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

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

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How to build a successful CEP application and avoid frequent deficiencies?

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Summary

- CEP process overview
- How to build up a successful Dossier and avoid deficiencies?
- Examples

CEP Process Overview

Validation	• Administrative • Technical
Evaluation 1	• CEP granted or • Additional information requested
Evaluation 2	• CEP granted or • Additional information requested
Evaluation 3	• CEP granted or • Application closed without the CEP being granted

Technical validation at receipt

- Commercial history
  - Clear summary. Information on IF and in WHAT product THIS source of API is on the EUROPEAN market. Information on ASMF submitted for the same substance.
  - Give as much information as possible (companies, products names, countries, registration dates, marketing dates)

→ Impact on Qualification (limits) of impurities and applicability of guidelines

- Is dossier content suitable to start the evaluation process?

e.g. - Use of Class I solvents without justification and control
- Sterile substances: absence of validation data on the sterilisation
- Alternative routes of synthesis (significantly different?)
- Absence of quantitative method to replace a non-specific TLC test of the monograph

NO

Application blocked (≈20%)

The clock does not start until suitable information is given

=

An incomplete application delays the CEP!

Technical validation at receipt

Cyclophosphamide (01/2017:0711)

- *Related substances by TLC* → General acceptance criterion «any spot (except main spot) NMT 1.0%»
- No transparency statement in the monograph

Applicant must propose additional «state of the art» quantitative methods (e.g. HPLC), together with limits for specified, unspecified and total related substances (cf. GM 2034)

CEP Process Overview

		EDQM	Applicant
Validation	• Administrative • Technical ☺		
Evaluation 1	• CEP granted or • Additional information requested	5 months	6 months
Evaluation 2	• CEP granted or • Additional information requested	4 months	3 months
Evaluation 3	• CEP granted or • Application closed without the CEP being granted	4 months	

CEP

See monthly report published on www.edqm.eu

CERTIFICATION OF SUITABILITY (CEP) / PROCEDURE OF CERTIFICATION (GENERAL) | NEWS | 12 JUNE 2020 | STRASBOURG, FRANCE

Certification Monthly Report of Activities: May 2020

The latest monthly activity report for the Certification of Substances Department (DCEP) is now available.

Deficiencies: How to avoid them ?

Reference documents

PA/PH/CEP (04) 1 6R (December 2018)
"Content of the dossier for chemical purity and microbiological quality"

PA/PH/CEP (16) 58 (December 2016)
"Top Ten Deficiencies – New applications for certificates of suitability for chemical purity (2015-2016)"

- Publicly available on the EDQM website
- They describe what we expect to see in the dossier

Deficiencies: How to avoid them ?

To be kept in mind…

- The scheme is Certification of suitability to the monographs of the EUROPEAN Pharmacopoeia.
- References, terminology, etc. should be to the Ph. Eur. or at least traceable to it
- There is a requirement to show that the monograph is suitable to control the actual quality of your substance.

Starting materials

Top 4 **Redefinition of starting materials**

Top 5 **Quality of starting materials**

Top 2 **Fate and carryover of impurities from starting materials**

Top 10 **Information on starting materials**

Definition of starting materials

- For synthetic processes the production of an API starts with the introduction of the starting materials (ICH Q7)
- The approved starting materials are the starting point for GMP and variations and must be representative of the overall synthetic process.

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging

Definition of starting materials

Reference documents: **ICH Q11 and its Q&A document**

In order to assess the adequacy of control on the drug substance, its manufacturing process and control of impurities, **enough** of the process should be described.

➡ Relationship between risk and number of synthetic steps

- The definition of starting materials is expected to be justified by the applicant.
- If not acceptable, a redefinition is required.

What are the consequences?

Redefinition of starting materials - consequences

Top 4

Manufacturers of non-acceptable starting materials become manufacturers of intermediates and:

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

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

Quality of starting materials - Fate and carryover of impurities

Top 5

What do we expect?

1. The impurity profile of the starting material should be adequately characterised;
2. Analytical specifications with justified acceptance criteria should be proposed to control the impurity profile of starting materials. Analytical specification should be representative of the process adopted;
3. Discussion on fate and carry-over of impurities.

