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

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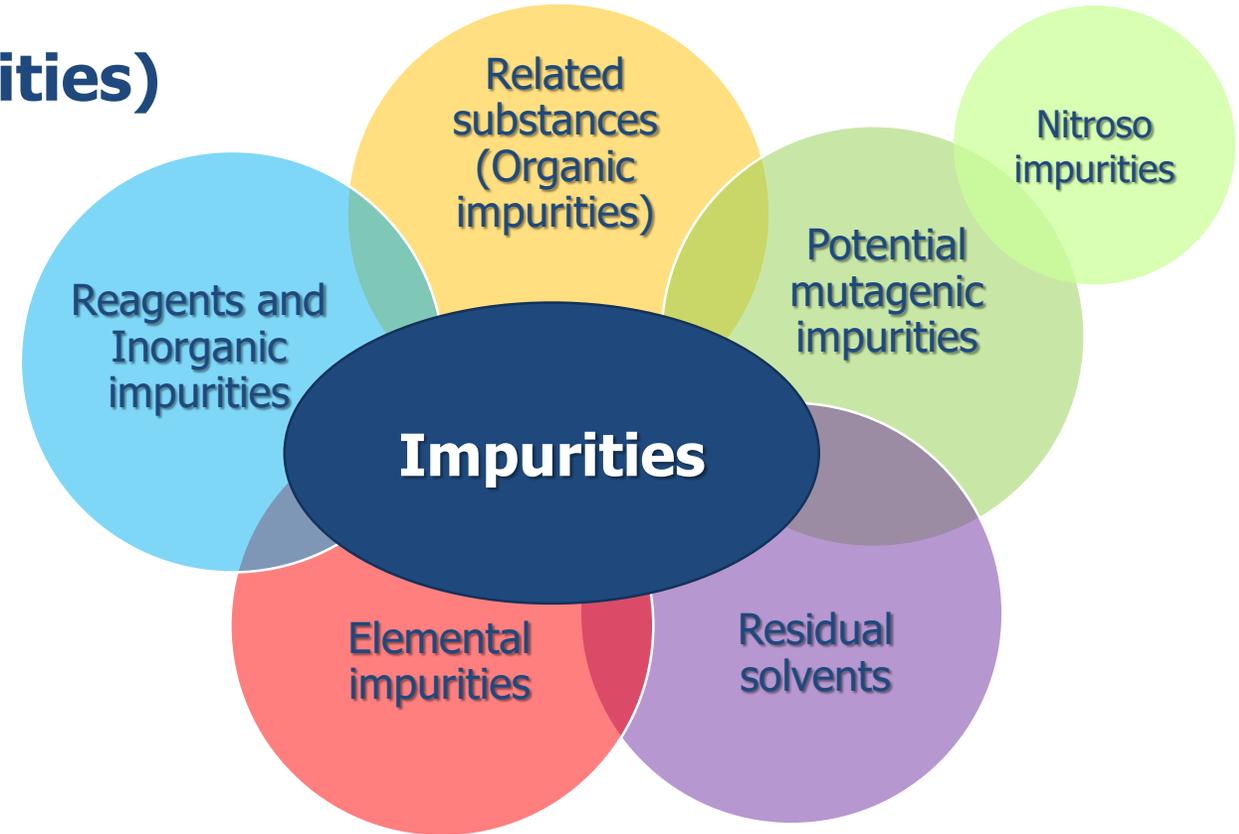# Control of impurities : CEP approach

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EDQM training 2023
6 July 2023

Impurities & Control strategy in Active Substances

- Related Substances (Organic impurities)

- Mutagenic Impurities

- Nitroso impurities

- Residual Solvents

- Elemental Impurities

- Inorganic impurities

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

How to set specifications accordingly?

Which key guidance? *A brief recap...*

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

ICH Q6A Specifications:
Test procedures and acceptance criteria for new chemical substances

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

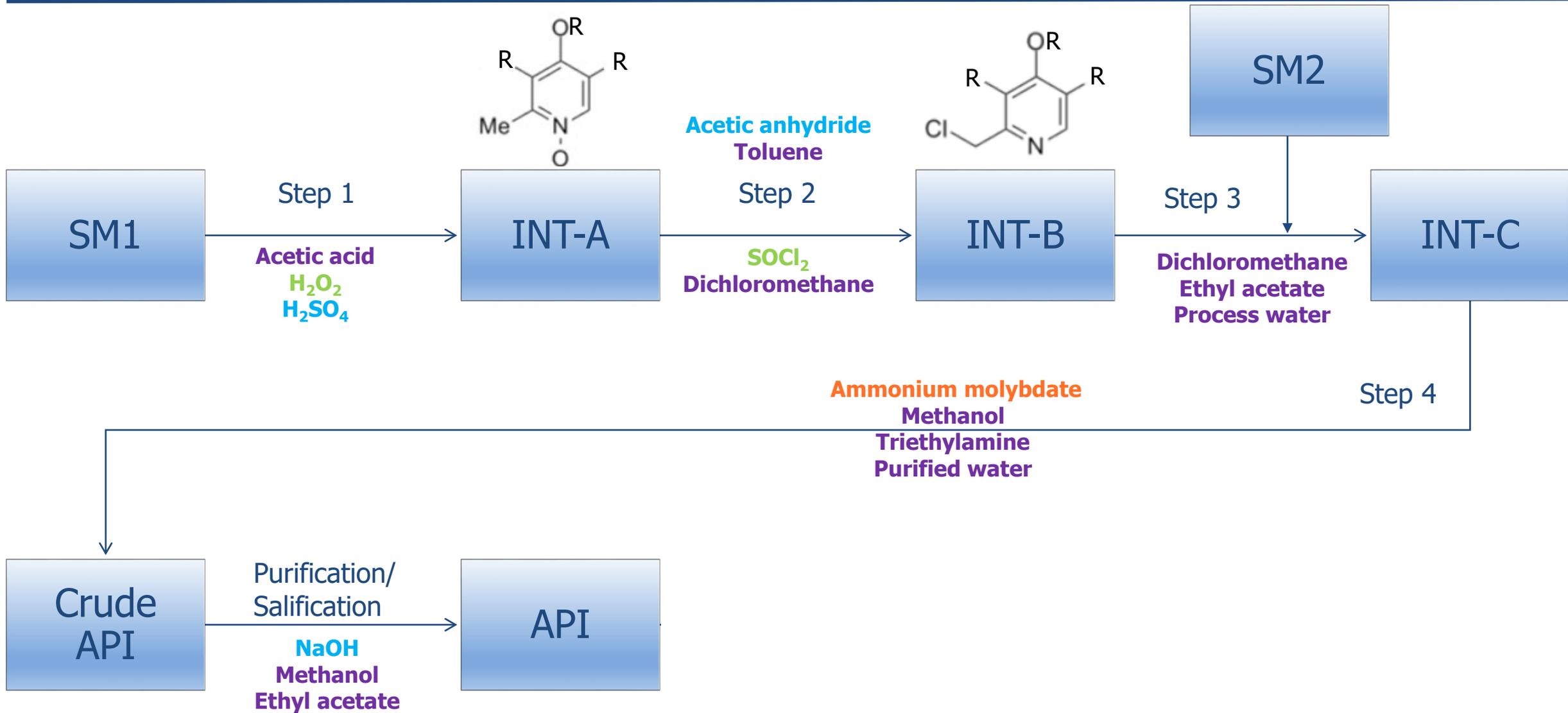| Type of impurity	ICH/EMA	EDQM
Related substances	ICH Q3A	Ph.Eur. 5.10, Ph.Eur. GM 2034 *Antibiotics only: Guideline on setting specifications for related impurities in antibiotics (EMA/CHMP/CVMP/ QWP/199250/2009)*
Mutagenic impurities	ICH M7 and its Q&A document	-
Elemental impurities	ICH Q3D	Ph.Eur. 5.20 PA/PH/CEP(16)23: Implementation of policy on elemental impurities in the Certification Procedure
Residual solvents	ICH Q3C CPMP/QWP/450/03 -Rev.1 (Annex I)	Ph.Eur. 5.4
Analytical procedures	ICH Q2 (R1)	Ph.Eur. 2.2.46 (for Pharmacopoeial methods)

Expectations ?

Impurity profile of the material should be **known** in detail
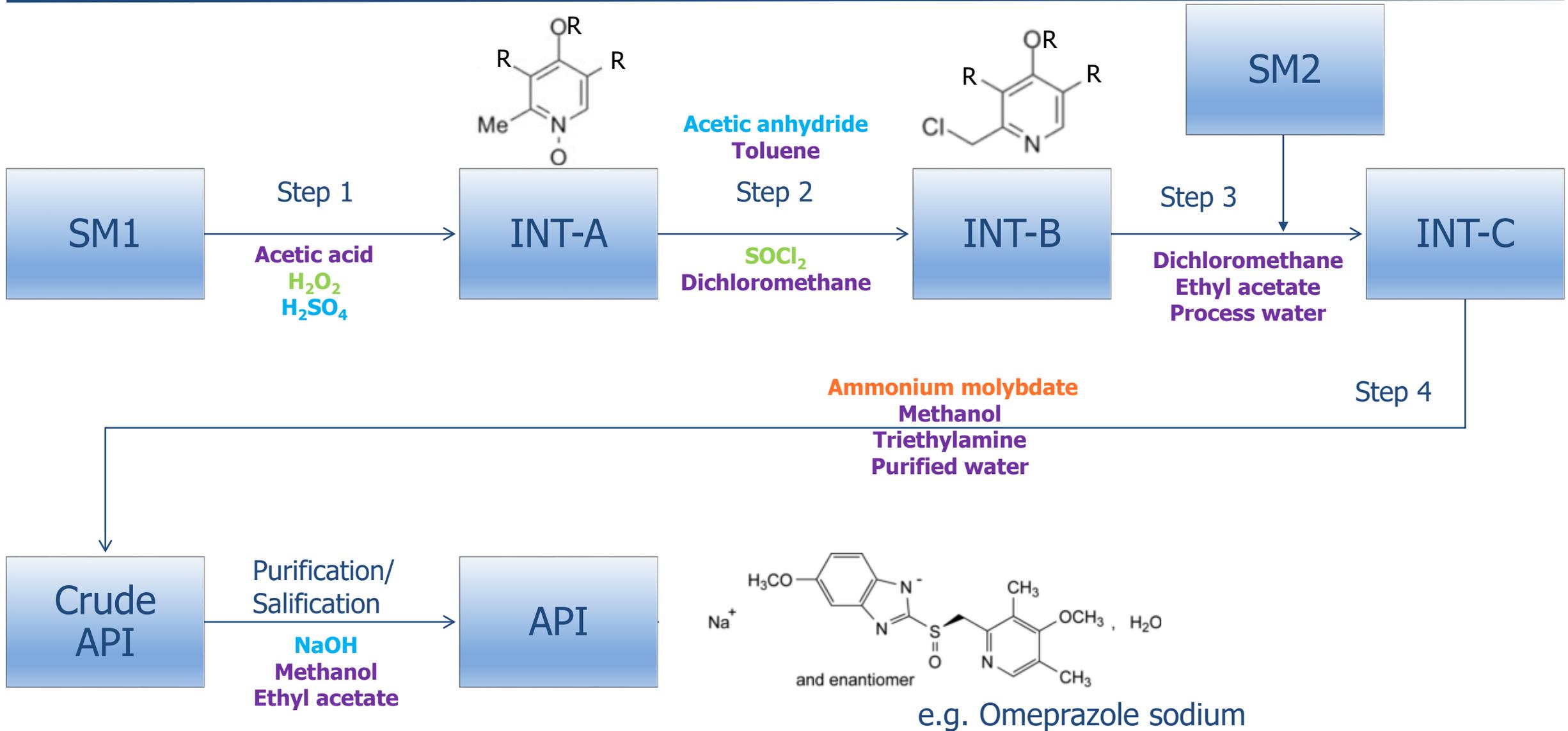
Analytical specifications should **control** the impurity profile and be **representative** of the process adopted

