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

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Module 8:

Control of impurities : CEP approach

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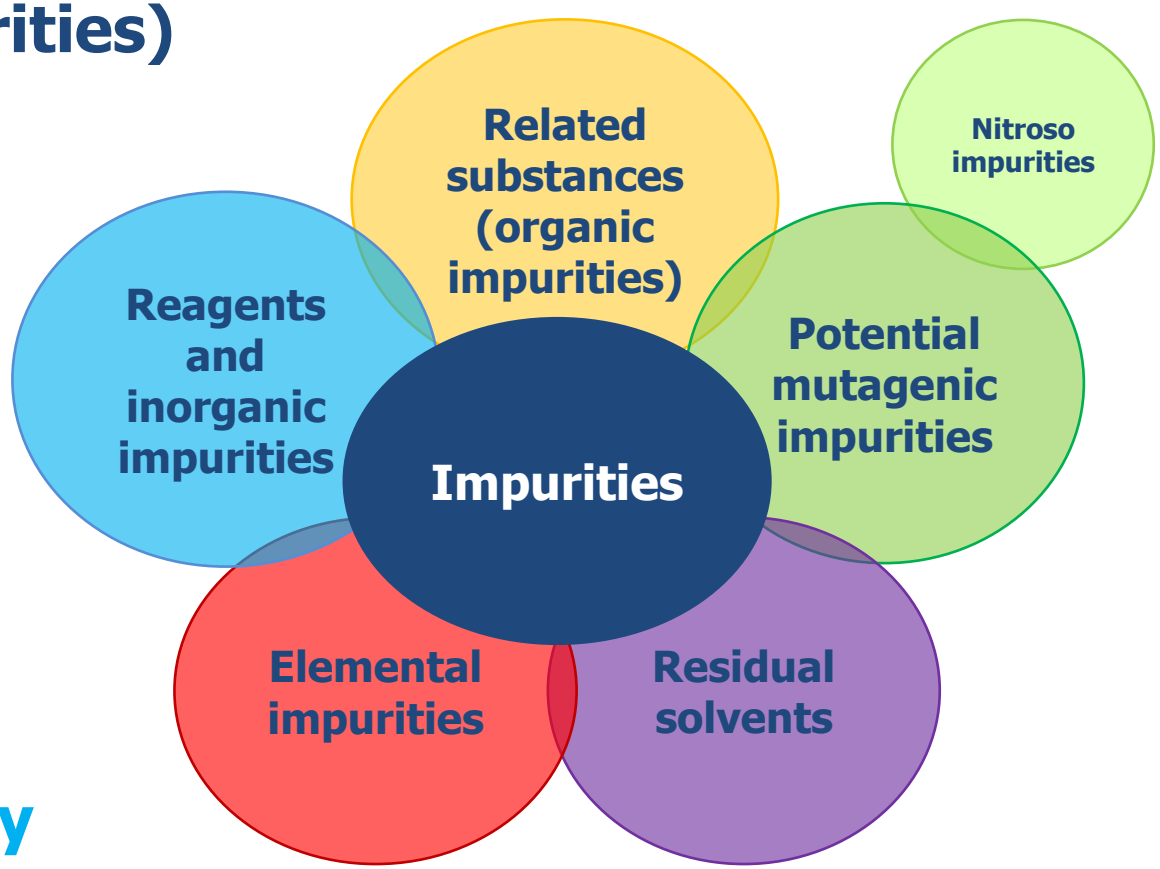
EDQM training 2024
12 December 2024 (10:00 – 11h30)

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?

**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 :
Content of the dossier for chemical purity and microbiological quality

PA/PH/CEP (23) 21:
Requirements for the content of the CEP dossier according to CEP 2.0

ICH / EMA

EDQM

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

Antibiotics only, where applicable: 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**

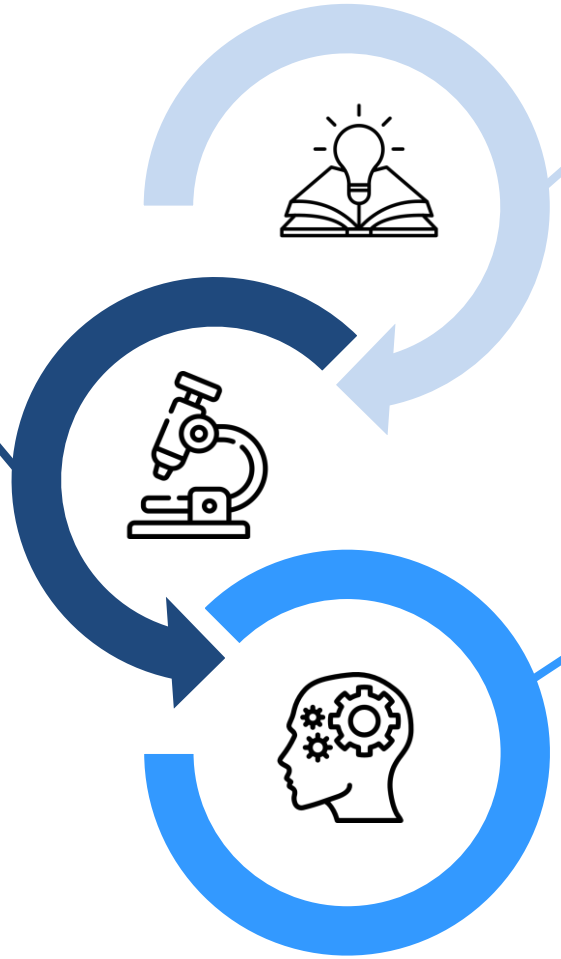
ICH Q3D ← Elemental impurities → **Ph. Eur. 5.20**
PA/PH/CEP(16)23: Implementation of policy on elemental impurities in the Certification Procedure

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

Expectations ?

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



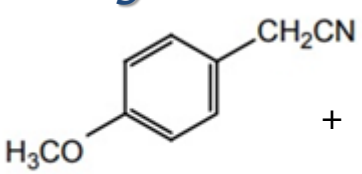
Analytical specifications should **control** the impurity profile and be **representative** of the process adopted

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)

Venlafaxine hydrochloride:

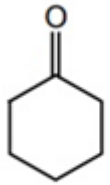
Stage-1



p-Methoxy phenyl acetonitrile

SM1

+



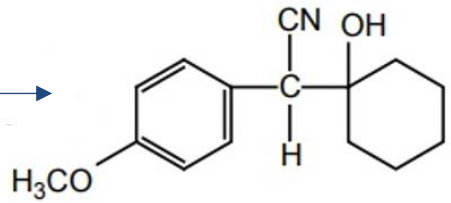
Cyclohexanone

SM2

Sodium hydroxide
TBAB

Toluene
Water

Stage-2

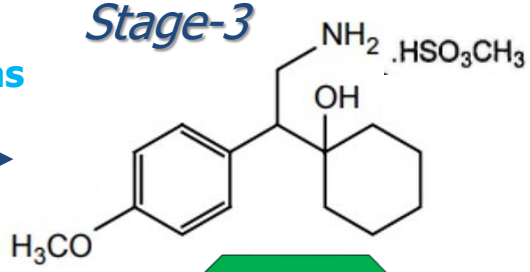


INT-A

Palladium/ hydrogen gas
methane sulfonic acid

Isopropanol
Methanol

Stage-3

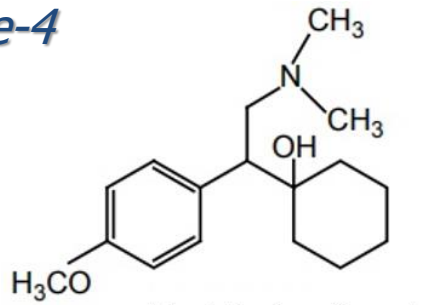


INT-B

Isopropanol
Toluene

Formic acid
Formaldehyde

Stage-4

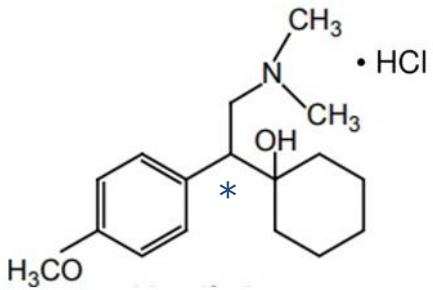


Venlafaxine (base)

INT-C

Hydrochloric acid

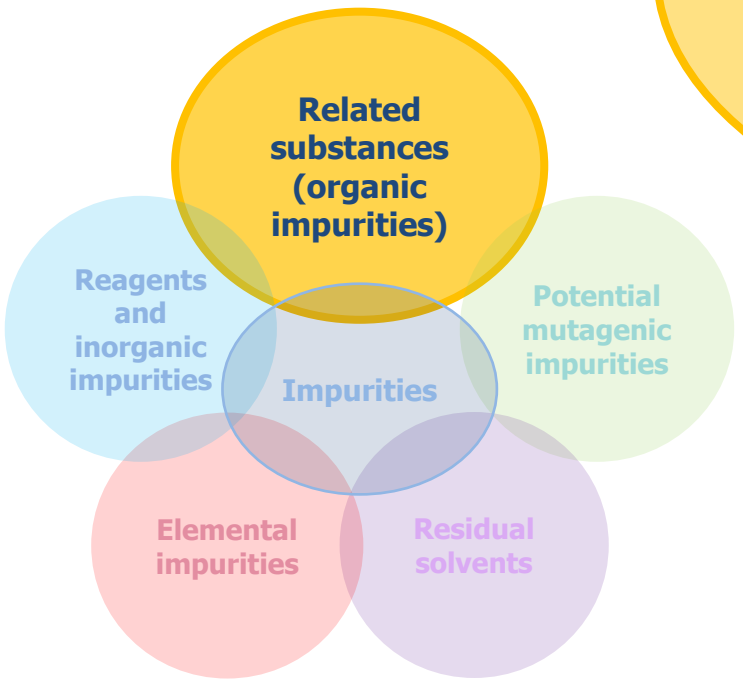
Ethanol



Venlafaxine hydrochloride

Racemic mixture

Organic impurities



Related substances (organic impurities)

Organic impurities

Related substances (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…

Related substances (Organic impurities)

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 of having uncontrolled impurities up to the API to ensure compliance

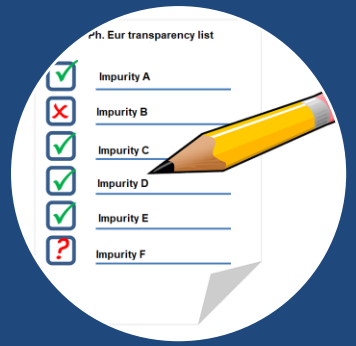
Special attention to be given to:

* **Intermediates late in the process** including the crude API
* Related substances controlled upstream by an analytical procedure **different** from the one at release
* **API-like impurities**

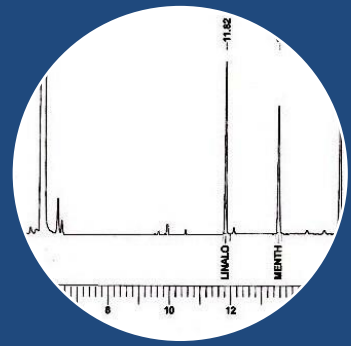
Certification of suitability to Ph. Eur. monographs

Related substances (Organic impurities)

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

Limits:

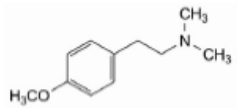
- *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
- *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Other detectable impurities may not be present in all processes. They are listed as detectable by the Ph. Eur. Monograph method.

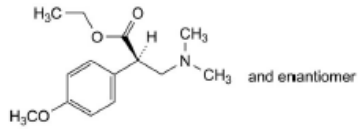
IMPURITIES

Specified impurities: F.

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, D, E, G, H.*

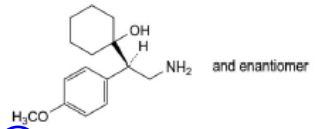


A. 2-(4-methoxyphenyl)-*N*,*N*-dimethylethanamine,

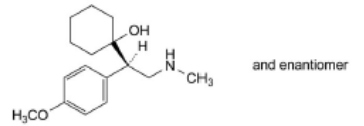


B. ethyl (2*RS*)-3-(dimethylamino)-2-(4-methoxyphenyl)-propanoate,

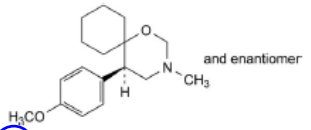
Other detectable (unspecified) impurities from the transparency list: NMT 0.10%



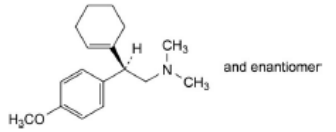
C. 1-[(1*RS*)-2-amino-1-(4-methoxyphenyl)ethyl]-cyclohexanol,



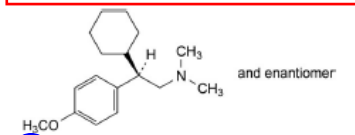
D. 1-[(1*RS*)-1-(4-methoxyphenyl)-2-(methylamino)ethyl]-cyclohexanol,



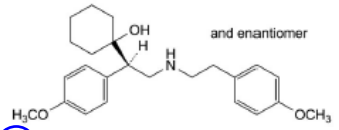
E. (5*RS*)-5-(4-methoxyphenyl)-3-methyl-1-oxa-3-azaspiro[5.5]undecane,



F. (2*RS*)-2-(cyclohex-1-enyl)-2-(4-methoxyphenyl)-*N*,*N*-dimethylethanamine,



G. (2*RS*)-2-cyclohexyl-2-(4-methoxyphenyl)-*N*,*N*-dimethylethanamine,



H. 1-[(1*RS*)-1-(4-methoxyphenyl)-2-[[2-(4-methoxyphenyl)-ethyl]amino]ethyl]cyclohexanol.

Related substances (Organic impurities)

Only specified impurity from the transparency list: NMT 0.1%

Case study: Venlafaxine hydrochloride

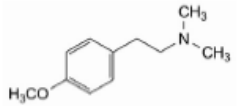
Related substances (Organic impurities)

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

IMPURITIES

Specified impurities: F.

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, D, E, G, H.*



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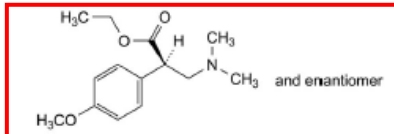
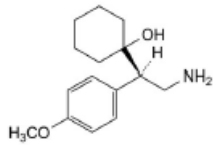
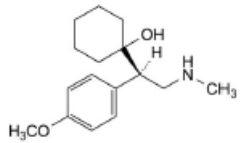


B. ethyl (2*RS*)-3-(dimethylamino)-2-(4-methoxyphenyl)-propanoate,

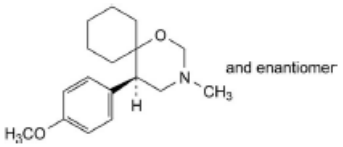
INT-B



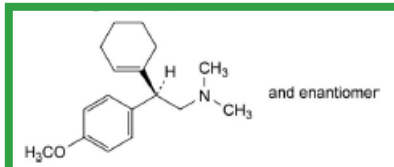
C. 1-[(1*RS*)-2-amino-1-(4-methoxyphenyl)ethyl]-cyclohexanol,



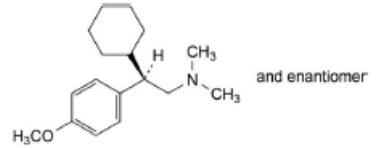
D. 1-[(1*RS*)-1-(4-methoxyphenyl)-2-(methylamino)ethyl]-cyclohexanol,



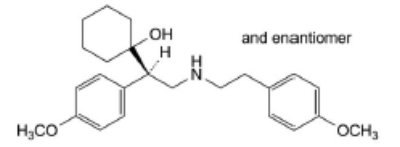
E. (5*RS*)-5-(4-methoxyphenyl)-3-methyl-1-oxa-3-azaspiro[5.5]undecane,



F. (2*RS*)-2-(cyclohex-1-enyl)-2-(4-methoxyphenyl)-*N*,*N*-dimethylethanamine,



G. (2*RS*)-2-cyclohexyl-2-(4-methoxyphenyl)-*N*,*N*-dimethylethanamine,



H. 1-[(1*RS*)-1-(4-methoxyphenyl)-2-[[2-(4-methoxyphenyl)-ethyl]amino]ethyl]cyclohexanol.

Ph. Eur. Imp A: unreacted SM1 carried over in Stage-1 and transformed, further carried over and transformed in Stage-2

Ph. Eur. Imp B: not from the same route of synthesis.

