Changing EU Requirements and their National Impact

DIA AC Europe

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Toxicity of Impurities

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IMPURITIES **Relevant Information**

- Commission Directive 2001/83
- Notice to Applicants
- Expert Report(s) / Nonclinical Overview
- Guideline on the Assessment Report
- ICH Guideline Q3A Impurities in New Drug Substances
- ICH Guideline Q3B Impurities in New Drug Products
- ICH Guideline Q3C Impurities: Residual Solvents
- Draft Residues of Metal Catalysts
- Draft Limits for Genotoxic Impurities

Impurities ICH Q 3 A

Impurities can be **classified** into the following categories:

- Organic impurities (process- and drug-related)
- Inorganic impurities
- Residual solvents

Organic impurities **can arise** during the manufacturing process and/or storage of the new drug substance. They can be identified, volatile or non-volatile, and include:

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands and catalysts

Inorganic impurities **can result from** the manufacturing process. They are normally known and identified and include:

- Reagents, ligands and catalysts
- Heavy metals or other residual metals
- Inorganic salts
- Other materials (e.g., filter aids, charcoal)

When Toxicity Assessment needed?

Safety Aspects include specific guidance for qualifying those impurities that were not present, or
were present at substantially lower levels,
in batches of a new drug substance
used in safety and clinical studies.

RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

Organic Impurities

•summarise the **actual and potential impurities** most likely to arise during the synthesis, purification, and storage of the new drug substance

•summarise the **laboratory studies** conducted to detect

impurities in the new drug substance characterise the structure of actual impurities present in the new drug substance at a level greater than (>) the identification threshold

•**analytical procedures** should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than (≤) the identification threshold

Inorganic Impurities

Inorganic impurities are normally detected
and quantified using
pharmacopoeial or
other appropriate procedures

QUALIFICATION OF IMPURITIES

- Qualification is the process of acquiring and evaluating data that establishes the **biological safety** of an individual impurity or a given impurity profile at the level(s) specified.

- The applicant should provide a **rationale** for establishing impurity acceptance criteria that includes safety considerations.

- The **level** of any impurity present in a new drug substance that has been adequately tested in safety and/or clinical studies would be considered qualified.

- Impurities that are also significant **metabolites** present in animal and/or human studies are generally considered qualified.

- A level of a qualified impurity higher than that present in a new drug substance can also **be justified** based on an analysis of the actual amount of impurity administered in previous relevant safety studies.

Decision Tree for Identification and Qualification" (Attachment 3)

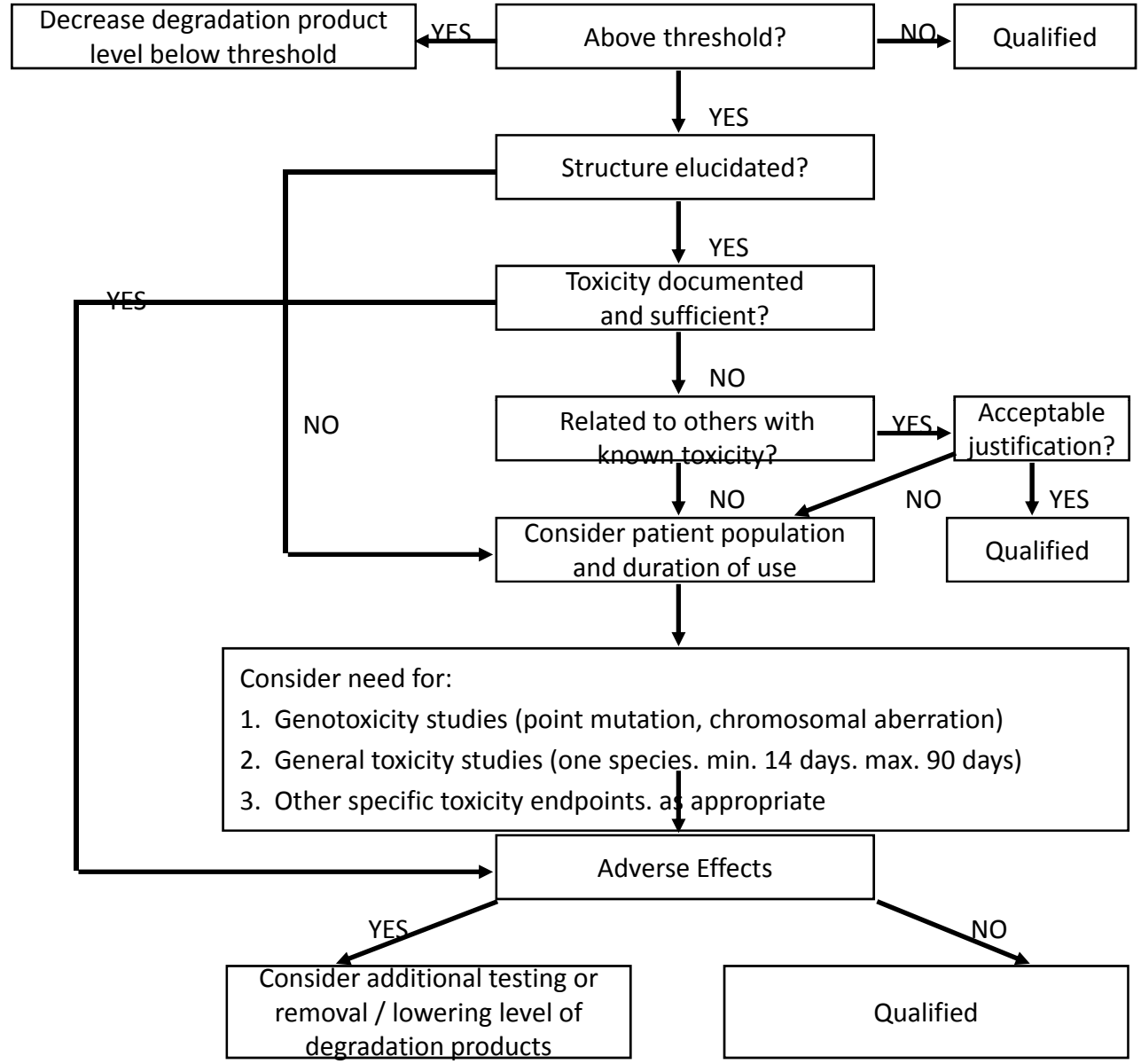
- The “Decision Tree”describes **considerations** for the qualification of impurities when thresholds are exceeded.