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)

SM1 → **Step 1** (Acetic acid, H₂O₂, H₂SO₄) → INT-A → **Step 2** (Acetic anhydride, Toluene / SOCl₂, Dichloromethane) → INT-B → **Step 3** (SM2; Dichloromethane, Ethyl acetate, Process water) → INT-C → **Step 4** (Ammonium molybdate, Methanol, Triethylamine, Purified water) → Crude API → **Purification/Salification** (NaOH, Methanol, Ethyl acetate) → API

Case study (fictitious)

SM1 → Step 1 → INT-A → Step 2 → INT-B → Step 3 → INT-C → Step 4 → Crude API → Purification/Salification → API

Step 1
Acetic acid
H_2O_2
H_2SO_4

Step 2
Acetic anhydride
Toluene
$SOCl_2$
Dichloromethane

Step 3
SM2
Dichloromethane
Ethyl acetate
Process water

Step 4
Ammonium molybdate
Methanol
Triethylamine
Purified water

Purification/Salification
NaOH
Methanol
Ethyl acetate

and enantiomer

e.g. Omeprazole sodium

Organic impurities

- ICH Q3A

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

- Ph. Eur. GM 2034 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

Do not forget …

Scope:

Certification of suitability to the monographs of the **EUROPEAN** Pharmacopoeia

Terminology should refer to the **Ph. Eur.** or at least traceable to it

Show suitability of the monograph to control the actual quality of your substance

- Cross-check with transparency list of the monograph
- Additional impurities/in-house impurities:
  - Suitability of the monograph test and specification to control it
  - For in-house impurities: chemical structures and INN/chemical names should be given as far as possible

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 impurities as specified impurities

Show the risk of having uncontrolled impurities up to the API is under control

- Special attention to be given to:
- Intermediates late in the process including the crude substance
- Related substances controlled by a method which is different comparing to the one adopted at release
- API-like impurities

Case study (fictitious)

SM1 → Step 1 → INT-A → Step 2 → INT-B → Step 3 → INT-C → Step 4 → Crude API → Purification/Salification → API

Step 1
Acetic acid
H_2O_2
H_2SO_4

INT-A structure:
OR, R, R, Me, N, O

Step 2
Acetic anhydride
Toluene
$SOCl_2$
Dichloromethane

INT-B structure:
OR, R, R, Cl, N

SM2

Step 3
Dichloromethane
Ethyl acetate
Process water

Step 4
Ammonium molybdate
Methanol
Triethylamine
Purified water

Purification/Salification
NaOH
Methanol
Ethyl acetate

e.g. Omeprazole sodium

and enantiomer

Starting materials (3.2.S.2.3)

Precursor 1 → Precursor 2 → SM1

Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
Precursor 1	Precursor. Found <0.05% in INT-A.	0.71%	Controlled as specified impurity in the SM at NMT 0.80%
Precursor 2	Precursor. Found <0.05% in SM.	0.02%	Controlled as unspecified impurity in the SM
Impurity RRT=1.2	Likely by-product. Found <0.05% in INT-A.	0.25%	Controlled as unspecified impurity in the SM

Which specification ?

Impurity	Limit
Related substances	
Precursor 1	NMT 0.80%
Unspecified imp.	NMT 0.30%
Total	NMT 1.0%

Potential by-products, side-reactions should be considered as well!
Same exercise for SM2

Intermediates (3.2.S.2.4)

Related substances (Organic impurities)

Intermediate INT-A:

Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
SM1	SM. Absent (<0.05%) in INT-B	0.89%	Controlled as specified impurity at NMT 1.0%
Precursor 1	From SM	0.03%	Controlled as unspecified impurity

Which specification ?

Impurity	Limit
Related substances	
SM1	NMT 1.0%
Unspecified imp.	NMT 0.20%
Total	NMT 1.2%

Intermediate INT-B:

Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
SM1	SM. Absent (<0.05%)	0.02%	Controlled as unspecified impurity
INT-A	Process impurity. Potentially mutagenic. Aromatic N-oxide alerting structure	0.68%	Controlled as specified impurity at NMT 0.70% in INT-B & in line with ICH M7 unless demonstrated not mutagenic

Impurity	Limit
INT-A	NMT 0.70%
Unspecified imp.	NMT 0.20%
Total	NMT 1.0%

Potential by-products, side-reactions should be systematically considered!

Intermediates (3.2.S.2.4)

Related substances (Organic impurities)

Intermediate INT-C, **Ph. Eur. imp. C** :

Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
INT-B	Process impurity. Potentially mutagenic. Alkyl chloride alerting structure	0.90%	Controlled as specified impurity at NMT 1.0% in INT-C & in line with ICH M7 unless demonstrated not mutagenic
SM2	SM	0.16%	Ph.Eur. Impurity A. Controlled as unspecified impurity in INT-C and API
Impurity RRT=0.4	Likely by-product. Found <0.05% in crude API	0.12%	Controlled as unspecified impurity in INT-C

Which specification ?

Impurity	Limit
INT-B	NMT 1.0%
Unspecified imp.	NMT 0.20%
Total	NMT 1.2%

Crude API

Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
INT-C	Process impurity	0.17%	Ph.Eur. Impurity C
Sulfone impurity	Process impurity	0.21%	Ph.Eur. Impurity D
Impurity RRT=0.4	Likely by-product	0.04%	Controlled as unspecified impurity in crude API

Assuming Ph.Eur. Monograph method for Related Substances is used for control of the API

Impurity	Limit
INT-C	NMT 0.20%
Sulfone impurity	NMT 0.25%
Unspecified imp.	NMT 0.15%
Total	NMT 0.7%

Potential by-products, side-reactions should be systematically considered!

Case study: omeprazole sodium

Ph.Eur. 1032

Related substances (Organic impurities)

Case study: omeprazole sodium

IMPURITIES

Specified impurities: D, E.

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.

SM2
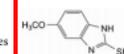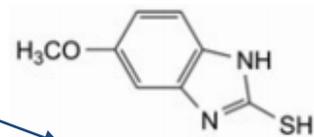
A. 5-methoxy-1*H*-benzimidazole-2-thiol,
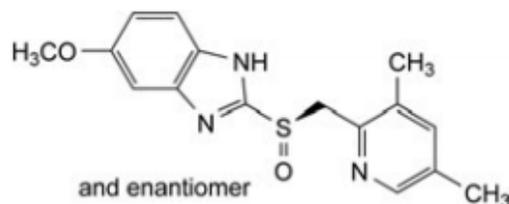
B. 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole,

and enantiomer

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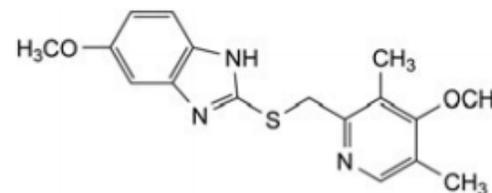
C. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfanyl]-1*H*-benzimidazole (ufiprazole),
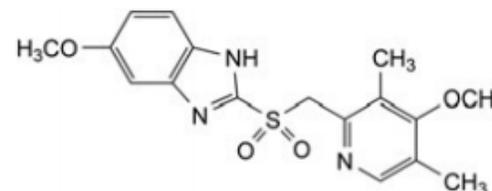
D. 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1*H*-benzimidazole (omeprazole-sulfone),

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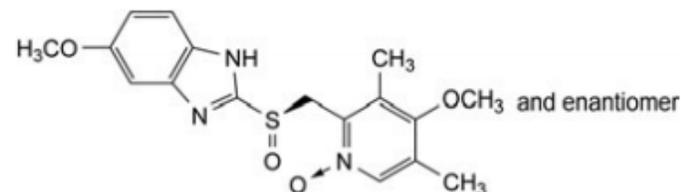
E. 4-methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulfinyl]methyl]-3,5-dimethylpyridine 1-oxide.

Case study: omeprazole sodium

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 sodium specifications :

Impurity	Limit	Batch data	Method
Ph.Eur. Impurity D	NMT 0.15 %	0.10-0.11%	HPLC, Ph.Eur. 1032 & 2.2.29
Ph.Eur. Impurity E	NMT 0.15%	0.07-0.09%	
Unspecified	NMT 0.10%	0.08-0.09%	
Total	NMT 0.5%	0.25-0.29%	

In this case related substances controlled by the transparency list of the monograph
No in-house impurity present (i.e. >0.05%) in the API

But life is not perfect….

