The place of the Certification Procedure in the global regulatory environment

19-20/09/2017 - Prague

Workshop 1: how to build up a good CEP application

Top ten deficiencies

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Reference documents chemical applications

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 our website
- They describe what we expect to find in the dossier

How to deal with mutagenic impurities

Reference documents
ICH M7 (R1) (March 2017)
"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
- 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

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

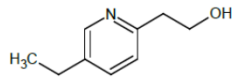
- **Option 1**: test the impurity in the drug substance specification with an acceptance criterion at or below the acceptable limit;
- **Option 2**: test the impurity in starting materials or intermediates or as an in-process control, with an acceptance criterion at or below the acceptable limit;
- **Option 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 (2)

Pioglitazone, antidiabetic. MDD= 45 mg

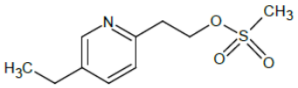
Methanesulphonyl chloride
- Washing step with water?

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)*

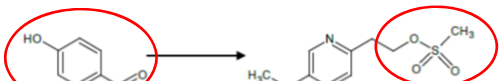
How to develop a control strategy (3)

4-HB: aromatic aldehyde

PGL-1: mesilate

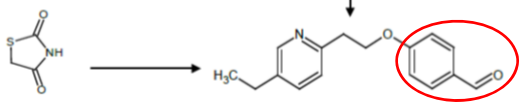
PGL-2: aromatic aldehyde

Options 2 or 3



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

Isopropyl alcohol
Toluene
Process water

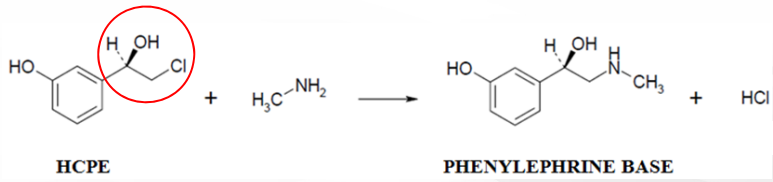


2,4 thiazolidine dione — **PGL-2** *(4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde)*

Final API

How to develop a control strategy (4)

Phenylephrine, symptomatic relief of nasal congestion, treatment of hypotensive states. MDD= 60 mg



HCPE **PHENYLEPHRINE BASE**

HCPE recognised as mutagenic (by Ames test) → **option 1** (control in the final API).

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**

Redefinition of starting materials

As per **ICH Q11**:

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 (2) - 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 manufacturer of the API 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

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 (2)

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 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 API.

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 API manufacturer, taking into account fate and carryover of impurities from starting materials to the API (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.

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

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.

The maximum batch size or the batch size range the process refers to should be given. Batch data in section 3.2.S.4.4 should be representative of the production capability of the process.

Sections 3.2.S.2.2 and 3.2.S.2.4 should be harmonised.

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 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 API of reagents and solvents should be discussed, as applicable.

Conclusions

- 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 API. 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 very much for your attention!

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