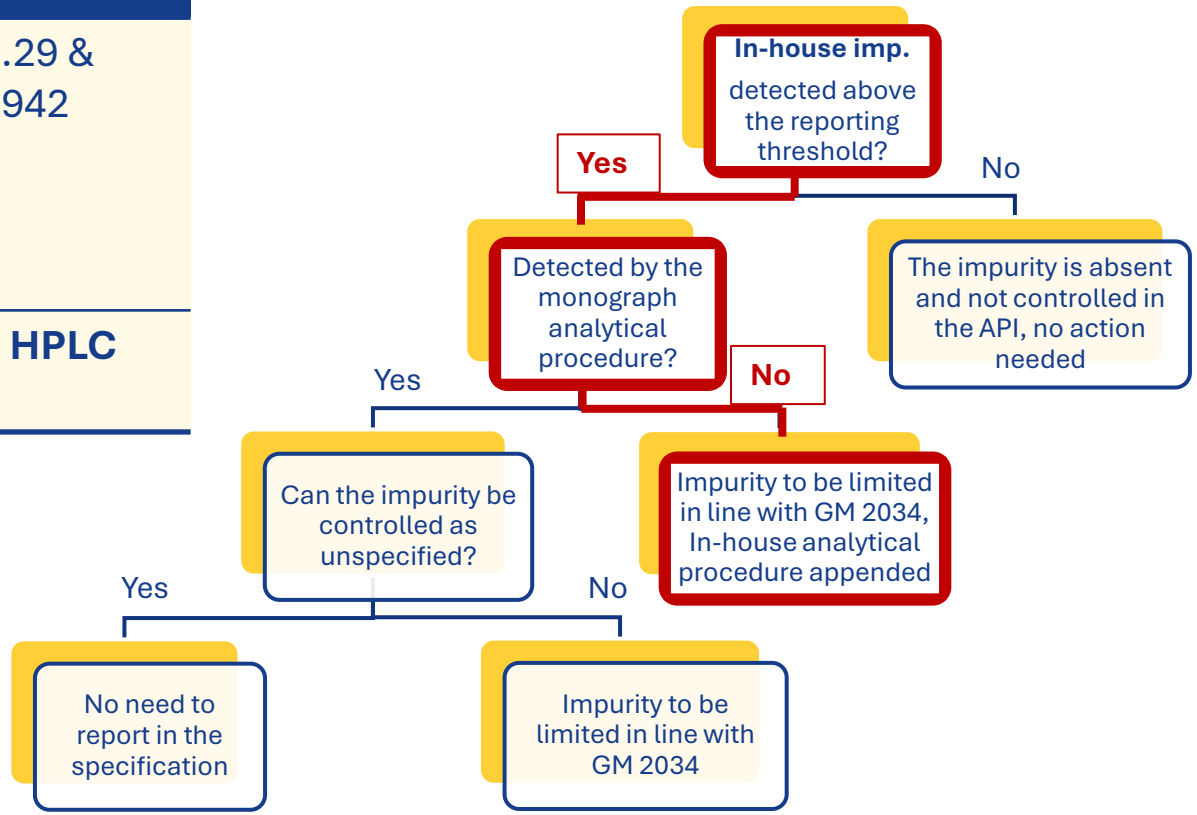
- Suitability of Ph. Eur. to be demonstrated
- If not suitable, in-house analytical procedure to be appended

Case study: Omeprazole

Other situations : specifications for in-house impurities 4 and 5?

Impurity	Limit	Batch data	analytical procedure
Ph. Eur. Impurity D	NMT 0.15%	0.05-0.08%	HPLC 2.2.29 & Ph. Eur. 0942
Ph. Eur. Impurity E	NMT 0.15%	0.05-0.11%	
Unspecified impurity	NMT 0.10%	0.01-0.06%	
Total impurities	NMT 0.5%	0.19-0.31%	
In-house impurity 5 (RRT 1.10)	**?**	**0.05-0.11%**	**In-house HPLC**

Reporting threshold: 0.05%



Impurity detected above the identification threshold:

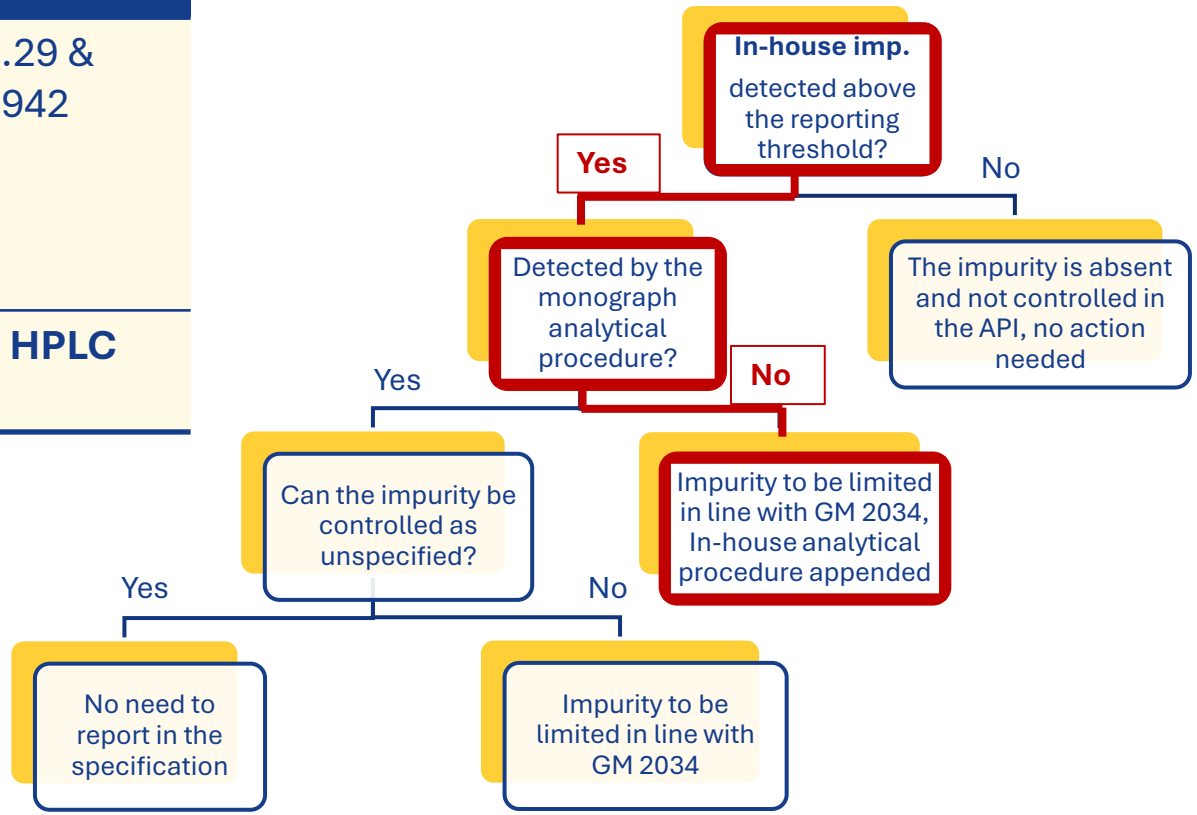
- **The in-house impurity should be individually specified in the specification with a limit set according to GM 2034**
- **The in-house analytical procedure will be appended to the CEP.**

Case study: Omeprazole

Other situations : specifications for in-house impurities 4 and 5?

Impurity	Limit	Batch data	analytical procedure
Ph. Eur. Impurity D	NMT 0.15%	0.05-0.08%	HPLC 2.2.29 & Ph. Eur. 0942
Ph. Eur. Impurity E	NMT 0.15%	0.05-0.11%	
Unspecified impurity	NMT 0.10%	0.01-0.06%	
Total impurities	NMT 0.5%	0.19-0.31%	
In-house impurity 5 (RRT 1.10)	**NMT 0.15%**	**0.05-0.11%**	**In-house HPLC**

Reporting threshold: 0.05%



Impurity detected above the identification threshold:

- **The in-house impurity should be individually specified in the specification with a limit set according to GM 2034**
- **The in-house analytical procedure will be appended to the CEP.**

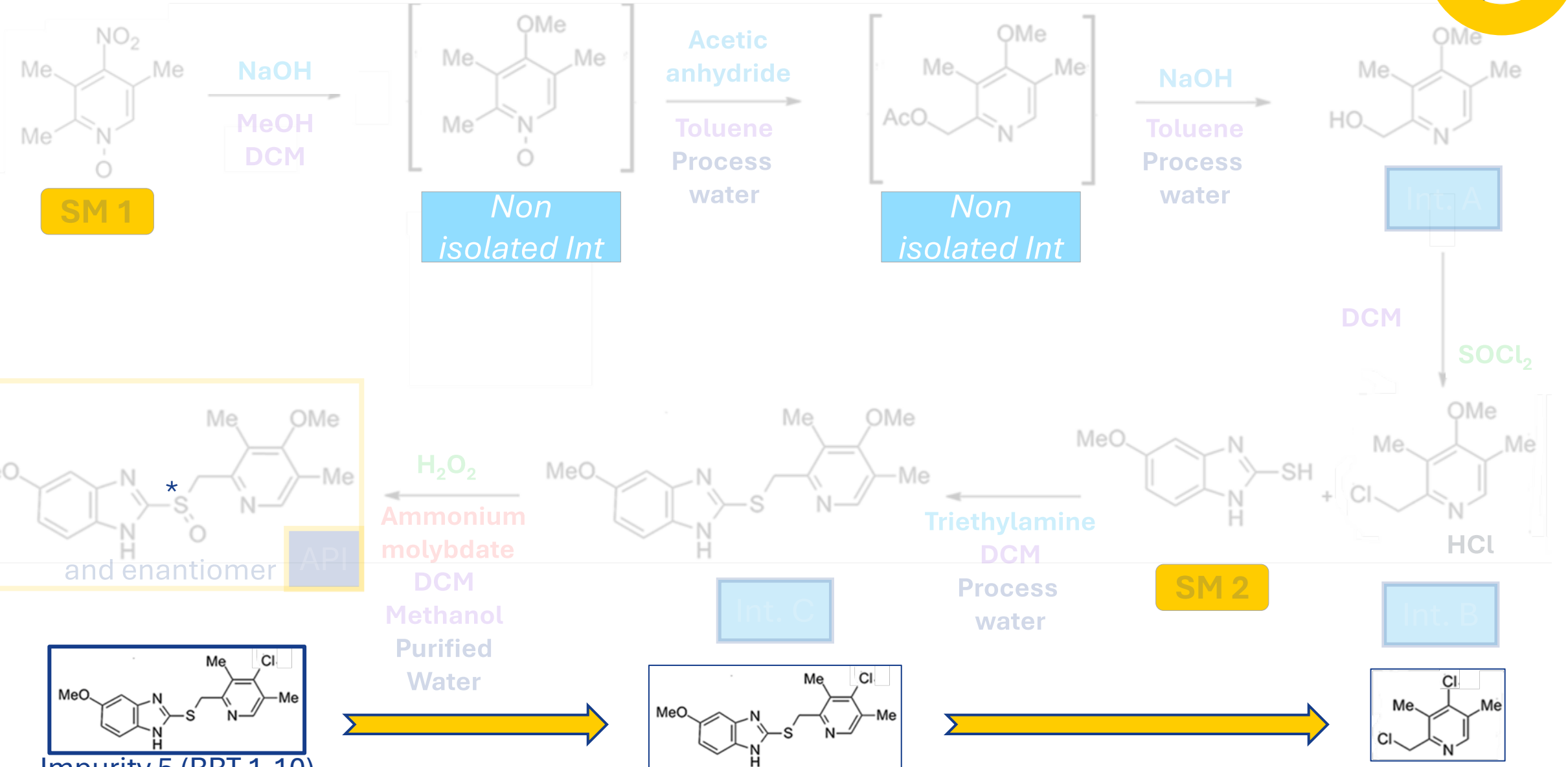
Case study: Omeprazole

Specification for related substances:

Impurity	Limit	Batch data	analytical procedures
Ph. Eur. Impurity D	NMT 0.15%	0.05 – 0.08%	
Ph. Eur. Impurity E	NMT 0.15%	0.01 – 0.03%	Ph. Eur. current edition
Unspecified impurity	NMT 0.10%	0.01 – 0.06%	
Total impurities	NMT 0.5%	0.18 – 0.23%	
In-house impurity 5 (RRT 1.10)	NMT 0.15%	0.05 – 0.11%	**In-house**

Specification for the final substance in section 3.2.S.4.1 should make reference to the analytical procedure being used (i.e. "Ph. Eur. current edition" or "in-house").
The in-house analytical procedure for impurity 5 is additional to Ph. Eur. and will be appended to the CEP.

Case study (fictitious): Omeprazole



- Related Substances (Organic impurities)
- **Mutagenic impurities**
- Nitrosamine impurities
- Residual solvents
- Elemental impurities
- Inorganic impurities

Mutagenic impurities

Reference guideline:

ICH M7(R2) Guideline on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk

- ★ **ICH M7(R2) Addendum** on application of the principles of the ICH M7 guideline to calculation of compound-specific acceptable intake
- ★ **ICH M7(R2) Questions and Answers** on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk

For veterinary products: Guideline on assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products (EMA/CVMP/SWP/377245/2016)

Definition of mutagenic: Inducing or capable of inducing genetic mutation.