Other examples…

In-house impurities

Suitability of the Monograph to control the impurity profile of the final substance
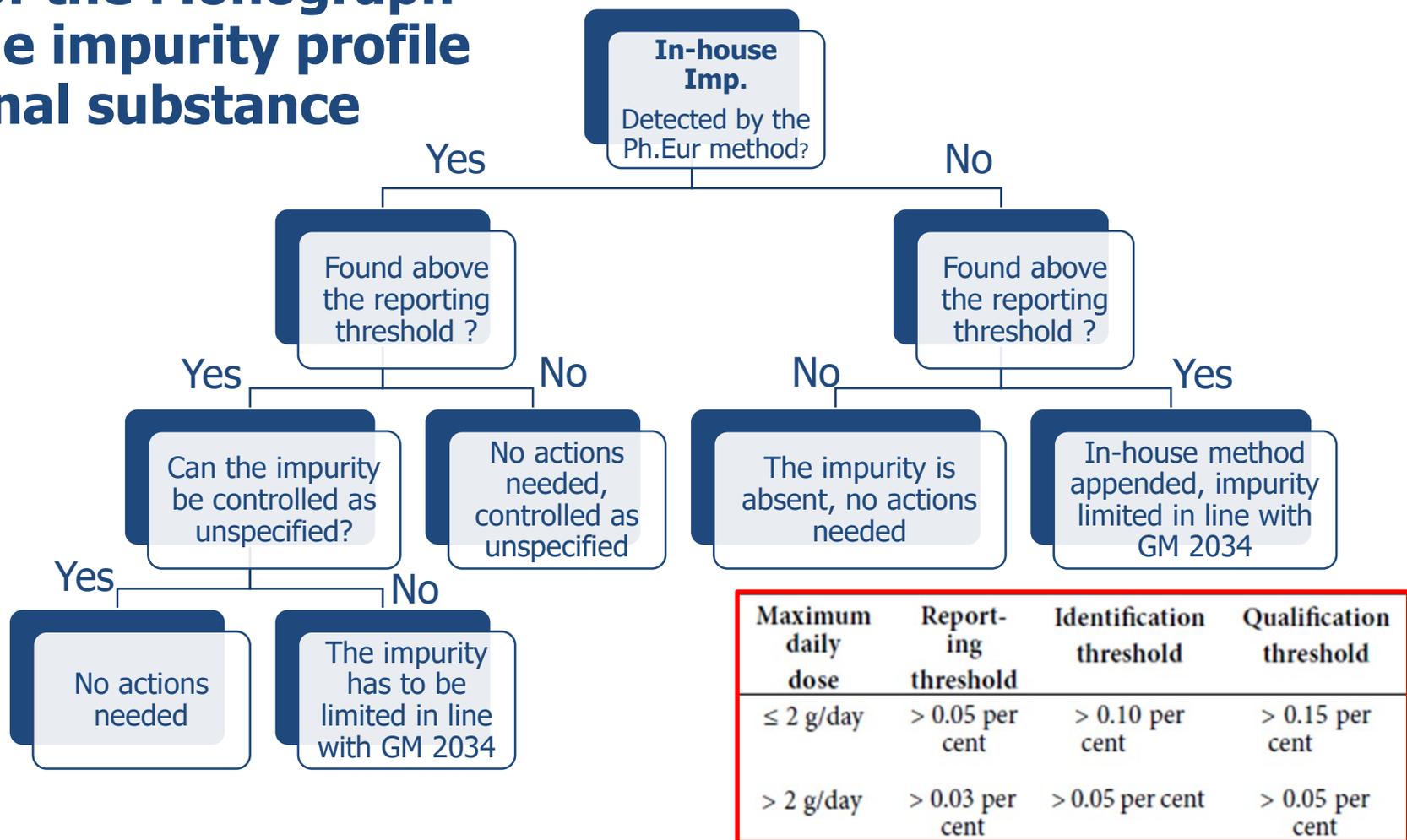
In-house Imp.
Detected by the Ph.Eur method?

Yes → Found above the reporting threshold?

- **Yes** → Can the impurity be controlled as unspecified?
  - **Yes** → No actions needed
  - **No** → The impurity has to be limited in line with GM 2034
- **No** → No actions needed, controlled as unspecified

No → Found above the reporting threshold?

- **No** → The impurity is absent, no actions needed
- **Yes** → In-house method appended, impurity limited in line with GM 2034

Maximum daily dose	Reporting 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 method of the monograph to control all the related substances should be demonstrated

Alternative method

- When: Ph. Eur method **is suitable** to control in-house impurities but In-house methods may be used

- Equivalent results comparing to the corresponding Ph.Eur. method(s): cross-validation data on the same batches, using spiked solutions if necessary

- Validation in line with ICH Q2(R1)

Additional method

- When : Ph. Eur. method is **not suitable** to control in-house impurities

- To supplement monograph method(s)

- Unless absence of corresponding impurities is demonstrated, it will be reported on CEP

- Validation in line with ICH Q2(R1)

Case study: omeprazole sodium

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

Impurity	Limit	Batch data	Method
Ph.Eur. Impurity D	NMT 0.15%	0.10-0.11%	HPLC, Ph.Eur. 1032 & 2.2.29
Ph.Eur. Impurity E	NMT 0.15%	0.05-0.09%	
In-house impurity 1	**?**	**0.001-0.03%**	
In-house impurity 2	**?**	**0.06-0.08%**	
In-house impurity 3 (RRT 0.9)	**?**	**0.09-0.14%**	
Unspecified	NMT 0.10%	0.06-0.07%	
Total	NMT 0.5%	0.36-0.49%	
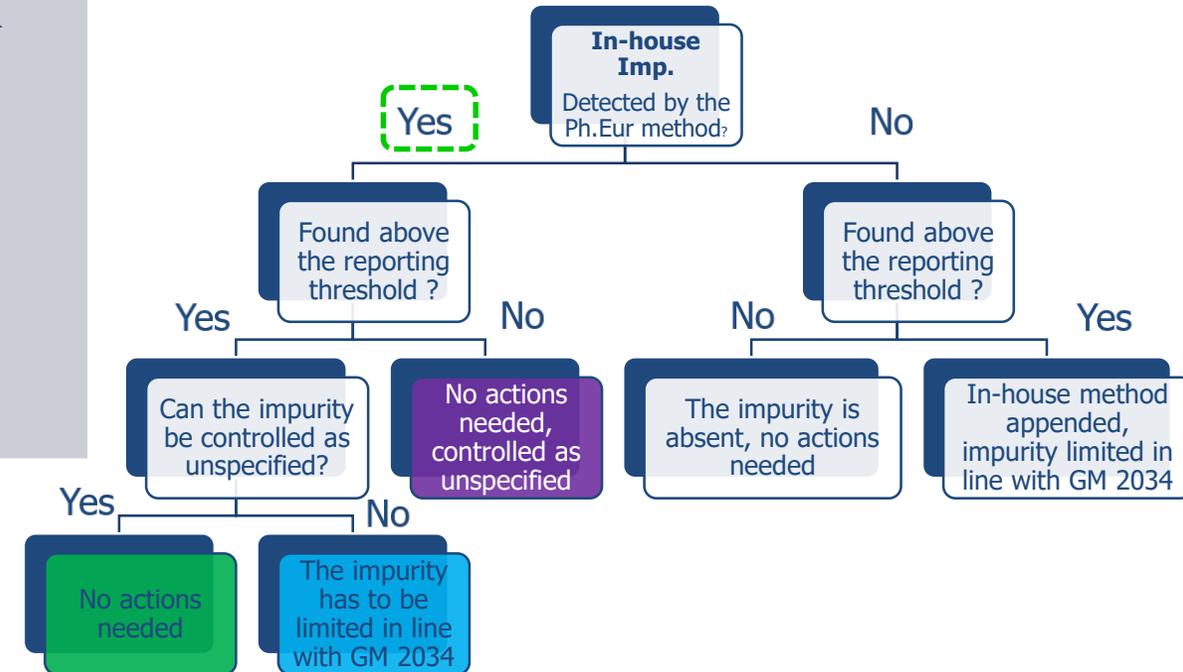
Case study: omeprazole sodium

Related substances
(Organic impurities)

Impurity	Limit	Batch data	Method
Ph.Eur. Impurity D	NMT 0.15%	0.10-0.11%	HPLC, Ph.Eur. 1032 & 2.2.29
Ph.Eur. Impurity E	NMT 0.15%	0.05-0.09%	
In-house impurity 3 (RRT 0.9)	**NMT 0.15%**	0.09-0.14%	
Unspecified *In-house impurity 2*	NMT 0.10%	0.06-0.08%	
Total	NMT 0.5%	0.36-0.49%	
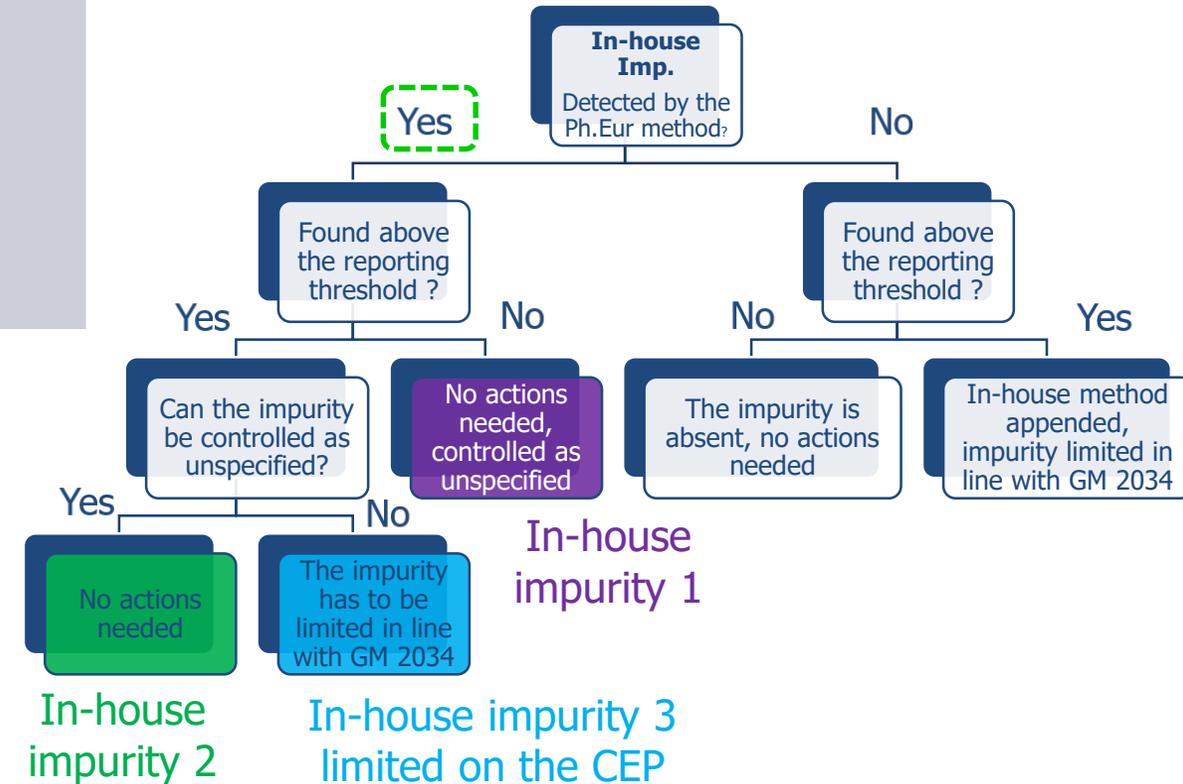
If in-house impurity 3 is found above the qualification threshold (0.15%) → → → qualification needed

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

In-house Imp. Detected by the Ph.Eur method?

