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

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How to build a good new CEP application

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Module 6: Building successful CEP dossiers (Live Webinar)
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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

EDQM — Applicant

115 WD — **1st Round:** 5% CEP 95% AI — 180 CD

92 WD — 90/30 CD

92/23 WD

CEP

Deficient application delays the CEP!

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

Top 4

- 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

Top 4

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

Annex 1 to ICH Q11 Q&A-Decision tree

→ Relationship between risk for the quality of the final substance and number of synthetic steps

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

Redefinition of starting materials - consequences

Top 4

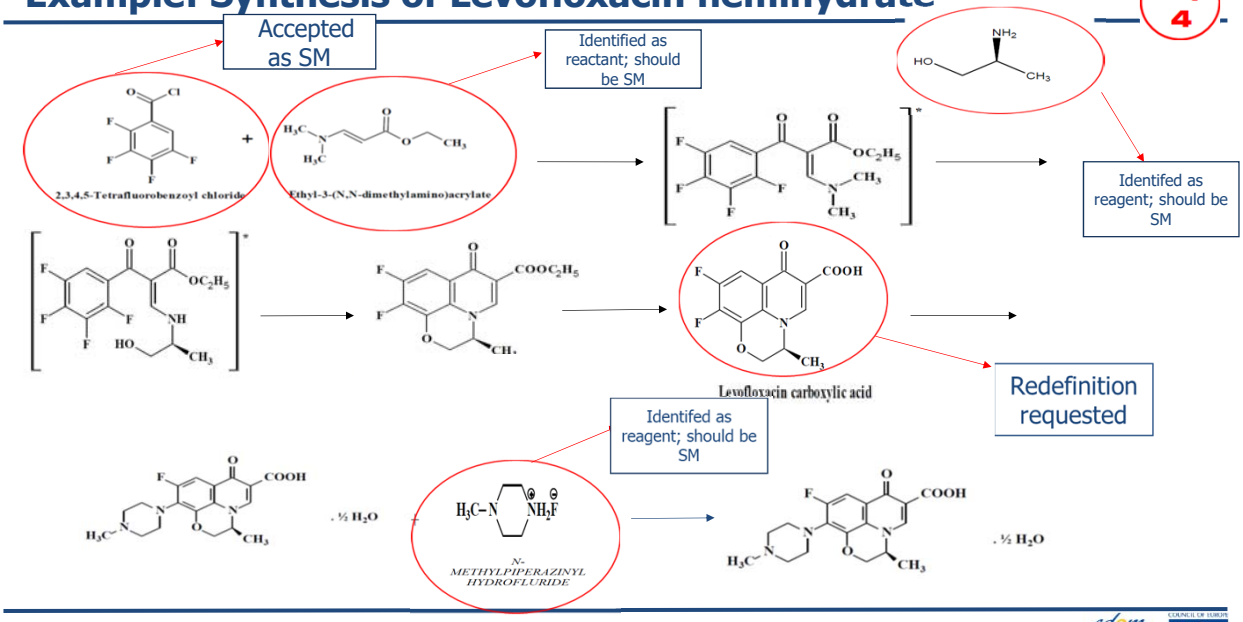
- The definition of starting materials is expected to be justified by the applicant. If not acceptable, a redefinition is required. What are the consequences?

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)

Example: Synthesis of Levofloxacin hemihydrate

Top 4



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

Example of non-acceptable analytical specification

Top 5

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

Top 5

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 %

Batch data 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 10

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.

These requirements apply equally for outsourced intermediates

Top 3

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

- the maximum batch size for which manufacturer has acquired experience and which correspond to batches referred in the dossier should be given

Absence of information related to recovery procedures:

- approved procedures exist for recovery and it should be described where recovered material is re-introduced in the process;
- justified specification should be described for recovered material(s)

Absence of information related to reprocessing procedures:

- routine reprocessing should be identified and justified;
- reprocessing method should be clearly described, as well as criteria for deciding when reprocessing will be performed

EU Guideline on the chemistry of active substance (EMA/454576/2016)

Mutagenic impurities

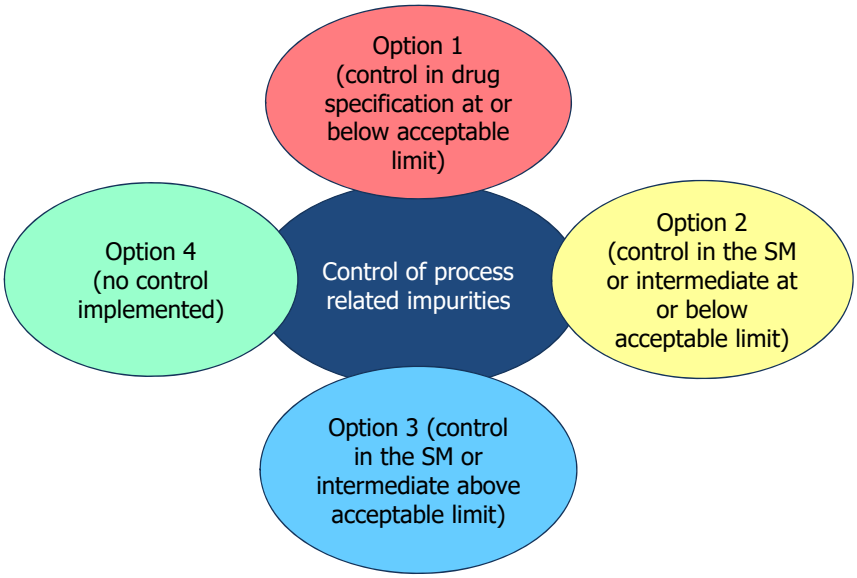
Reference documents
ICH M7 (R1)
"Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk"