Mutagenic impurities

1. Active substance assessment for mutagenic impurities

- Actual impurities
- Potential impurities

2) Hazard assessment and classification as per ICH M7

- Known mutagens
- Structural alert for mutagenicity

3) Setting acceptable limits and propose a control strategy

- Threshold of Toxicological Concern: TTC limit
- Other specific acceptable limits

Mutagenic impurities

1) Active substance assessment

Actual and potential impurities that are likely to arise during the synthesis (synthetic impurities) and storage (degradation products) of a drug substance are to be assessed for **MUTAGENIC POTENTIAL**

Actual impurities
Identified, known structure

Impurities found above ICH Q3A reporting threshold

Potential impurities
Likely to be present in the final substance

Starting materials (its impurities & depending on where introduced in the process, also their synthesis), reagents, intermediates and by-products in the route of synthesis from the starting material to the active substance

Mutagenic impurities

2) Hazard assessment and classification as per ICH M7

ICH M7:

- ★ **Initial analysis from database and literature searches for classification into class 1, 2 or 5**
- ★ **If no data available, identification of an alerting structure using computational *in silico* assessment to predict the mutagenicity of the impurity, based on Quantitative Structure-Activity Relationships (Q)SAR principles**

→ Absence of structural alerts from two complementary (Q)SAR methodologies (expert rule- based and statistical) is sufficient to conclude that the impurity is not of mutagenic concern.

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

ICH M7 Table 1 Classification of impurities with respect to mutagenic and carcinogenic potential

Mutagenic impurities

2) Hazard assessment and classification as per ICH M7

Initial analysis – *Available literature and database searches*

Impurities with **unknown mutagenicity**

Impurities with presence / absence of **mutagenic concern**

Class 1, 2 or 5

Run Q(SAR) prediction to identify the presence of alerting structure

(2 complementary methodologies)

Negative
Class 4 or 5

Inconclusive
→ *Worst case*
Class 3

Positive
Class 3

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

ICH M7 Table 1 Classification of impurities with respect to mutagenic and carcinogenic potential

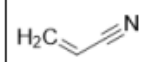
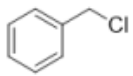
Mutagenic impurities

3) Setting acceptable limits and propose a control strategy

For class 1, 2 and 3 impurities, control strategy in line with ICH M7 requirements.

$$\text{Acceptable limit (ppm)} = \frac{\textbf{PDE} \text{ (µg/day)}}{\textbf{MDD} \text{ (g/day)}}$$

Compound-specific limit (Class 1)
Defined according to the **specific acceptable intake** (*ICH M7 addendum*)

Compound	CAS#	Chemical Structure	AI or PDE (µg/day)	Comment
Linear extrapolation from TD50				
Acrylonitrile	107-13-1		6	TD50 linear extrapolation
Benzyl chloride	100-44-7		41	TD50 linear extrapolation

TTC Limit (Class 2 and 3)
Defined according to the **duration of treatment**

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 Years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

Mutagenic impurities

3) Setting acceptable limits and propose a control strategy

For class 1, 2 and 3 impurities, control strategy in line with ICH M7 requirements.

$$\text{Acceptable limit (ppm)} = \frac{\text{PDE (µg/day)}}{\text{MDD (g/day)}}$$

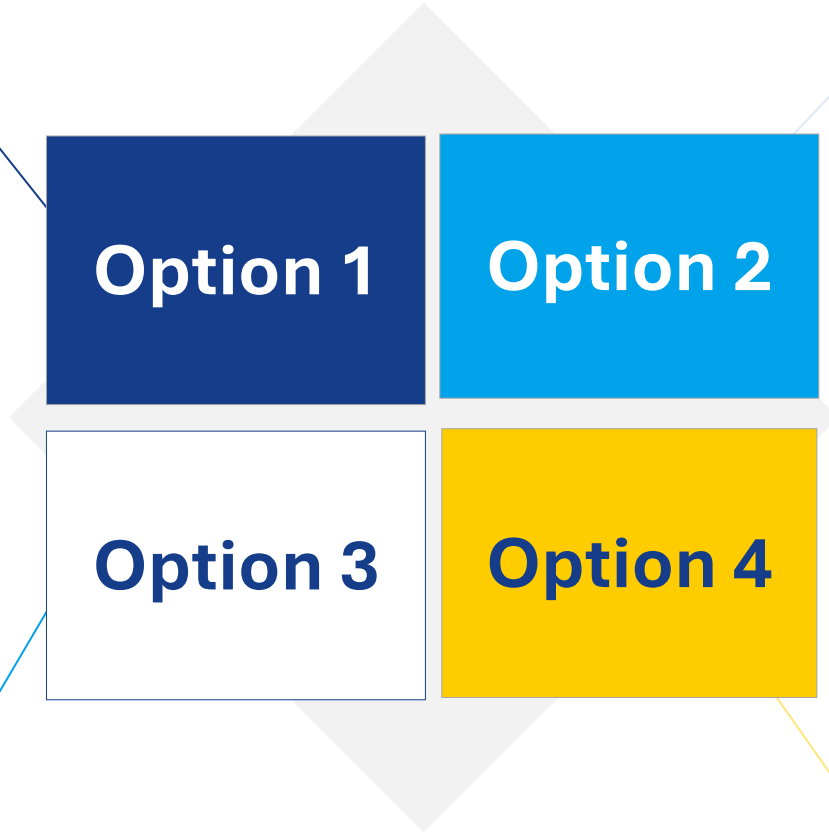
CEP 2.0

MDD and information regarding the use of the substance to be included in 3.2.S.1.3 along with route of administration and treatment duration considered for development of the control strategy and specification.

Mutagenic impurities

3) Setting acceptable limits and propose a control strategy

For class 1, 2 and 3 impurities, control strategy in line with ICH M7 requirements.



Control ≤ acceptable limit in the final substance

Control ≤ acceptable limit in a raw material, SM or intermediate or as an IPC

Control > acceptable limit in a raw material, SM or intermediate or as an IPC.

Absence of control, based on process understanding

Mutagenic impurities

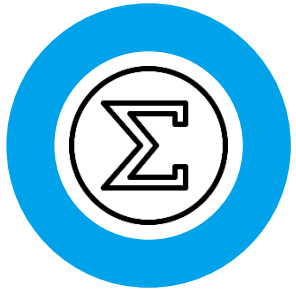
3) Setting acceptable limits and propose a control strategy

For class 1, 2 and 3 impurities, control strategy in line with ICH M7 requirements.

Option 1	**Control ≤ acceptable limit in the final substance** Impurities introduced in the last step of the synthesis, unless otherwise justified (*Refer to ICH M7 Q&A document*)
Option 2	**Control ≤ acceptable limit in a raw material, SM or intermediate or as an IPC.** *No further justification needed.*
Option 3	**Control > acceptable limit in a raw material, SM or intermediate or as an IPC.** Suitability of the proposed limit is to be justified by demonstrating levels of the impurity being <30% acceptable limit in the API. Spike-purge studies are highly encouraged.
Option 4	**Understanding the process and its effects on impurities**, with sufficient confidence that the level of the impurity in the drug substance will be below the acceptable limit. Option to be supported by predictive purge calculations and if relevant batch data (if introduced or formed late in the process). For impurities inherently unstable, introduced early and well purged etc.

Mutagenic impurities

3) Setting acceptable limits and propose a control strategy



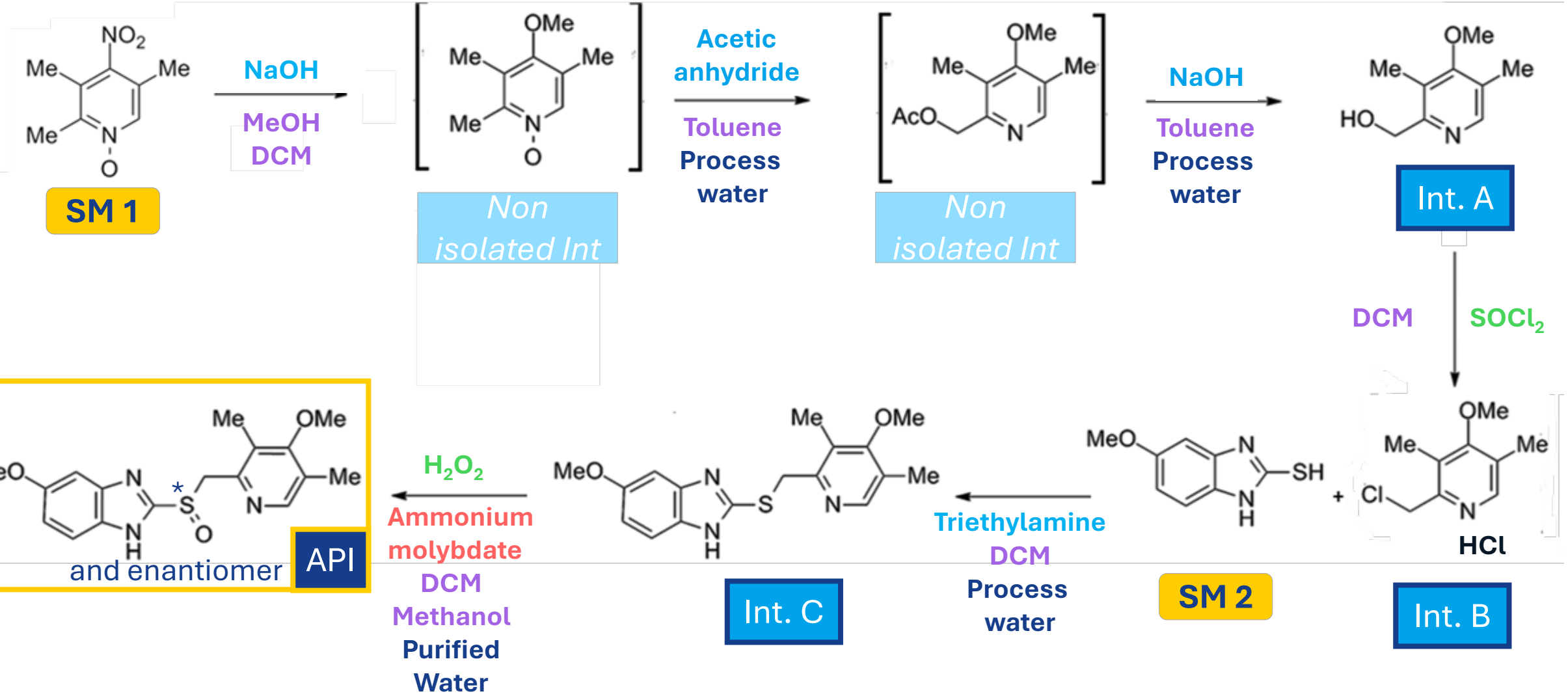
If three or more class 2 or class 3 impurities are controlled in the API:
→Implement a limit for **total mutagenic impurities** in addition to individual limits (ICH M7 table 3)

Regarding periodic verification testing (i.e. testing on pre-selected batches or at predetermined intervals instead of on a batch-to-batch basis):
→ To be applied only when **option 1** control strategy is in place
→ Not appropriate for options 2 and 3

For all carry-over studies, **suitable and relevant validation data in line with ICH Q2 (R2)** of the analytical procedure used have to be provided.

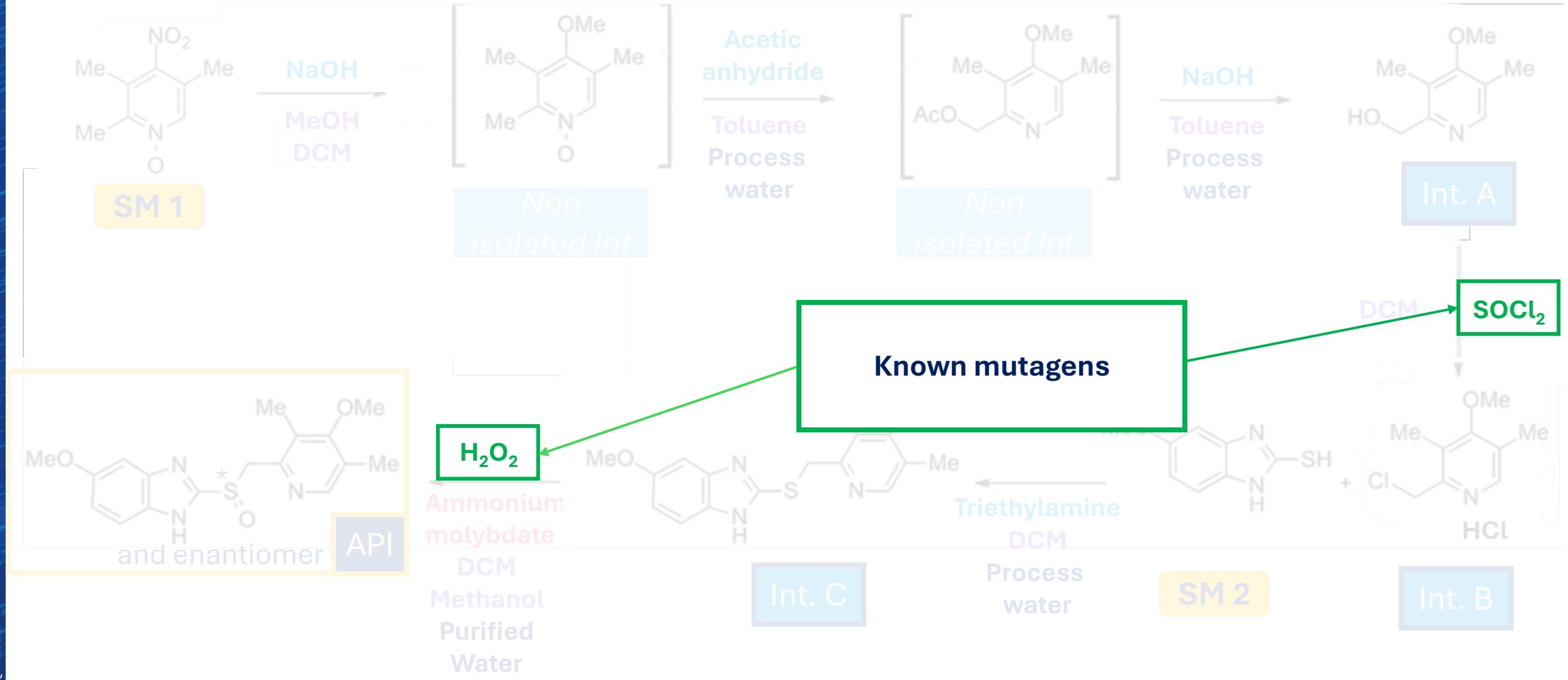
Mutagenic impurities: Case study (fictitious)