Yes — No

Found above the reporting threshold ?

Found above the reporting threshold ?

Yes — No

No — Yes

Can the impurity be controlled as unspecified?

No actions needed, controlled as unspecified

The impurity is absent, no actions needed

In-house method appended, impurity limited in line with GM 2034

In-house impurity 1

Yes — No

No actions needed

The impurity has to be limited in line with GM 2034

In-house impurity 2

In-house impurity 3 limited on the CEP

Case study: omeprazole sodium

Other situations : specifications for in-house impurities 10, and 11 ?

Impurity	Limit	Batch data	Method
Ph.Eur. Impurity D	NMT 0.15%	0.10-0.11%	HPLC, Ph.Eur. 1032 & 2.2.29
Ph.Eur. Impurity E	NMT 0.15%	0.05-0.09%	
Unspecified	NMT 0.10%	0.08-0.09%	
Total	NMT 0.5%	0.23-0.30%	
In-house impurity 10	**?**	**0.01-0.03%**	**In-house HPLC method**
In-house impurity 11	**?**	**0.08-0.13%**	

In-house Imp. Detected by the Ph.Eur method?

Yes

No

Found above the reporting threshold ?

Yes → Can the impurity be controlled as unspecified?

Yes → No actions needed

No → The impurity has to be limited in line with GM 2034

No → No actions needed, controlled as unspecified

Found above the reporting threshold ?

No → The impurity is absent, no actions needed

Yes → In-house method appended, impurity limited in line with GM 2034

Case study: omeprazole sodium

Related substances (Organic impurities)

Impurity	Limit	Batch data	Method
Ph.Eur. Impurity D	NMT 0.15%	0.10-0.11%	HPLC, Ph.Eur. 1032 & 2.2.29
Ph.Eur. Impurity E	NMT 0.15%	0.05-0.09%	
Unspecified	NMT 0.10%	0.08-0.09%	
Total	NMT 0.5%	0.31-0.42%	
In-house impurity 11	**NMT 0.15%**	**0.08-0.13%**	**In-house HPLC method**

In-house Imp. Detected by the Ph.Eur method?

Yes

No

Found above the reporting threshold ?

Yes

No

Can the impurity be controlled as unspecified?

No actions needed, controlled as unspecified

Yes

No

No actions needed

The impurity has to be limited in line with GM 2034

Found above the reporting threshold ?

No

Yes

The impurity is absent, no actions needed

In-house method appended, impurity limited in line with GM 2034

In-house impurity 10

In-house impurity 11 limited on the CEP & method appended

Mutagenic impurities

Potential mutagenic impurities

ICH M7 (R2) "Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk"

ICH M7(R2), Questions and Answers *Step 4*

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

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 to be assessed for **MUTAGENIC POTENTIAL**

Mutagenic impurities

Active substance assessment

1. **Actual impurities**
Identified, known structure

➡ Impurities found
> ICH Q3A reporting threshold

2. **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

Actual and potential impurities of known structure

Hazard assessment & classification

- **Known mutagen**: Database and literature searches

- **Alerting structure of unknown mutagenicity**
  = no data available... often the case...

In-silico assessment

Computational toxicology assessment using (Quantitative) Structure-Activity Relationships (SAR) that predict bacterial mutagenicity

- Two complementary (Q)SAR systems:
  Expert rule based and statistical based

- Expert review and discussion to support conclusions, if necessary

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

Alerting structures and mutagenicity

Potential mutagenic impurities

**Alerting structure,
Unknown mutagenic potential**

(Class 3)

(Q)SAR based on
bacterial mutagenicity predictions

Adequate control measures

Negative
Class 5

Positive
Class 2

Absence of structural alerts from two complementary (Q)SAR methodologies is sufficient to conclude that the impurity is of no mutagenic concern

Bacterial mutagenicity assay
(e.g. AMES test)

Negative
Class 5

Positive
Class 2

AMES negative result
over-rules (Q)SAR result

In vivo gene mutation studies in case control not possible at appropriate acceptable limit
→ Class 1 or 5

Case study (fictitious)

SM1 → (Step 1, H_2O_2) → INT-A → (Step 2, $SOCl_2$) → INT-B → (Step 3, SM2) → INT-C → (Step 4) → Crude API → (Purification/Salification) → API

Hazard assessment

Potential mutagenic impurities

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

Impurity	Origin	Hazard assessment	Class
Precursor SM 2	SM2	Nitro aromatic alerting structure.	?
Hydrogen peroxide	Step 1	Known mutagenic carcinogens. Database and literature data. ICH M7 "addendum".	Class 1
INT-A	Step 2	N-oxide alerting structure.	?
Thionyl chloride	Step 2	Known mutagenic carcinogens. Database and literature data. ICH M7.	Class 1
INT-B	Step 3	Alkyl chloride alerting structure.	?

Hazard assessment

Potential mutagenic impurities

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

Impurity	Origin	Hazard assessment	Class
Precursor SM 2	SM2	Nitro aromatic alerting structure.	?
Hydrogen peroxide	Step 1	Known mutagenic carcinogens. Database and literature data. ICH M7 addendum.	Class 1
INT-A	Step 2	N-oxide alerting structure.	?
Thionyl chloride	Step 2	Known mutagenic carcinogens. Database and literature data. ICH M7.	Class 1
INT-B	Step 3	Alkyl chloride alerting structure.	?

Hazard assessment

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

Impurity	Origin	Hazard assessment	Class
Precursor SM 2	SM2	Nitro aromatic alerting structure. (Q)SAR study & Expert review. Negative. Non-mutagenic.	Class 5
Hydrogen peroxide	Step 1	Known mutagenic carcinogens. Database and literature data. ICH M7 addendum.	Class 1
INT-A	Step 2	N-oxide alerting structure. No database or literature data. No mutagenicity data.	Class 3
Thionyl chloride	Step 2	Known mutagenic carcinogens. Database and literature data. ICH M7.	Class 1
INT-B	Step 3	Alkyl chloride alerting structure. No database or literature data. In-vitro bacterial mutagenicity assay (e.g. AMES test). Positive. Mutagenic.	Class 2

How to set an acceptable limit ?

Potential mutagenic impurities

$$\textbf{\textit{Acceptable limit}} = \frac{PDE \left(\frac{\mu g}{day}\right)}{MDD \left(\frac{g}{day}\right)}$$

MDD 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

NEW CEP 2.0

- **Compound-specific acceptable limit**

→ Class 1 impurities

ICH M7 Appendix 3

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

$$H_2O_2 \text{ Acceptable limit} = \frac{68,000\left(\frac{\mu g}{day}\right)}{0.0426\left(\frac{g}{day}\right)} = 170\%, \text{ Thus } <0.5\%$$

How to set an acceptable limit ?

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

Note 7

- **TTC-based limit** → Class 2 and 3 impurities
  - Threshold of Toxicological Concern (TTC) concept was developed to define an **acceptable intake** for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects.
  - Acceptable intake in relation to Less-than-lifetime exposure
  - Does not apply to high potency mutagenic carcinogens referred to as the "cohort of concern", comprises *aflatoxin-like-*, *N-nitroso-*, and *alkyl-azoxy compounds*.

$$\text{TTC-based limit} \ = \ \frac{1.5\left(\frac{\mu g}{day}\right)}{0.0426\left(\frac{g}{day}\right)} = \textbf{35 ppm}$$

MDD Omeprazole sodium in long-term use. Worst case scenario.

Table 4. Examples of clinical use scenarios with different treatment durations for applying acceptable intakes

Scenario	Acceptable Intake (µg/day)
Treatment duration of ≤ 1 month: e.g., drugs used in emergency procedures (antidotes, anesthesia, acute ischemic stroke), actinic keratosis, treatment of lice	120
Treatment duration of > 1-12 months: e.g., anti-infective therapy with maximum up to 12 months treatment (HCV), parenteral nutrients, prophylactic flu drugs (~ 5 months), peptic ulcer, Assisted Reproductive Technology (ART), pre-term labor, preeclampsia, pre-surgical (hysterectomy) treatment, fracture healing (these are acute use but with long half-lives)	20
Treatment duration of >1-10 years: e.g., stage of disease with short life expectancy (severe Alzheimer's), non-genotoxic anticancer treatment being used in a patient population with longer term survival (breast cancer, CML), drugs specifically labeled for less than 10 years of use, drugs administered intermittently to treat acute recurring symptoms (chronic Herpes, gout attacks, substance dependence such as smoking cessation), macular degeneration, HIV	10
Treatment duration of >10 years to lifetime: e.g., chronic use indications with high likelihood for lifetime use across broader age range (hypertension, dyslipidemia, asthma, Alzheimer's (except severe AD), hormone therapy (e.g., GH, TH, PTH), lipodystrophy, schizophrenia, depression, psoriasis, atopic dermatitis, COPD, cystic fibrosis, seasonal and perennial allergic rhinitis	1.5

Control options

Potential mutagenic impurities

**For Class 1, 2 and 3 impurities,
a control in line with one of ICH M7 Options is <u>expected</u> and should be <u>justified</u>**

Option 1	Control ≤ acceptable limit in the final substance Impurities introduced in the last step of the synthesis, unless otherwise justified *Certification procedure does not take position on skip testing*
Option 2	Control ≤ acceptable limit in a raw material, SM or intermediate or as an IPC
Option 3	Control > acceptable limit in a raw material, SM or intermediate or as an IPC. Suitability of the acceptable limit to be demonstrated by spike-purge studies: impurity <30% acceptable limit
Option 4	Understanding the process and its effects on impurities, so that risk of an impurity residing in the final substance above the acceptable limit is determined to be negligible

- Limit on CEP
- Analytical method appended
- Validation in line with ICH Q2 (R1) to be provided

For all carry-over studies:
- Identify method (e.g. GC-MS)
- Validation data: at least LOD, LOQ, selectivity.

