

Content of the dossier – The Top Deficiencies identified in dossiers

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Summary

- Overview of CEP process
- Top 10 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

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Administrative validation at receipt

Dossier is complete

- The clock starts

Dossier is not complete

- The clock does not start: dossier is blocked



- Dossier not in eCTD
- QOS is missing
- Dossier is not written in one of the official languages

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Administrative validation at receipt

- Electronic submission not in accordance with the requirements (eCTD since 01/2018)
- Missing information on the application form:
 - Names and addresses of the parties involved
 - Agreement letters
- Declaration of manufacture according to the dossier and GMP
- Declaration of willingness to be inspected
- Use of animal or human origin material
- Holder's commitments

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Technical validation at receipt

- Summarise the commercial history - make clear if, and in what product THIS source of substance is on the EUROPEAN market. Information on ASMF submitted for the 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

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Technical validation at receipt

- Specify the proposed re-test period:
 - Justified by stability data based on ICH conditions studies
 - Recommended storage conditionsOr tick the box "No re-test period requested"
- Specify the packaging material (the container closure system is summarised on the CEP)

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Technical validation at receipt

Applications are blocked when:

- Reference is made to an old version of the Ph. Eur. monograph
- Use of Class I solvents without justification and control
- Unsuitable information on the impurity profile of the substance
- Sterile substances: absence of validation data on the sterilisation
- **Absence of quantitative method to replace a non-specific TLC test of the monograph**

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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)

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Technical validation at receipt

Application blocked (in general 20% of the total)

- information not suitable to start the evaluation process
- the clock does not start until suitable information is given

An incomplete application delays the CEP!

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Evaluation

- After validation is satisfactorily completed, the dossier is then evaluated. The EDQM has 5 months to complete the evaluation and inform the applicant of the outcome.
- Currently the deadlines are being respected.
- See monthly report published on www.edqm.eu

CERTIFICATION OF SUITABILITY (CEP) PROCEDURE OF CERTIFICATION (GENERAL) | NEWS | 09 APRIL 2018 | STRASBOURG, FRANCE |

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

- ▶ [March 2018 Certification Monthly Report.](#)

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After first round of evaluation

- Less than 5% of CEPs are usually granted after the first round of evaluation, a request for additional information is sent for the other 95% of dossiers.
- The applicant has up to 6 months to respond to this request

➔ Deficient application delays the CEP!

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Administrative validation at receipt of additional information response

Dossier is complete

- The clock starts

Dossier is not complete

- The clock does not start: dossier is blocked



- Updated sections of dossier impacted by responses not provided.
- Responses to all questions not provided.

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Technical validation at receipt of additional information responses

- The technical validation at the reception of the response involves checking that all the questions have been answered and that they seem coherent. The responses are not assessed at this stage.
 - Evaluation of additional information takes 4 months
- After two rounds of requests for additional information, dossiers still deficient may lead to their rejection!

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Dossier and deficiencies

Reference documents

- **PA/PH/CEP (04) 1 5R (September 2015)**
“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

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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 Ph. Eur. monograph is suitable to control the actual quality of the substance.

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Deficiencies concerning starting materials

Top 4

Redefinition of starting materials

Top 5

Quality of starting materials

Top 2

Fate and carry-over of impurities from starting materials

Top 10

Information on starting materials

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Definition of starting materials

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

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

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Definition of starting material

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

Relationship between risk and number of synthetic steps

Length of the synthesis and Control strategy-both have to be taken into account

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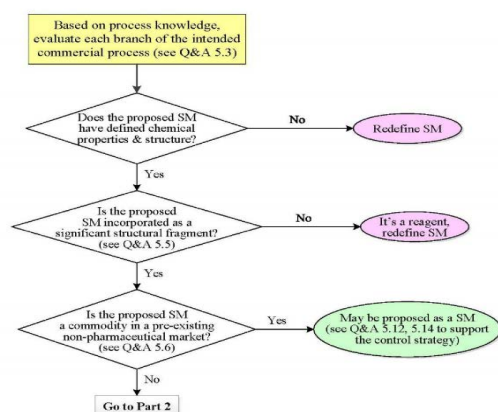
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Definition of starting material

Annex 1 to ICH Q11 Q&A-Decision Tree :