1) Active substance assessment for mutagenic impurities



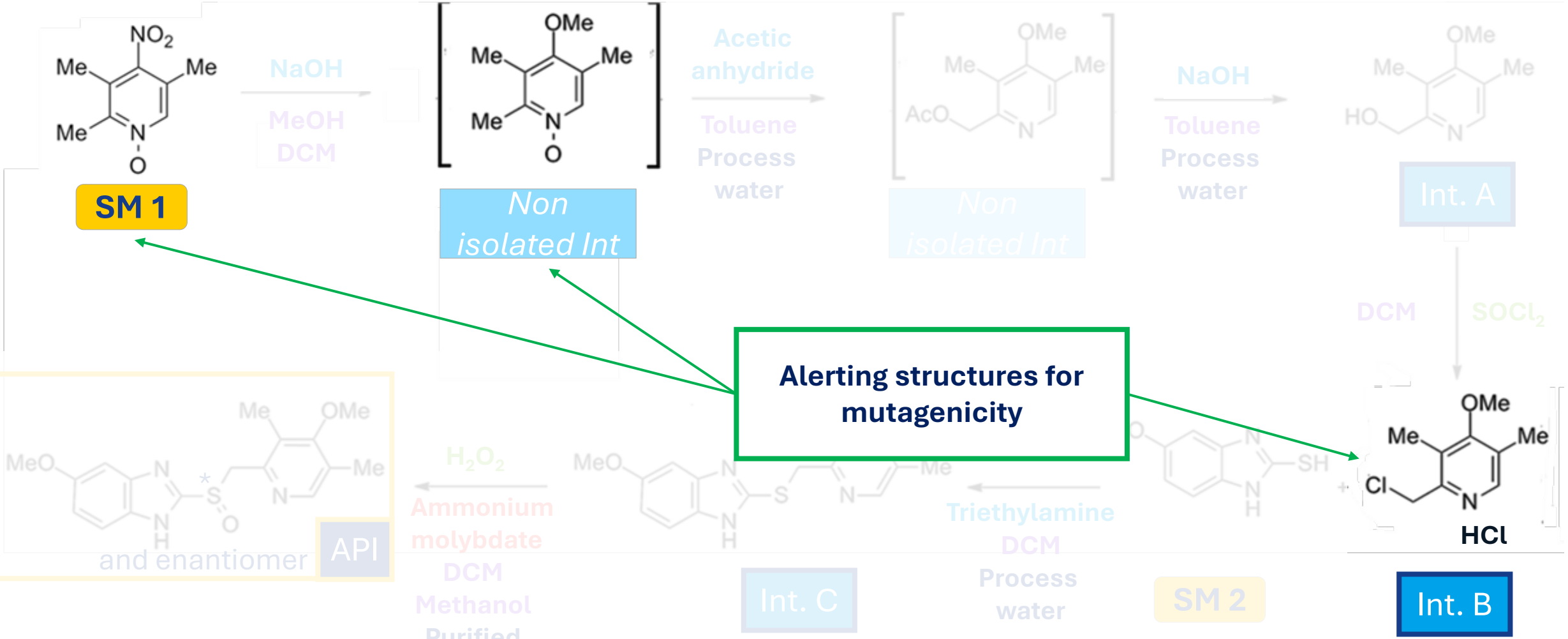
Mutagenic impurities: Case study (fictitious)

1) Active substance assessment for mutagenic impurities



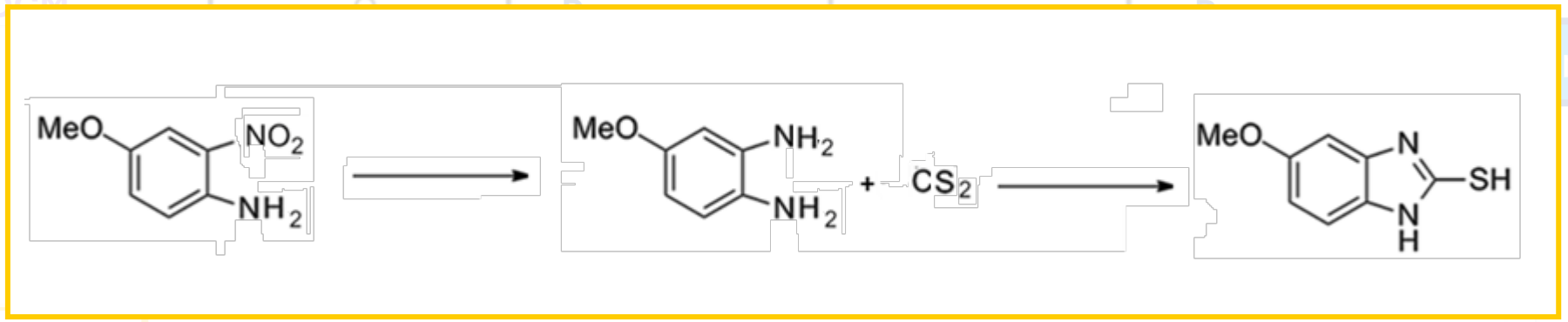
Mutagenic impurities: Case study (fictitious)

1) Active substance assessment for mutagenic impurities



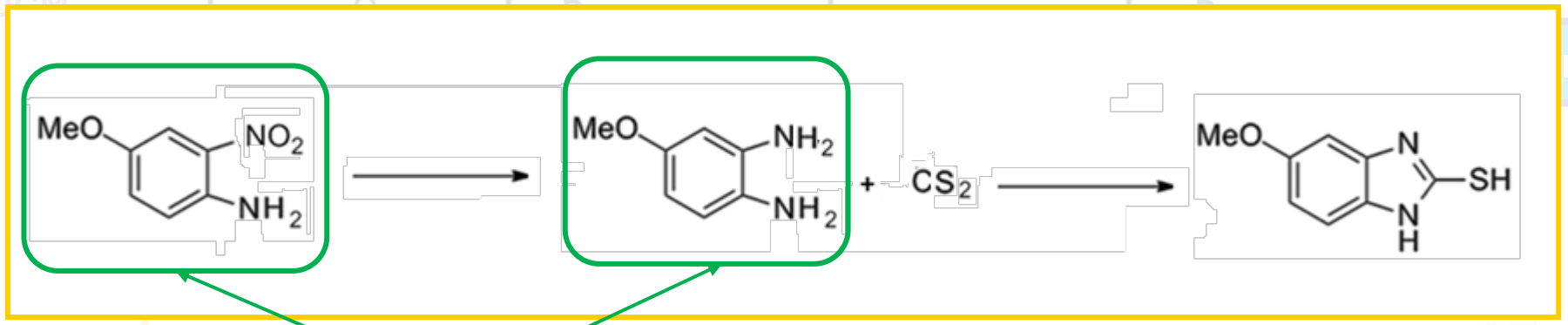
Mutagenic impurities: Case study (fictitious)

1) Active substance assessment for mutagenic impurities



Mutagenic impurities: Case study (fictitious)

1) Active substance assessment for mutagenic impurities



Alerting structures for mutagenicity

Mutagenic impurities: Case study (fictitious)

2) Hazard assessment and classification as per ICH M7

Impurity	Origin	Hazard assessment	Class
Thionyl chloride	2	Known mutagenic carcinogen. Database / literature data, ICH M7.	Class 1
Hydrogen peroxide	**4**	Known mutagenic carcinogen. Database / literature data, ICH M7	Class 1
SM1	1	Nitro aromatic alerting structure → ***In-vitro bacterial mutagenicity assay (e.g. AMES test). Positive. Mutagenic***	**Class 2**
In-situ intermediate	1	N-oxide alerting structure. → ***(Q)SAR study: Inconclusive outcome (positive and negative).***	**Class 3**
Intermediate B	2	Alkyl chloride alerting structure. → ***In-vitro bacterial mutagenicity assay (e.g. AMES test). Negative. Non-mutagenic.***	**Class 5**
Precursor 1 SM2	SM2	Nitro aromatic alerting structure → ***(Q)SAR study & Expert review: Negative. Non-mutagenic.***	**Class 5**
Precursor 2 SM2	SM2	Diamine alerting structure → ***(Q)SAR study: Positive outcome from 2 methodologies.***	**Class 3**

Mutagenic impurities: Case study (fictitious)

3) Setting acceptable limits and propose a control strategy

Impurity	Classification	Control as per ICH M7	Justification
Thionyl chloride	Class 1	?	?
Hydrogen peroxide	Class 1	?	?
SM1	Class 2	?	?
In-situ intermediate	Class 3	?	?
Precursor SM2	Class 3	?	?

$$\textbf{Acceptable limit (ppm)} = \frac{\textbf{PDE} \text{ (µg/day)}}{\textbf{MDD} \text{ (g/day)}}$$

Information regarding the substance:

→ MDD: 40 mg/d

→ Route of administration: Oral

→ Treatment duration: >10 years to lifetime

Mutagenic impurities: Case study (fictitious)

3) Setting acceptable limits and propose a control strategy

Impurity	Classification	Control as per ICH M7	Justification
Thionyl chloride	Class 1	**Option 4**	Reactivity: Highly reactive with water
Hydrogen peroxide	Class 1	**?**	**?**
SM1	Class 2	**?**	**?**
In-situ intermediate	Class 3	**?**	**?**
Precursor SM2	Class 3	**?**	**?**

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

Information regarding the substance:

→ MDD: 40 mg/d

→ Route of administration: Oral

→ Treatment duration: >10 years to lifetime

Mutagenic impurities: Case study (fictitious)

3) Setting acceptable limits and propose a control strategy

Impurity	Classification	Control as per ICH M7	Justification
Thionyl chloride	Class 1	Option 4	Reactivity: Highly reactive with water
Hydrogen peroxide	Class 1	?	?
SM1	Class 2	?	?
In-situ intermediate	Class 3	?	?
Precursor SM2	Class 3	?	?

$$H_2O_2 \text{ Acceptable limit (ppm)} = \frac{68{,}000 \text{ (µg/day)}}{0.040 \text{ (g/day)}} = 170\%$$

H_2O_2 to be limited at **NMT 0.5%** (>ICH Q3A treshold)
→ **Option 4 control strategy proposed**

Acceptable intakes (AIs) or Permissible Daily Exposures (PDEs)

Compound	CAS#	Chemical Structure	AI or PDE (µg/day)	Comment
Hydrogen peroxide	7722-84-1	HO–OH	68,000 or 0.5%, whichever is lower	68 mg/day is 1% of estimated endogenous production

Mutagenic impurities: Case study (fictitious)

3) Setting acceptable limits and propose a control strategy

Impurity	Classification	Control as per ICH M7	Justification
Thionyl chloride	Class 1	Option 4	Reactivity: Highly reactive with water
Hydrogen peroxide	Class 1	**Option 4**	Understanding of purge + Carry-over data
SM1	Class 2	**?**	**?**
In-situ intermediate	Class 3	**?**	**?**
Precursor SM2	Class 3	**?**	**?**

$$\textbf{H}_2\textbf{O}_2\ \textbf{Acceptable limit (ppm)} = \frac{\textbf{68,000}\ (\mu g/day)}{\textbf{0.040}\ (g/day)} = \textbf{170\%}$$

H_2O_2 to be limited at **NMT 0.5%** (>ICH Q3A treshold)
→ **Option 4 control strategy proposed**

Acceptable intakes (AIs) or Permissible Daily Exposures (PDEs)

Compound	CAS#	Chemical Structure	AI or PDE (µg/day)	Comment
Hydrogen peroxide	7722-84-1	HO–OH	68,000 or 0.5%, whichever is lower	68 mg/day is 1% of estimated endogenous production

Justification: Understanding of purge + Carry-over data H_2O_2 not detected (LOD 0.012%) in three API batches (last synthetic step)

Mutagenic impurities: Case study (fictitious)

3) Setting acceptable limits and propose a control strategy

Impurity	Classification	Control as per ICH M7	Justification
Thionyl chloride	Class 1	**Option 4**	Reactivity: Highly reactive with water
Hydrogen peroxide	Class 1	**Option 4**	Understanding of purge + carry-over data
SM1	Class 2	**?**	**?**
In-situ intermediate	Class 3	**?**	**?**
Precursor SM2	Class 3	**?**	**?**

$$\textbf{TTC limit (ppm)} = \frac{\textbf{1.5}\ (\mu g/day)}{\textbf{0.040}\ (g/day)} = \textbf{37.5 ppm}$$

Proposed control:

NMT 30 ppm in the specification for Intermediate A. The SM1 was not detected (LOD 1 ppm) in the API.