Control options

If **three or more Class 2 or 3 impurities** controlled in the API ➡ Individual limits & Total limit for Class 2 and 3 impurities
ICH M7 table 3

Option 3 & 4: Where justification based on scientific principles alone is not considered sufficient… ➡ Supportive analytical data is expected

Option 4

When?

- Impurities introduced early in the synthesis and effectively purged

- Impurities inherently unstable in process conditions (e.g. highly reactive substances, soluble, ionisable, gaseous and early reagents/ impurities that are purged/destroyed through/by the process (e.g. acyl halides, thionyl chloride)).

Justification?

- Generally, elements of a scientific risk assessment can be used. ICH M7 Ref. 11 & estimation of Purge factors

- When the impurity is known to form or introduced late in the process, process-specific data expected. **Case-by-case**

Case study (fictitious)

SM1 —Step 1 H_2O_2→ INT-A —Step 2 $SOCl_2$→ INT-B —Step 3 Process water→ INT-C

SM2 → INT-C

INT-C —Step 4 Purified water→ Crude API —Purification/ Salification→ API

Control

Potential mutagenic impurities

Impurity	Origin	Classification	Control in line with ICH M7	Justification
Precursor SM2	SM2	Class 5	Treat as non-mutagenic impurity	
Hydrogen peroxide	Step 1	Class 1	Option 4	Used in the 1st step of the process. Decomposes in water used widely ahead in the process (Steps 3 and 4).
INT-A	Step 2	Class 3	?	?
Thionyl chloride	Step 2	Class 1	Option 4	Used in the step 2 of the process. Highly reactive in water used widely ahead in the process (Steps 3 and 4).
INT-B	Step 3	Class 2	?	?

Control

Potential mutagenic impurities

Impurity	Origin	Classification	Control in line with ICH M7	Justification
Precursor SM2	SM2	Class 5	Treat as non-mutagenic impurity	
Hydrogen peroxide	Step 1	Class 1	Option 4	Used in the 1st step of the process. Decomposes in water used widely ahead in the process (Steps 3 and 4).
INT-A	Step 2	Class 3	?	?
Thionyl chloride	Step 2	Class 1	Option 4	Used in the step 2 of the process. Highly reactive in water used widely ahead in the process (Steps 3 and 4).
INT-B	Step 3	Class 2	?	?

INT-A limited in INT-B at NMT 0.70%

Proposed limit > TTC-based limit

Option 3 →→ Spike/purge studies
e.g. INT-B spiked with 0.74% INT-A → Pursue synthetic process
↓
INT-A shown <u>absent</u>, i.e., <u><30% TTC-based limit</u>,
in suitable intermediate or final substance
by GC-MS (LOD=3ppm, LOQ= 7ppm).

Control

Potential mutagenic impurities

Impurity	Origin	Classification	Control in line with ICH M7	Justification
Precursor SM2	SM2	Class 5	Treat as non-mutagenic impurity	
Hydrogen peroxide	Step 1	Class 1	Option 4	Used in the 1st step of the process. Decomposes in water used widely ahead in the process (Steps 3 and 4).
INT-A	Step 2	Class 3	Option 3 NMT 0.70% in INT-B	INT-A purged to levels < 30% TTC-based limit (35ppm) in API when present at 0.74% in INT-B as per spiking experiments by GC-MS (LOD=3ppm, LOQ= 7ppm).
Thionyl chloride	Step 2	Class 1	Option 4	Used in the step 2 of the process. Highly reactive in water used widely ahead in the process (Steps 3 and 4).
INT-B	Step 3	Class 2	?	?

Control

Impurity	Origin	Classification	Control in line with ICH M7	Justification
Precursor SM2	SM2	Class 5	Treat as non-mutagenic impurity	
Hydrogen peroxide	Step 1	Class 1	Option 4	Used in the 1st step of the process. Decomposes in water used widely ahead in the process (Steps 3 and 4).
INT-A	Step 2	Class 3	Option 3 NMT 0.70% in INT-B	INT-A purged to levels < 30% TTC-based limit (35ppm) in API when present at 0.74% in INT-B as per spiking experiments by GC-MS (LOD=3ppm, LOQ= 7ppm).
Thionyl chloride	Step 2	Class 1	Option 4	Used in the step 2 of the process. Highly reactive in water used widely ahead in the process (Steps 3 and 4).
INT-B	Step 3	Class 2	?	?

Alkyl chloride Acceptable limit? ➡ ICH M7 Note 5
Monofunctional alkyl chlorides
Lifetime and LTL daily intakes 10x default ones ➡ Acceptable limit = 350 ppm

Control

Potential mutagenic impurities

Impurity	Origin	Classification	Control in line with ICH M7	Justification
Precursor SM2	SM2	Class 5	Treat as non-mutagenic impurity	
Hydrogen peroxide	Step 1	Class 1	Option 4	Used in the 1st step of the process. Decomposes in water used widely ahead in the process (Steps 3 and 4).
INT-A	Step 2	Class 3	Option 3 NMT 0.70% in INT-B	INT-A purged to levels < 30% TTC-based limit (35ppm) in API when present at 0.74% in INT-B as per spiking experiments by GC-MS (LOD=3ppm, LOQ= 7ppm).
Thionyl chloride	Step 2	Class 1	Option 4	Used in the step 2 of the process. Highly reactive in water used widely ahead in the process (Steps 3 and 4).
INT-B	Step 3	Class 2	**Option 1 NMT 350ppm in API**	Monofunctional alkyl chloride. ICH M7 Note 5. Despite control in INT-B, Option 1 chosen to be implemented.

Mutagenic impurities

Potential mutagenic impurities

Impurity	Origin	Classification	Control in line with ICH M7	Justification
Precursor SM2	SM2	Class 5	Treat as non-mutagenic impurity	
Hydrogen peroxide	Step 1	Class 1	Option 4	Used in the 1st step of the process. Decomposes in water used widely ahead in the process (Steps 3 and 4).
INT-A	Step 2	Class 3	Option 3 NMT 0.70% in INT-B	INT-A purged to levels < 30% TTC-based limit (35ppm) in API when present at 0.74% in INT-B as per spiking experiments by GC-MS (LOD=3ppm, LOQ= 7ppm).
Thionyl chloride	Step 2	Class 1	Option 4	Used in the step 2 of the process. Highly reactive in water used widely ahead in the process (Steps 3 and 4).
INT-B	Step 3	Class 2	Option 1 NMT 350ppm in API	Monofunctional alkyl chloride. ICH M7 Note 5. Despite control in INT-B, Option 1 chosen to be implemented.

**Exercise and outcome of discussion to be summarised
in section 3.2.S.3.2 – Mutagenic impurities**

Specification as provided in relevant sections (3.2.S.2.3, 3.2.S.2.4, 3.2.S.4.1)

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Nitroso 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.

- Example of formation conditions: concomitant presence of a secondary/tertiary amine and a nitrosating agent (e.g. $NaNO_2$) under acidic conditions

$$NaNO_2 + H^+ \longrightarrow \text{H-O-N=O} \xrightarrow{\;H^+\;} {}^+N=O$$

(sodium/alkyl nitrite)   (nitrous acid)   (nitrosonium ion)
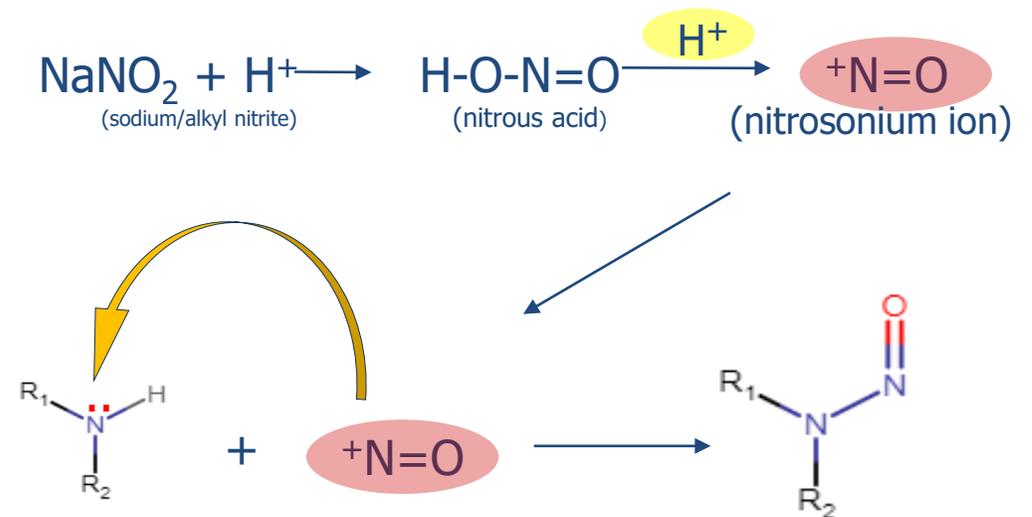
Risk assessment in CEP dossiers - Principles

Q & A for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products (EMA website)

Risk identified?

Presence confirmed?