Ph. Eur. Imp C: intermediate B unreacted and carried over in final API,

Ph. Eur. Imp D: monomethylated impurity, derived from intermediate B,

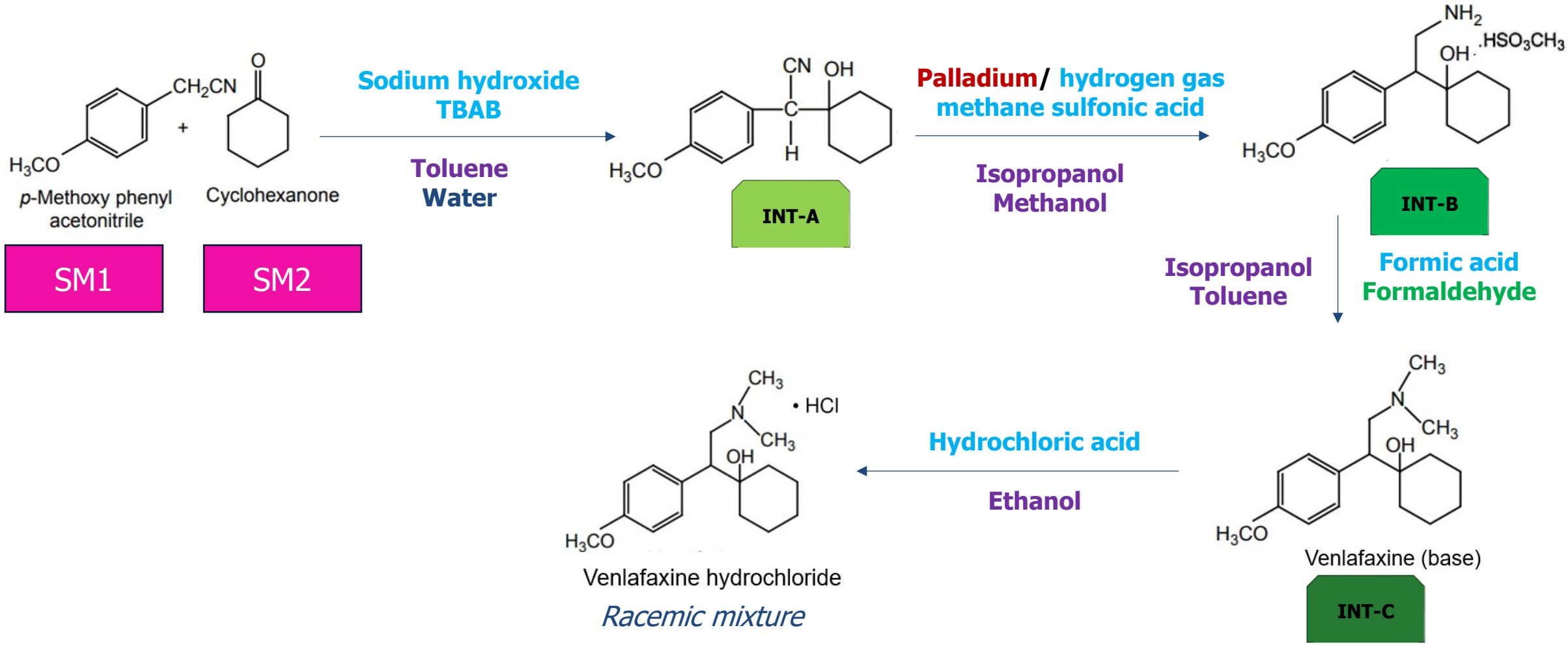
Ph. Eur. Imp E: cyclization with formaldehyde and Ph. Eur. Imp D during Stage-3,

Ph. Eur. Imp G: potentially formed by reduction of precursor impurity of Ph. Eur. Imp F,

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

Case study (fictitious)

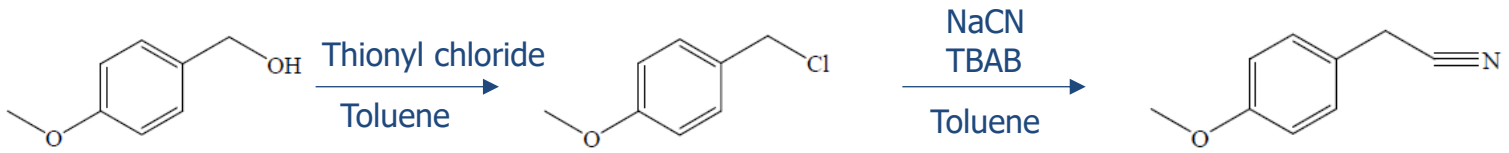
Venlafaxine hydrochloride:



Starting materials (3.2.S.2.3)

Related substances (Organic impurities)

SM1



Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
Thionyl chloride	Reactive reagent, hydrolyzed during work-up	ND	See **mutagenic impurities**
Precursor 1 4-methoxybenzyl alcohol	Precursor. Found <0.05% in INT-A.	0.21%	Controlled as specified impurity in the SM at NMT 1.0%
Precursor 2 4-methoxybenzyl chloride	Precursor, alerting structure (see **mutagenic impurities**).	0.02%	Controlled as specified impurity in the SM at NMT 0.15%
Impurity RRT 0.92	Likely by-product. Found <0.05% in INT-A. Fate impurity RRT 1.15, found 0.21% in INT-A.	0.25%	Controlled as specified impurity in the SM at NMT 0.40%

Which specification ?

Impurity	Limit
Precursor 1	NMT 1.0%
Precursor 2	NMT 0.15%
Impurity RRT 0.92	NMT 0.40%
Unspecified imp.	NMT 0.25%
Total	NMT 1.5%

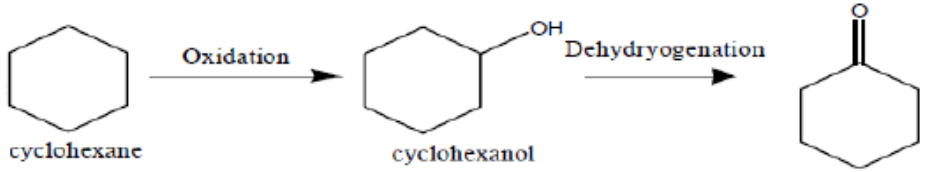
Fate: potential by-products, side-reactions should be considered as well!

Same exercise for SM2

Starting materials (3.2.S.2.3)

Related substances (Organic impurities)

SM2



Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
Precursor 1 (cyclohexane)	Precursor. Eliminated during filtration in INT-A. Found <0.05% in INT-A and in INT-B.	0.11%	Controlled as specified impurity in the SM at NMT 1.0%
Precursor 2 (cyclohexanol)	Precursor. Eliminated during filtration in INT-A. Found <0.05% in INT-A. Tested ND in INT-B.	0.13%	Controlled as specified impurity in the SM at NMT 0.20%
Impurity RRT 0.88	Likely by-product. Found <0.05% in INT-A.	0.06%	Controlled as unspecified impurity in the SM at NMT 0.15%

Which specification ?

Impurity	Limit
Precursor 1	NMT 1.0%
Precursor 2	NMT 0.20%
Unspecified imp.	NMT 0.15%
Total	NMT 1.5%

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

Intermediates (3.2.S.2.4)

Related substances (Organic impurities)

INT-A

Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
SM1	SM. Absent (<0.05%) in INT-B. Tested ND in API.	0.19%	Controlled as specified impurity at NMT 0.3%
Impurity RRT 1.15	From Imp RRT 0.92. Tested ND in API. Fate impurity found in Int-B (0.15%).	0.21%	Controlled as specified impurity at NMT 0.25%
SM2	SM. Absent (<0.05%) in INT-B. Tested ND in API. Fate impurity cyclohexanol, tested ND in INT-B.	0.53%	Controlled as specified impurity at NMT 1.0%

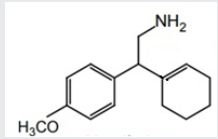
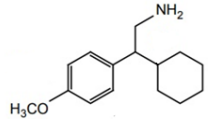
Which specification ?

Impurity	Limit
SM 1	NMT 0.3%
SM 2	NMT 1.0%
Impurity RRT 1.15	NMT 0.25%
Unspecified imp.	NMT 0.15%
Total	NMT 1.5%

Intermediates (3.2.S.2.4)

Related substances (Organic impurities)

INT-B

Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
SM1	SM. Absent (<0.05%) in Int-C	0.02%	Controlled as unspecified impurity
INT-A	Unreacted intermediate carried over. Eliminated during crystallisation of INT-C. When spiked at 2.0%, found ND in INT-C	0.58%	Controlled as specified impurity at NMT 2.0% in INT-B
Deshydrated impurity 	Dehydration of Int-B. Found ND in INT-C. Fate impurity: Ph. Eur. Imp F in Int-C/API, controlled as specified	0.32%	Controlled as specified impurity at NMT 0.80% in INT-B
Hydrogenated impurity 	Reduced impurity, found ND (< 0.05%) in Int-C. Fate impurity: Ph. Eur. Imp G in Int-C/API, controlled as unspecified	0.06%	Controlled as unspecified impurity at NMT 0.15% in INT-B
Impurity RRT 1.20	Process impurity, originating from Int A	0.15%	Controlled as specified impurity at NMT 0.20% in INT-B

Which specification ?

Impurity	Limit
Int-A	NMT 2.0%
Dehydrated imp	NMT 0.80%
Impurity RRT 1.20	NMT 0.20%
Unspecified imp.	NMT 0.15%
Total	NMT 3.0%

Intermediates (3.2.S.2.4)

Related substances (Organic impurities)

INT-C

Impurity	Origin, fate and carry over	Batch data	Limit/Control strategy
Ph. Eur. Imp F	Dehydration impurity. Removed during crystallization stage	0.38%	Controlled as specified impurity at NMT 0.50% in INT-C and at NMT 0.1% in API
INT-B (Ph. Eur. Imp C)	Process impurity. Removed during crystallization. Found <0.05% in API	0.27%	Controlled as specified impurity at NMT 0.40% in INT-C and as unspecified impurity in the API
Ph. Eur. Imp D	Process impurity, uncomplete methylation. Found <0.05% in API	0.09%	Controlled as unspecified impurity at NMT 0.10% in INT-C and in the API
Impurity RRT 1.10	From previous step. Found <0.05% in API	0.11%	Controlled as specified impurity at NMT 0.15% in INT-C and in the API as unspecified impurity

Which specification ?

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

Impurity	Limit
Ph. Eur. Imp F	NMT 0.50%
INT-B	NMT 0.40%
Impurity RRT 1.10	NMT 0.15%
Unspecified imp.	NMT 0.10%
Total	NMT 1.0%

It is expected that special attention should be paid to the impact of impurities generated/carried-over from the latest intermediates to the API.

Overview of the control strategy

Related substances (Organic impurities)

		SM1	SM2	Int-A	Int-B	Int-C	API	Origin, fate and carry over	Limit/Control strategy
SM1	**Precursor 1**	0.21%		ND				Precursor SM1. Found ND in Int-A & B	Controlled in SM1 at NMT 1.0%.
	Precursor 2	0.02%		ND	ND		ND	Precursor SM1, potential mutagenic impurity (Class 3). Found ND in Int-A.	Controlled in SM1 at NMT 0.15%. Discussed under mutagenic impurities.
	RRT 0.92	0.25%		ND				By-product. Found ND in Int-A	Controlled in SM1 at NMT 0.40%, as unsp. in INT-A.
SM2	**Cyclohexane**		0.11%	0.02%	ND	ND		Precursor of SM2, eliminated through washings, absent in Int-B, C and API	Controlled in SM2 at **NMT 1.0%**, tested ND in INT-C as residual solvent
	Cyclohexanol		0.08%	ND	ND			Precursor of SM2, absent in Int-B	Controlled in SM2 at **NMT 0.25%.**
Int-A	**SM1**			0.89%	0.02%		ND	Unreacted SM1, 0.02% in Int-B, tested ND in API	Controlled in INT-A at **NMT 1.0%**, as unsp. in INT-B.
	SM2			0.53%	ND		ND	Unreacted SM2, absent in Int-B, tested ND in API	Controlled in Int-A at **NMT 1.0%** and in INT-B and API as unspecified.
	RRT 1.15			0.21%	ND			ate imp. RRT 1.20	Controlled in Int-A at NMT 0.25%.
Int-B	**INT-A**				0.58%			ND in Int-C	Controlled in INT-B as specified at **NMT 2.0%**.
	Dehydro				0.32%	ND		Process imp. Found ND in Int-C.	Controlled in INT-B as specified at **NMT 0.80%**.
	Hydrogenated				0.06%	ND		Process imp. Found ND in Int-C.	Controlled in INT-B as unspecified at **NMT 0.15%**.
	RRT 1.20				0.15%	ND	ND	From imp RRT 1.15, fate imp. RRT 1.10	Controlled in INT-B as specified at **NMT 0.20%**.
Int-C	**INT-B (Ph. Eur. Imp. C)**					0.27%	*Unsp.*	Int. carried in Int-C. Eliminated during crystallization of API.	Controlled in INT-C as specified at **NMT 0.40%** and as unspec. impurity in API.
	Ph. Eur. Imp F					0.38%	Spec.	Process impurity from dehydro imp. & deg API.	Controlled in Int-C as specified at **NMT 0.50%**, in API at **NMT 0.1%**.
	RRT 1.10					0.11%	*Unsp.*	From imp. RRT 1.20. Found at 0.02% in API	Controlled in Int-C at **NMT 0.15%**, in API as unspec. impurity.

Can be included in the Quality Overall Summary

Case study: Venlafaxine hydrochloride

Related substances (Organic impurities)

Related substances. Liquid chromatography (*2.2.29*).

Limits:

- *impurity F*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
- *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Venlafaxine hydrochloride specification:

Impurity	Limit	Batch data	Method
Ph. Eur. Impurity F	NMT 0.1 %	0.09-0.13%	Ph. Eur. Current edition
Unspecified impurity	NMT 0.10%	<0.05-0.07%	
Total impurities	NMT 0.2%	0.14-0.20%	

In this case, related substances are controlled by the transparency list of the monograph

No in-house impurity present (i.e. >0.05%) in the API

Different situations…

Related substances (Organic impurities)

If in-house impurities are present?

If you are using an in-house analytical procedure?

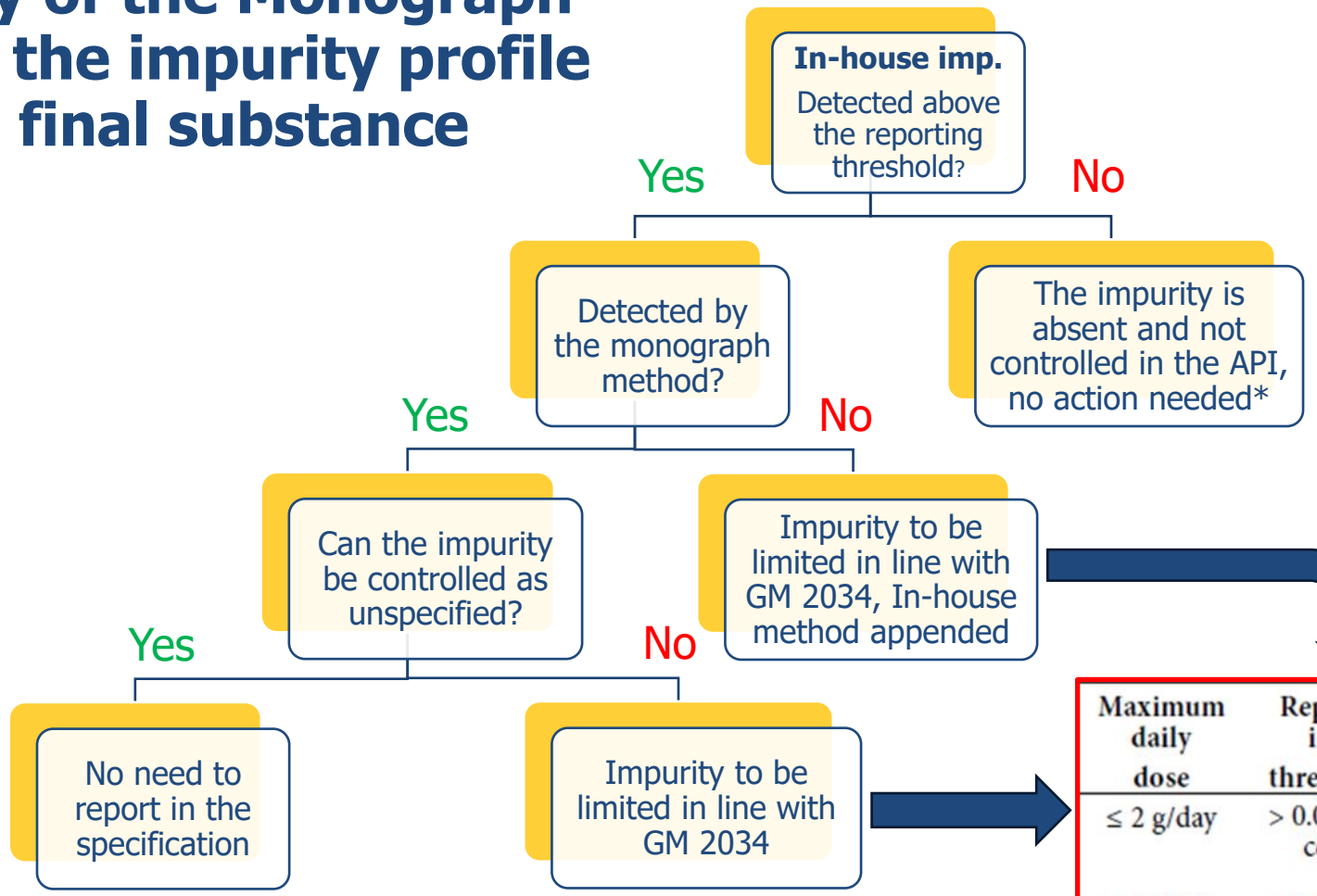
How to handle the situation?