Quality of starting materials - Fate and carryover of impurities

Top 5

Example of non-acceptable analytical specification

Chromatographic purity (By GC) Purity	Not less than 98.00 %
Impurity X	Not more than 0.50%
Unknown single impurity	Not more than 1.00%
Total impurities	Not more than 2.00%

Quality of starting materials - Fate and carryover of impurities

Top 5

Example of non-acceptable analytical specification

Chromatographic purity (By GC) Purity	Not less than 98.00 %
Impurity X	Not more than 0.50%
Unknown single impurity	Not more than 1.00%
Total impurities	Not more than 2.00%

It is not clear what the major impurity is → risks of having uncontrolled impurities → risks for the quality of final API

It is understandable and acceptable that there may be limitations in characterizing the impurity profile of a starting material but these limitations should not prevent the manufacturer from demonstrating that the level of characterization reached does not pose risks for the quality of the final substance.

Quality of starting materials - Fate and carryover of impurities

Other information

Acceptance criteria in place to control impurities in starting materials should be justified by the manufacturer, taking into account fate and carryover of impurities from starting materials to the final substance (ability of the process to purge unreacted impurities and potential by-products). Assurance should be given on the risk of having uncontrolled impurities later in the process.

Purity by HPLC		
a) Impurity at RRT 0.14	Not more than 2.5 % w/w	1.54 %
b) Single max unknown impurity	Not more than 1.0 % w/w	0.21 %
c) Total impurities	Not more than 3.0 % w/w	2.27 %

Quality of starting materials - Fate and carryover of impurities

Other information

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Batch data not expected for SMs and on their own DO NOT justify limits!

Other than analytical specification, we expect to have in the Dossier a description of the analytical procedures used, names and addresses of manufacturers (not vendors or suppliers) and a brief description of the process/synthesis adopted for the starting material.

Top 3

Manufacturing Process

Manufacturing process

Description of the manufacturing process and process controls

The description of the manufacturing process in place from the introduction of starting materials should contain complete information on:

- Chemicals used and their quantities;
- Operations conducted with conditions adopted.

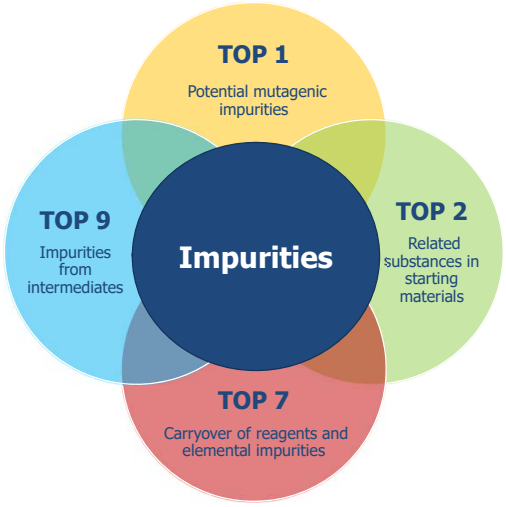
Manufacturing process

Absence of information related to the maximum batch size for the approved process

- The maximum batch size for which the manufacturer has acquired experience with the defined process and which should correspond to batches referred to in the dossier, should be stated
- Where the substance has yet to be produced in commercial quantities, the CEP may be granted provided scale-up is reported to the EDQM via an appropriate revision

Impurities

- **Related Substances**
- **Mutagenic Impurities**
- **Elemental Impurities**
- **Residual Solvents**

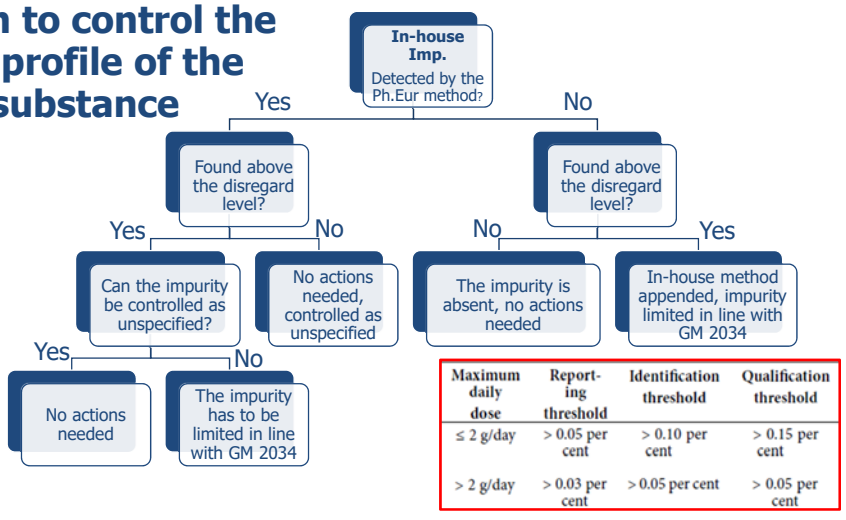


Impurities – Related substances

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

- Suitability (or unsuitability) of the method(s) of the monograph to control all the related substances should be demonstrated
- If the Ph. Eur method is not suitable to control in-house impurities then it has to be supplemented with an additional (validated) method, unless absence of the concerned impurities is demonstrated