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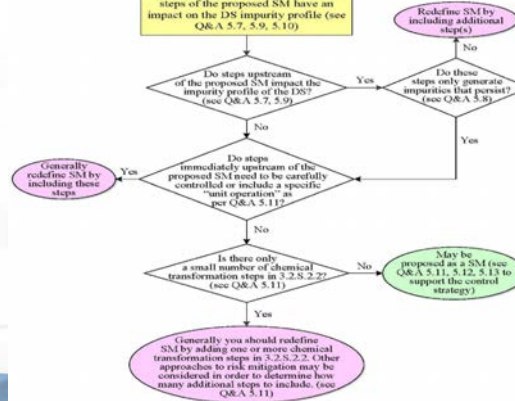
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Definition of starting material

Part 2:

Examine the DS impurity profile based on process knowledge of the intended commercial process in order to assess whether upstream and downstream steps of the proposed SM have an impact on the DS impurity profile (see Q&A 5.7, 5.9, 5.10)



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Redefinition of starting materials - consequences -

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

→ 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
- Sections 3.2.S.2.2, S.2.3, S.2.4 and S.3.2 need to be updated;
- **Information submitted from third parties is not acceptable. The final substance 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)**

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Quality of starting materials Fate and carry-over of impurities

- The impurity profile of the starting materials should be adequately characterised
- 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.
- Discussion on fate and carry-over of impurities.

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Quality of starting materials Fate and carry-over of impurities

Example of non-acceptable analytical specification

Chromatographic purity (By GC)	
Purity	Not less than 98.00 % (Including 4-Methoxy phenacyl chloride)
4-Methoxy acetophenone	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 substance

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.

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Quality of starting materials Fate and carry-over of impurities

Acceptance criteria in place to control impurities in starting materials should be justified by the manufacturer, taking into account fate and carry-over 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 %

Batch data on their own
DO NOT justify limits!

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Information on the starting materials

Besides analytical specification, the following information are expected in 3.2.S.2.3 :

- Brief synthetic pathway of starting materials including all solvents and reagents, sufficient steps should be disclosed to enable an assessment of potential impurities.
- Names and addresses of the manufacturers (not traders, vendors or suppliers).
- If more than one manufacturer of the SM is used, quality equivalence should be demonstrated by batch data on the final substance manufactured using all the possible sources of the SM.

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Description of the manufacturing process and process controls

**Top
3**

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 (temperatures, pressures, times, etc.)

Same level of detail is requested for outsourced intermediates.

In-process controls should be mentioned in S.2.2. part (as a part of description of manufacturing process), and details of in-process control in terms of acceptance criteria and analytical methods in section S.2.4. (information in both sections should be coherent)

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Description of the manufacturing process and process controls

- Re-working is not allowed as typically implies the use of different reagents and/or solvents and consequently it leads to a different impurity profile
- Usage of recovered solvents: justified specification should be provided

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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 (information in section S.2.2. should be in line with batch size in S.4.4).
- Where the substance has yet to be produced in commercial quantities, the CEP can be granted provided scale-up is reported to the EDQM via an appropriate revision.

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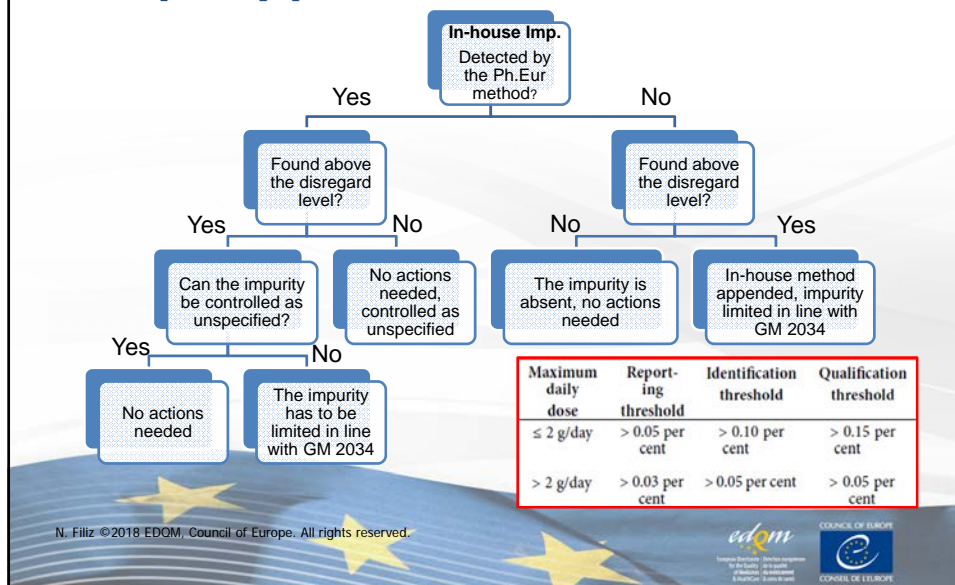
Related substances and suitability of the Monograph to control the impurity profile of the final substance