Which impurity to include in the specification?

In-house impurities

Related substances (Organic 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 method 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 …

Related substances (Organic impurities)

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 CEP
  - Validation in line with ICH Q2(R2)

Case study: Venlafaxine hydrochloride

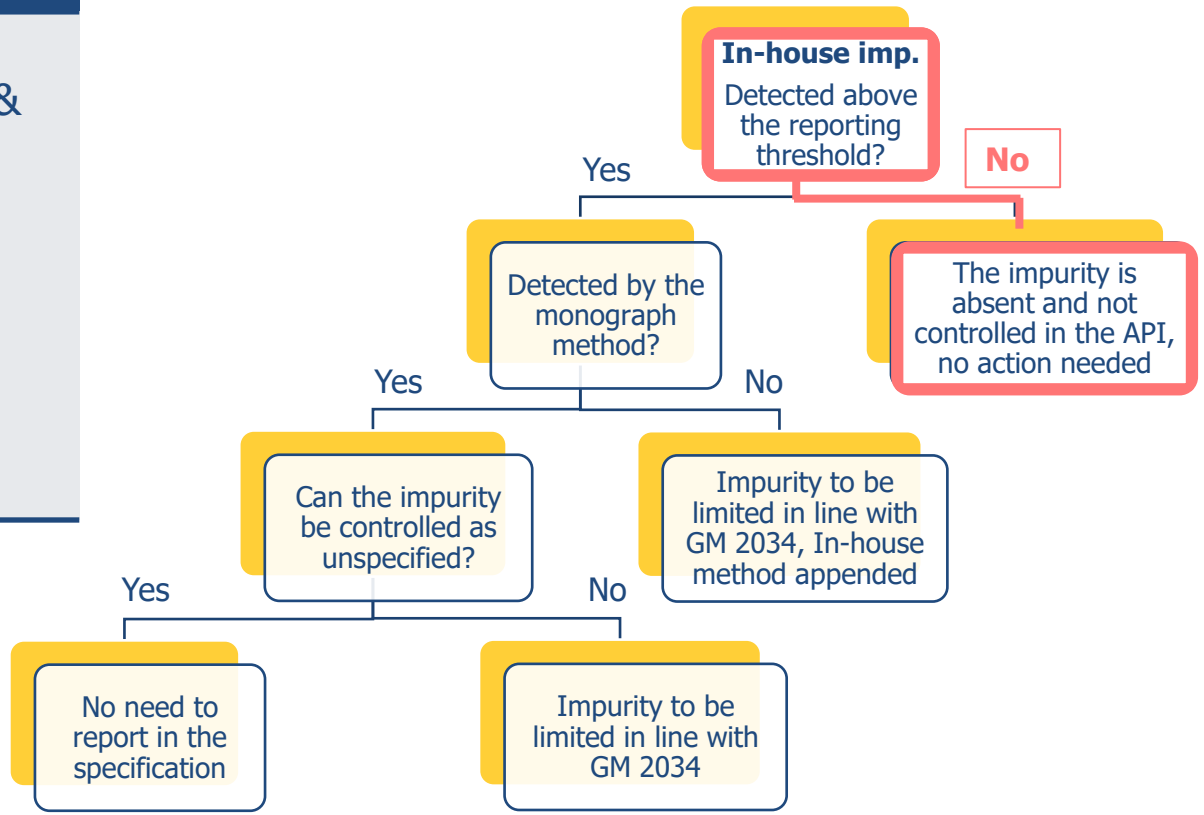
Related substances (Organic impurities)

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

Impurity	Limit	Batch data	Method
Ph.Eur. Impurity F	NMT 0.1%	0.05-0.08%	HPLC 2.2.29 & Ph. Eur. 2119
In-house impurity 1	**?**	**0.001-0.02%**	
In-house impurity 2		**0.04-0.06%**	
In-house impurity 3 (RRT 1.10)		**0.08-0.12%**	
Unspecified impurity	NMT 0.10%	0.01-0.04%	
Total impurities	NMT 0.2%	0.14-0.23%	

Reporting threshold: 0.05%

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



Case study: Venlafaxine hydrochloride

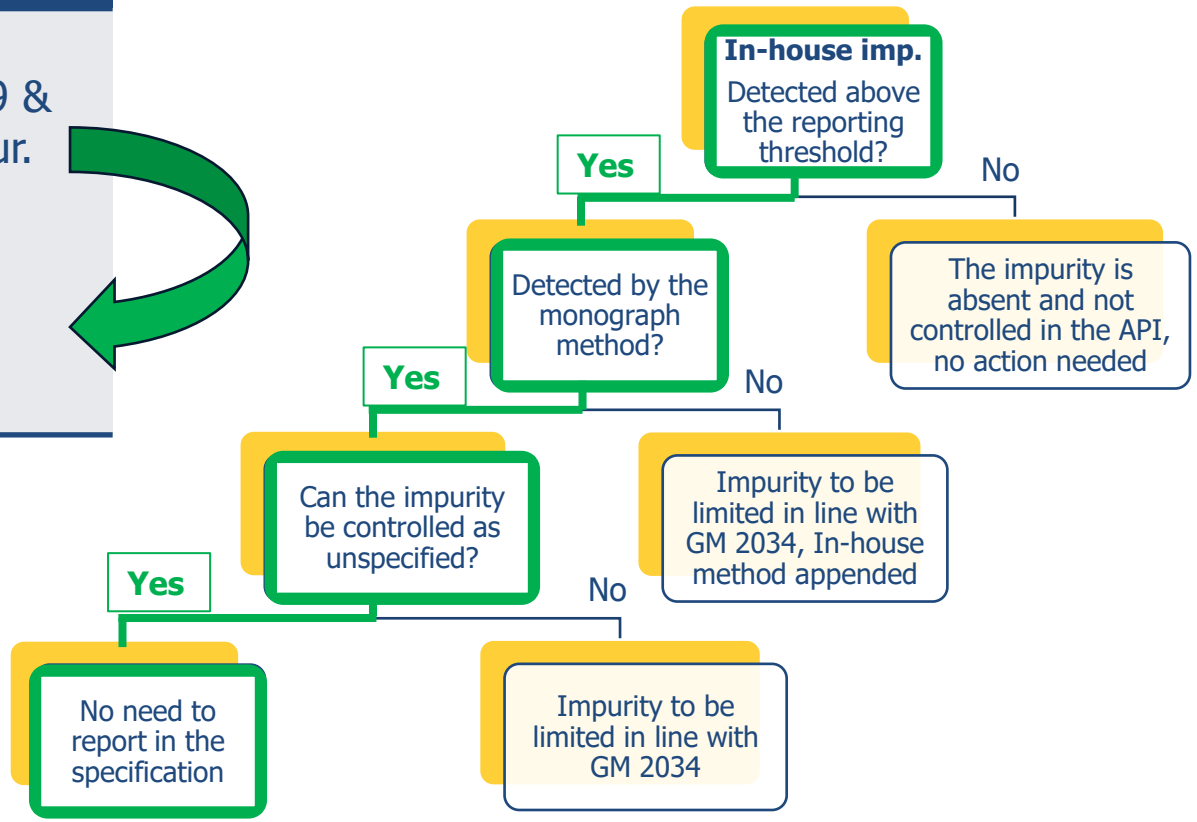
Related substances (Organic impurities)

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

Impurity	Limit	Batch data	Method
Ph.Eur. Impurity F	NMT 0.1%	0.05-0.08%	HPLC 2.2.29 & Ph. Eur. 2119
In-house impurity 2	**?**	**0.04-0.06%**	
In-house impurity 3 (RRT 1.10)		**0.08-0.12%**	
Unspecified impurity	NMT 0.10%	0.01-0.06%	
Total impurities	NMT 0.2%	0.14-0.23%	

Reporting threshold: 0.05%

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



Case study: Venlafaxine hydrochloride

Related substances (Organic impurities)

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

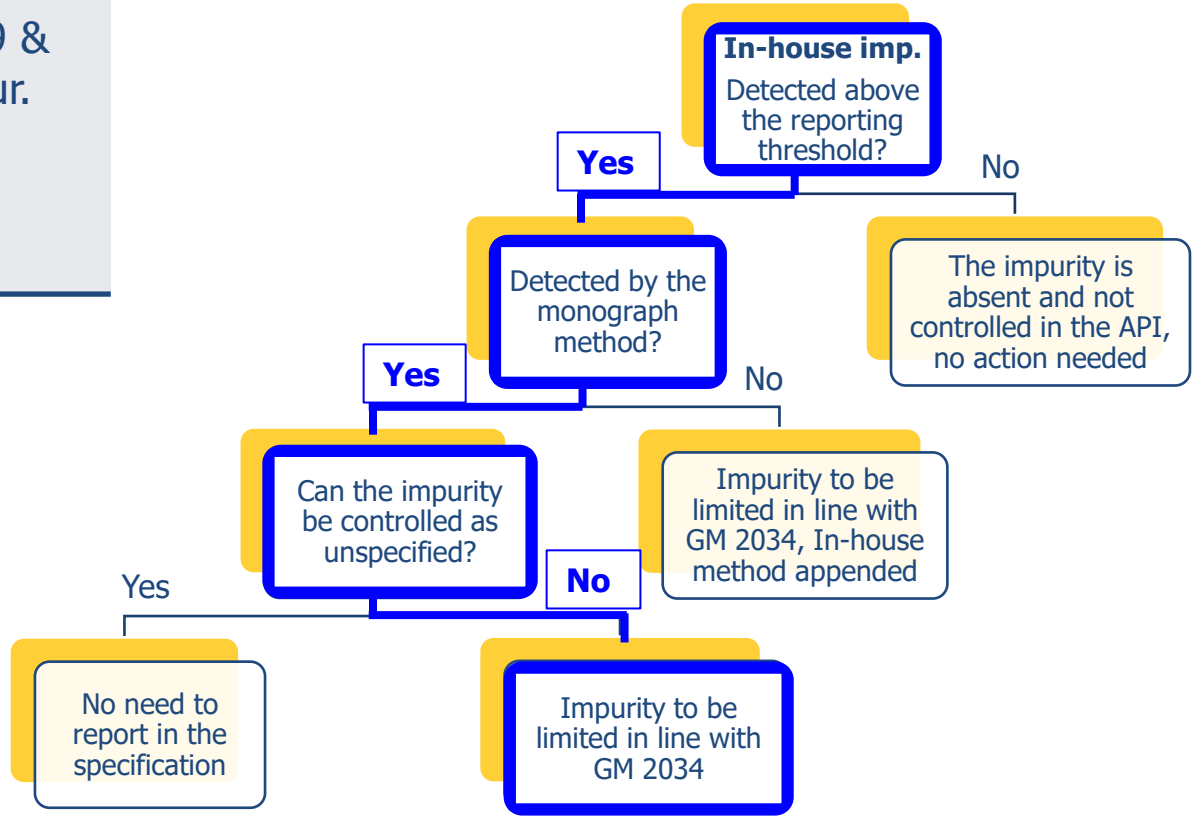
Impurity	Limit	Batch data	Method
Ph.Eur. Impurity F	NMT 0.1%	0.05-0.08%	HPLC 2.2.29 & Ph. Eur. 2119
In-house impurity 3 (RRT 1.10)	**NMT 0.15%**	**0.08-0.12%**	
Unspecified impurity	NMT 0.10%	0.01-0.06%	
Total impurities	NMT 0.2%	0.14-0.23%	

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

Have to demonstrate biological safety of the impurity at its level



Case study: Venlafaxine hydrochloride

Related substances (Organic impurities)

Specification for related substances:

Impurity	Limit	Batch data	Method
Ph.Eur. Impurity F	NMT 0.1%	0.05 - 0.08%	Ph. Eur. current edition
In-house impurity 3 (RRT 1.10)	NMT 0.15%	0.08 - 0.12%	
Unspecified impurity	NMT 0.10%	<0.05 - 0.06%	
Total impurities	NMT 0.2%	0.14 - 0.23%	

CEP 2.0

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

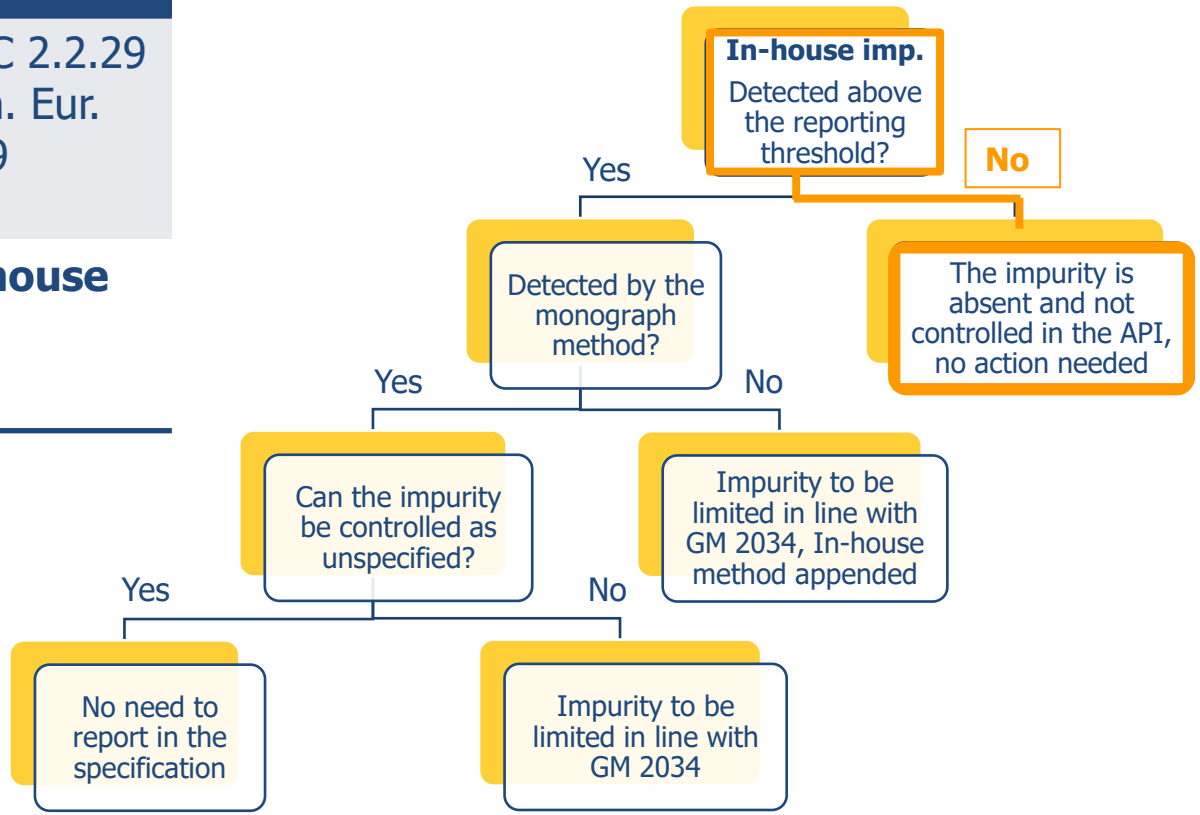
Case study: Venlafaxine hydrochloride

Related substances (Organic impurities)

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

Impurity	Limit	Batch data	Method
Ph. Eur. Impurity F	NMT 0.1%	0.05-0.08%	HPLC 2.2.29 & Ph. Eur. 2119
Unspecified impurity	NMT 0.10%	0.01-0.06%	
Total impurities	NMT 0.2%	0.18-0.23%	
In-house impurity 4	**?**	**0.01-0.03%**	**In-house**
In-house impurity 5 (RRT 1.10)		**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 method to be appended