ICH M7 option 2 → No further justification needed.

Mutagenic impurities: Case study (fictitious)

3) Setting acceptable limits and propose a control strategy

Impurity	Classification	Control as per ICH M7	Justification
Thionyl chloride	Class 1	**Option 4**	Reactivity: Highly reactive with water
Hydrogen peroxide	Class 1	**Option 4**	Understanding of purge + carry-over data
SM1	Class 2	**Option 2**	**No further justification needed.**
In-situ intermediate	Class 3	**?**	**?**
Precursor SM2	Class 3	**?**	**?**

$$\textbf{TTC limit (ppm)} = \frac{\textbf{1.5}\ (\mu g/day)}{\textbf{0.040}\ (g/day)} = \textbf{37.5 ppm}$$

<u>Proposed control:</u>

NMT 30 ppm in the specification for Intermediate A. The SM1 was not detected (LOD 1 ppm) in the API.

ICH M7 option 2 → No further justification needed.

Mutagenic impurities: Case study (fictitious)

3) Setting acceptable limits and propose a control strategy

Impurity	Classification	Control as per ICH M7	Justification
Thionyl chloride	Class 1	**Option 4**	Reactivity: Highly reactive with water
Hydrogen peroxide	Class 1	**Option 4**	Understanding of purge + carry-over data
SM1	Class 2	**Option 2**	No further justification needed.
In-situ intermediate	Class 3	**?**	**?**
Precursor SM2	Class 3	**?**	**?**

$$\textbf{TTC limit (ppm)} = \frac{\textbf{1.5}\ (\mu g/day)}{\textbf{0.040}\ (g/day)} = \textbf{37.5 ppm}$$

Proposed control:
NMT 0.25% in intermediate A

ICH M7 option 3 → Spike/purge studies

Justification:

a) Spiking Intermediate A with 0.5% of *in-situ* intermediate
Results: Not detected (LOD 0.1 ppm; LOQ 0.9 ppm)
in the final substance by LC-MS

→ **Found <30% of the TTC limit**

b) Carry-over data to the API:
Not detected (LOD 0.1 ppm; LOQ 0.9 ppm) in three batches

→ **Found <30% of the TTC limit**

Mutagenic impurities: Case study (fictitious)

3) Setting acceptable limits and propose a control strategy

Impurity	Classification	Control as per ICH M7	Justification
Thionyl chloride	Class 1	**Option 4**	Reactivity: Highly reactive with water
Hydrogen peroxide	Class 1	**Option 4**	Understanding of purge + carry-over data
SM1	Class 2	**Option 2**	No further justification needed.
In-situ intermediate	Class 3	**Option 3**	Spiking study + Carry-over data
Precursor SM2	Class 3	**?**	**?**

$$\textbf{TTC limit (ppm)} = \frac{\textbf{1.5}\ (\mu g/day)}{\textbf{0.040}\ (g/day)} = \textbf{37.5 ppm}$$

Proposed control:
NMT 0.25% in intermediate A

ICH M7 option 3 → Spike/purge studies

Justification:

a) Spiking Intermediate A with 0.5% of *in-situ* intermediate
Results: Not detected (LOD 0.1 ppm; LOQ 0.9 ppm)
in the final substance by LC-MS

→ **Found <30% of the TTC limit**

b) Carry-over data to the API:
Not detected (LOD 0.1 ppm; LOQ 0.9 ppm) in three batches

→ **Found <30% of the TTC limit**

Mutagenic impurities: Case study (fictitious)

3) Setting acceptable limits and propose a control strategy

Impurity	Classification	Control as per ICH M7	Justification
Thionyl chloride	Class 1	**Option 4**	Reactivity: Highly reactive with water
Hydrogen peroxide	Class 1	**Option 4**	Understanding of purge + carry-over data
SM1	Class 2	**Option 2**	No further justification needed.
In-situ intermediate	Class 3	**Option 3**	Spiking study + Carry-over data
Precursor SM2	Class 3	**?**	**?**

$$\textbf{TTC limit (ppm)} = \frac{\textbf{1.5}\ (\mu g/day)}{\textbf{0.040}\ (g/day)} = \textbf{37.5 ppm}$$

Proposed control:
NMT 0.10% in SM2

ICH M7 option 3 → Spike/purge studies

Justification:

a) Spiking SM2 with 0.15% of precursor 2
Results: Not detected (LOD 1.8 ppm; LOQ 3.0 ppm)
in **Intermediate C** by LC-MS

→ **Found <30% of the TTC limit**

b) Carry-over data :
Not detected (LOD 1.8 ppm; LOQ 3.0 ppm) in **Intermediate C**

→ **Found <30% of the TTC limit**

Mutagenic impurities: Case study (fictitious)

3) Setting acceptable limits and propose a control strategy

Impurity	Classification	Control as per ICH M7	Justification
Thionyl chloride	Class 1	**Option 4**	Reactivity: Highly reactive with water
Hydrogen peroxide	Class 1	**Option 4**	Understanding of purge + carry-over data
SM1	Class 2	**Option 2**	No further justification needed.
In-situ intermediate	Class 3	**Option 3**	Spiking study + Carry-over data
Precursor SM2	Class 3	**Option 3**	Spiking study + Carry-over data

$$\textbf{TTC limit (ppm)} = \frac{\textbf{1.5}\ (\mu g/day)}{\textbf{0.040}\ (g/day)} = \textbf{37.5 ppm}$$

Proposed control:
NMT 0.10% in SM2

ICH M7 option 3 → Spike/purge studies

Justification:

a) Spiking SM2 with 0.15% of precursor 2
Results: Not detected (LOD 1.8 ppm; LOQ 3.0 ppm)
in **Intermediate C** by LC-MS
→ **Found <30% of the TTC limit**

b) Carry-over data :
Not detected (LOD 1.8 ppm; LOQ 3.0 ppm) in **Intermediate C**
→ **Found <30% of the TTC limit**

Mutagenic impurities: Case study (fictitious)

Impurity	Origin	Classification	Control as per ICH M7	Justification
Thionyl chloride	2	Class 1	Option 4	Reactivity: Highly reactive with water
Hydrogen peroxide	**4**	Class 1	Option 4	Understanding of purge + carry-over data
SM1	1	Class 2	Option 2	No further justification needed
In-situ intermediate	1	Class 3	Option 3	Spiking study + Carry-over data
Intermediate B	2	Class 5	***Not applicable***	***Treat as non-mutagenic***
Precursor 1 SM2	SM2	Class 5	***Not applicable***	***Treat as non-mutagenic***
Precursor 2 SM2	SM2	Class 3	*Option 3*	Spiking study + Carry-over data

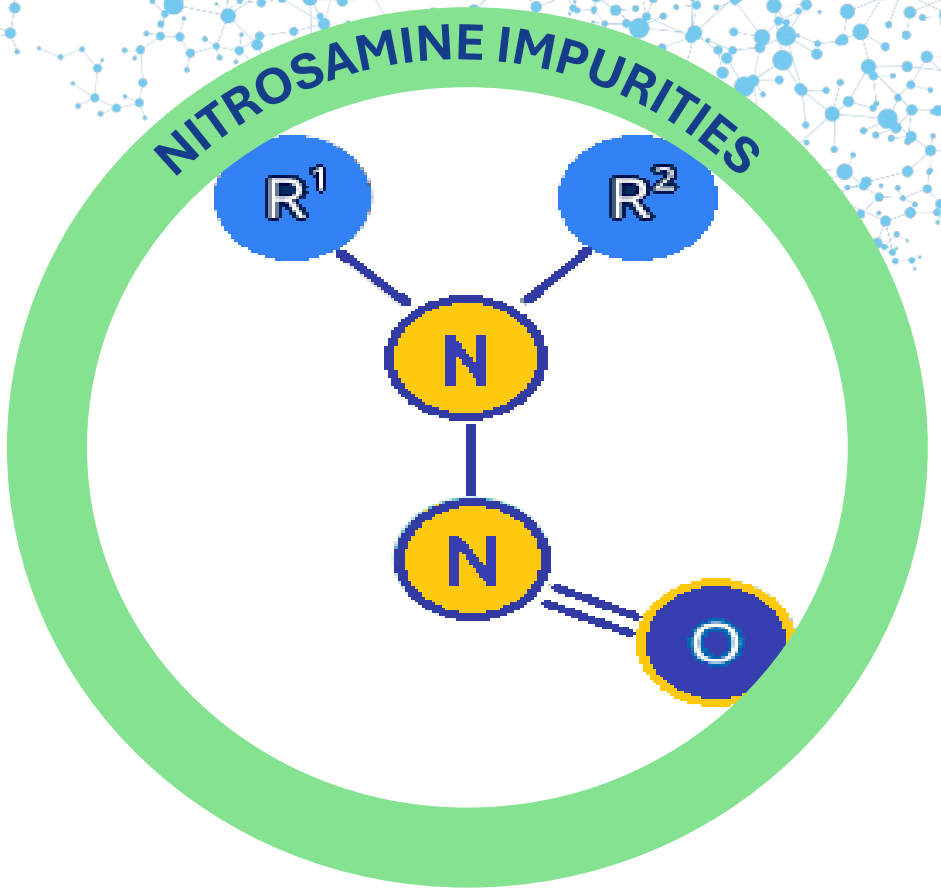
Control strategy and the outcome of discussion to be summarised in section 3.2.S.3.2 – Mutagenic impurities (QSARs data may be provided to support classification as per ICH M7)

Overview of the control strategy

		SM1	Int-A	Int-B	SM2	Int-C	API	Origin, fate and carry over	Limit/Control strategy
SM1	**Precursor A**	0.26%	ND					Precursor SM1. Removed during crystallisation.	Controlled in SM1 at NMT 0.50%.
	Precursor B	0.08%	ND	ND			ND	Precursor SM1. Eliminated in the mother liquor.	Controlled in SM1 at NMT 0.15%.
	3,5-Lutidine	0.24%	ND					By-product,not reactive in the downstream process	Controlled in SM1 at NMT 0.50%, as unsp. in INT-A.
Int-A	**SM1**		11 ppm				ND	Unreacted SM1, mutagenic impurity (Class 2), tested ND (LOD 1 ppm) in API.	Controlled in INT-A at **30 ppm** as per **ICH M7 option 2.**
	4-OMe		0.15%				ND	In-situ intermediate, potential mutagenic impurity (Class 3).	Controlled in Int-A at **NMT 0.25%** as per **ICH M7 option 3** based on spiking and carry-over data.
	4-Cl derivative		0.18%				*Unsp*	By-product, precursor of Ph. Eur. Impurity H	Controlled in Int-A at NMT 0.25%. If carried over,its fate impuirty is controlled as unsp. In the API.
	Acetyl derivative		0.53%	ND				intermediate	Controlled in Int-A at NMT 1.0%, and at NMT 0.25% in Int-B.
Int-B	**INT-A**			0.38%		ND		inated during 2%, ND in Int-C	Controlled in INT-B as specified at **NMT 1.0%**.
	Acetyl derivative			0.18%		ND		In-situ int	Controlled in INT-B as specified at **NMT 0.25%**.
	4-Cl Cl-impurity			0.14%		ND		Process impurity.	Controlled in INT-B as unspecified at **NMT 0.15%**.
SM2	**Precursor 1**				0.13%	ND		Precursor of SM2, discussed as mutagenic impurity (Class 5), absent (<0.05%) in Int-C.	Controlled in SM2 at **NMT 0.30%**.
	Precursor 2				0.06%	ND		Precursor of SM2, potential mutagenic impurity (Class 3), ND (LOD 1.8 ppm) in Int-C	Controlled in SM2 at **NMT 0.10% as per ICH M7 option 3,** based on spiking and carry-over data.
Int-C	**INT-B**					0.17%	*Unsp*	Int. carried in Int-C. Eliminated during crystallization of API. Found <0.05% in the API.	Controlled in INT-C as specified at **NMT 0.40%** and as unspec. impurity in API.
	Ph. Eur. Imp A (SM2)					0.38%	*Unsp*	Unreacted SM2, removed during crystallisation.	Controlled in Int-C as specified at **NMT 0.50%**, in API as unspecified impurity.
	RRT 1.10					0.12%	*Unsp*	Unidentified impurity, found 0.05-0.13% in the API.	Controlled in Int-C at **NMT 0.20%**, in API as unspec. impurity.

Can be included in the Quality Overall Summary

- Related Substances (Organic impurities)
- Mutagenic impurities
- **Nitrosamine impurities**
- Residual solvents
- Elemental impurities
- Inorganic impurities



Nitrosamine impurities

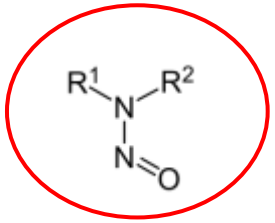
ICH M7 : structural groups identified to be of such high potency that intakes even below the TTC would theoretically be associated with a potential for a significant carcinogenic risk. This group is referred to as the "cohort of concern", comprises aflatoxin-like-, N-nitroso-, and alkyl-azoxy compounds.