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



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

Absence of cross validation between Ph.Eur. and in-house method for the control of related substances

Alternative methods may be used but they have to be shown to give equivalent results comparing to the corresponding Ph.Eur methods:

- They have to be fully validated in line with ICH Q2 (R1)
- Cross-validation on the same batches against the corresponding Ph.Eur method (using spiked solutions if necessary)
- Comparative and typical chromatograms

Modifications to the Ph.Eur methods allowed within the ranges set by the Ph.Eur 2.2.46.

Antibiotics
(products of fermentation and semi-synthetic substances)

- Guideline on setting specifications for related impurities in antibiotics (EMA/CHMP/CVMP/QWP/199250/2009 corr)

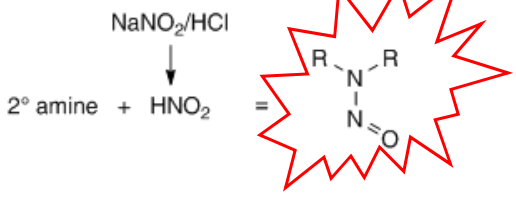
  It does not apply to already marketed products.

→ Limit for "any other impurity" of the individual monograph applies to impurities of the monograph and to any other specified impurity. A suitable limit for "unspecified impurities" has to be proposed by applicant.

Impurities – Nitrosamines

- Nitrosamines are known as possible carcinogens for humans: only very low amounts are acceptable according to current regulatory requirements (ICH M7 "cohort of concern").
- Origin linked to several factors, e.g.
  - from processing conditions (e.g. temperature, duration of reaction)
  - accidental introduction due to cross-contamination (from processes running in parallel on the same production lines)
  - recovery procedures for solvents,
  - degradation of the substances.

Concomitant presence of a secondary amine and a nitrosating agent



Impurities – Nitrosamines

NEW

Risk assessment

- Systematically expected for **ALL** New applications and also Renewals, Sister files and changes to the synthesis
- Risk evaluation with regards to nitrosamine formation
  - addressing risks from the manufacturing process and materials introduced (e.g. starting materials, reagents, solvents – fresh & recovered….)
  - using quality risk management principles, as per ICH Q9 & principles in ICH M7 guideline.
- EMA & CMDh joint Questions and Answers document

  EMA/CHMP/428592/2019 Rev. 3

Impurities – Nitrosamines

NEW

Risk assessment → **Confirmatory testing** → **Control strategy**

Risk identified

- Systematic
- Validated and sensitive method

Limits expected

Impurities – Mutagenic impurities

How to deal with mutagenic impurities?

Reference documents
ICH M7 (R1)
"Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk"

- Hazard assessment in order to classify actual and potential impurities (class from 1 to 5)
- Guideline on how to develop an adequate control strategy according to the nature of the impurities
- Applies to new sources of active substances
- A specific discussion is expected in the dossier (section 3.2.S.3.2)

Classification of impurities with respect to mutagenic and carcinogenic potential

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

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5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

How to set an acceptable limit

Application of the "less-than-lifetime" (LTL) concept

Scenario[1]	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, chronic myelogenous leukemia), drugs specifically labeled for less than 10 years of use, drugs administered intermittently to treat acute recurring symptoms[2] (chronic Herpes, gout attacks, substance dependence such as smoking cessation), macular degeneration, HIV[3]	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 Alzheimer disease), hormone therapy (e.g., growth hormone, thyroid hormone, parathyroid hormone), lipodystrophy, schizophrenia, depression, psoriasis, atopic dermatitis, Chronic Obstructive Pulmonary Disease (COPD), cystic fibrosis, seasonal and perennial allergic rhinitis	1.5

$$\frac{acceptable\ intake\ (\frac{\mu g}{day})}{MDD\ (\frac{g}{day})}$$

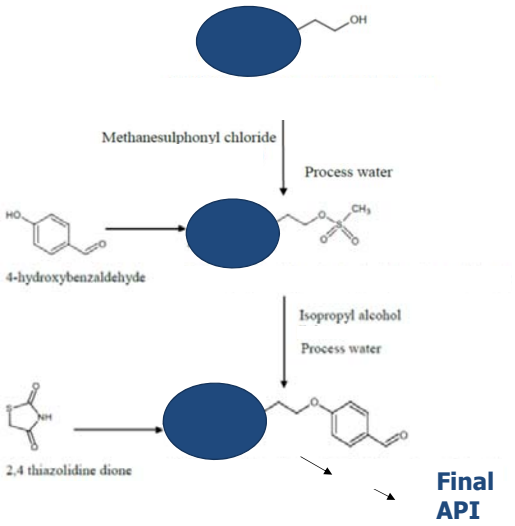
How to develop a control strategy?