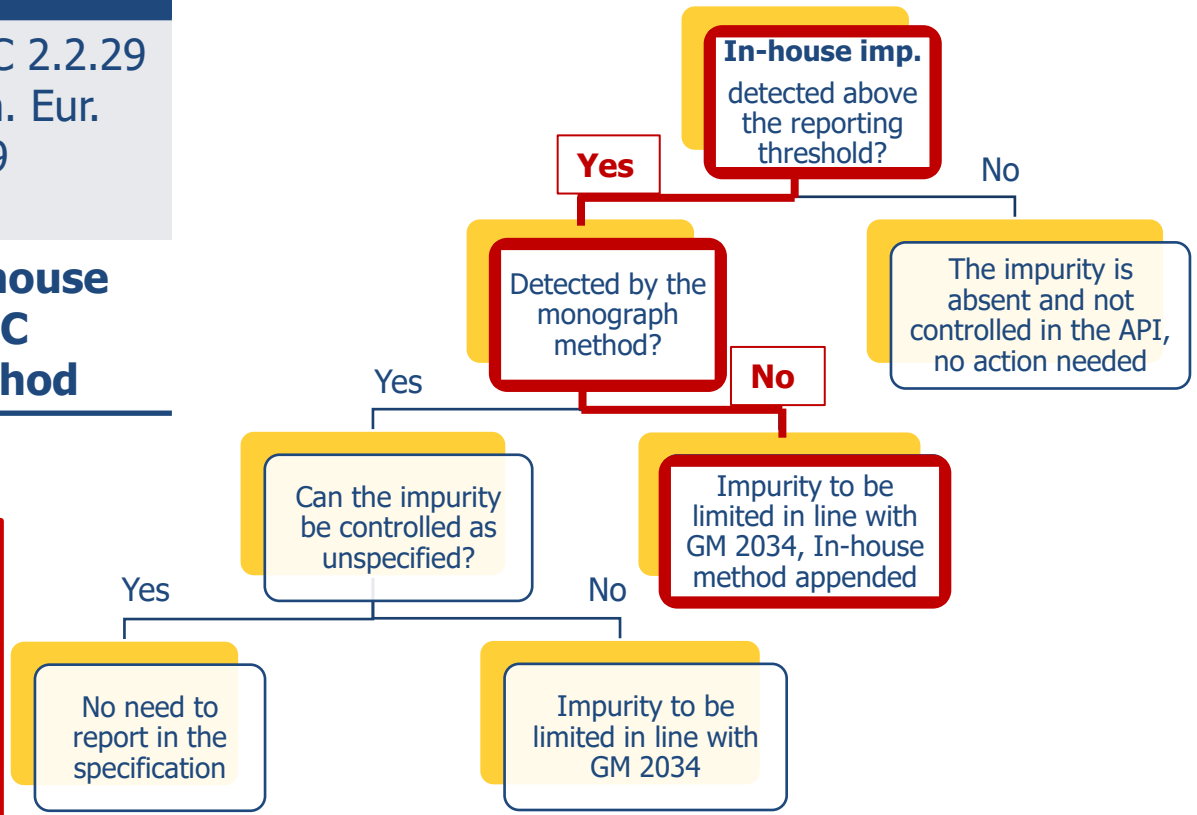
Case study: Venlafaxine hydrochloride

Related substances (Organic impurities)

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

Impurity	Limit	Batch data	Method
Ph. Eur. Impurity F	NMT 0.1%	0.05-0.08%	HPLC 2.2.29 & Ph. Eur. 2119
Unspecified impurity	NMT 0.10%	0.01-0.06%	
Total impurities	NMT 0.2%	0.18-0.23%	
In-house impurity 5 (RRT 1.10)	**?**	**0.05-0.11%**	**In-house HPLC method**

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 method will be appended to the CEP.

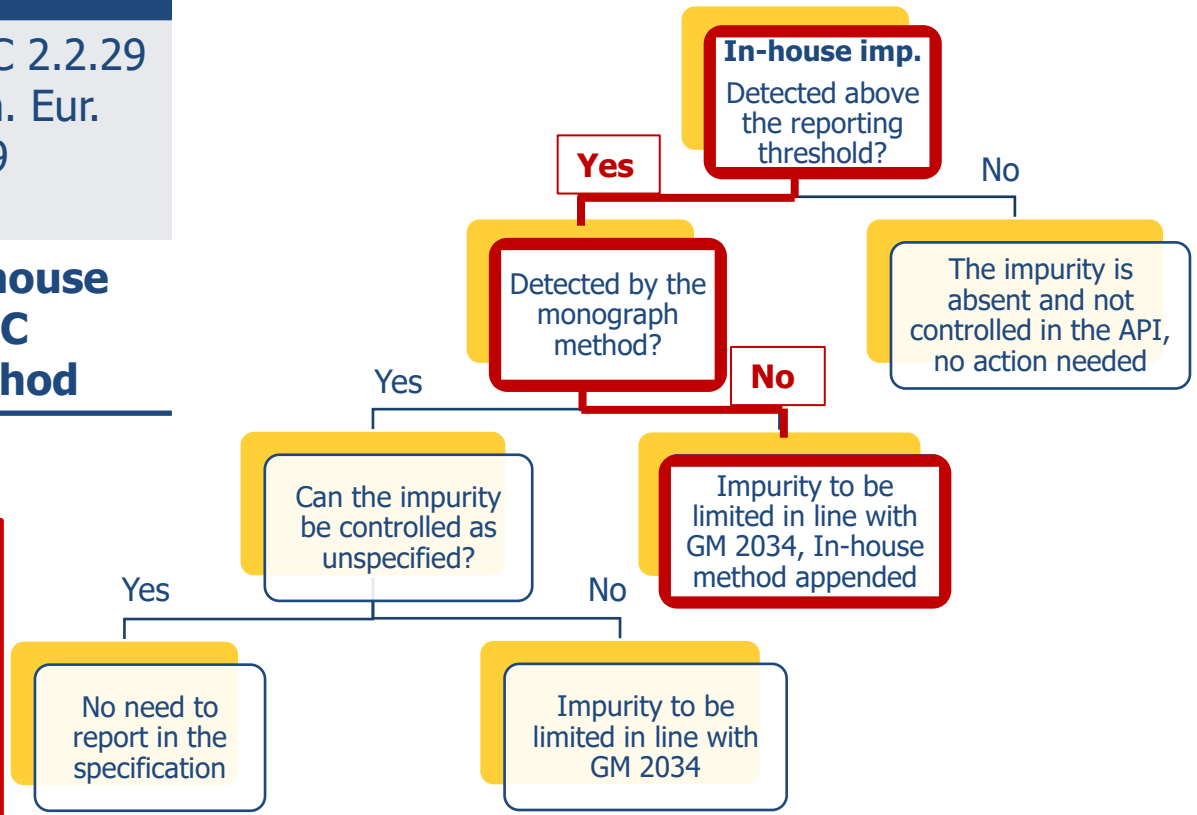
Case study: Venlafaxine hydrochloride

Related substances (Organic impurities)

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

Impurity	Limit	Batch data	Method
Ph. Eur. Impurity F	NMT 0.1%	0.05-0.08%	HPLC 2.2.29 & Ph. Eur. 2119
Unspecified impurity	NMT 0.10%	0.01-0.06%	
Total impurities	NMT 0.2%	0.18-0.23%	
In-house impurity 5 (RRT 1.10)	**NMT 0.15%**	**0.05-0.11%**	**In-house HPLC method**

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 method will be appended to the CEP.

Case study: Venlafaxine hydrochloride

Related substances (Organic impurities)

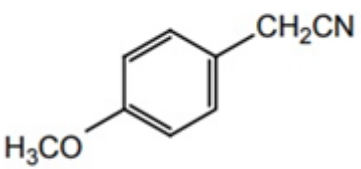
Specification for related substances:

Impurity	Limit	Batch data	Method
Ph.Eur. Impurity F	NMT 0.1%	0.05 – 0.08%	Ph. Eur. current edition
Unspecified impurity	NMT 0.10%	0.01 – 0.06%	
Total impurities	NMT 0.2%	0.18 – 0.23%	
In-house impurity 5 (RRT 1.10)	NMT 0.15%	0.05 – 0.11%	**In-house**

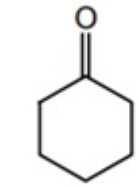
CEP 2.0

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

Carry-over of impurities



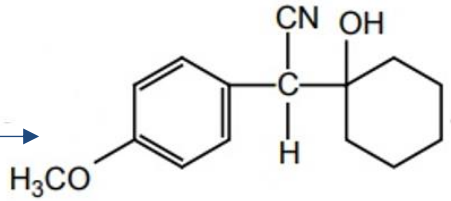
p-Methoxy phenyl acetonitrile

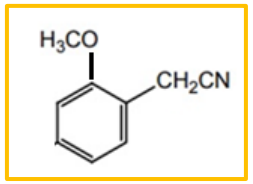


Cyclohexanone

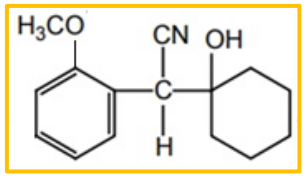
Sodium hydroxide
TBAB

Toluene
Water





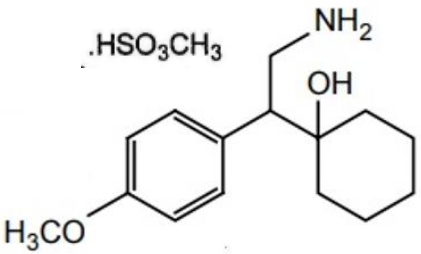
Imp RRT 0.92
NMT 0.40%

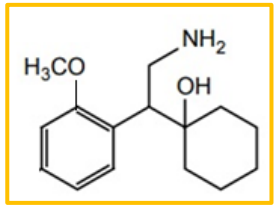


Imp RRT 1.15
NMT 0.25%

Palladium/ hydrogen gas
methane sulfonic acid

Isopropanol
Methanol

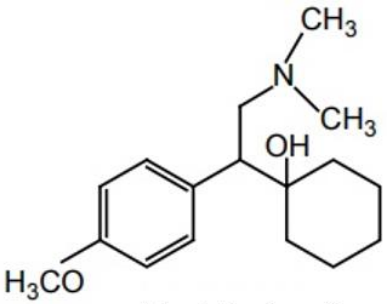




Imp RRT 1.20
NMT 0.20%

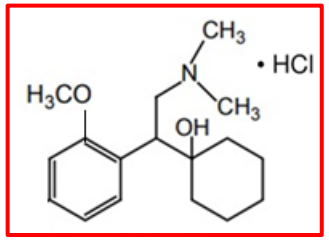
Isopropanol
Toluene

Formic acid
Formaldehyde

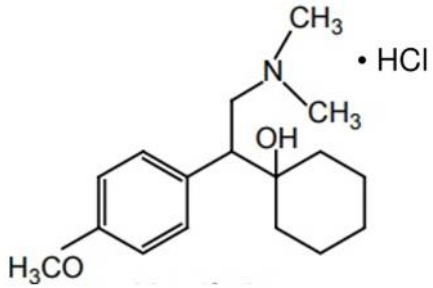


Venlafaxine (base)

No alerting structure



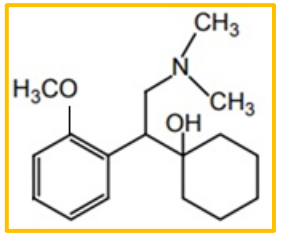
Impurity RRT 1.10
NMT 0.15%



Venlafaxine hydrochloride
Racemic mixture

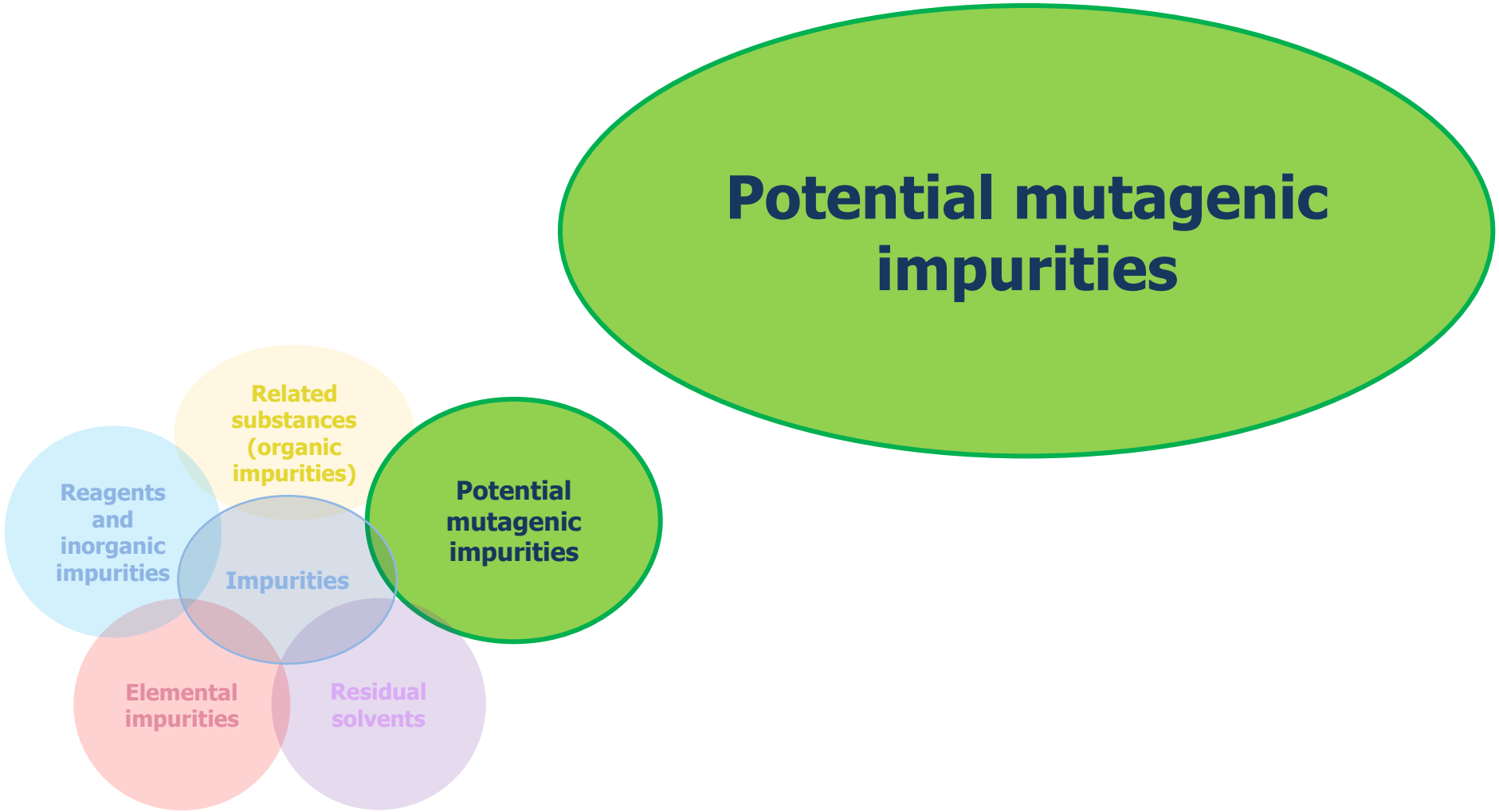
Hydrochloric acid

Ethanol



Imp RRT 1.10
NMT 0.15%

Mutagenic impurities



Mutagenic impurities

Potential 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 intakes
- **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 mutagen	**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

Potential 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

Potential mutagenic impurities

2) Hazard assessment and classification as per ICH M7

ICH M7: There is an expectation that structural alert assessment will be conducted using (Q)SAR prediction.