Specific references for nitrosamine impurities:

→ Ph. Eur. 2.5.42

→ EMA assessment report of the CHMP's Article 5(3) of Regulation (EC) No 726/2004 opinion on nitrosamine impurities in human medicinal products (EMA/369136/2020): General guidance

→ Corresponding Q&A document:



Questions and answers document (EMA/409815/2020)

- **Appendix 1**: Acceptable intakes established for N-nitrosamines
- **Appendix 2**: Carcinogenic Potency Categorisation Approach for N-nitrosamines
- **Appendix 3:** Enhanced AMES test conditions for N-nitrosamines

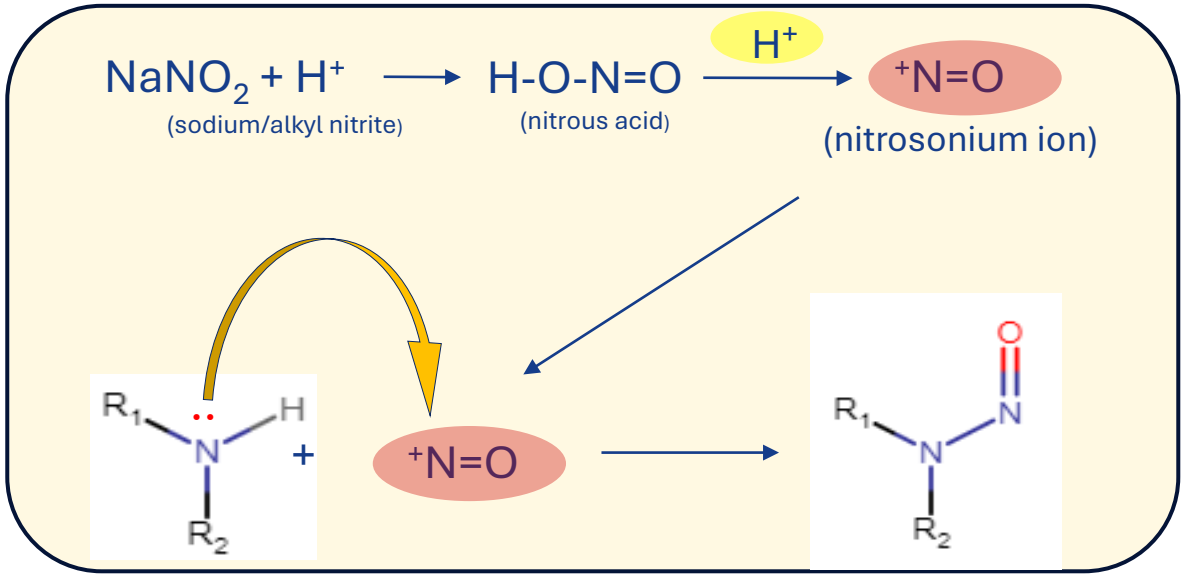
Risk assessment in CEP dossiers – EMA Principles

Step I | Step II | Step III

Comprehensive risk assessment

Nitrosating agent + secondary/tertiary amine + favourable conditions

- Manufacturing process conditions (same synthetic step or in different steps)
- Contaminated starting materials, intermediates, recovered or recycled materials, cross-contamination
- Degradation of API, intermediates, reagents or solvents etc.



***Special attention for the potential formation of nitroso-API (containing secondary amine + favourable conditions or if a risk is known i.e. reported in appendix 1). Case-by-case.**

Same principles to be used for Veterinary products

Risk assessment in CEP dossiers – EMA Principles

Step I

Risk identified? If yes →

Step II

Step III

Comprehensive risk assessment

Nitrosating agent + secondary/tertiary amine + favourable conditions

- Manufacturing process conditions (same synthetic step or in different steps)
- Contaminated starting materials, intermediates, recovered or recycled materials, cross-contamination
- Degradation of API, intermediates, reagents or solvents etc.

Perform confirmatory testing

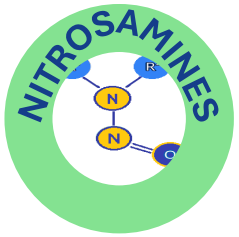
To confirm or refute the presence of nitrosamines

- Omission of control justified only if levels found are below 10% of the acceptable limit
- Using a suitably validated analytical procedure with adequate LOQ (description and full validation data should be provided)

Analytical procedure should be **sufficiently sensitive**:
the LOQ should **be ≤ 10%** of the acceptable limit to omit a control in the API

Same principles to be used for Veterinary products

Risk assessment in CEP dossiers – EMA Principles



Step I → *Risk identified? If yes →* **Step II** → *Presence confirmed? If yes →* **Step III**

Comprehensive risk assessment

Nitrosating agent + secondary/tertiary amine + favourable conditions

- Manufacturing process conditions (same synthetic step or in different steps)
- Contaminated starting materials, intermediates, recovered or recycled materials, cross-contamination
- Degradation of API, intermediates, reagents or solvents etc.

Perform confirmatory testing

To confirm or refute the presence of nitrosamines

- Omission of control justified only if levels found are below 10% of the acceptable limit,
- Using a suitably validated analytical procedure with adequate LOQ (description and full validation data should be provided)

Control strategy

In case levels of nitrosamine impurity is found above 10% of the acceptable limit

- Control at the acceptable limit in the final substance
- Root cause analysis to be performed
- Implement effective risk mitigating measures – CAPA (e.g. changes in manufacturing process)

Same principles to be used for Veterinary products

Nitrosamine impurities – Acceptable limit

How to define an acceptable limit for a nitrosamine impurity?

Questions and answers document (EMA/409815/2020 Rev.21)

Appendix 1:
Acceptable intakes established for N-nitrosamines

Summarizes **specific acceptable intake (AI)** for a specific nitrosamine to be used for limit calculation

Appendix 2:
Carcinogenic Potency Categorisation Appraoch for N-nitrosamines

Describes "CPCA" approach to **find the acceptable intake (AI)** to be applied for the limit calculation

Appendix 3:
Enhanced AMES test conditions for N-nitrosamines

Calculation of applicable limit:

$$\textbf{Acceptable limit (ppm)} = \frac{\textbf{AI} \text{ (ng/day)}}{\textbf{MDD} \text{ (mg/day)}}$$

Nitrosamine impurities – *Key point*

The EDQM relies on the EMA Q&A for the assessment of the risk nitrosamine impurities.

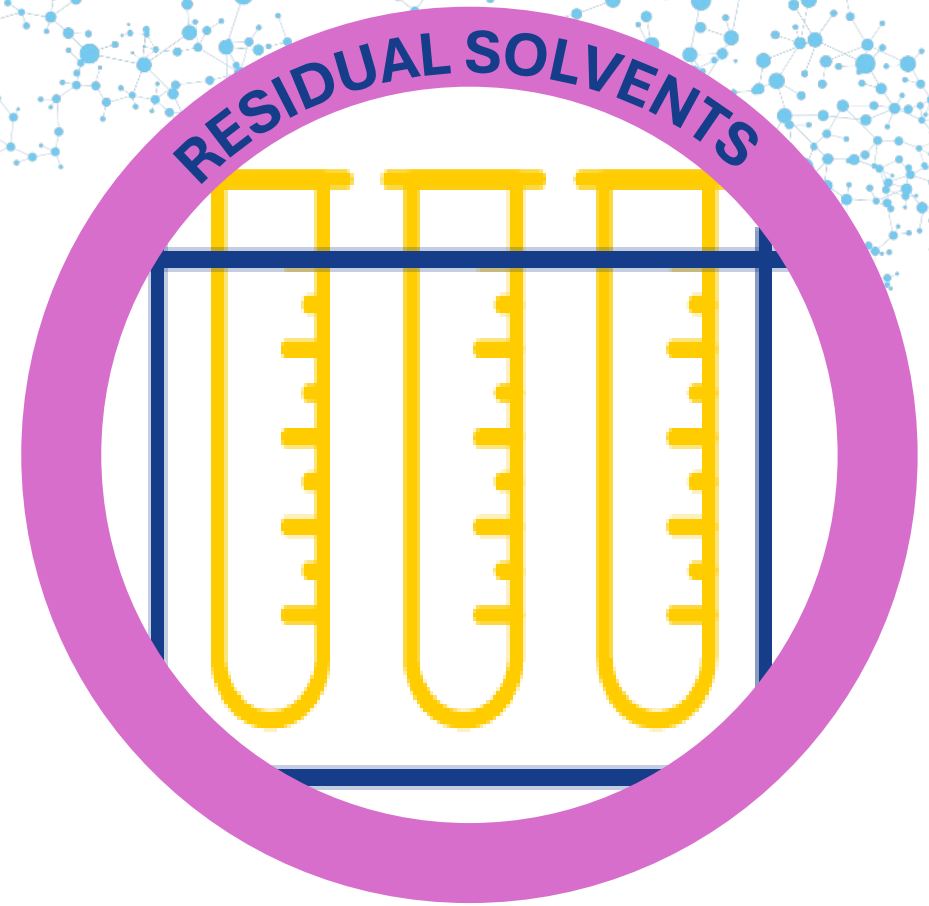
Frequent revision of the Q&A or its corresponding appendixes:

- Specific acceptable intakes (AI) for nitrosamines may be updated following toxicological assessment (e.g. Bacterial Reverse Mutation Test, in vivo studies etc.)
- Additional nitrosamine impurities are frequently newly included in appendix 1.

⟶ **CEP holders are expected to perform the risk assessment for nitrosamine impurities, and if relevant propose a control strategy according to most recent EU requirements.**

Risk assessment to be included in 3.2.S.3.2 – Nitrosamine impurities

- ★Related Substances (Organic impurities)
- ★Mutagenic impurities
- ★Nitrosamine impurities
- ★**Residual solvents**
- ★Elemental impurities
- ★Inorganic impurities



Residual solvents

- **ICH Q3C / Ph.Eur. 5.4** classification and recommended limits
- **CPMP/QWP/450/03 -Rev.1 (Annex I)**

ICH Class 1 solvent
(as contaminants of other solvents)

Solvents to be avoided, usually contaminants of solvents (e.g. benzene is a potential contaminant of acetone, toluene, methanol,...)

Control needed in the API unless...

Option 1

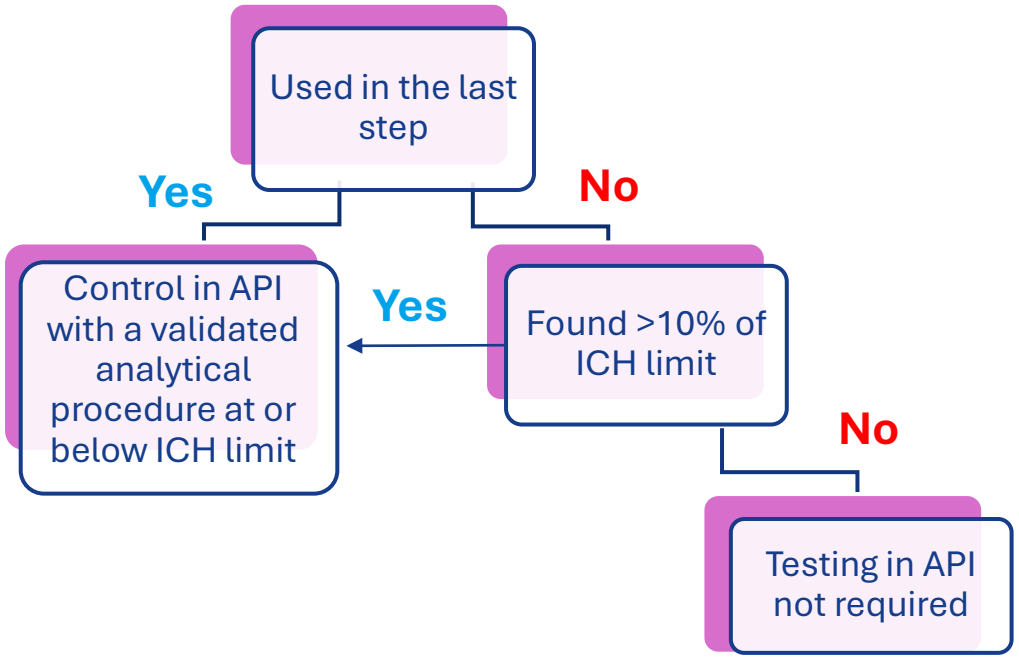
- Limit in originator solvent ensuring class 1 solvent in the API <30% ICH limit based on a rationale.

Option 2

- Demonstrated < 30% ICH limit in intermediate or API by a validated analytical procedure on 3 consecutive batches (or 6 pilot batches).

ICH Class 2 solvent
(solvents to be limited)

Control needed in the API if...