Control of process-related impurities

- **Option 1**: test the impurity in the drug substance specification with an acceptance criterion at or below the acceptable limit;
- **Option 2**: test the impurity in starting materials or intermediates or as an in-process control, with an acceptance criterion at or below the acceptable limit;
- **Option 3**: test the impurity in starting materials or intermediates or as an in-process control, with an acceptance criterion above the acceptable limit of the impurity in the drug substance. The control should be coupled with demonstrated understanding of fate and purge, without the need for any additional testing later in the process. This option can be justified when the level of the impurity in the drug substance is less than 30% of the acceptable limit;
- **Option 4**: Understand process parameters and impact on residual impurity levels (including fate and purge knowledge) with sufficient confidence that the level of the impurity in the drug substance will be below the acceptable limit such that no analytical testing is recommended for this impurity.

How to develop a control strategy

Active substance X, MDD= 45 mg

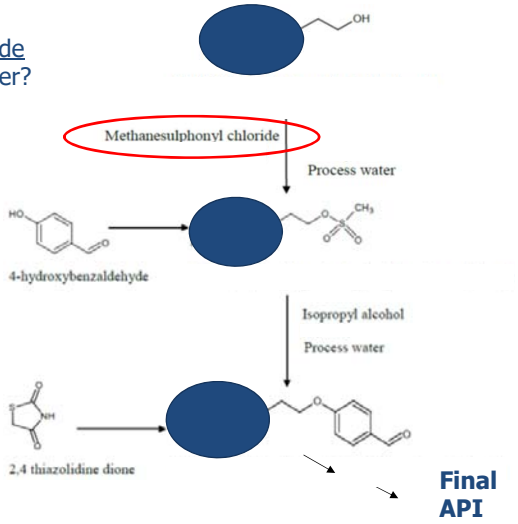


How to develop a control strategy

Active substance X, MDD= 45 mg

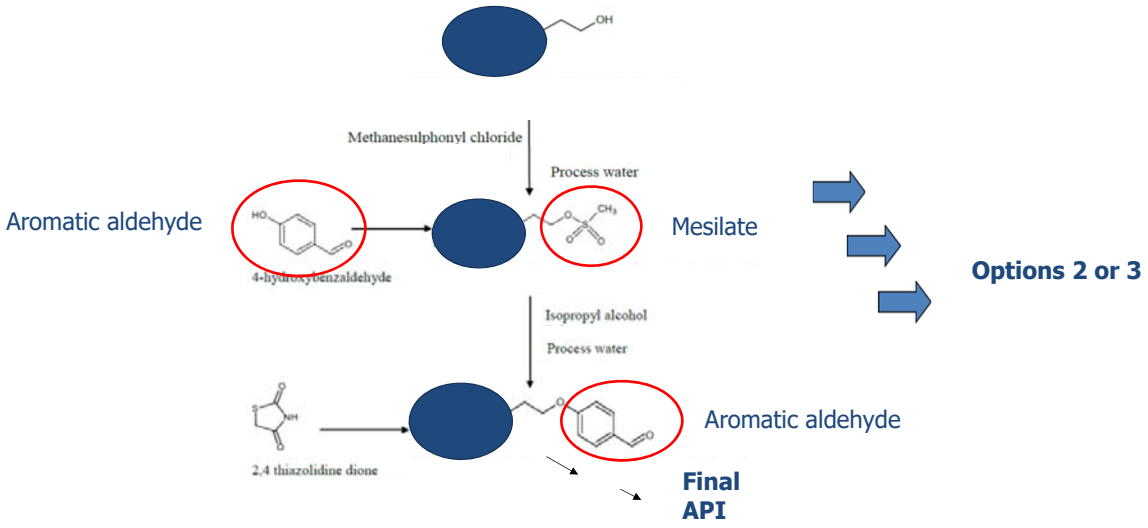
Methanesulphonyl chloride
- Washing step with water?