→ *In-silico* assessment is expected using (Quantitative) Structure-Activity Relationships (SAR) that predict bacterial mutagenicity

→ Two complementary (Q)SAR systems:

Expert-rule based and statistical based

Class 1 : Specific permitted daily exposure (ICH M7 addendum)

Class 2 : No specific permitted daily exposure (TTC approach)

Class 3 : Unstudied mutagenicity

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

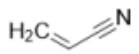
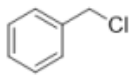
Potential mutagenic impurities

3) Setting acceptable limits and propose a control strategy

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

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

<u>Compound-specific limit (Class 1)</u>
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

<u>TTC Limit (Class 2 and 3)</u>
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

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

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

CEP 2.0

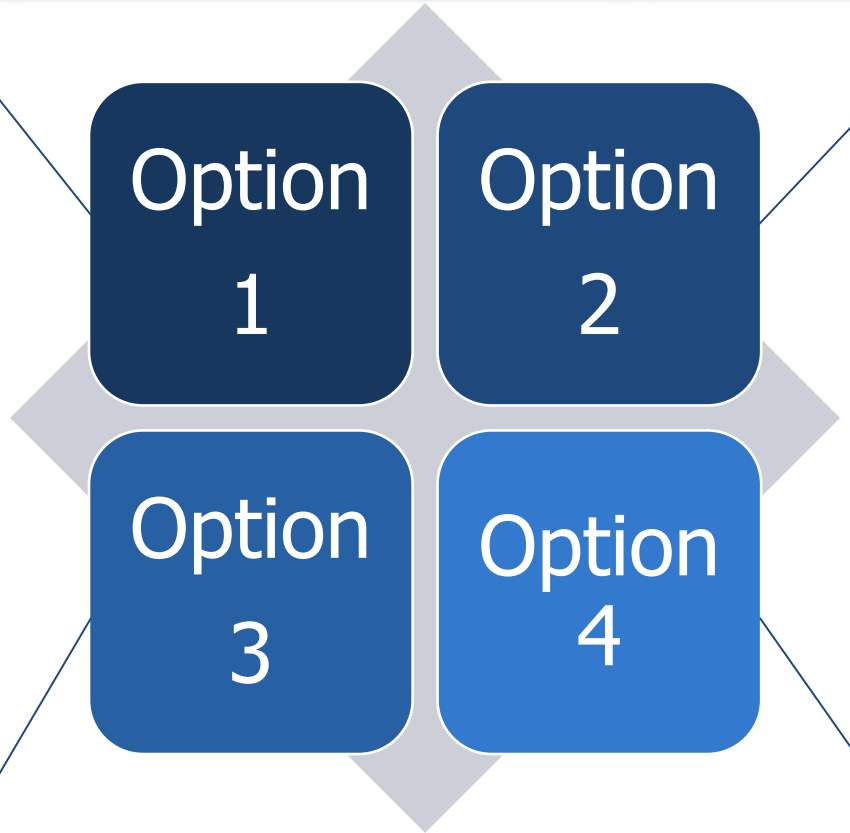
MDD and information regarding the use of the substance to be included in 3.2.S.1.3 along with route of administration and treatment duration considered for development of the control strategy and specification.

Mutagenic impurities

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



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

Potential mutagenic impurities

3) Setting acceptable limits and propose a control strategy

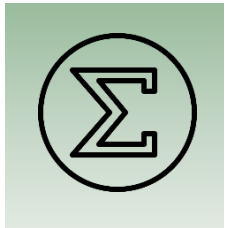
For class 1, 2 and 3 impurities, control strategy in line with ICH M7 requirements

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**
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, 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, so that risk of an impurity residing in the final substance above the acceptable limit is determined to be negligible. Supported by calculated purge factors and if relevant batch data (if introduced or formed late in the process). (e.g. impurities inherently unstable, introduced early and well purged etc.)

Mutagenic impurities

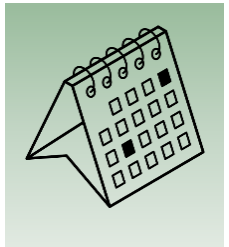
Potential mutagenic impurities

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)

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.



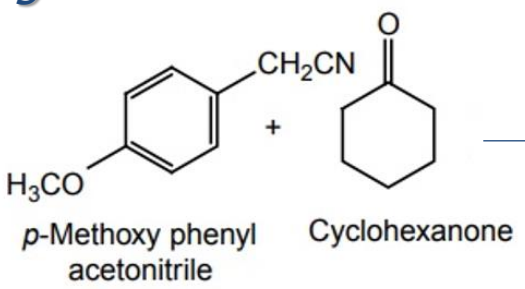
Regarding periodic verification testing (i.e. testing on pre-selected batches or at predetermined intervals instead of on a batch-to-batch basis):
→ To be applied only when **option 1** control strategy is in place
→ Not appropriate for options 2 and 3

Mutagenic impurities - Case study (fictitious)

Venlafaxine hydrochloride:

Ph. Eur. impurity C

Stage-1



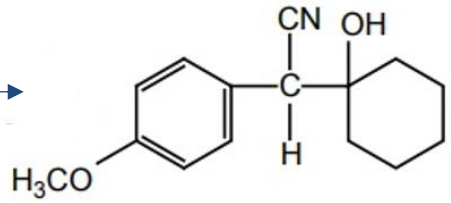
p-Methoxy phenyl acetonitrile + Cyclohexanone

SM1 SM2

Sodium hydroxide
TBAB

Toluene
Water

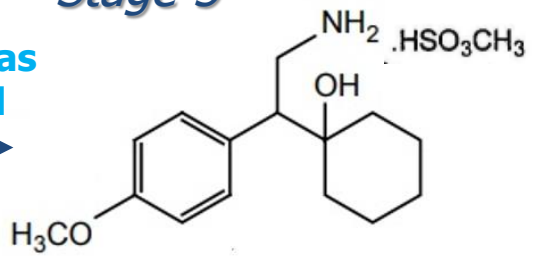
Stage-2



Palladium/ hydrogen gas
methane sulfonic acid

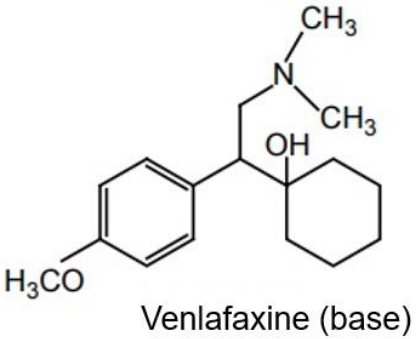
Isopropanol
Methanol

Stage-3



Isopropanol
Toluene

Formic acid
Formaldehyde

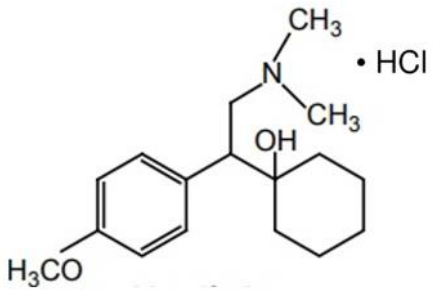


Venlafaxine (base)

Stage-4

Hydrochloric acid

Ethanol

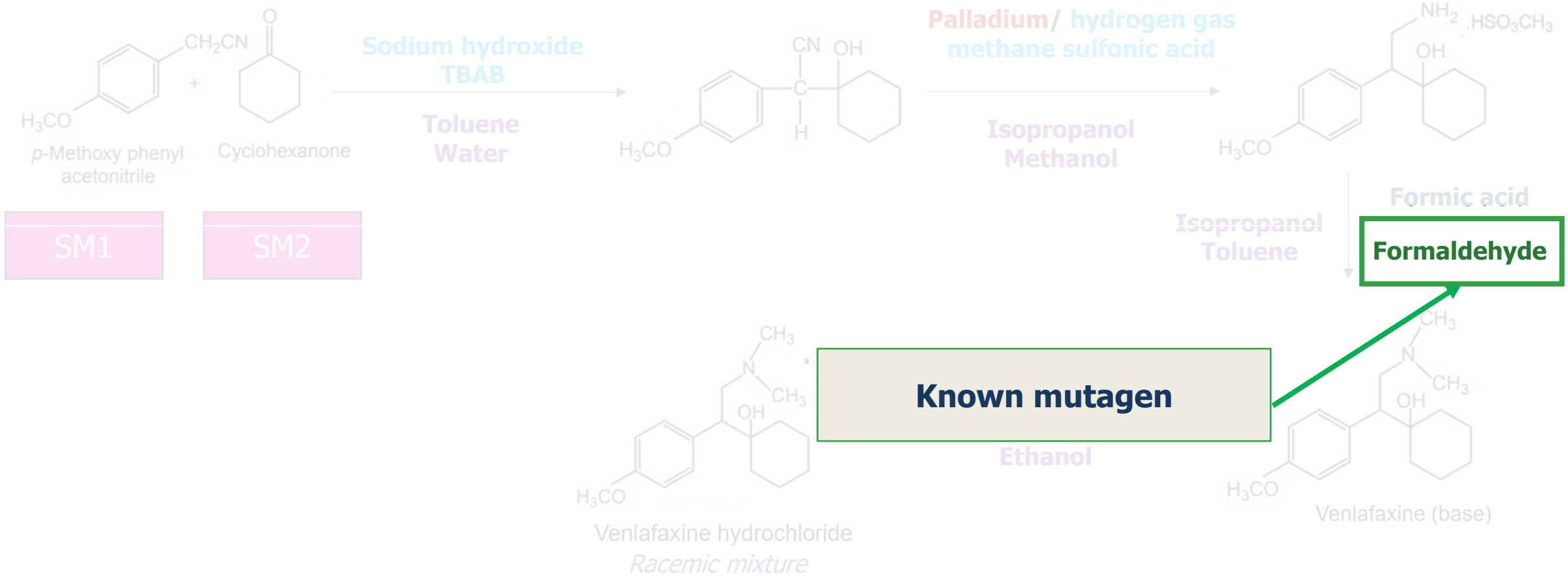


Venlafaxine hydrochloride

Racemic mixture

Mutagenic impurities - Case study (fictitious)

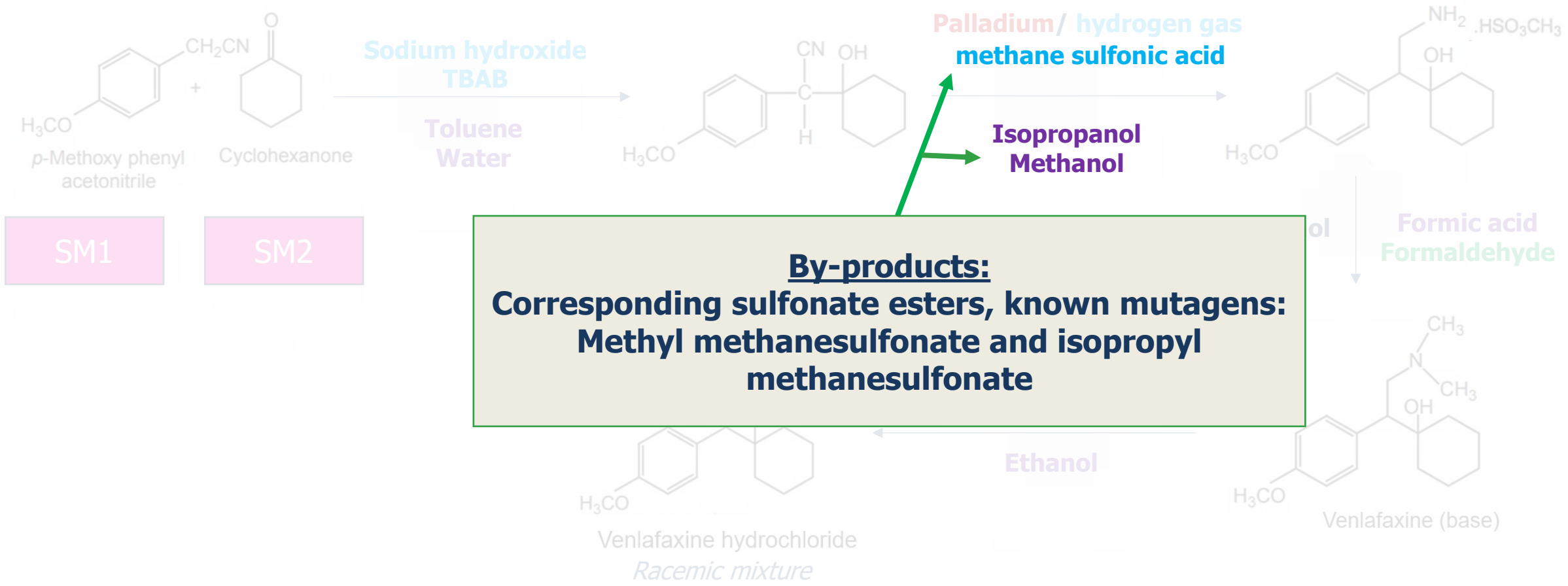
2) Hazard assessment for mutagenic impurities



Mutagenic impurities - Case study (fictitious)

2) Hazard assessment for mutagenic impurities

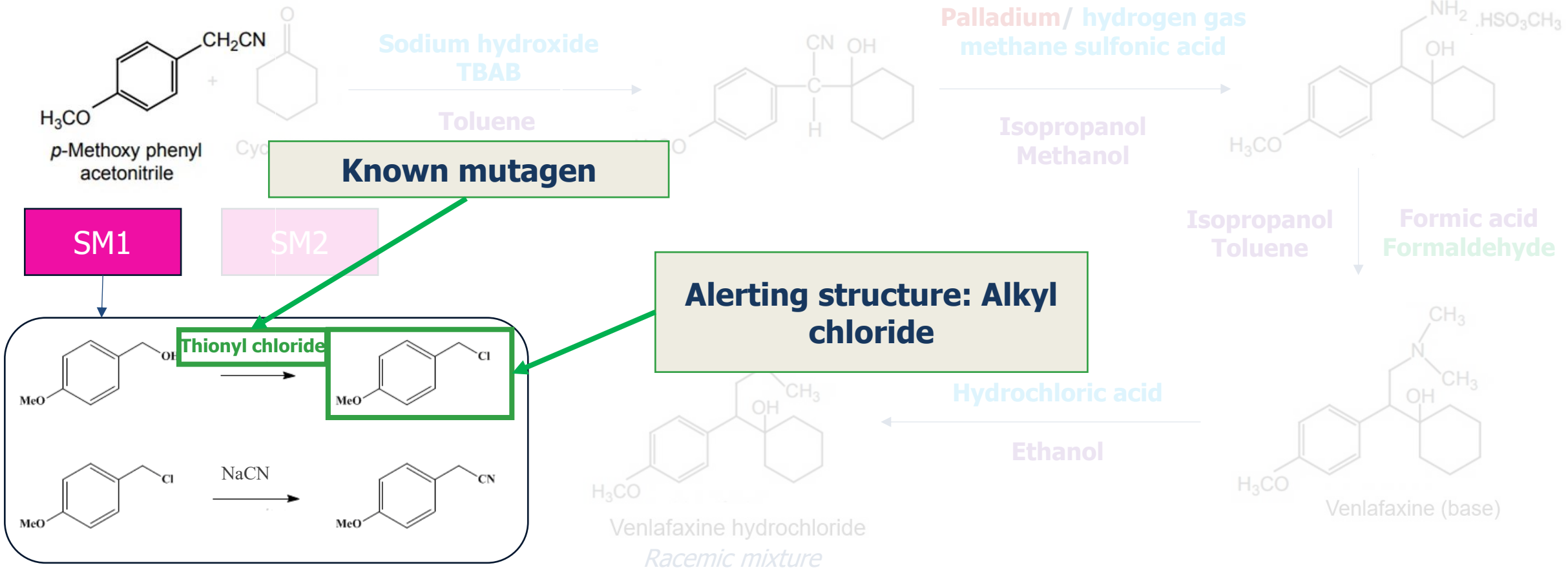
Ph.Eur. impurity C



By-products:
Corresponding sulfonate esters, known mutagens: Methyl methanesulfonate and isopropyl methanesulfonate

Mutagenic impurities - Case study (fictitious)

2) Hazard assessment for mutagenic impurities



Mutagenic impurities - Case study (fictitious)

Potential mutagenic impurities

2) Hazard assessment and classification as per ICH M7

Impurity	Origin	Hazard assessment	Class
Formaldehyde	Step 3	Known mutagenic carcinogen (ICH M7 addendum) → ***Not considered mutagenic when taken orally*** ***(PDE 10000µg/d – acceptable limit is > as ICH Q3A thresholds)***	Class 1
Methyl methanesulfonate (MMS) & isopropyl methanesulfonate (IPMS)	Step 2	Mesylates : Known mutagens with unknown carcinogenic potential → ***In-vitro mutagenicity data (literature)*** ***Positive outcome.***	Class 2
Precursor SM1	SM 1	Alkyl chloride alerting structure → ***No database or literature data. No mutagenicity data.***	Class 3
Thionyl chloride	SM 1	Known mutagen	Class 1

Mutagenic impurities - Case study (fictitious)

Potential mutagenic impurities

3) Setting acceptable limits and propose a control strategy

Impurity	Origin	Classification	Control in line with ICH M7	Justification
Paraformaldehyde	Step 3	***Treat as non-mutagenic as the substance is administered orally only***		
MMS & IPMS	Step 2	Class 2	**?**	**?**
Precursor SM1	SM 1	Class 3	**?**	**?**
Thionyl chloride	SM 1	Class 1	**?**	**?**