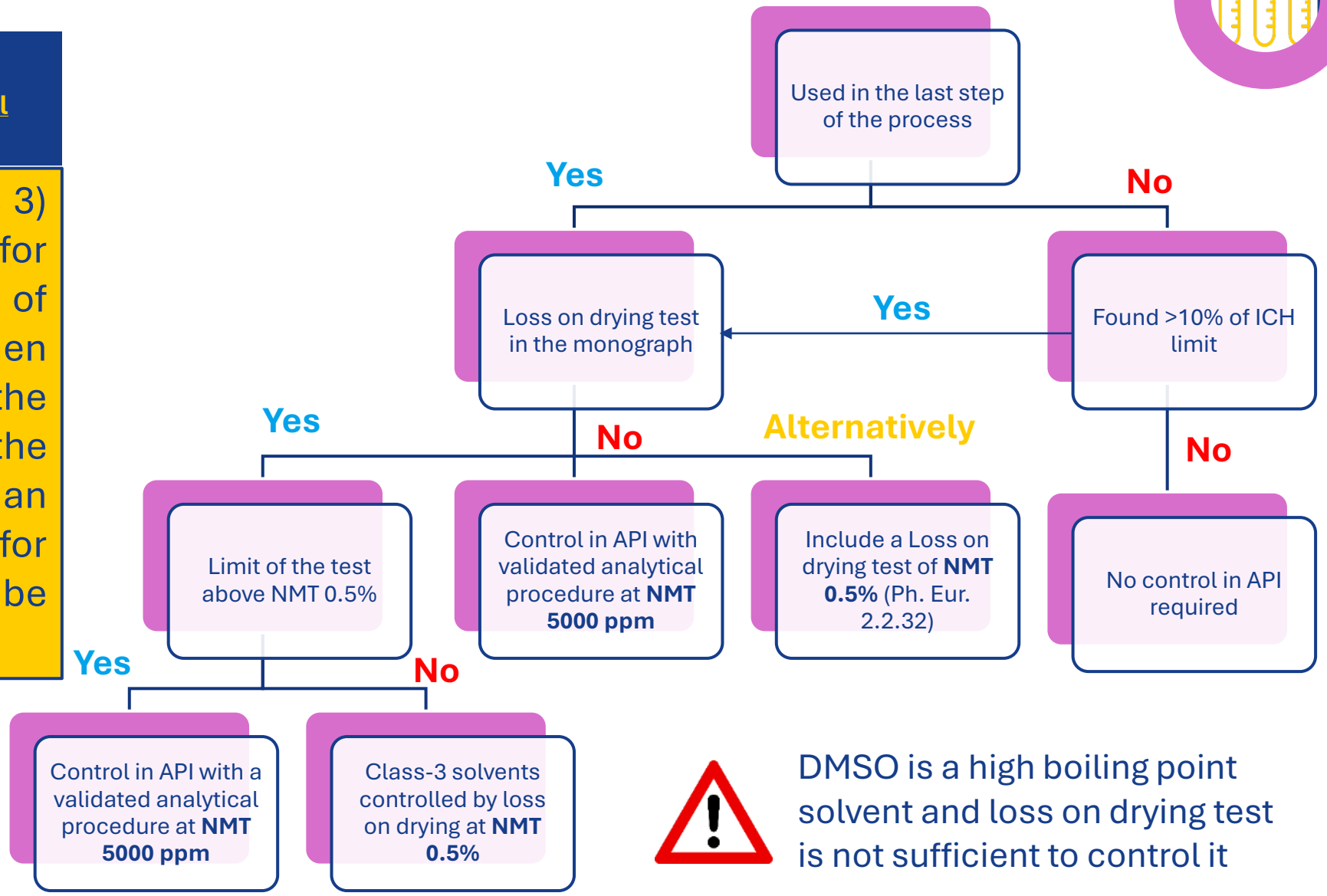


Non-classified ICH Q3C Solvents: toxicological justification for any proposed limit.

Class 3 solvents & Certification Procedure

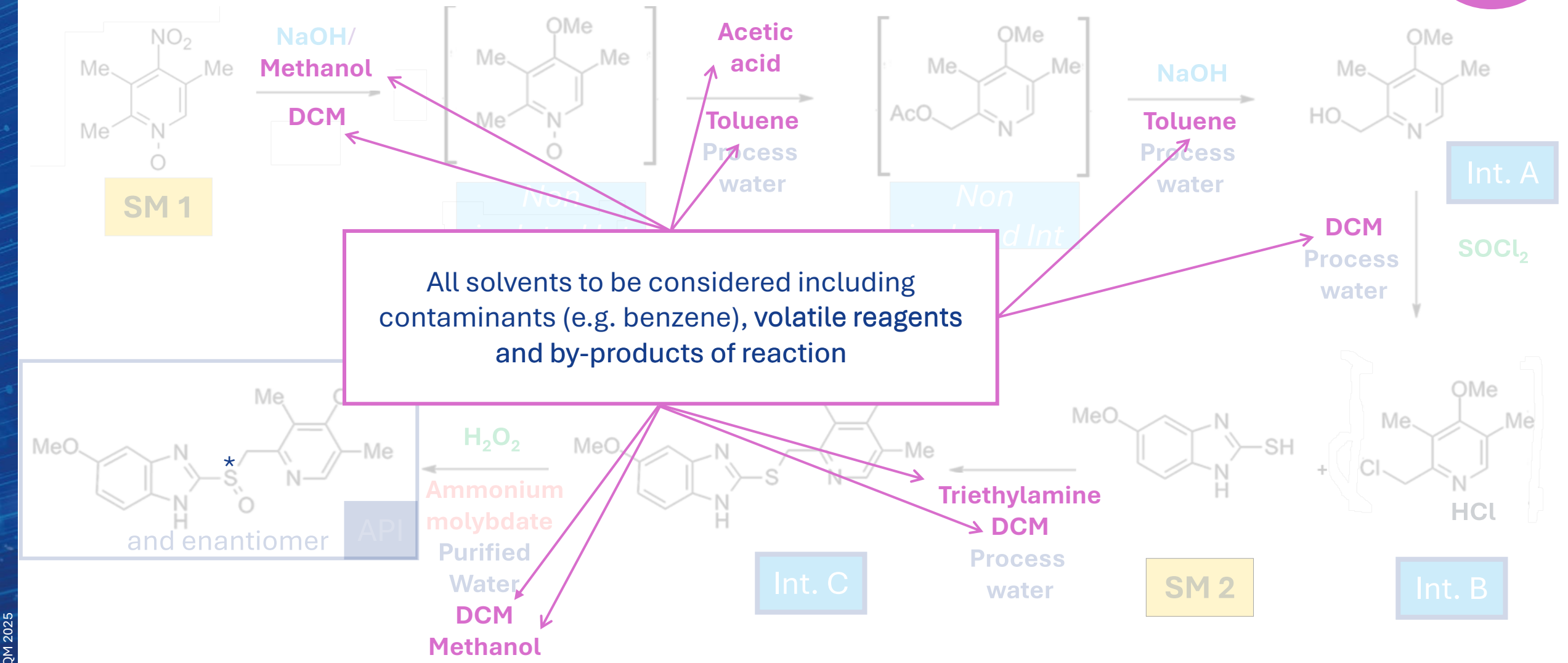
PA/PH/CEP (04) 1, 7R :
Content of the dossier for chemical purity and microbiological quality

Low toxicity solvents (Class 3) can be limited by a test for loss on drying with a limit of not more than 0.5%, when appropriate. If the limit of the loss on drying test of the monograph is higher than 0.5%, then a specific test for residual solvents should be introduced.



DMSO is a high boiling point solvent and loss on drying test is not sufficient to control it

Case study (fictitious)



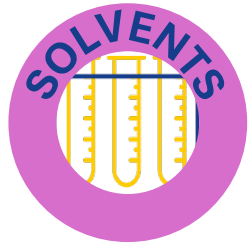
Case study : Which specifications?

Solvent	Used in stage X / 4	ICH classification	Typical levels in API	LOD (ppm)	Limit in API
Methanol	Stages 1 & **4**	Class 2 NMT 3000 ppm	88 – 184 ppm	7	?
Toluene	Stage 1	Class 2 NMT 890 ppm	BDL	16	?
Dichloromethane	Stages 2, 3 & **4**	Class 2 NMT 600 ppm	54 – 102 ppm	54	?
Acetic acid	Stage 1	Class 3 NMT 5000 ppm	BDL	6	?
Triethylamine	Stage 3	Class 3 NMT 5000 ppm	ND – 16 ppm	12	?
Benzene	As contaminant	Class 1 NMT 2 ppm	BDL	0.5	?

Data obtained from controls in intermediates may also be used to show absence.

Testing using GC analytical procedures (or other suitable) validated in line with ICH Q2 (R2).

Case study : Which specifications?



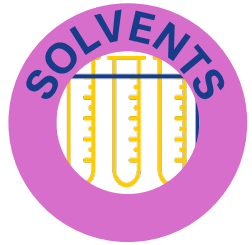
Solvent	Used in stage X / 4	ICH classification	Typical levels in API	LOD (ppm)	Limit in API
Methanol	Stages 1 & **4**	Class 2 NMT 3000 ppm	88 – 184 ppm	7	?
Toluene	Stage 1	**Class 2** NMT 890 ppm	**BDL**	16	✖
Dichloromethane	Stages 2, 3 & **4**	Class 2 NMT 600 ppm	54 – 102 ppm	54	?
Acetic acid	Stage 1	**Class 3** NMT 5000 ppm	**BDL**	6	✖
Triethylamine	Stage 3	**Class 3** NMT 5000 ppm	**ND – 16 ppm**	12	✖
Benzene	As contaminant	Class 1 NMT 2 ppm	BDL	0.5	?

<10%ICH, not used last step

No control in the API requested

Testing using GC analytical procedures (or other suitable) validated in line with ICH Q2 (R2).

Case study : Which specifications?



Solvent	Used in stage X / 4	ICH classification	Typical levels in API	LOD (ppm)	Limit in API
Methanol	Stages 1 & **4**	**Class 2** NMT 3000 ppm	**188 – 1284 ppm**	7	?
Toluene	Stage 1	Class 2 NMT 890 ppm	BDL	16	-
Dichloromethane	Stages 2, 3 & **4**	**Class 2** NMT 600 ppm	**54 – 102 ppm**	54	?
Acetic acid	Stage 1	Class 3 NMT 5000 ppm	BDL	6	-
Triethylamine	Stage 3	Class 3 NMT 5000 ppm	ND – 16 ppm	12	-
Benzene	As contaminant	Class 1 NMT 2 ppm	BDL	0.5	?

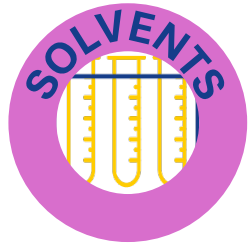
Used in the last step, Class 2 solvents

⇩

Control in API using a validated analytical analytical procedure

Testing using GC analytical procedures (or other suitable) validated in line with ICH Q2 (R2).

Case study : Which specifications?



Solvent	Used in stage X / 4	ICH classification	Typical levels in API	LOD (ppm)	Limit in API
Methanol	Stages 1 & **4**	**Class 2** NMT 3000 ppm	**188 – 1284 ppm**	7	**NMT 3000 ppm**
Toluene	Stage 1	Class 2 NMT 890 ppm	BDL	16	-
Dichloromethane	Stages 2, 3 & **4**	**Class 2** NMT 600 ppm	**54 – 102 ppm**	54	**NMT 600 ppm**
Acetic acid	Stage 1	Class 3 NMT 5000 ppm	BDL	6	-
Triethylamine	Stage 3	Class 3 NMT 5000 ppm	ND – 16 ppm	12	-
Benzene	As contaminant	Class 1 NMT 2 ppm	BDL	0.5	?

Used in the last step, Class 2 solvents

⇩

Control in API using a validated analytical analytical procedure

⇩

Specification limit according to ICH Q3C

Testing using GC analytical procedures (or other suitable) validated in line with ICH Q2 (R2).

Case study : Which specifications?

Solvent	Used in stage X / 4	ICH classification	Typical levels in API	LOD (ppm)	Limit in API
Methanol	Stages 1 & 4	Class 2 NMT 3000 ppm	188 – 1284 ppm	7	NMT 3000ppm
Toluene	Stage 1	Class 2 NMT 890 ppm	BDL	16	-
Dichloromethane	Stages 2, 3 & 4	Class 2 NMT 600 ppm	54 – 102 ppm	54	NMT 600ppm
Acetic acid	Stage 1	Class 3 NMT 5000 ppm	BDL	6	-
Triethylamine	Stage 3	Class 3 NMT 5000 ppm	ND – 16 ppm	12	-
Benzene	As contaminant	**Class 1** NMT 2 ppm	**BDL**	**0.5**	✖

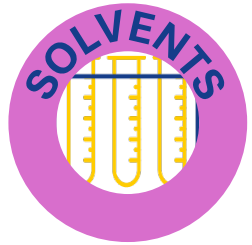
No control in API requested

⇧

Class 1 solvent as contaminant, <30% ICH limit

Testing using GC analytical procedures (or other suitable) validated in line with ICH Q2 (R2).

Specification of the active substance



Solvent	ICH classification	Limit in API	
Methanol	Class 2 NMT 3000 ppm	NMT 3000 ppm	*Used in the last step*
Dichloromethane	Class 2 NMT 600 ppm	NMT 600 ppm	*Used in the last step*

If other solvents are included in section 3.2.S.4.1, it will be transparent on the CEP and the analytical procedure(s) used to detect them will be appended to the CEP.

Exercise to be summarised in section 3.2.S.3.2 - Residual solvents

- Related Substances (Organic impurities)
- Mutagenic impurities
- Nitrosamine impurities
- Residual solvents
- **Elemental impurities**
- Inorganic impurities

Elemental impurities: references and control strategy

ICH Q3D

- Covers **24** elements classified as : Class-1, Class-2A, Class-2B and Class-3
- Gives permitted daily exposure (PDE) according to the route of administration.