Theoretical impurity
Option 4



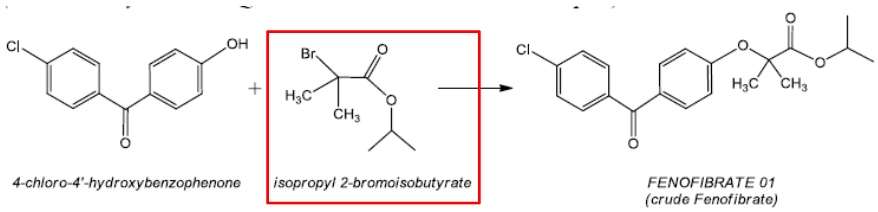
How to develop a control strategy

Active substance X, MDD= 45 mg



How to develop a control strategy

- **Fenofibrate**, lipid regulation drug.



According to ECHA website: mutagenic compound both in vivo and in vitro

Introduced in the last synthetic step → **Option 1** (control in the final API)

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Impurities - Elemental impurities

Reference documents

- **ICH Q3D**
- **PA/PH/CEP (16) 23** published in July 2018

Only applicable to substances used in products within the scope of Q3D (e.g. not implemented for vet. only, herbals, etc.)

- Serve the Component Approach as per Q3D: provide necessary information to MAH for their risk assessment on the Drug Product;
- Be useful for substances manufacturers and MAH and keep the benefits of the centralized assessment

Elemental impurities

Two different scenarios:

1. The substance manufacturer can submit a risk management summary (RMS) for elemental impurities (component approach). This helps the DP manufacturer's risk assessment and it is evaluated by assessors
2. No RMS given by the substance manufacturer.

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

Applicants are also reminded that it is a requirement to submit the synthesis of the substance in the Dossier including information on metal catalysts or reagents used.

Elemental impurities

1. If the RMS is included in the Dossier…

- It should be apparent that this approach is followed
- The intended route of administration/use should be indicated
- Details on the risk assessment performed should be provided
- The RMS should provide the reasons why certain impurities are considered and the justification of the chosen control strategy
- A screening alone is not a risk management summary
- Analytical methods used should be described including demonstration of specificity and sensitivity. Full validation should be given for methods adopted to release the substance.

Elemental impurities

1. If the RMS is included in the Dossier…

On the CEP…

A risk management summary for elemental impurities has been provided.	(Annex 2)

… and if applicable…

– Test for elemental impurities by ICP-MS Palladium	not more than 10 ppm	(Annex 3)

Intended route of administration / Use of the substance: ……

Element	Class	Intentionally added?	Considered in risk management?	Conclusion
Cd	1	*	Yes	**
Pb	1	*	Yes	**
As	1	*	Yes	**
Hg	1	*	Yes	**
Co	2A	*	Yes	**
V	2A	*	Yes	**
Ni	2A	*	Yes	**
Tl	2B	*	*	**
Au	2B	*	*	**
Pd	2B	*	*	**
Ir	2B	*	*	**
Os	2B	*	*	**
Rh	2B	*	*	**
Ru	2B	*	*	**
Se	2B	*	*	**
Ag	2B	*	*	**
Pt	2B	*	*	**
Li	3	*	*	**
Sb	3	*	*	**
Ba	3	*	*	**
Mo	3	*	*	**
Cu	3	*	*	**
Sn	3	*	*	**
Cr	3	*	*	**

Does not restrict the use of the CEP!

"Yes" for all which have been discussed

*** Yes / No**

** The following statements may be used as explained under 3.1:
- **"Absent"** with its meaning definition (e.g. "less than 30% of ICH Q3D option 1 limit", or "less than X ppm"),
- **or "< X ppm",**
- **or "No risk identified"**

Elemental impurities

2. If the RMS is NOT provided…

It is expected to have in the Dossier:

- Information on Class 1, 2 and 3 elements intentionally added, as part of description of the manufacturing process
- For elements intentionally added in early steps (all but the last synthetic step), data showing levels in the final substance and controls applied, if any.

On the CEP…

> No elemental impurity classified in ICH Q3D is intentionally introduced in the manufacture of the substance.

… or …

> The following elemental impurity classified in ICH Q3D is intentionally introduced in the manufacture of the substance: Palladium

In this case no information on levels of elemental impurities are reported on the CEP.