<u>Comprehensive</u> risk assessment. <u>ALL</u> risk factors to be considered. Refer to Q&A document, Topic 4. E.g.:

Nitrosating agent + secondary/tertiary amine + favourable conditions

- Manufacturing process conditions, either within same synthetic step or in different steps
- Contaminated starting materials, intermediates, recovered or recycled materials
- Degradation of API, intermediates, reagents or solvents.
- Cross-contaminations, etc.

YES, risk identified:

- **confirmatory testing to confirm or refute the presence of nitrosamines**

YES, presence confirmed:

- **implement effective risk mitigating measures** (e.g. changes in manufacturing process)
- **suitable control strategy**

Same principles to be used for Veterinary products

Risk & Presence confirmed

Control strategy in line with:
- Q & A document, Question 10
- ICH M7 principles, as applicable

Calculation of applicable limit:

$$\text{Limit (ppm)} = \frac{\text{AI (ng)}}{\text{MDD (mg)}}$$

N-nitrosamine with insufficient substance specific data :

→ **default class specific TTC of 18 ng/d**

→ if not possible, interim requirements Q 21

Multiple N-nitrosamines (more than one)

→ **Total** nitrosamines

→ Q & A, Annex 1, Decision tree with control options for products containing multiple N-nitrosamines

Q&A, Table 1 (refer to current version for full table):
Following limits have been established for:

N-Nitrosamine (CAS number)	ng/day*
N-Nitrosodimethylamine, NDMA[1] (62-75-9)	96.0
N-Nitrosodiethylamine, NDEA[1] (55-18-5)	26.5
N-Nitrosoethylisopropylamine, EIPNA[2] (16339-04-1)	26.5
N-Nitrosodiisopropylamine, DIPNA[2] (601-77-4)	26.5
N-Nitroso-N-methyl-4-aminobutyric acid, NMBA[3] (61445-55-4)	96.0
1-Methyl-4-nitrosopiperazine, MeNP[2] (16339-07-4)	26.5
N-Nitroso-di-n-butylamine, NDBA[2] (924-16-3)	26.5
N-Nitroso-N-methylaniline, NMPA[1] (614-00-6)	34.3
N-nitroso-morpholine, NMOR[4] (59-89-2)	127
N-nitroso-varenicline, NNV [5]	37.0
N-nitrosodipropylamine, NDPA (621-64-7)[2]	26.5
N-nitrosomethylphenidate[6]	1300
N-nitrosopiperidine (100-75-4)	1300

…Etc.

These limits are applicable only if a FP contains a single N-nitrosamine.

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Risk & Presence confirmed

Or... Non-mutagenic?

Toxicological data needed to
classify a nitrosamine as a Class 5 impurity

↓

Q&A, Q10, Guidance on use of Ames test

- **Negative** *in vitro* bacterial reverse mutation tests:
  - **Not sufficient** as **sole** evidence for **lack of mutagenic potential** for nitrosamines
  - Can be used as **part** of a weight of evidence approach, but additional supporting evidence would be required

- Internationally centralised assessment

- **Analytical methods** need sufficient sensitivity

- Quantitative test → LOQ ≤ acceptable limit based on the AI of the nitrosamine impurity.

- Quantitative testing to justify omission of a specification → LOQ of the analytical method ≤ 10% of the acceptable limit based on the AI of the nitrosamine impurity.

Reminder…

- To be provided for all new CEP applications

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

- For existing CEP applications:

Completion of *Step 2: Confirmatory Testing & Step 3: Update of CEP Application*
(refer to Q&A principles) by **1st October 2023**

**Summary and outcome of Risk Assessment to be provided in section 3.2.S.3.2
&
Other sections to be amended as needed**

**CEP holders should be supportive to MAHs
and provide them with relevant information**

Residual solvents

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

Control in API when

ICH Class 2 solvent		ICH Class 3 solvent		ICH Class 1 solvents as contaminant of another solvent
Used in last step	Used before last step **but** found >10% ICH limit in the API	Used in last step	Used before last step **but** found >10% ICH limit in the API *(CEP procedure)*	

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

Class 1 solvents as contaminant of another solvent

Control needed unless…

Option 1. Limit in originator solvent ensures that the class 1 solvent will be present in the API at levels <30% ICH limit. Taking into account the maximum likely level of contamination of the Class 1 solvent and volatility of both solvents.

Benzene (bp : 80.1°C) limited in toluene: NMT 500 ppm
Toluene (bp : 110.6 °C, purity NLT 99.5%) in API :
NMT 200 ppm, eliminated by **drying** in process

→ Theoretical Max level of benzene in API: 0.1 ppm
(ICH limit : 2 ppm)

Option 2. Class 1 solvent demonstrated < 30% ICH limit in an intermediate or API. Using a validated method, data on 6 consecutive pilot scale batches or 3 consecutive industrial scale batches.

Class 3 solvents & Certification Procedure

PA/PH/CEP (04) 1 :
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%. If the limit in the loss on drying test of the monograph is more than 0.5% then generally a specific test for residual solvents should be introduced.

```
Product monograph includes a test for
Loss on drying at NMT 0.5 %?
                │
      ┌─────────┴──────────────────┐
     Yes                           No
      │                             │ Alternatively
      │                   ┌─────────┴─────────────┐
Solvent can be       Specific method          Loss on drying
controlled in        - Validated ICH Q2 (R1)  Ph. Eur. 2.2.32
API by test for      - Appended to the CEP
Loss on drying of    Limit at NMT 5000 ppm    Limit at NMT 0.5%
the monograph        or 0.5%
```

Case study (fictitious)

SM2

SM1 — Step 1 / Acetic acid → INT-A

INT-A — Toluene / Step 2 / Dichloromethane → INT-B

INT-B — Step 3 / Dichloromethane / Ethyl acetate / Process water → INT-C

INT-C — Step 4 / Methanol / Triethylamine / Purified water → Crude API

Crude API — Purification/ Salification / Methanol / Ethyl acetate → API
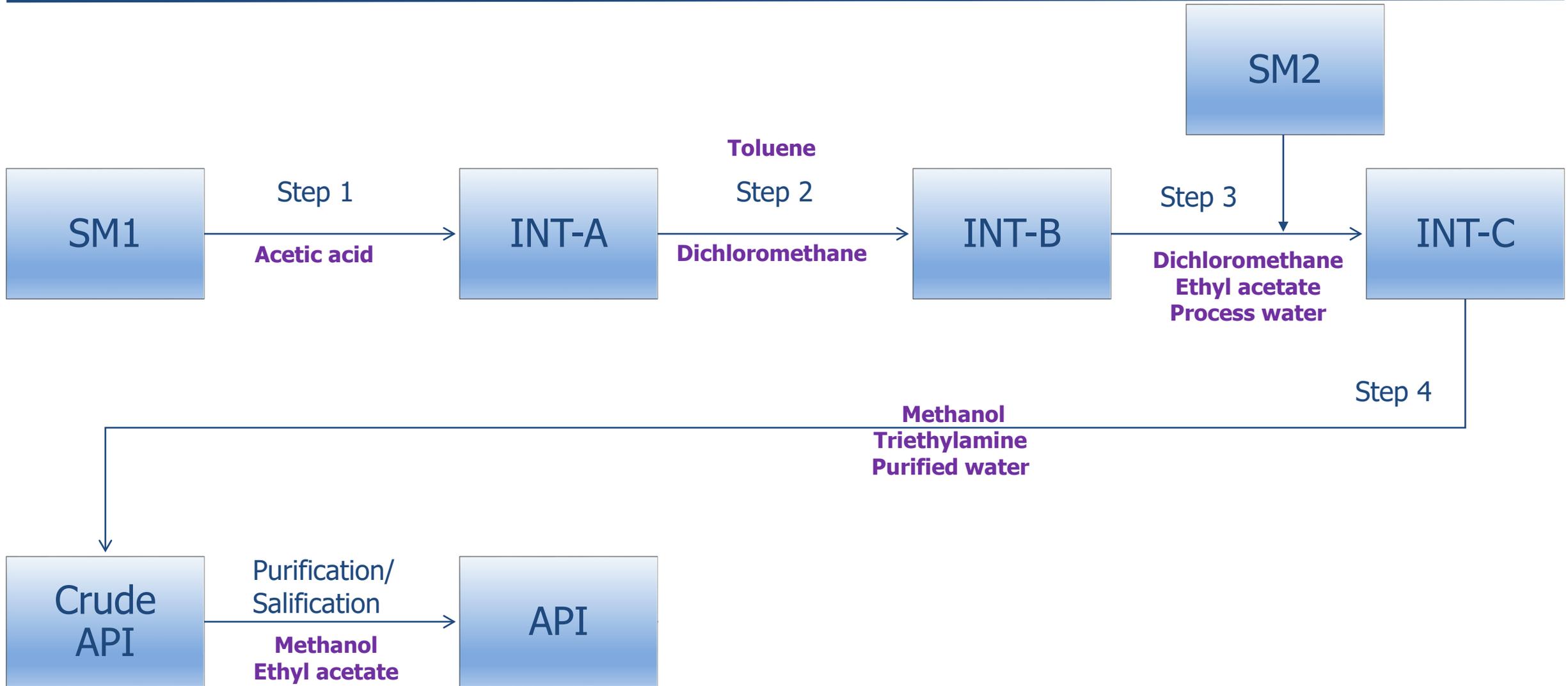
Case study : Which specifications?

Residual solvents

Solvent	Used in step X / 5	ICH classification	Typical levels in API	LOD (ppm)	Limit in API
Acetic acid	Step 1	Class 3 NMT 5000 ppm	ND	68	?
Toluene	*SM1,* Step 2	Class 2 NMT 890 ppm	ND-42ppm	7	?
Dichloromethane	*SM1,* Step 3, 4	Class 2 NMT 600 ppm	28-94 ppm	15	?
Ethyl acetate	Step 3, 5	Class 3 NMT 5000 ppm	BDL-567 ppm	49	?
Triethylamine	Step 4	Class 3 NMT 5000 ppm	ND	77	?
Methanol	Step 4, 5	Class 2 NMT 3000 ppm	ND	6	?
Benzene	As contaminant	Class 1 NMT 2 ppm	ND	0.5	?

Only water used as solvent in the manufacturing of SM2

Testing using GC methods (or other suitable) validated in line with ICH Q2 (R1)

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

Which specifications?