Mutagenic impurities - Case study (fictitious)

Potential mutagenic impurities

3) Setting acceptable limits and propose a control strategy

Impurity	Origin	Classification	Control in line with ICH M7	Justification
Paraformaldehyde	Step 3	***Treat as non-mutagenic as the substance is administered orally only***		
MMS & IPMS	Step 2	Class 2	**?**	**?**
Precursor SM1	SM 1	Class 3	**?**	**?**
Thionyl chloride	SM 1	Class 1	Option 4	Used pre-SM, Highly reactive in water used widely ahead in the process

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

Information regarding the substance:

→ MDD: 424.5 mg/d

→ Route of administration: Oral

→ Treatment duration: >10 years to lifetime

Mutagenic impurities - Case study (fictitious)

Potential mutagenic impurities

3) Setting acceptable limits and propose a control strategy

	Origin	Classification	Control in line with ICH M7	Justification
MMS & IPMS	Step 2	Class 2	**?**	**?**
Precursor SM1	SM 1	Class 3	**?**	**?**

$$\textbf{TTC limit} = \frac{1.5\ (\frac{\mu g}{day})}{0.4245\ (\frac{g}{day})} = \textbf{3.53 ppm}$$

Proposed control in Venlafaxine base

MMS : NMT 100 ppm

IPMS: NMT 100 ppm

ICH M7 option 3 → Spike/purge studies

Justification:

a) Spiking the base with 200 ppm of MMS and IPMS
Results: Not detected (LOD 0.3 ppm; LOQ 1.0 ppm) in the API by GC-MS
→ **Found <30% of the TTC limit**

b) Carry-over data to the API:
Not detected (LOD 0.3 ppm; LOQ 1.0 ppm)
→ **Found <30% of the TTC limit**

Mutagenic impurities - Case study (fictitious)

Potential mutagenic impurities

3) Setting acceptable limits and propose a control strategy

	Origin	Classification	Control in line with ICH M7	Justification
MMS & IPMS	Step 2	Class 2	**Option 3**	**Spiking study + Carry-over data**
Precursor SM1	SM 1	Class 3	**?**	**?**

$$\textbf{TTC limit} = \frac{1.5\ (\frac{\mu g}{day})}{0.4245\ (\frac{g}{day})} = \textbf{3.53 ppm}$$

Proposed control in Venlafaxine base

MMS : NMT 100 ppm

IPMS: NMT 100 ppm

ICH M7 option 3 → Spike/purge studies

Justification:

a) Spiking the base with 200 ppm of MMS and IPMS
Results: Not detected (LOD 0.3 ppm; LOQ 1.0 ppm) in the API by GC-MS
→ **Found <30% of the TTC limit**

b) Carry-over data to the API:
Not detected (LOD 0.3 ppm; LOQ 1.0 ppm)
→ **Found <30% of the TTC limit**

Mutagenic impurities - Case study (fictitious)

Potential mutagenic impurities

3) Setting acceptable limits and propose a control strategy

	Origin	Classification	Control in line with ICH M7	Justification
MMS & IPMS	Step 2	Class 2	**Option 3**	**Spiking study + Carry-over data**
Precursor SM1	SM 1	Class 3	**?**	**?**

$$\text{TTC limit} = \frac{1.5\ (\frac{\mu g}{day})}{0.4245\ (\frac{g}{day})} = \mathbf{3.53\ ppm}$$

Proposed control for the precursor:
NMT 0.15% in the SM1

ICH M7 option 3 → Spike/purge studies

Justification:

a) Spiking SM1 with 0.5% of precursor 1

Results: Not detected (LOD 0.1 ppm; LOQ 0.9 ppm) in Venlafaxine base by LC-MS

→ **Found <30% of the TTC limit**

b) Carry-over data to Venlafaxine base:

Not detected (LOD 0.1 ppm; LOQ 0.9 ppm)

→ **Found <30% of the TTC limit**

Mutagenic impurities - Case study (fictitious)

Potential mutagenic impurities

3) Setting acceptable limits and propose a control strategy

	Origin	Classification	Control in line with ICH M7	Justification
MMS & IPMS	Step 2	Class 2	**Option 3**	**Spiking study + Carry-over data**
Precursor SM1	SM 1	Class 3	**Option 3**	**Spiking study + Carry-over data**

$$\textbf{TTC limit} = \frac{1.5\ (\frac{\mu g}{day})}{0.4245\ (\frac{g}{day})} = \textbf{3.53 ppm}$$

Proposed control for the precursor:
NMT 0.15% in the SM1

ICH M7 option 3 → Spike/purge studies

Justification:

a) Spiking SM1 with 0.5% of precursor 1

Results: Not detected (LOD 0.1 ppm; LOQ 0.9 ppm) in Venlafaxine base by LC-MS

→ **Found <30% of the TTC limit**

b) Carry-over data to Venlafaxine base:

Not detected (LOD 0.1 ppm; LOQ 0.9 ppm)

→ **Found <30% of the TTC limit**

Mutagenic impurities - Case study (fictitious)

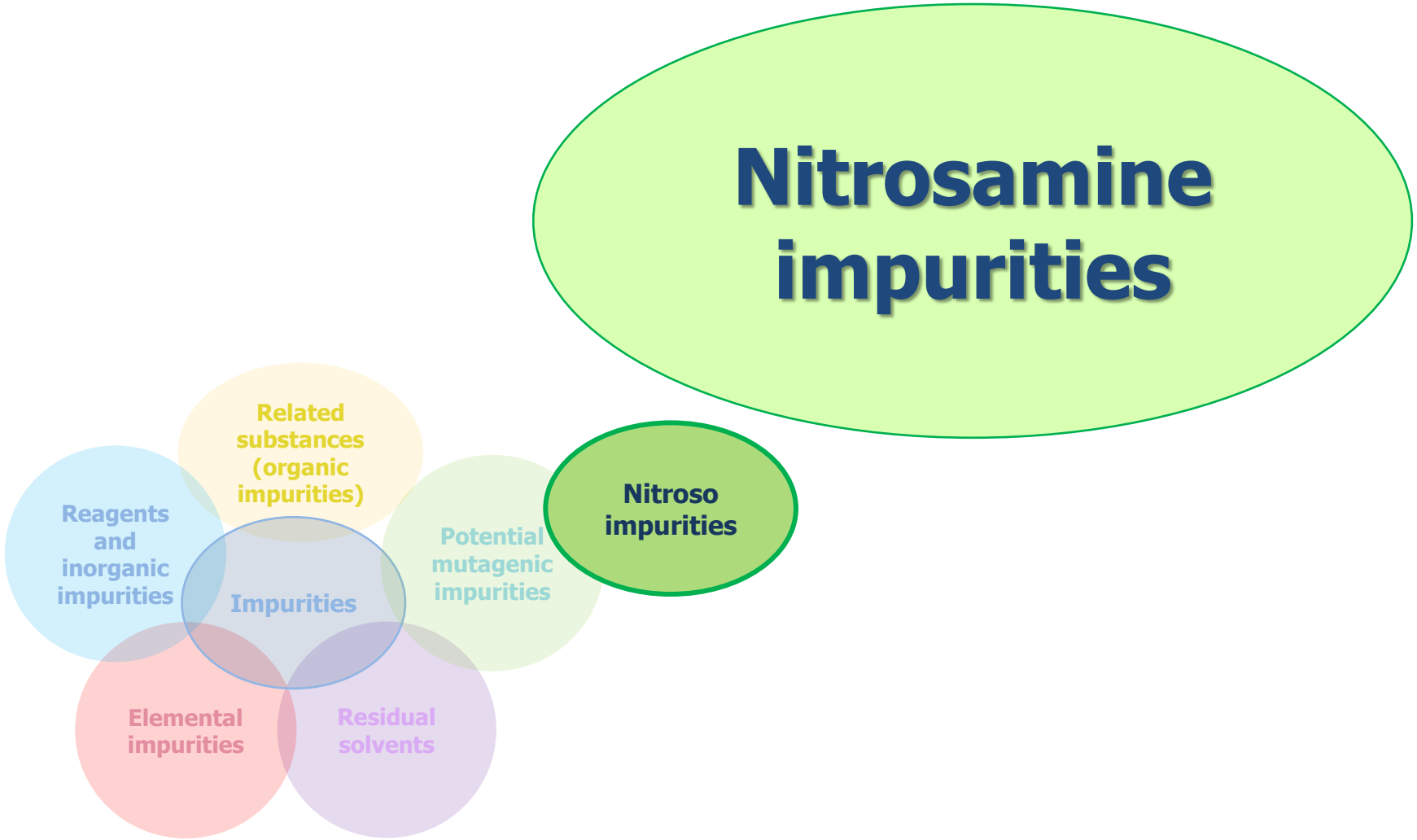
Potential mutagenic impurities

3) Setting acceptable limits and propose a control strategy

Impurity	Origin	Classification	Control in line with ICH M7	Justification
Formaldehyde	Step 3	Class 1	***Treat as non-mutagenic for the oral route → ICH Q3A***	
MMS & IPMS	Step 2	Class 2	Option 3	MMS and IPMS purged to levels <30% of the TTC limit in the API when present at 200 ppm in venlafaxine base
Precursor SM1	SM 1	Class 3	Option 3	Precursor purged to levels <30% of the TTC limit in a relevant intermediate when present at 0.5% in SM1
Thionyl chloride	SM 1	Class 1	Option 4	Used pre-SM. Highly reactive in water used widely ahead in the process

Control strategy and the outcome of discussion to be summarised in section 3.2.S.3.2 – Mutagenic impurities

Nitrosamine impurities



Nitrosamine impurities

Nitroso impurities

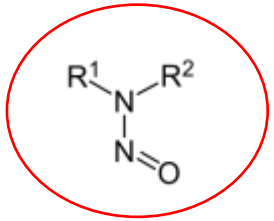
ICH M7 : structural groups identified to be of such high potency that intakes even below the TTC would theoretically be associated with a potential for a significant carcinogenic risk. This group is referred to as the "cohort of concern", comprises aflatoxin-like-, N-nitroso-, and alkyl-azoxy compounds.

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

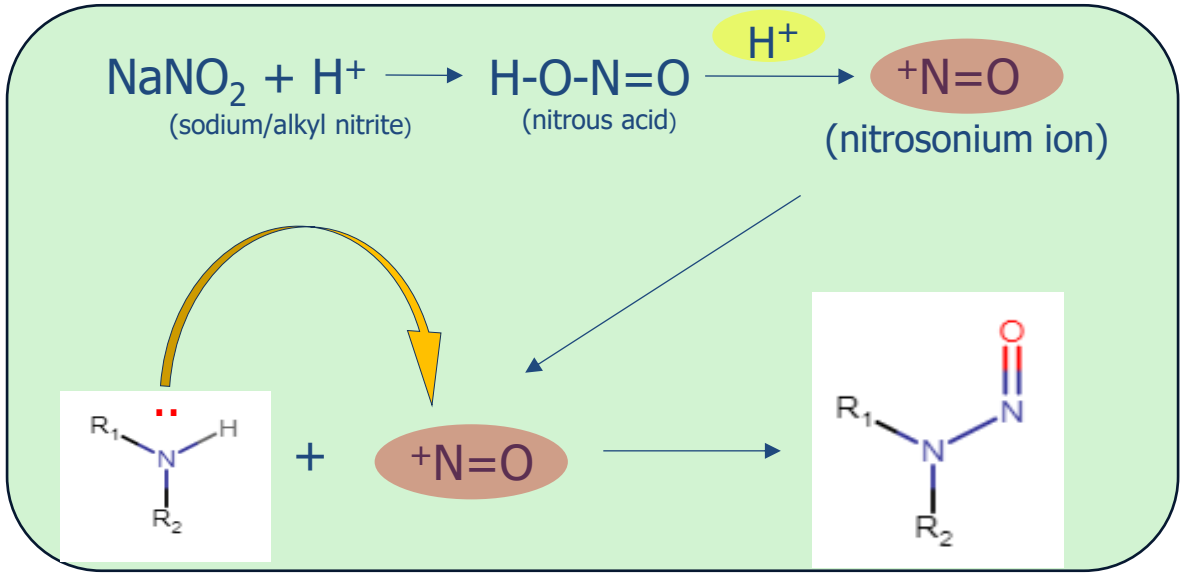
Step II

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)

IMPORTANT

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:

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

Nitrosamine impurities – *Key point*

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

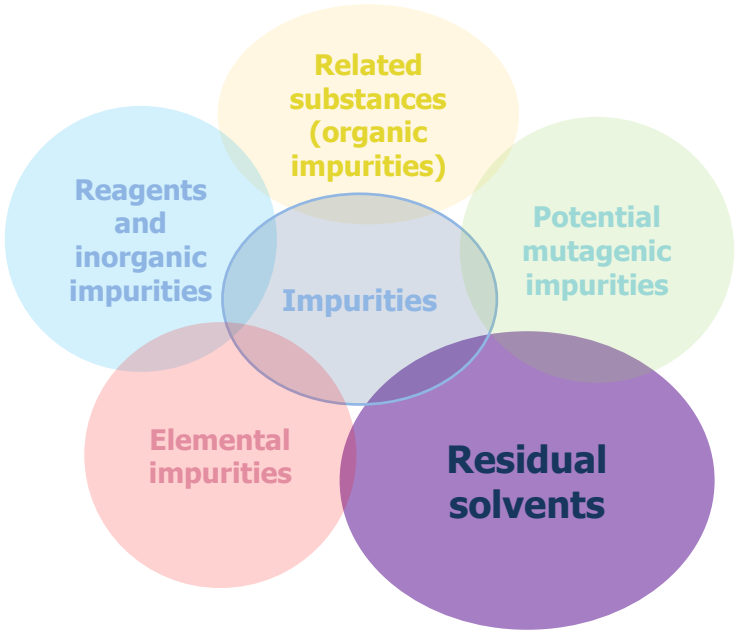
Frequent revision of the Q&A or its corresponding appendixes:

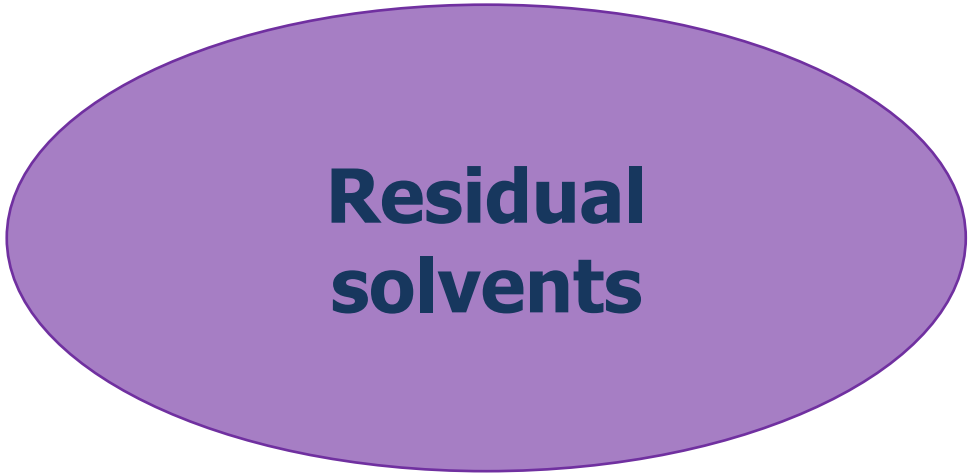
- Specific acceptable intakes (AI) for nitrosamines may be updated following toxicological assessment (e.g. Bacterial Reverse Mutation Test, in vivo studies etc.)
- Additional nitrosamine impurities are frequently newly included in appendix 1.