Elemental impurities

For both scenarios:

EI intentionally introduced prior to the last step:

- Specification at release if proposed by the applicant, is mentioned on CEP (irrespective of presence/absence of the elemental impurities)

EI intentionally introduced in last synthetic step:

- Specification for final substance is normally expected unless levels are below 30% of ICH Q3D option 1 limit

In general the control strategy should focus on absence or presence of elemental impurities in the final substance relying on the process capabilities and on the control of elemental impurities (using preferably option 1, or alternatively option 2a of ICH Q3D).

Impurities – Residual solvents

Absence of discussion for Class 1 solvents as contaminant of another solvent

Many solvents are known to be contaminated by class 1 solvents.

E.g., benzene is potentially present in acetone, toluene, ethanol, methanol, isopropanol, xylene, hexane and petroleum ether

Reference documents

ICH Q3C / Ph.Eur. General Chapter 5.4

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

Where a class 1 solvent might be present in another solvent, a routine test for this class 1 solvent is not required if one of the 2 options reported is met.

Residual solvents

Absence of discussion for Class 1 solvents as contaminant of another solvent

Option 1. Limit applied to originator solvent is such that the class 1 solvent will be present in the API at levels below 30% of the ICH limit, taking into account the maximum likely level of contamination of the Class 1 solvent.

Toluene in API: NMT 200 ppm

Benzene in toluene: NMT 500 ppm → Max level of benzene in the API: 0.1 ppm

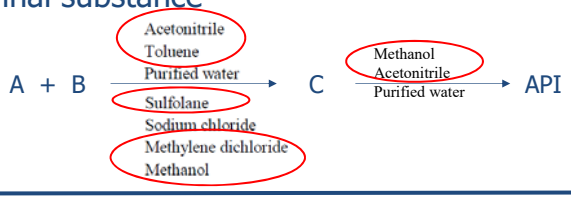
Option 2. Demonstration (validated method) that the class 1 solvent is NMT 30% of its ICH limit in a suitable intermediate or final API. Supporting data on 6 consecutive pilot scale batches or 3 consecutive industrial scale batches.

Residual solvents

Control of class 2 residual solvents

Reference document **Annex 1 (CPMP/QWP/450/03) to the EU Guideline for residual solvents**

- Class 2 solvents used in the last step of the synthesis should be routinely controlled in API
- The routine testing of a class 2 solvent used prior to the last step is not required if its content is demonstrated to be < 10% of the limit in an intermediate or the final substance



ICH limits class 2 solvents used

Acetonitrile	NMT 410 ppm
Toluene	NMT 890 ppm
Sulfolane	NMT 160 ppm
Methylene Dichloride	NMT 600 ppm
Methanol	NMT 3000 ppm

Quality of intermediates
Fate and carryover of impurities

Top 8 Top 9

The proposed control strategy is evaluated keeping in mind the risk of having uncontrolled impurities in the final substance above acceptable limits.

The impurity profile of isolated intermediates should be characterised and this becomes particularly important in case of:

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

Quality of intermediates
Fate and carryover of impurities

Top 8 Top 9

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

Information should be given on the impact the quality of isolated intermediates can have on the quality of the final substance. Hence:

- Fate and carryover of impurities from intermediates to the final substance should be discussed;
- Absence of residues of intermediates (isolated and non-) in the final substance should be demonstrated;
- The suitability of the monograph to control the quality of the final substance coming from the presented synthesis should be discussed.

Analytical specifications for reagents and solvents and their carry-over

Top 6 Top 7

- Specifications of reagents and solvents used to manufacture the substance from the introduction of the starting materials is needed. Purity should be defined and a reasonable mass balance should be observed;
- Specifications of recycled material before being re-introduced in the process should be given and justified;
- Particular attention should be paid to the quality of solvents (both fresh and recovered) used in the last steps;
- Carryover to the final substance of reagents and solvents should be discussed, as applicable.

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Deficient application delays the CEP!

Conclusions: how to avoid deficiencies?

- Build up your Dossier taking into account applicable policies and addressing the requirements discussed in this workshop.
- With your Dossier you should give assurance on the ability of the process to remove impurities and to reduce the risk of having uncontrolled impurities above acceptable limits. Hence:
  - do not build up your Dossier on your purest batches of starting materials, intermediates and final substance. This would just lead to questions
  - include in the Dossier any relevant (recent and non-) analytical results and studies in support, even though performed during development phase
- Suitability of the specific monograph to control the quality of your substance should be demonstrated
- Deficient Dossiers delay the granting of your CEP and might lead to the closure of your application without the CEP being granted.

Thank you for your attention

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