Residual solvents

Solvent	Used in step X / 5	ICH classification	Limit in API	Typical levels in API	LOD (ppm)
Acetic acid	Step 1	Class 3 NMT 5000 ppm	?	ND	68
Toluene	SM1, Step 2	Class 2 NMT 890 ppm	?	ND-42ppm	7
Dichloromethane	SM1, Step 3, 4	Class 2 NMT 600 ppm	?	28-94 ppm	15
Ethyl acetate	Step 3, 5	Class 3 NMT 5000 ppm	?	BDL-567 ppm	49
Triethylamine	Step 4	Class 3 NMT 5000 ppm	?	ND	77
Methanol	Step 4, 5	Class 2 NMT 3000 ppm	?	ND	6
Benzene	As contaminant	Class 1 NMT 2 ppm	?	ND	0.5

<10%ICH, not used last step

<10%ICH, not used last step

Only water used as solvent in the manufacturing of SM2

Which specifications?

Residual solvents

Solvent	Used in step X / 5	ICH classification	Limit in API	Typical levels in API	LOD (ppm)
Acetic acid	Step 1	Class 3 NMT 5000 ppm	X	ND	68
Toluene	SM1, Step 2	Class 2 NMT 890 ppm	X	ND-42ppm	7
Dichloromethane	SM1, Step 3, 4	Class 2 NMT 600 ppm	?	28-94 ppm	15
Ethyl acetate	Step 3, 5	Class 3 NMT 5000 ppm	?	BDL-567 ppm	49
Triethylamine	Step 4	Class 3 NMT 5000 ppm	X	ND	77
Methanol	Step 4, 5	Class 2 NMT 3000 ppm	?	ND	6
Benzene	As contaminant	Class 1 NMT 2 ppm	?	ND	0.5

<10%ICH, not used last step

<10%ICH, not used last step

Only water used as solvent in the manufacturing of SM2

Which specifications?

Solvent	Used in step X / 5	ICH classification	Limit in API	Typical levels in API	LOD (ppm)
Acetic acid	Step 1	Class 3 NMT 5000 ppm	X	ND	68
Toluene	SM1, Step 2	Class 2 NMT 890 ppm	X	ND-42ppm	7
Dichloromethane	SM1, Step 3, 4	Class 2 NMT 600 ppm	?	28-94 ppm	15
Ethyl acetate	Step 3, 5	Class 3 NMT 5000 ppm	?	BDL-567 ppm	49
Triethylamine	Step 4	Class 3 NMT 5000 ppm	X	ND	77
Methanol	Step 4, 5	Class 2 NMT 3000 ppm	?	ND	6
Benzene	As contaminant	Class 1 NMT 2 ppm	?	ND	0.5

⟹ Class 2, > 10%ICH limit

Only water used as solvent in the manufacturing of SM2

Which specifications?

Residual solvents

Solvent	Used in step X / 5	ICH classification	Limit in API	Typical levels in API	LOD (ppm)
Acetic acid	Step 1	Class 3 NMT 5000 ppm	X	ND	68
Toluene	SM1, Step 2	Class 2 NMT 890 ppm	X	ND-42ppm	7
Dichloromethane	SM1, Step 3, 4	Class 2 NMT 600 ppm	**NMT 600 ppm**	28-94 ppm	15
Ethyl acetate	Step 3, **5**	Class 3 NMT 5000 ppm	?	BDL-567 ppm	49
Triethylamine	Step 4	Class 3 NMT 5000 ppm	X	ND	77
Methanol	Step 4, **5**	Class 2 NMT 3000 ppm	?	ND	6
Benzene	As contaminant	Class 1 NMT 2 ppm	?	ND	0.5

⟹ Class 2, > 10%ICH limit

Only water used as solvent in the manufacturing of SM2

Which specifications?

Residual solvents

Solvent	Used in step X / 5	ICH classification	Limit in API	Typical levels in API	LOD (ppm)
Acetic acid	Step 1	Class 3 NMT 5000 ppm	x	ND	68
Toluene	SM1, Step 2	Class 2 NMT 890 ppm	x	ND-42ppm	7
Dichloromethane	SM1, Step 3, 4	Class 2 NMT 600 ppm	**NMT 600 ppm**	28-94 ppm	15
Ethyl acetate	Step 3, **5**	Class 3 NMT 5000 ppm	**?**	BDL-567 ppm	49
Triethylamine	Step 4	Class 3 NMT 5000 ppm	x	ND	77
Methanol	Step 4, **5**	Class 2 NMT 3000 ppm	**?**	ND	6
Benzene	As contaminant	Class 1 NMT 2 ppm	**?**	ND	0.5

Only water used as solvent in the manufacturing of SM2

Class 2, > 10%ICH limit

⟹ Used last step, no loss on drying test in the monograph

⟹ Used last step

Which specifications?

Residual solvents

Solvent	Used in step X / 5	ICH classification	Limit in API	Typical levels in API	LOD (ppm)
Acetic acid	Step 1	Class 3 NMT 5000 ppm	x	ND	68
Toluene	SM1, Step 2	Class 2 NMT 890 ppm	x	ND-42ppm	7
Dichloromethane	SM1, Step 3, 4	Class 2 NMT 600 ppm	**NMT 600 ppm**	28-94 ppm	15
Ethyl acetate	Step 3, **5**	Class 3 NMT 5000 ppm	**NMT 5000 ppm**	BDL-567 ppm	49
Triethylamine	Step 4	Class 3 NMT 5000 ppm	x	ND	77
Methanol	Step 4, **5**	Class 2 NMT 3000 ppm	**NMT 3000 ppm**	ND	6
Benzene	As contaminant	Class 1 NMT 2 ppm	?	ND	0.5

Class 2, > 10%ICH limit

→ Used last step, no loss on drying test in the monograph

→ Used last step

Only water used as solvent in the manufacturing of SM2

Which specifications?

Solvent	Used in step X / 5	ICH classification	Limit in API	Typical levels in API	LOD (ppm)
Acetic acid	Step 1	Class 3 NMT 5000 ppm	x	ND	68
Toluene	SM1, Step 2	Class 2 NMT 890 ppm	x	ND-42ppm	7
Dichloromethane	SM1, Step 3, 4	Class 2 NMT 600 ppm	**NMT 600 ppm**	28-94 ppm	15
Ethyl acetate	Step 3, **5**	Class 3 NMT 5000 ppm	**NMT 5000 ppm**	BDL-567 ppm	49
Triethylamine	Step 4	Class 3 NMT 5000 ppm	x	ND	77
Methanol	Step 4, **5**	Class 2 NMT 3000 ppm	**NMT 3000 ppm**	ND	6
Benzene	As contaminant	Class 1 NMT 2 ppm	**?**	ND	0.5

Only water used as solvent in the manufacturing of SM2

Class 2, > 10%ICH limit

⟹ Used last step

⟹ Used last step

Class 1 solvent as contaminant, <30% ICH limit

Which specifications?

Solvent	Used in step X / 5	ICH classification	Limit in API	Typical levels in API	LOD (ppm)
Acetic acid	Step 1	Class 3 NMT 5000 ppm	x	ND	68
Toluene	SM1, Step 2	Class 2 NMT 890 ppm	x	ND-42ppm	7
Dichloromethane	SM1, Step 3, 4	Class 2 NMT 600 ppm	**NMT 600 ppm**	28-94 ppm	15
Ethyl acetate	Step 3, **5**	Class 3 NMT 5000 ppm	**NMT 5000 ppm**	BDL-567 ppm	49
Triethylamine	Step 4	Class 3 NMT 5000 ppm	x	ND	77
Methanol	Step 4, **5**	Class 2 NMT 3000 ppm	**NMT 3000 ppm**	ND	6
Benzene	As contaminant	Class 1 NMT 2 ppm	**X**	ND	0.5

Class 2, > 10%ICH limit

Used last step

Used last step

Class 1 solvent as contaminant , <30% ICH limit

Only water used as solvent in the manufacturing of SM2

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

Specifications in Active substance

Residual solvents

> Outcome of discussion in section 3.2.S.3.2 → Specification as provided in section 3.2.S.4.1

Solvent	ICH classification	Limit in API
Dichloromethane	Class 2 NMT 600 ppm	NMT 600 ppm
Ethyl acetate	Class 3 NMT 5000 ppm	NMT 5000 ppm
Methanol	Class 2 NMT 3000 ppm	NMT 3000 ppm

NEW CEP 2.0

If other solvents included in section 3.2.S.4.1., these will be transparent on the CEP

Elemental impurities

- **ICH Q3D**

  - Covers 24 elements (classified under the classes 1, 2A, 2B and 3) and 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

Note

Principles also to be applied for substances for « veterinary use only » :

Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products (EMA/CVMP/QWP/153641/2018)

How to define the control strategy

The control strategy should focus on absence or presence of elemental impurities (e.g. metal catalysts) in the API

Absence in the API of an elemental impurity intentionally added
i.e. purged to a level consistently and convincingly **below 30% of the limit** which is defined considering:
- the indicated route of administration
- the ICH Q3D option 1 (API daily intake of NMT 10g) or option 2a when justified
- Analytical method identified, at least sensitivity (LOD/LOQ) to be provided

Presence in API for an elemental impurity intentionally added : if not demonstrated absent, a justified **specification** should be applied
- Analytical methods should be described in 3.2.S.4.2, validation in line with Q2(R1)

→ Specification limit in the API is usually expected for any elemental impurity introduced into the *last synthetic step* not demonstrated absent

Implementation of ICH Q3D in the CEP procedure

Elemental impurities

Two possible approaches :

No Risk management summary is prepared.

OR

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

Option encouraged by EDQM = facilitates risk assessment for medicinal product

→ besides the intentionally added elements the assessment should also cover all other potential elemental impurities from other sources

- Risk Management Summary **report** (summarised) which details the rationale of the study. Provide the reasons why impurities are considered + justification of the chosen control strategy + indicate the intended route of administration on which the risk assessment is based.