→ **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.**

The risk assessment is to be included in section 3.2.S.3.2 – Nitrosamine impurities

Residual solvents





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

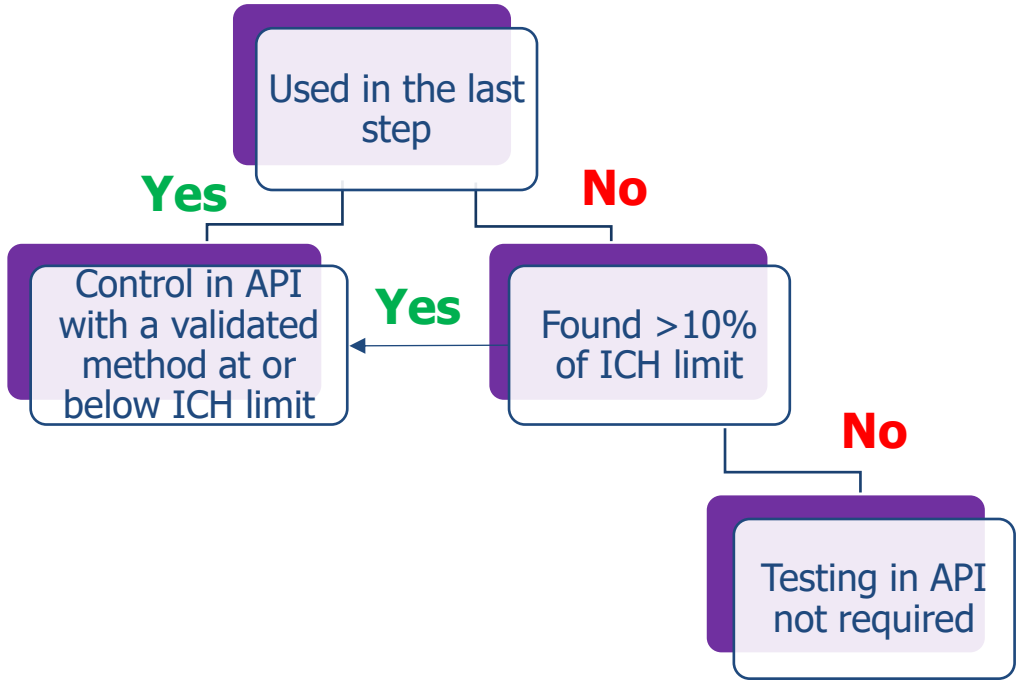
- Limit in originator solvent ensuring class 1 solvent in the API <30% ICH limit based on a rationale.

Option 2

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

ICH Class 2 solvent
(solvents to be limited)

Control needed in the API if…



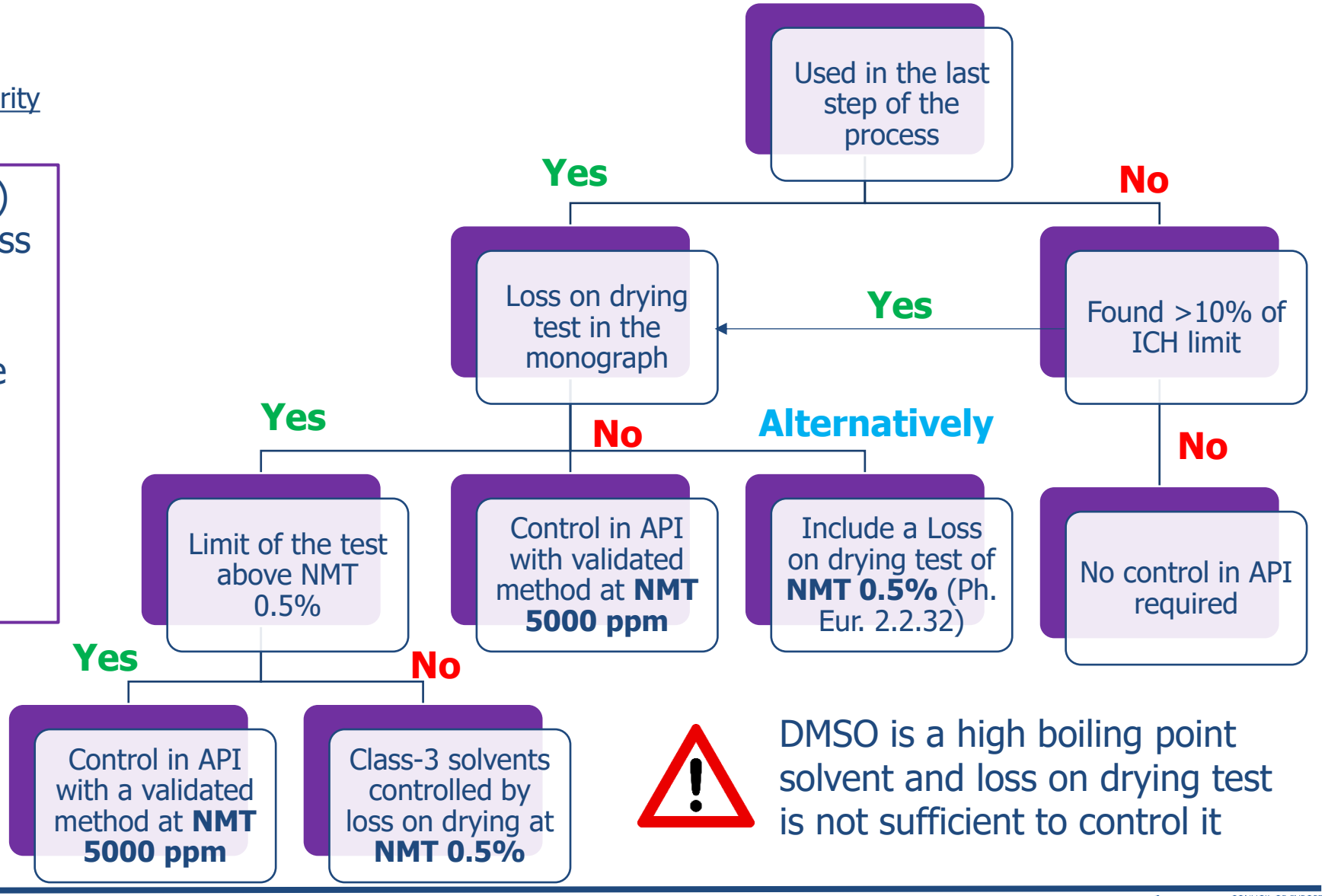
Non-classified ICH Q3C Solvents: toxicological justification for any proposed limit.

Class 3 solvents & Certification Procedure

Residual solvents

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

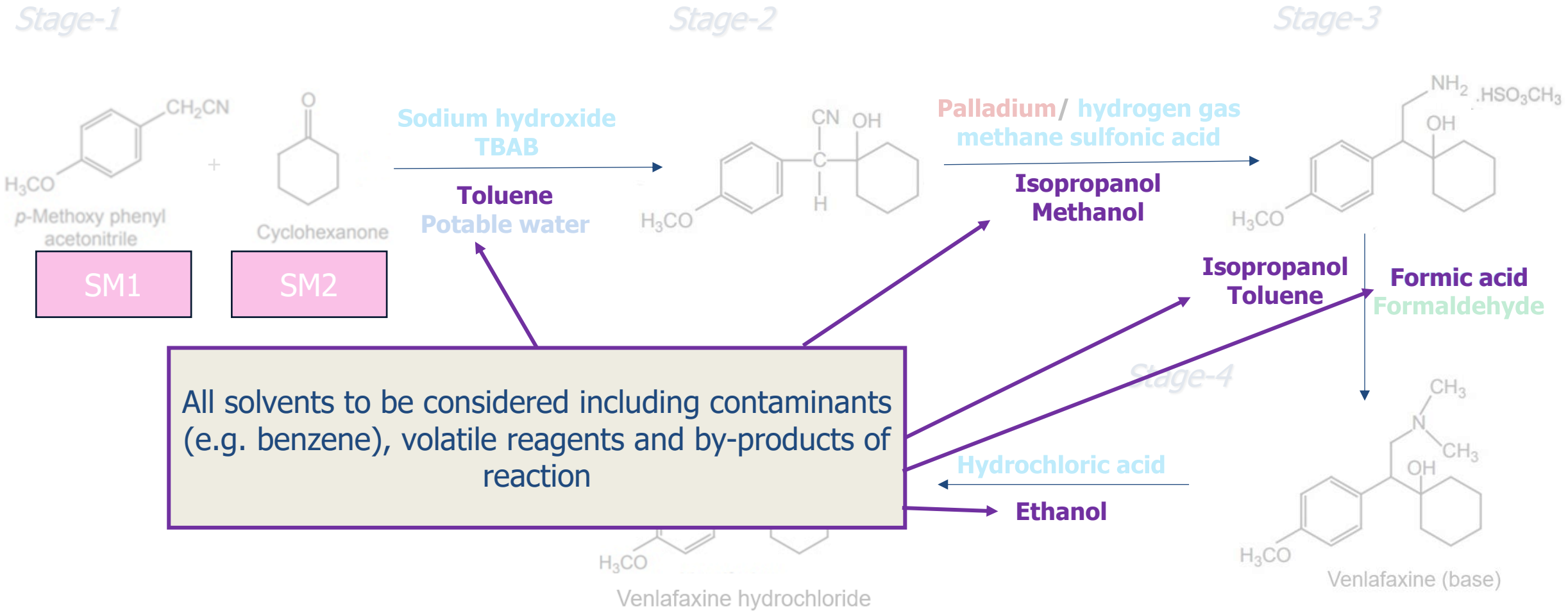
Low toxicity solvents (Class 3) can be limited by a test for loss on drying with a limit of not more than 0.5%, when appropriate. If the limit of the loss on drying test of the monograph is higher than 0.5%, then a specific test for residual solvents should be introduced.



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

Case study (fictitious)

Residual solvents



All solvents to be considered including contaminants (e.g. benzene), volatile reagents and by-products of reaction

Case study : Which specifications?

Residual solvents

Solvent	Used in stage X / 4	ICH classification	Typical levels in API	LOD (ppm)	Limit in API
Toluene	Stages 1 & 3	Class 2 NMT 890 ppm	7 – 93 ppm	7	?
Ethanol	Stage **4**	Class 3 NMT 5000 ppm	154 – 567 ppm	49	?
Isopropanol	Stages 2 & 3	Class 3 NMT 5000 ppm	ND	77	?
Methanol	Stage 2	Class 2 NMT 3000 ppm	ND	6	?
Formic acid	Stage 3	Class 3 NMT 5000 ppm	ND	12	?
Benzene	As contaminant	Class 1 NMT 2 ppm	ND	0.5	?

Data obtained from controls in intermediates may also be used to show absence.
Testing using GC methods (or other suitable) validated in line with ICH Q2 (R2)

Case study : Which specifications?

Residual solvents

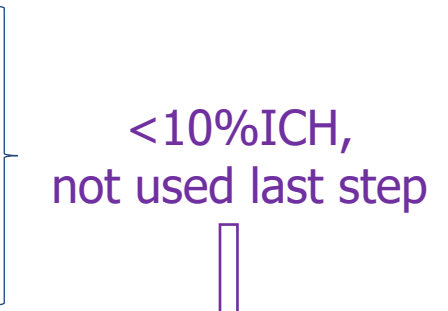
Solvent	Used in stage X / 4	ICH classification	Typical levels in API	LOD (ppm)	Limit in API
Toluene	Stages 1 & 3	Class 2 NMT 890 ppm	7 – 93 ppm	7	?
Ethanol	Stage **4**	Class 3 NMT 5000 ppm	154 – 567 ppm	49	?
Isopropanol	Stages 2 & 3	**Class 3** NMT 5000 ppm	**ND**	77	**?**
Methanol	Stage 2	**Class 2** NMT 3000 ppm	**ND**	6	**?**
Formic acid	Stage 3	**Class 3** NMT 5000 ppm	**ND**	12	**?**
Benzene	As contaminant	Class 1 NMT 2 ppm	ND	0.5	?

Data obtained from controls in intermediates may also be used to show absence.
Testing using GC methods (or other suitable) validated in line with ICH Q2 (R2)

Case study : Which specifications?

Residual solvents

Solvent	Used in stage X / 4	ICH classification	Typical levels in API	LOD (ppm)	Limit in API
Toluene	Stages 1 & 3	Class 2 NMT 890 ppm	7 – 93 ppm	7	?
Ethanol	Stage **4**	Class 3 NMT 5000 ppm	154 – 567 ppm	49	?
Isopropanol	Stages 2 & 3	**Class 3** NMT 5000 ppm	**ND**	77	
Methanol	Stage 2	**Class 2** NMT 3000 ppm	**ND**	6	
Formic acid	Stage 3	**Class 3** NMT 5000 ppm	**ND**	12	
Benzene	As contaminant	Class 1 NMT 2 ppm	ND	0.5	?



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

Case study : Which specifications?

Residual solvents

Solvent	Used in stage X / 4	ICH classification	Typical levels in API	LOD (ppm)	Limit in API
Toluene	Stages 1 & 3	Class 2 NMT 890 ppm	7 – 93 ppm	7	**?**
Ethanol	Stage **4**	Class 3 NMT 5000 ppm	154 – 567 ppm	49	**?**
Isopropanol	Stages 2 & 3	Class 3 NMT 5000 ppm	ND	77	**X**
Methanol	Stage 2	Class 2 NMT 3000 ppm	ND	6	**X**
Formic acid	Stage 3	Class 3 NMT 5000 ppm	ND	12	**X**
Benzene	As contaminant	Class 1 NMT 2 ppm	ND	0.5	**?**

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

Case study : Which specifications?

Residual solvents

Solvent	Used in stage X / 4	ICH classification	Typical levels in API	LOD (ppm)	Limit in API
Toluene	Stages 1 & 3	**Class 2** NMT 890 ppm	**7 – 93 ppm**	7	**?**
Ethanol	Stage **4**	Class 3 NMT 5000 ppm	154 – 567 ppm	49	?
Isopropanol	Stages 2 & 3	Class 3 NMT 5000 ppm	ND	77	**X**
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Formic acid	Stage 3	Class 3 NMT 5000 ppm	ND	12	**X**
Benzene	As contaminant	Class 1 NMT 2 ppm	ND	0.5	?

Class 2,
> 10% ICH limit

Control in the API using a validated analytical method

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

Case study : Which specifications?

Residual solvents

Solvent	Used in stage X / 4	ICH classification	Typical levels in API	LOD (ppm)	Limit in API
Toluene	Stages 1 & 3	**Class 2** NMT 890 ppm	**7 – 93 ppm**	7	**NMT 890 ppm**
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Formic acid	Stage 3	Class 3 NMT 5000 ppm	ND	12	**X**
Benzene	As contaminant	Class 1 NMT 2 ppm	ND	0.5	?

Class 2,
> 10% ICH limit

⇩

Control in the API using a validated analytical method

⇩

Specification limit according to ICH Q3C

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

Case study : Which specifications?

Residual solvents

Solvent	Used in stage X / 4	ICH classification	Typical levels in API	LOD (ppm)	Limit in API
Toluene	Stages 1 & 3	Class 2 NMT 890 ppm	7 – 93 ppm	7	NMT 890 ppm
Ethanol	Stage **4**	**Class 3** NMT 5000 ppm	**154 – 567 ppm**	49	**?**
Isopropanol	Stages 2 & 3	Class 3 NMT 5000 ppm	ND	77	**X**
Methanol	Stage 2	Class 2 NMT 3000 ppm	ND	6	**X**
Formic acid	Stage 3	Class 3 NMT 5000 ppm	ND	12	**X**
Benzene	As contaminant	Class 1 NMT 2 ppm	ND	0.5	?

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

Control in API using a validated analytical method

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

Case study : Which specifications?

Residual solvents

Solvent	Used in stage X / 4	ICH classification	Typical levels in API	LOD (ppm)	Limit in API
Toluene	Stages 1 & 3	Class 2 NMT 890 ppm	7 – 93 ppm	7	NMT 890 ppm
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Isopropanol	Stages 2 & 3	Class 3 NMT 5000 ppm	ND	77	**X**
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Benzene	As contaminant	Class 1 NMT 2 ppm	ND	0.5	?

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

Control in API using a validated analytical method

Specification limit according to ICH Q3C

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

Case study : Which specifications?

Residual solvents

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Isopropanol	Stages 2 & 3	Class 3 NMT 5000 ppm	ND	77	**X**
Methanol	Stage 2	Class 2 NMT 3000 ppm	ND	6	**X**
Formic acid	Stage 3	Class 3 NMT 5000 ppm	ND	12	**X**
Benzene	As contaminant	**Class 1** NMT 2 ppm	**ND**	0.5	

No control in API required

⇧

Class 1 solvent as contaminant, <30% ICH limit

Specification of the 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
Toluene	Class 2 NMT 890 ppm	NMT 890 ppm
Ethanol	Class 3 NMT 5000 ppm	NMT 5000 ppm

Class 2, > 10%ICH limit

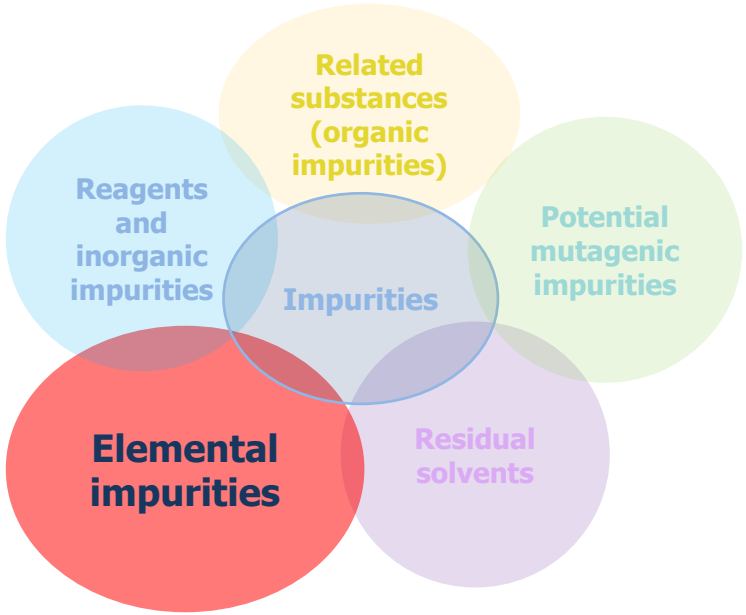
Used in the last step

CEP 2.0

If other solvents are included in section 3.2.S.4.1, these will be transparent on the CEP and the method used to detect them will be appended to the CEP.