- Suitability (or unsuitability) of the method(s) of the monograph to control all the related substances should be demonstrated; in particular where additional impurities (those not listed in the transparency statement of the monograph) are found above relevant reporting threshold or disregard limit of the monograph.
- 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.

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



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 Q2B
- Cross-validation on the same batches against the corresponding Ph. Eur. method (using spiked solutions if necessary)
- Comparative and typical chromatograms



Mutagenic impurities



Reference document:

ICH M7 (R1) (March 2017)

“Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk”

- 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)
- Hazard assessment in order to classify actual and potential impurities (class from 1 to 5)

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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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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

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

MDD ($\frac{\text{g}}{\text{day}}$)

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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.

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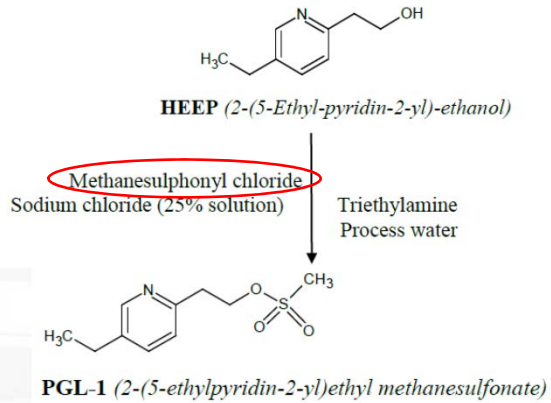


How to develop a control strategy

Pioglitazone, antidiabetic. MDD= 45 mg

Methanesulphonyl chloride
- Washing step with water?

↓
Theoretical impurity
Option 4

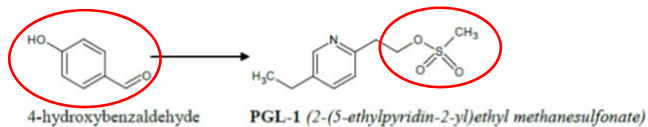


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How to develop a control strategy

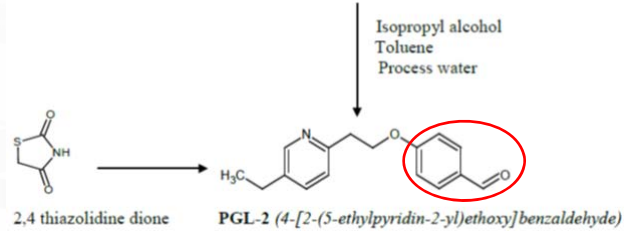
4-HB: aromatic aldehyde



PGL-1: mesilate

PGL-2: aromatic aldehyde

↓
Options 2 or 3



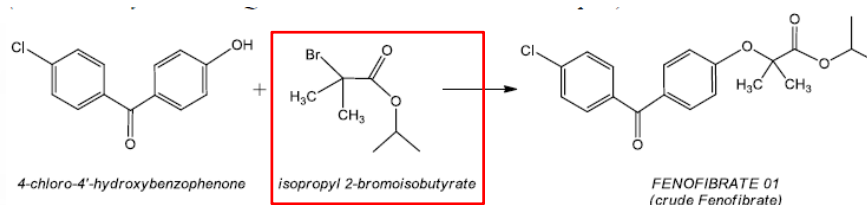
↓
Final API

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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 i.e. control in the final API

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Elemental impurities



Reference documents

- **ICH Q3D**
- **PA/PH/CEP (16) 23** published in August 2016
- Webinar on elemental impurities (2017)-training material available on EDQM website

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 centralised assessment

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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 CEP assessors
2. No RMS given by the substance manufacturer.

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Elemental impurities If the RMS is included in the Dossier...