- to be completed with a **summary table** → intended to be annexed to the CEP

A batch screening does not replace a risk management summary

RMS/no-RMS : *with both scenarios specification at release if proposed by the applicant → mentioned on CEP*
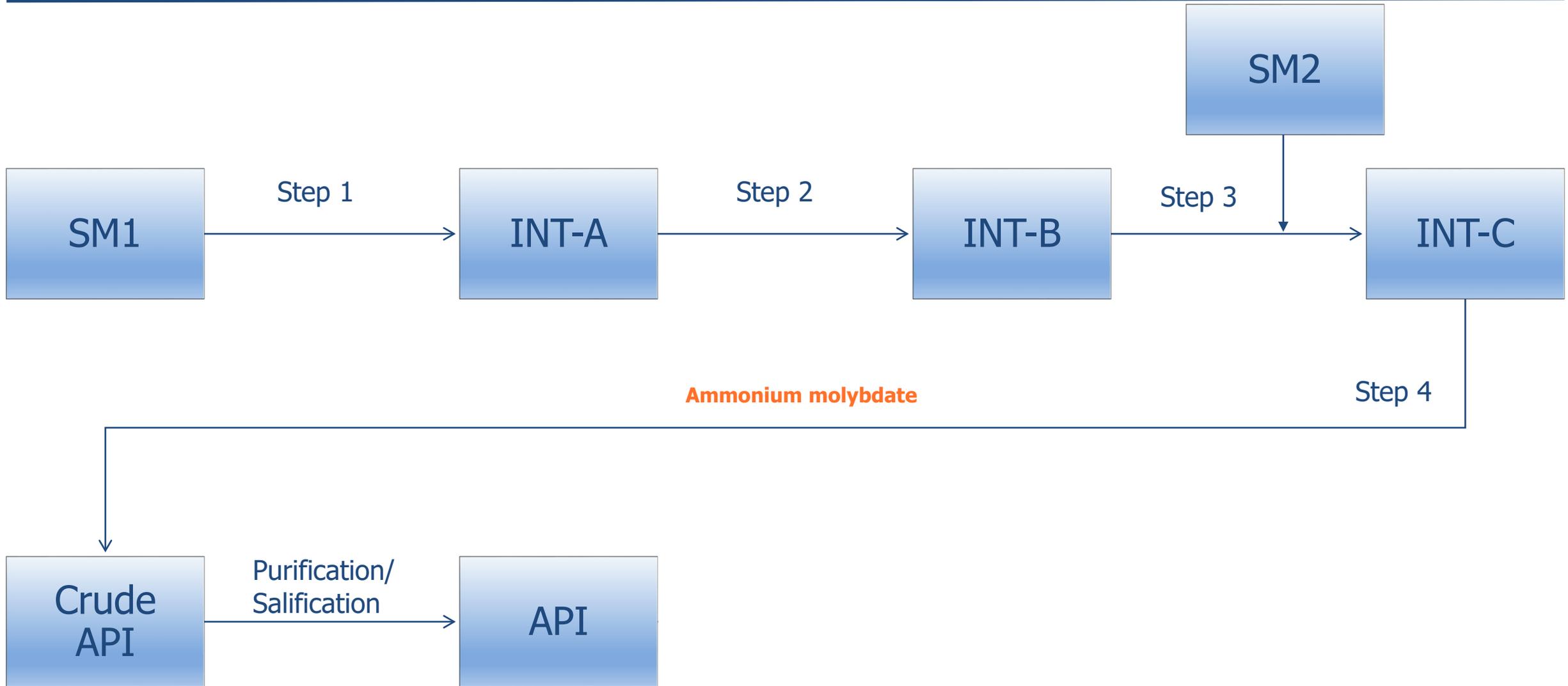
RMS approach:

Elements to be considered:

- elemental impurities derived from intentionally added catalysts and inorganic reagents

- Potential elemental impurities not intentionally added depending on the route of administration : see Table 5.1

- Potential elemental impurities derived from manufacturing equipment, water, leached from container closure system...
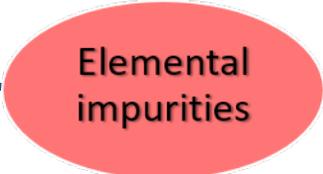
Table 5.1: Elements to be Considered in the Risk Assessment

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

Case study (fictitious)

SM2

SM1 →(Step 1)→ INT-A →(Step 2)→ INT-B →(Step 3)→ INT-C

Ammonium molybdate

Step 4

Crude API →(Purification/ Salification)→ API

Final substance (3.2.S.4.1) - Specification

Elemental impurities

Impurity	Limit	Batch data	Origin
Molybdenum	-	< 5 ppm	catalyst in step 4

- ICH Q3D Class 3 element
- Option 1 limit for parenteral administration: 1700 ppm
- → Control threshold : 510 ppm

Route of administration

Elements considered or not

Report a conclusion on absence or control

The control strategy followed should be clear and mentioned on the RMS:
- "**Absent**" should be defined (e.g. "less than 30% of ICH Q3D option 1 limit")
- or "**NMT limit in ppm**"calculated based on option 1 (or alternatively and if justified, based on option 2a)
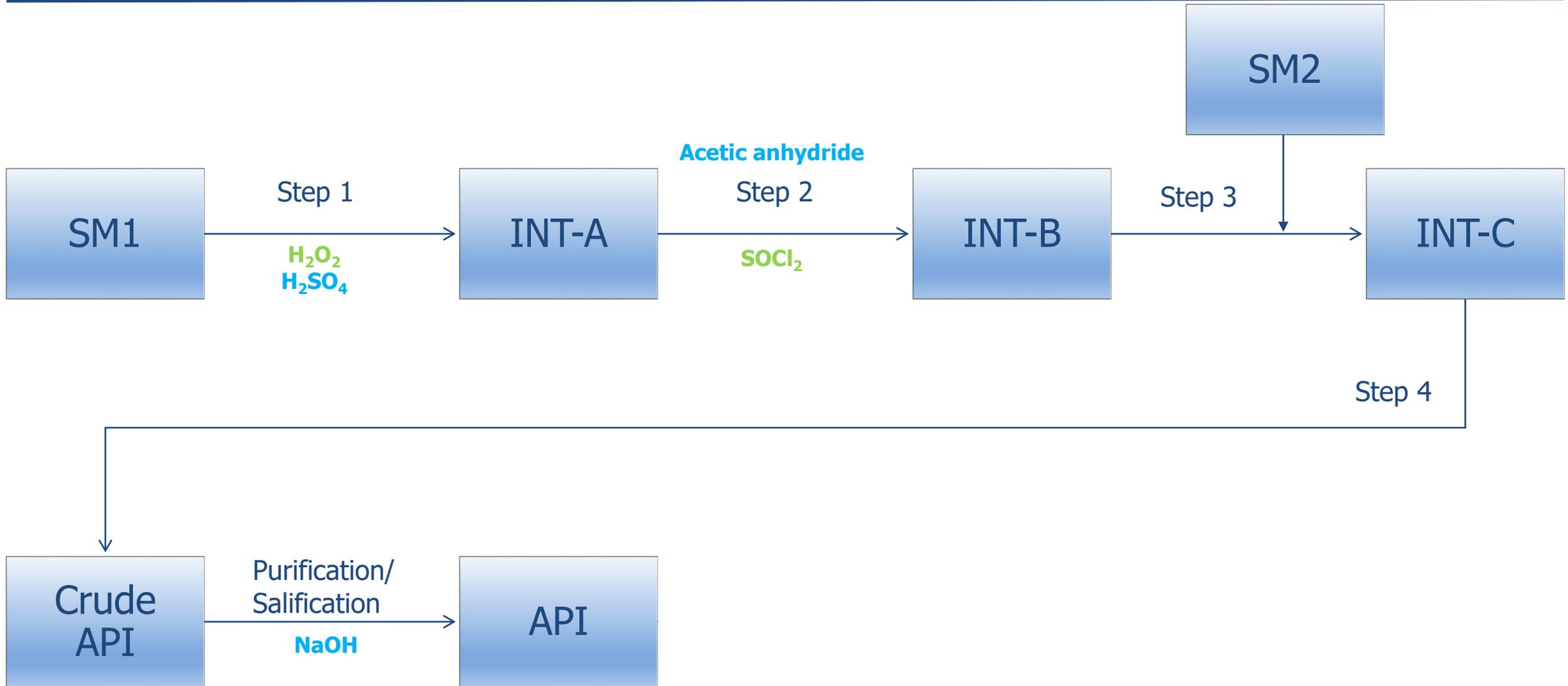- or "**No risk identified**"

If term « Absent » is used its definition is required

Route of administration considered in the risk assessment: parenteral

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	Absent
Au	2B	No	No	Absent
Pd	2B	No	No	Absent
Ir	2B	No	No	Absent
Os	2B	No	No	Absent
Rh	2B	No	No	Absent
Ru	2B	No	No	Absent
Se	2B	No	No	Absent
Ag	2B	No	No	Absent
Pt	2B	No	No	Absent
Li	3	No	Yes	Absent
Sb	3	No	Yes	Absent
Ba	3	No	No	Absent
Mo	3	Yes	Yes	Absent
Cu	3	No	Yes	Absent
Sn	3	No	No	Absent
Cr	3	No	No	Absent

NOTE: "Absent" means less than 30% of ICH Q3D option 1 limit

Reagents & Inorganic impurities

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

- Absence of carryover into the API is demonstrated using a validated method against a limit justified based on toxicological data

OR

- Routine control to be implemented at a suitable intermediate or final substance

Case study (fictitious)

Process flow diagram:

SM1 → Step 1 (H_2O_2, H_2SO_4) → INT-A → Step 2 (Acetic anhydride, $SOCl_2$) → INT-B → Step 3 → INT-C

SM2 → Step 3 → INT-C

INT-C → Step 4 → Crude API → Purification/Salification (NaOH) → API

Reagents & Inorganic impurities

Reagents	Origin, fate and carry over	Batch data	Limit
Acetic anhydride	Multiple steps up to the API. Low risk of carryover. Decomposes in water and NaOH, used ahead, to acetic acid which is demonstrated absent in the API.	x	x
Sulfuric acid	Washed along with water used in the manufacturing process.	x	x
Sodium hydroxide	Salt formation. Used last step. Carryover of residues controlled by the test for pH of the monograph.	x	x
Hydrogen peroxide	ICH M7 Class 1 impurity. Refer to section 3.2.S.3.2 – Mutagenic impurities.		
Thionyl chloride	ICH M7 Class 1 impurity. Refer to section 3.2.S.3.2 – Mutagenic impurities.		

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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