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

Elemental impurities



Elemental impurities

Elemental impurities: references and control strategy

Elemental impurities

- **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 <u>presence</u> or <u>absence</u> of elemental impurities in the API

Presence in API for an elemental impurity intentionally added :

- a justified **specification** should be applied
- Analytical methods 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 and convincingly **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 method identified (ICP/MS, ICP/OES,…), at least sensitivity (**LOD/LOQ**) to be provided

If elemental impurities are introduced into the ***<u>last synthetic step</u>***, specification limit in the API is usually expected

Implementation of ICH Q3D in the CEP procedure

Elemental impurities

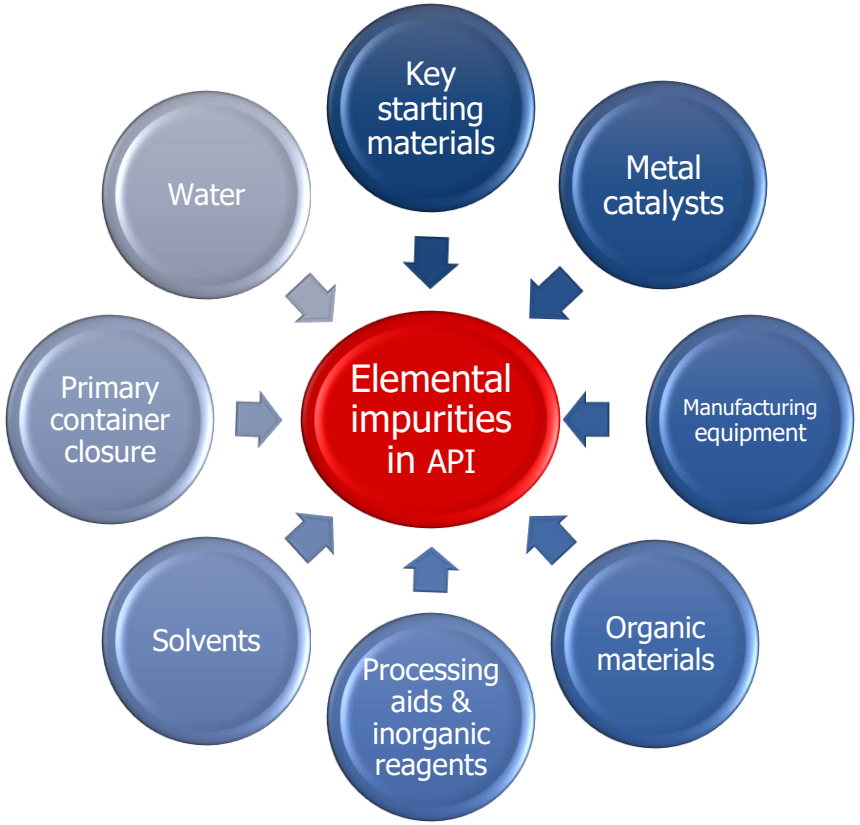
Two possible approaches :

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

- besides the intentionally added element[s], the assessment should also cover all oth[er] potential elemental impurities from other [sources]
- Risk Management Summary should detail the rationale of the study:
  - **why** impurities [were] considered
  - **justify** the [proposed] control strategy
  - intended **[route] of administration**
- to be co[mpleted] with a **RMS table** → intended to be [annexed] to the CEP

Option encouraged by EDQM = facilitates risk assessment for medicinal product

⚠ [Elemental] screening data do not replace a risk management summary



RMS approach:

Elemental impurities

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

Implementation of ICH Q3D in the CEP procedure

Elemental impurities

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

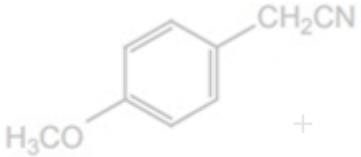
No Risk management summary is prepared.

- **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 method according to ICH Q2 (R2) should be provided and the **method** will be **appended** to the CEP
- If **no elemental impurity** is intentionally added, this will be reported on the CEP.

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

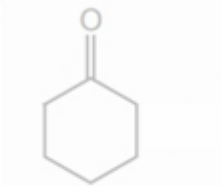
Case study (fictitious)

Stage-1



p-Methoxy phenyl acetonitrile

+



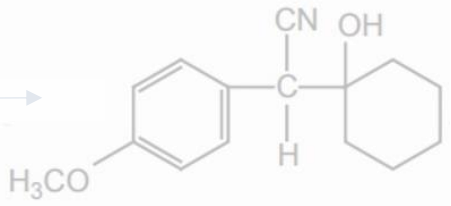
Cyclohexanone

SM1 SM2

Stage-2

Sodium hydroxide
TBAB

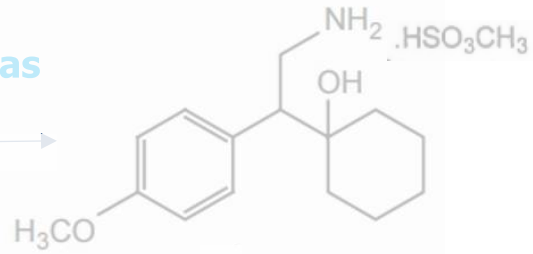
Toluene
Water



Palladium / hydrogen gas
methane sulfonic acid

Isopropanol
Methanol

Stage-3



Isopropanol
Toluene

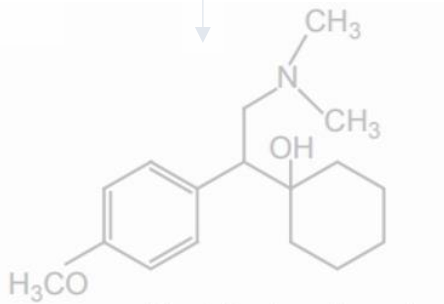
Formic acid
Formaldehyde

Catalyst used in stage-2

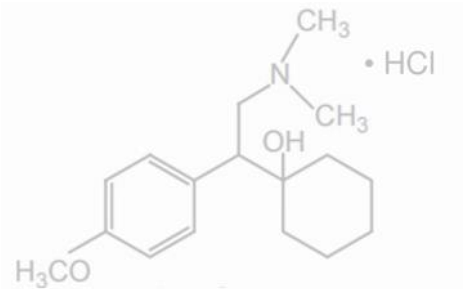
Stage-4

Hydrochloric acid

Ethanol



Venlafaxine (base)



Venlafaxine hydrochloride

Moreover, **Chromium** and **Molybdenum** have been considered as coming from the equipment used

RMS Table included in section 3.2.S.3.2

Impurity	Limit	Batch data	Origin
Palladium	10 ppm	< 1 ppm	Catalyst in step 2
Chromium	300 ppm	< 10 ppm	Equipment
Molybdenum	1100 ppm	< 100 ppm	Equipment

- 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** ».

Skip testing to be justified in line with ICH Q3D

CEP 2.0

RMS table will be appended to the CEP

Route of administration

Elements considered or not

Elements intentionally introduced or not

Report a conclusion on absence or control

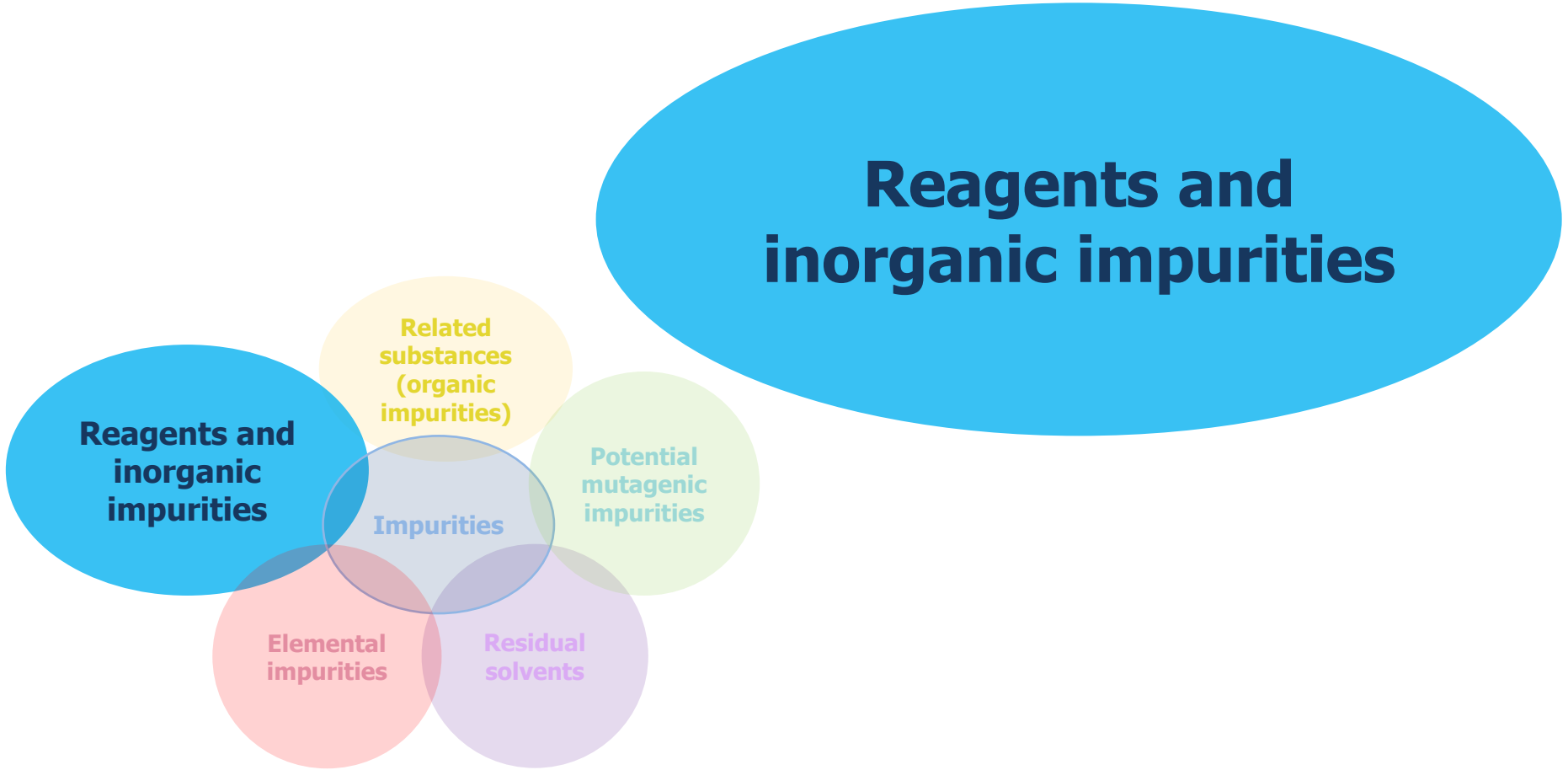
If term « Absent » is used its definition is required

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
Pd	2B	Yes	Yes	Absent
Ir	2B	No	No	Not applicable
Os	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	No	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

Reagents and inorganic impurities



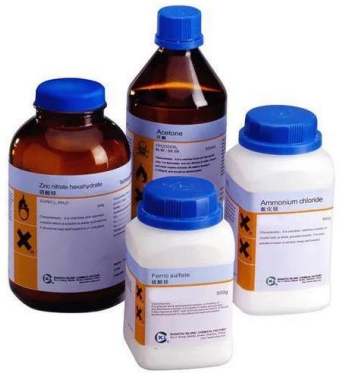
Reagents & Inorganic impurities

- 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 method against a limit justified based on toxicological data

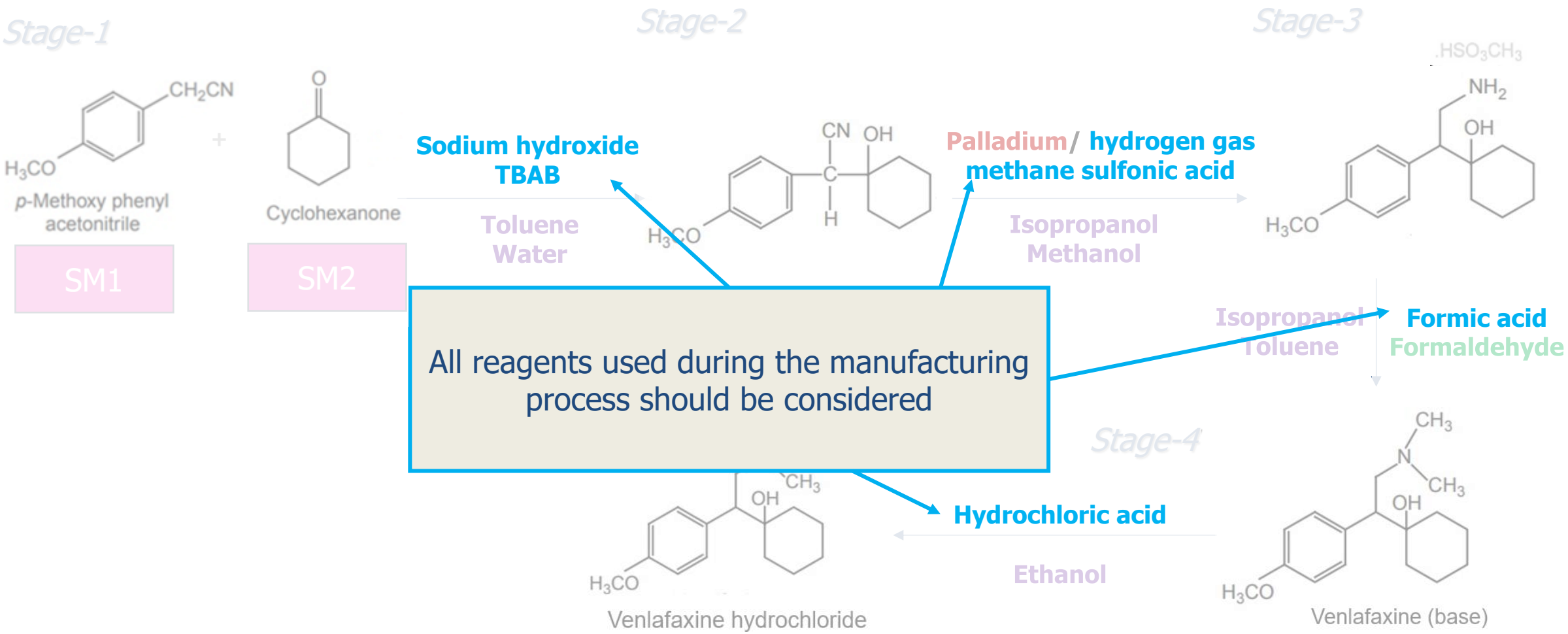
  OR

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



Case study (fictitious)

Reagents and Inorganic impurities



Reagents & Inorganic impurities

Reagents	Origin, fate and carry over	Batch data	Limit
Sodium cyanide	Used in SM1 manufacturing. Found <0.05% in SM. Tested in API, found ND.	**ND**	**X**
Tetrabutyl ammonium Bromide	Multiple steps up to the API. No risk of formation of nitrosamines identified. Low risk of carry-over. Tested in INT-B, found ND.	**ND**	**x**
Sodium hydroxide	Washed along with water used in the manufacturing process.	**x**	**x**
Formic acid	Discussed as solvent. *Refer to section 3.2.S.3.2 – Residual solvents*.	**ND**	**x**
Hydrogen gas	Gas removed at the end of the hydrogenation process.	**x**	**x**
Hydrochloric acid	Used in the last step, removed during washing and drying.	**x**	**x**
Methane sulfonic acid	Washed out during basic work-up. Absence demonstrated in INT-C.	**x**	**x**
Formaldehyde	ICH M7 Class 1 impurity. *Refer to section 3.2.S.3.2 – Mutagenic impurities.*		

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

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