PA/PH/CEP (16) 23, 2R

- Risk assessment requirements to control elemental impurities
- Component Approach as per ICH Q3D (contribution of each component is identified, evaluated and summarized)

The control strategy should focus on presence or absence of elemental impurities in the API

Presence in API of intentionally added elemental impurity :

- a justified **specification** should be applied
- Analytical procedure(s) should be described in 3.2.S.4.2, validation in line with ICH Q2(R2)

Absence in the API of intentionally added elemental impurity i.e. purged to a level consistently **below 30% of the defined limit** :

- the indicated **route of administration**
- the ICH Q3D **option 1** (API daily intake of NMT 10g) or **option 2a** when justified,
- Analytical procedure identified (ICP/MS, ICP/OES,...), at least sensitivity (**LOD/LOQ**) to be provided

If elemental impurities are introduced in the ***last synthetic step***, specification limit in the API is usually expected

Implementation of ICH Q3D in the CEP procedure

Two possible approaches :

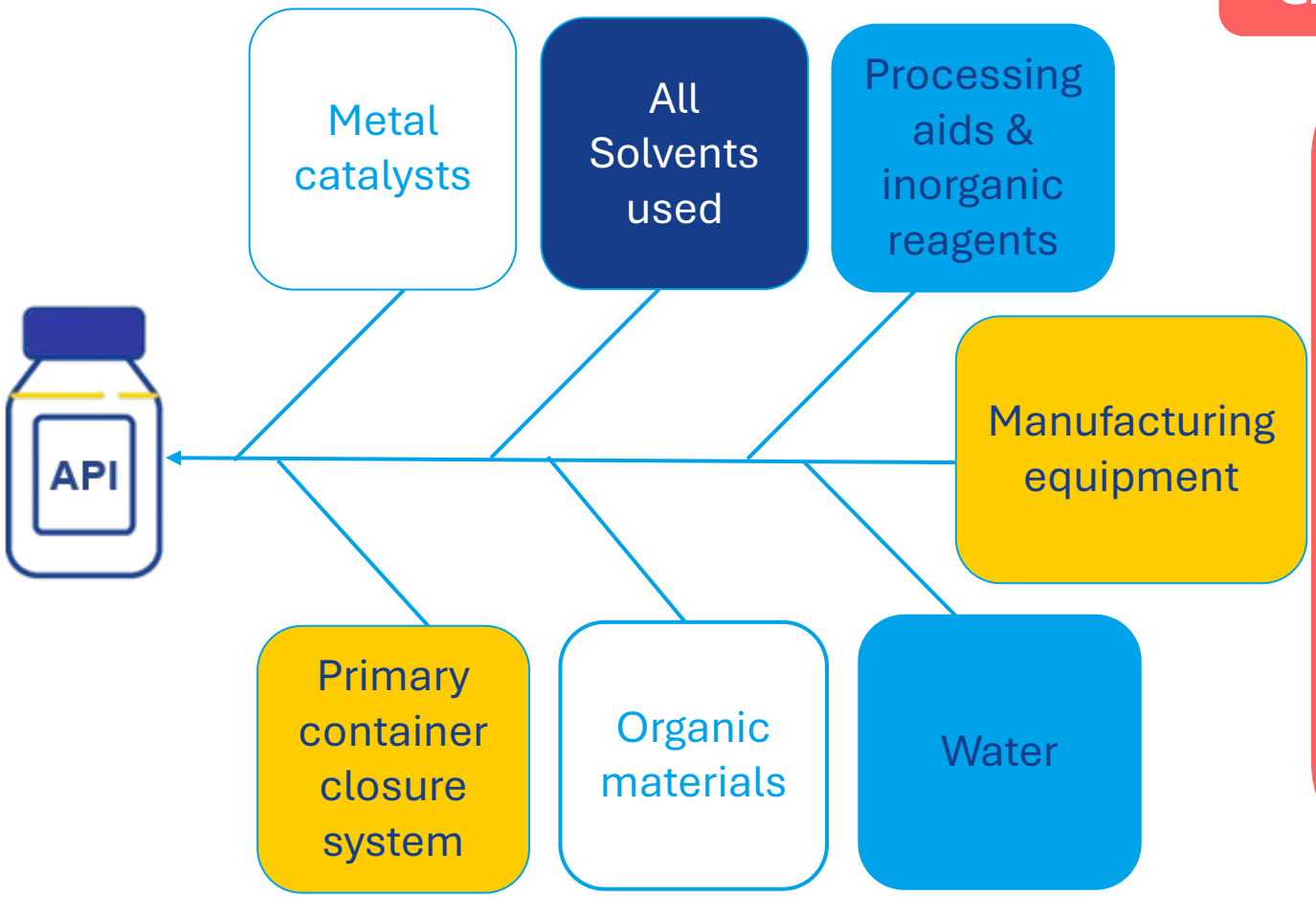
No Risk management summary is prepared.

- ★ **Any elemental impurity** used after the introduction of the SMs should be declared and will be **reported on the CEP**
- ★ If introduced in the **last synthetic step**, a **control** in the specification of the **API** should be included unless otherwise justified (e.g. levels below 30% of ICH Q3D limit)
- ★ If controlled in the final API, validation of the analytical procedure according to ICH Q2 (R2) should be provided and the **analytical procedure** will be **appended** to the CEP
- ★ If **no elemental impurity** is intentionally added, this will be reported on the CEP.

Implementation of ICH Q3D in the CEP procedure

Two possible approaches :

A Risk management summary for elemental impurities (RMS) is prepared:



- ★ Besides the intentionally added elements, the assessment should also cover all other potential elemental impurities from other sources
- ★ Risk Management Summary **report** should detail the rationale of the study:
  - ★ **why** impurities are considered
  - ★ **justify** the chosen control strategy
  - ★ intended **route of administration**
- ★ To be completed with a **RMS table** → intended to be **annexed** to the CEP

⚠ Batch screening data do not replace a risk management summary

Implementation of ICH Q3D in the CEP procedure

Two possible approaches :

No Risk management summary is prepared.

- **Any elemental impurity** after the introduction of the SMs should be declared and will be reported on the CEP
- If introduced in the **last synthetic step**, a **control** in the specification of the **API** should be included unless otherwise justified (levels below 30% of ICH Q3D limit)
- If control in the final API, validation of the analytical procedure according to ICH Q2 (R2) should be provided and the **analytical procedure** will be **appended** to the CEP
- If **no elemental impurity** is intentionally added, this will be reported on the CEP.

A Risk management summary for elemental impurities (RMS) is prepared:

- Besides the intentionally added element, the assessment should also cover all potential elemental impurities from sources
- Risk Management Summary should detail the rationale of:
  - **why** impurities considered
  - **justify** the control strategy
  - **route of administration**
- To be completed with a **RMS table** → to be annexed to the CEP

Option encouraged by EDQM = facilitates risk assessment for medicinal product

⚠ Such screening data do not replace a risk management summary

RMS/no-RMS : *Any limit for EI in the API **proposed** by the applicant will be transparent on the CEP in the specification.*

RMS approach:

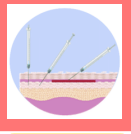
Elements to be considered:

Elemental impurities derived from intentionally added catalysts and inorganic reagents whatever the route of administration

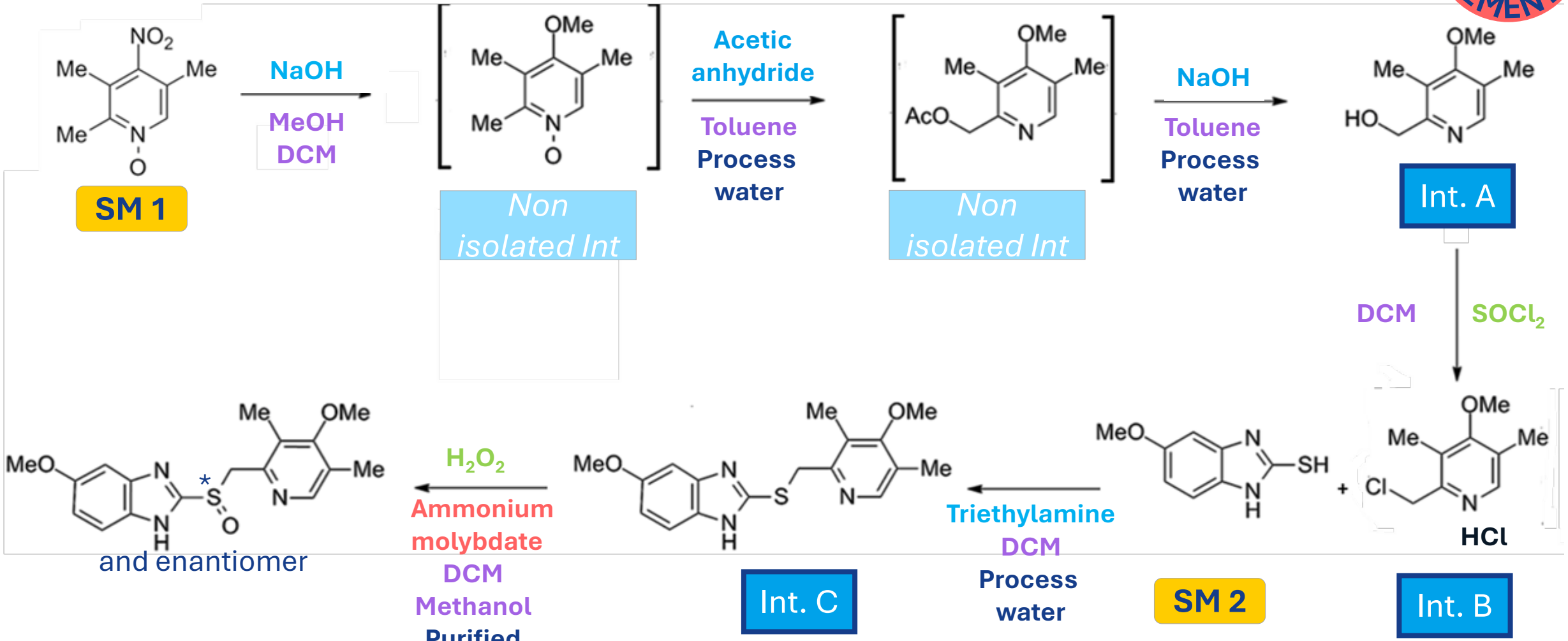
Potential elemental impurities not intentionally added depending on the route of administration

Potential elemental impurities derived from manufacturing equipment, water, leached from container closure system…

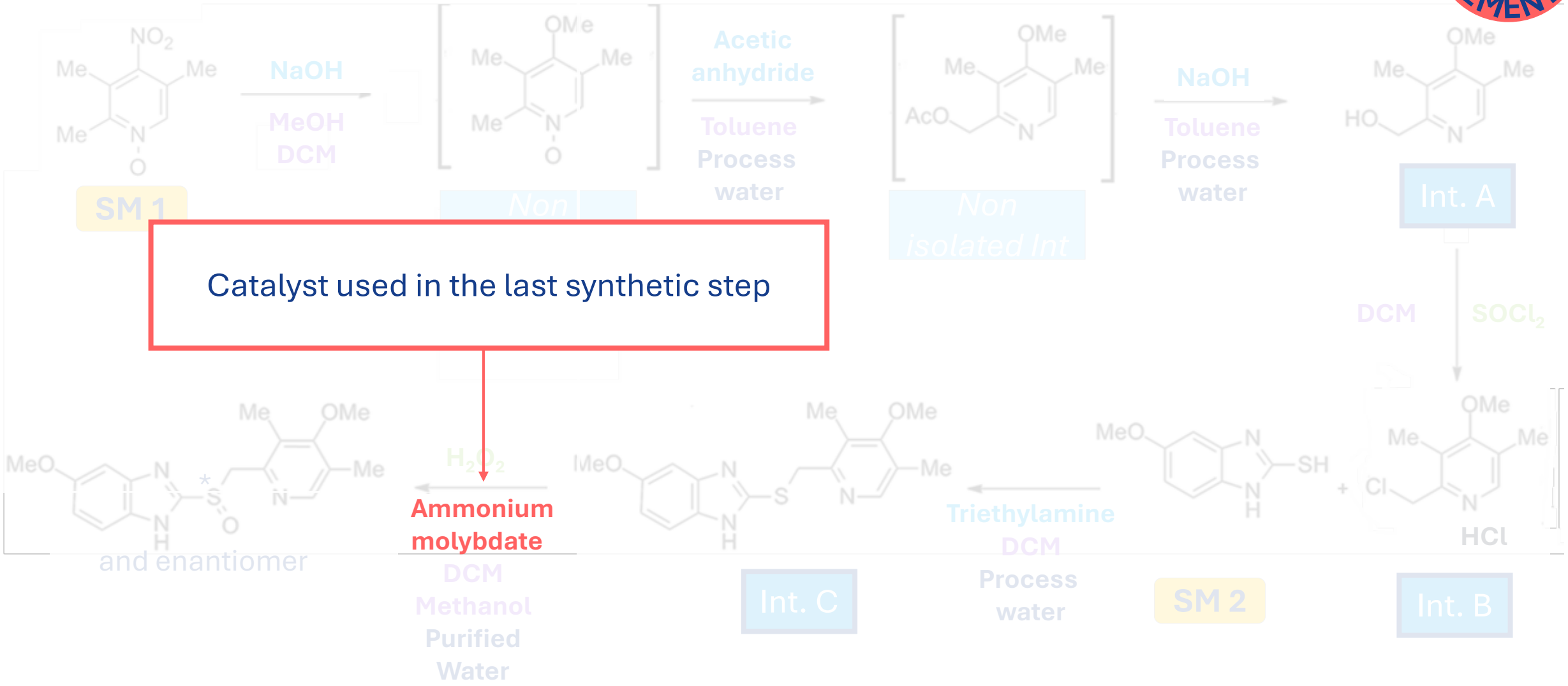
⚠ When multiple routes of administration possible for an API, the **worst-case scenario** has to be considered