- It should be apparent that this approach is followed
- The RMS should provide the reasons why certain impurities are considered and the justification of the chosen control strategy

How to build the RMS:

- All potential sources of contamination should be considered;
- The intended route of administration/use should be indicated;
- All elemental impurities mentioned in ICH Q3D (as per table 5.1) should be considered
- **A screening alone is not a RMS** (analytical methodology should be mentioned with demonstration of specificity and sensitivity)

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Elemental impurities If the RMS is included in the Dossier...

A possible way to present the RMS

Source	used in step X of 4	known/likely EI	Risk assessment	Risk of carry-over	Action
Catalyst	4	Pd	Homogeneous catalyst (Ph ₃ P) ₄ Pd used in last step.		Specification in final substance.
Process aids	4	Pb, Cu	Activated charcoal used in last step. Pot. impurities limited in raw material specification.		No further action required.
Reagents	1-4	Cd, Pb, As, Hg, Ni, Se, Sb, Cu, Cr	HCl, NaOH, H ₂ SO ₄ . Based on data on raw materials and the used quantities limited carry-over is expected.		Verify risk assessment for class 1 EI by screening.
Solvents	1-4	Ni	Cyclohexane used in last step. Purified by distillation. For other solvents no catalyst is used.		No further action required.
Water	4	Cd, Pb, As, Hg, Ni, Sb, Cu	Purified water is used.		No further action required.
Equipment	1-4	Ni, Mo, Cr	Glass-lined steel and steel 1.4435 is used. Harsh conditions (pH < 5.0) and high mechanical forces during particle size reduction.		Perform screening for these EI to check carry over.
Container closure system	-	Sb	Used as catalyst in PET synthesis. Low concentration of EI in packaging material. Solid substance and thus limited interaction.		No further action required.

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Elemental impurities If the RMS is NOT performed...

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.

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Elemental impurities For both scenarios:

EI intentionally introduced prior to the last step:

- Specification in the final substance if proposed by the applicant, mentioned on CEP (test appended, irrespective of presence/absence of the elemental impurities);
- No specification proposed by applicant: no test appended

EI intentionally introduced in last synthetic step:

- Specification for final substance is normally expected unless levels below 30% of ICH Q3D option 1 limit
- Suitable description of the analytical method used with full validation data (ICH Q2)

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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. For example, 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.

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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 → Max level of benzene
Benzene in toluene: NMT 500 ppm 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.

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Control of class 2 residual solvents

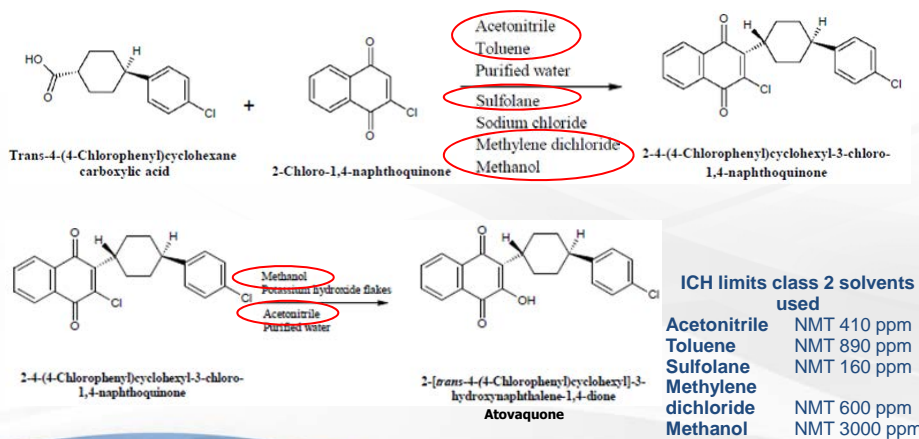
Reference document Annex 1 (CPMP/QWP/450/03) to the EU Guideline for residual solvents

- 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

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Control of class 2 residual solvents



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Quality of intermediates Fate and carryover of impurities from intermediates



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 which are controlled by a method which is different from the one adopted at release

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

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Quality of intermediates Fate and carryover of impurities

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.

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Analytical specifications for reagents and solvents and their carry-over



- 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 materials 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;
- Carry-over to the final substance of reagents and solvents should be discussed, as applicable.

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Conclusions: how to avoid deficiencies?

- Build up the Dossier taking into account applicable policies and addressing the requirements discussed in this workshop.
- With the Dossier, the applicant 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.

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