Complete discussion on mutagenic impurities 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);
- For impurities characterized as Class 1, 2, and 3 the principles of **risk characterization** (as in ICH M7) should be used to derive acceptable intakes;
-For Classes 1,2 and 3 impurities **Control strategy** according to one of the options as per ICH M7 should be developed

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

Risk assessments for nitrosamines to be systematically included by CEP applicants in new dossiers, renewals, and revisions where a risk of nitrosamine formation may be introduced (i.e. changes to the manufacturing process, change of suppliers of starting materials or intermediates, etc.) **since 1 October 2020**

How to develop a control strategy

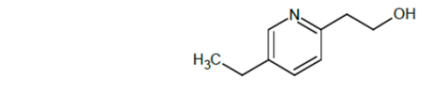


How to develop a control strategy

Pioglitazone, antidiabetic. MDD= 45 mg
- Acceptable limit NMT 33 ppm

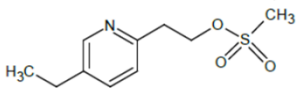
Methanesulphonyl chloride
- Washing step with water?

Theoretical impurity
Option 4



HEEP *(2-(5-Ethyl-pyridin-2-yl)-ethanol)*

Methanesulphonyl chloride
Sodium chloride (25% solution)
Triethylamine
Process water



PGL-1 *(2-(5-ethylpyridin-2-yl)ethyl methanesulfonate)*

How to develop a control strategy

4-HB: aromatic aldehyde

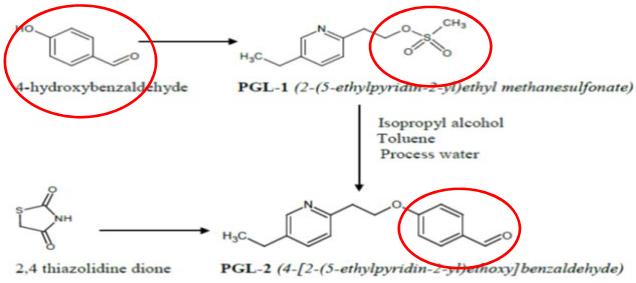
PGL-1: mesilate

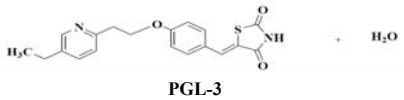
PGL-2: aromatic aldehyde

Options 2 or 3

Option 3: PGL-1 is controlled in PGL-3 with NMT 0.5 %

Justification of option 3 of control strategy



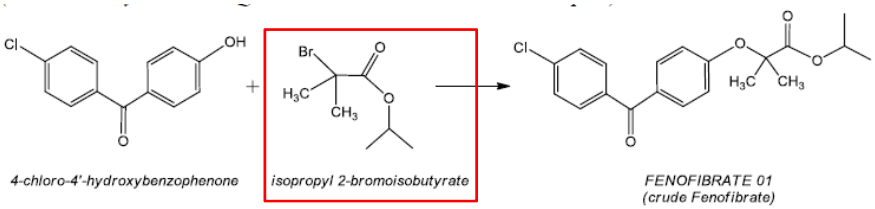


PGL-3

Final API

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)

Quality of intermediates Fate and carryover of impurities from intermediates

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

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 API. 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.

Elemental impurities

Top 7

Reference documents
- **ICH Q3D**
- **PA/PH/CEP (16) 23, 2R** published in April 2021

Specific discussion on elemental impurities is expected in the dossier (section 3.2.S.3.2)

Two different scenarios in CEP dossier:
- 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

- No RMS given by the substance manufacturer.

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

Elemental impurities

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

How to define control strategy for both scenario?

EI intentionally introduced in last synthetic step:
- Specification for final substance is normally expected unless levels below 30% of ICH Q3D option 1 limit (or alternatively and if justified, based on option 2a)

EI intentionally introduced prior to the last step:
- Specification at release if proposed by the applicant, to be mentioned on CEP (irrespective of presence/absence of the elemental impurities);
- No specification proposed by applicant: no questions

Method description with validation data according to ICH Q2 to be provided

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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