Element	Class	If intentionally added (all routes)	If not intentionally added			
			Oral 	Parenteral 	Inhalation 	Topical 
Cd	1	Yes	Yes	Yes	Yes	Yes
Pb	1	Yes	Yes	Yes	Yes	Yes
As	1	Yes	Yes	Yes	Yes	Yes
Hg	1	Yes	Yes	Yes	Yes	Yes
Co	2A	Yes	Yes	Yes	Yes	Yes
V	2A	Yes	Yes	Yes	Yes	Yes
Ni	2A	Yes	Yes	Yes	Yes	Yes
Tl	2B	Yes	No	No	No	No
Au	2B	Yes	No	No	No	No
Pd	2B	Yes	No	No	No	No
Ir	2B	Yes	No	No	No	No
Os	2B	Yes	No	No	No	No
Rh	2B	Yes	No	No	No	No
Ru	2B	Yes	No	No	No	No
Se	2B	Yes	No	No	No	No
Ag	2B	Yes	No	No	No	No
Pt	2B	Yes	No	No	No	No
Li	3	Yes	No	Yes	Yes	No
Sb	3	Yes	No	Yes	Yes	No
Ba	3	Yes	No	No	Yes	No
Mo	3	Yes	No	No	Yes	No
Cu	3	Yes	No	Yes	Yes	No
Sn	3	Yes	No	No	Yes	No
Cr	3	Yes	No	No	Yes	No

Case study (fictitious): Omeprazole



Case study (fictitious): Omeprazole



Moreover, **Chromium** has been considered as coming from the equipment used

RMS Table included in section 3.2.S.3.2

Impurity	Limit	Batch data	Origin
Chromium	300 ppm	< 10 ppm	Equipment
Molybdenum	1100 ppm	< 100 ppm	Catalyst in the last step

- Option 1 limit for oral administration

The control strategy followed should be clear and mentioned on the RMS:

- « **Absent** » should be defined (e.g. « less than 30% of ICHQ3D limit »)
- Or « **NMT limit in ppm** » calculated based on option 1 (or alternatively if justified, based on option 2a),
- Or « **No risk identified** ».

Route of administration

Elements considered or not

Elements intentionally introduced or not

Report a conclusion on absence or control

If term « Absent » is used its definition is required

Route of administration onsidered in the risk assessment: Oral				
Element	Class	Intentionally added?	Considered in risk management?	Conclusion
Cd	1	No	Yes	Absent
Pb	1	No	Yes	Absent
As	1	No	Yes	Absent
Hg	1	No	Yes	Absent
Co	2A	No	Yes	Absent
V	2A	No	Yes	Absent
Ni	2A	No	Yes	Absent
Tl	2B	No	No	Not applicable
Au	2B	No	No	Not applicable
Rh	2B	No	No	Not applicable
Ru	2B	No	No	Not applicable
Se	2B	No	No	Not applicable
Ag	2B	No	No	Not applicable
Pt	2B	No	No	Not applicable
Li	3	No	No	Not applicable
Sb	3	No	No	Not applicable
Ba	3	No	No	Not applicable
Mo	3	Yes	Yes	Absent
Cu	3	No	No	Not applicable
Sn	3	No	No	Not applicable
Cr	3	No	Yes	Absent
Note: "absent" means less than 30% of ICH Q3D option 1 limit				

RMS table will be appended to the **CEP**

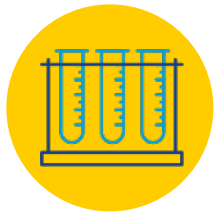
CEP 2.0

Skip testing to be justified in line with ICH Q3D

- ★ Related Substances (Organic impurities)
- ★ Mutagenic impurities
- ★ Nitrosamine impurities
- ★ Residual solvents
- ★ Elemental impurities
- ★ **Reagents and Inorganic impurities**

Reagents and inorganic impurities

Carry-over of reagents, in particular toxic reagents, to the final substance should be discussed, as applicable. (e.g. TBAB)

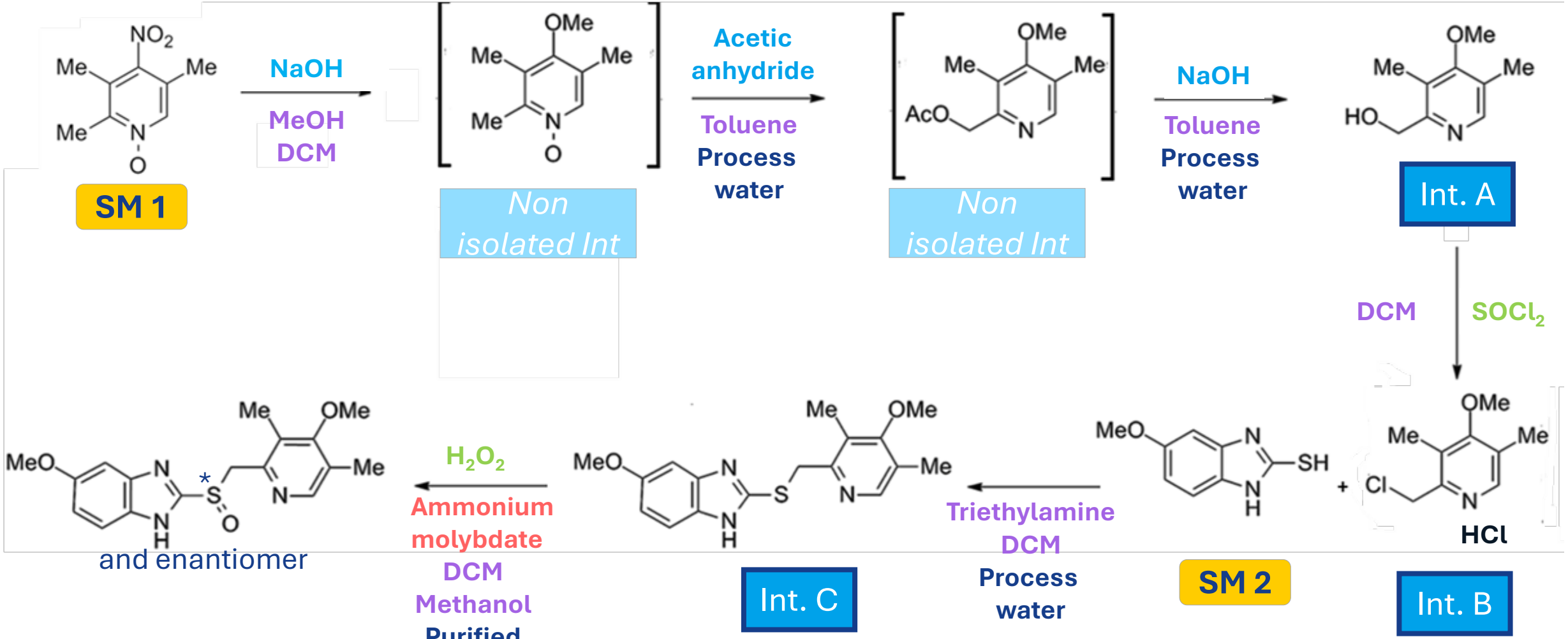


★Absence of carry-over into the API is demonstrated using a validated analytical procedure against a limit justified based on toxicological data

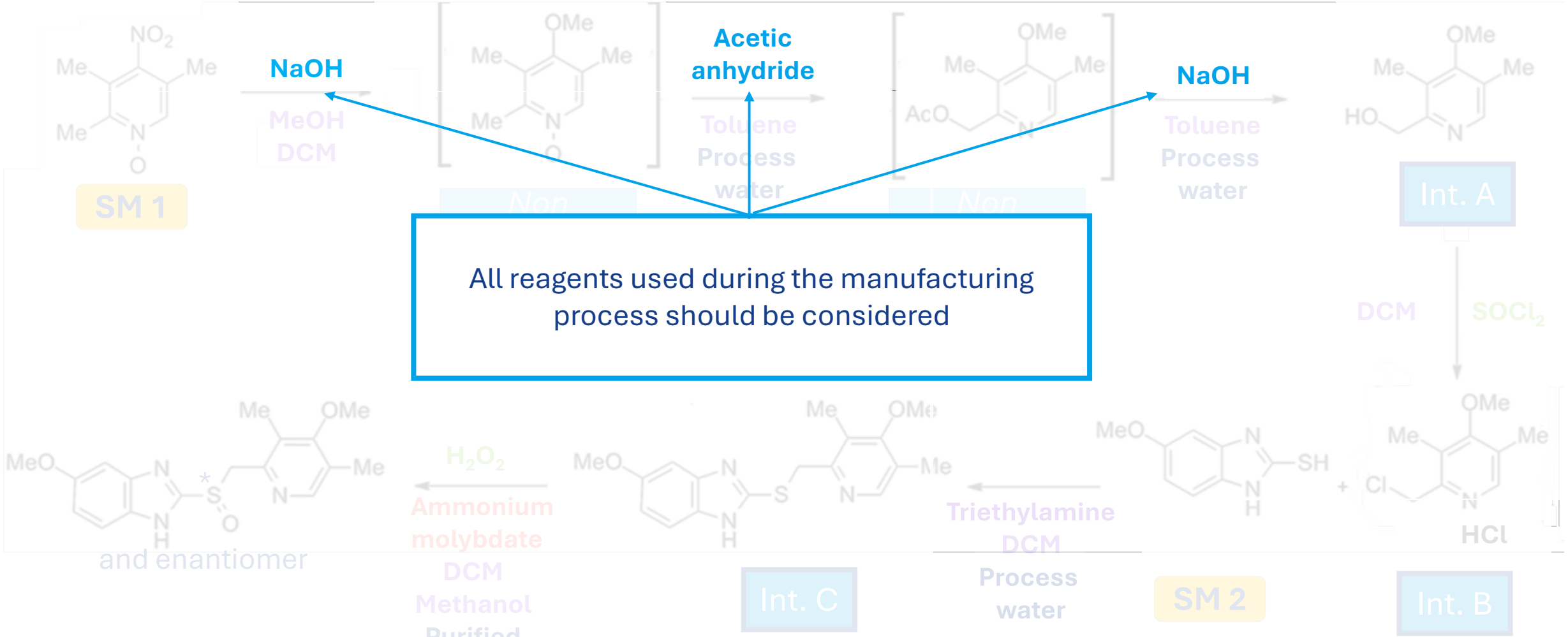
OR

★Routine control to be implemented in a suitable intermediate or final substance

Case study (fictitious): Omeprazole



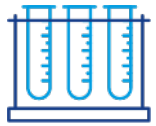
Case study (fictitious): Omeprazole



All reagents used during the manufacturing process should be considered

Reagents and inorganic impurities

	Origin, fate and carry over	Batch data	Limit
Sodium hydroxide	Washed along with water used in the manufacturing process.	**x**	**None**
Acetic anhydride	Hydrolyzed to acetic acid, itself not detected in the API. *Refer to residual sovents.*	**ND (LOD 15 ppm)**	**None**



Inorganic residues controlled by test of sulfated ash of the monograph.

Discussion to be included in 3.2.S.3.2 – Inorganic reagents / impurities.

Specification for the final API:

Test	Specification		Analytical procedure reference
Appearance	White or almost White powder		Ph. Eur. Current edition
Solubility	Very slightly soluble in water, soluble in methylene chloride, sparingly soluble in ethanol (96 per cent) and in methanol.		Ph. Eur. Current edition
Identification	IR spectrum should comply with that of the standard		Ph. Eur. Current edition
Appearance of solution	Solution S is clear		Ph. Eur. Current edition
Impurity F and Impurity G by UV	Maximum 350 ppm for the sum of impurity F & G. The absorbance of solution S determined at 440 nm is not greater than 0.10.		Ph. Eur. Current edition
Related substances	Ph. Eur Impurity D Ph. Eur. Impurity E Unspecified impurities (each) Total impurities	NMT 0.15% NMT 0.15% NMT 0.10% NMT 0.5%	Ph. Eur. Current edition
Loss on drying	Maximum 0.2%		Ph. Eur. Current edition
Sulfated ash	Maximum 0.1%		Ph. Eur. Current edition
Assay (dried substance)	99.0 per cent to 101.0 per cent		Ph. Eur. Current edition
Residual solvents	Methanol Dichloromethane	NMT 3000 ppm NMT 600 ppm	In-house

Take home message...

Show knowledge and understanding of your specific process and resulting impurity profile

Show you have identified the risks for the quality of your active substance

Show your control strategy mitigates the risks you have identified for the quality of your active substance

Thank you for your attention

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