- In some cases, **decreasing the level** of impurity to not more than the threshold can be simpler than providing safety data.

- Alternatively, adequate data could be available in the **scientific literature** to qualify an impurity.

- If neither is the case, **additional safety testing** should be considered

DECISION TREE FOR SAFETY STUDIES



ICH-Q3A1.ppt

IMPURITIES **Nonclinical Overview**

- „An assessment of the impurities and degradants present in the drug substance and product should be included along with the knowledge of their potential pharmacologic and toxicologic effects.“

- „This assesment should form part of the justification for proposed impurity limits in the drug substance and product, and be appropriately cross-referenced to the quality documentation.“

IMPURITIES **Nonclinical Overview**

Consider the proposed impurity limits in relation to:

- toxicology of the impurity in relation to the active substance
- route of administration
- daily dose
- target population
- duration of therapy
- proposed indication

3D Toxicology **Drug Substance** **Test Article:**

Batch No.	Purity (%)	Specified Impurities ( )	Study Number	Type of Study

PROPOSED SPECIFICATION:

IMPURITIES

Ph. Eur. monograph for Hydroxyethylcellulose (HEC)

- Limit of nitrates in HEC
  - Limit present = 0,2 %
  - Proposed limit = 3 %
- Expert Report
  - Dietary exposure
  - Drinking water exposure
  - Pharmaceutical exposure
  - Smokers
  - Endogenous nitrate production
  - Intoxication
- Conclusion
  - The increase in nitrate "is not expected to result in any increase for nitrate induced toxicity."

IMPURITIES Non-clinical Assessment Report

- General Considerations
  - Consider the acceptability of the impurity profile in the specification of material destined for marketing in relation to that pertaining to the batches of material used in the preclinical safety studies.

- Abridged Applications
  - Where there is a change in the impurity profile of an active substance compared to an earlier synthetic method, or another already marketed product.

IMPURITIES

New Drug Substances

Consider need for:

1. **Genotoxicity studies** (point mutation, chromosomal aberration)[a]
2. **General toxicity** studies (one species, min. 14 days, max. 90 days)[b]
3. **Other specific** toxicity endpoints, as appropriate

IMPURITIES

„Remember :

Test material in toxicology tests should optimally be less pure than that to be used in the clinic:

The toxicologists should be asking for a supply of characterised bulk medicinal product, taken from the manufacturing process before its final recrystallisation."

The Regulatory Affairs Journal, May 1996

IMPURITIES Example

Batch	Identified Impurity (%)	Field of Applications
1	< 0,01	Mutagenicity/ Carcinogenicity Rat
2	0,2	Carcinogenicity Mouse
3	0,5	Humans

Genotoxic Impurities

The toxicological assessment of genotoxic impurities is difficult.

Data providing evidence for a threshold mechanism of genotoxicity is lacking.

Therefore. a generally applicable approach as defined by the Threshold of Toxicological Concern (TTC) is proposed.

A TTC value of 1.5 µg/day intake of a genotoxic impurity is considered to be associated with an acceptable risk (excess cancer risk of <1 in 100,000 over a lifetime) for most pharmaceuticals.

From this threshold value, a permitted level in the active substance can be calculated based on the expected daily dose.

Higher limits may be justified under certain conditions such as short-term exposure periods.

Genotoxic compound **with** evidence of threshold

Permitted Daily Exposure (PDE) Calculation

- Interaction with spindel apparatus
- Topoisomerase inhibition
- Inhibition of DNA synthesis
- Overloading of defense mechanisms
- Metabolic overload
- Induction of erythopoeisis
- Hyper-hypothermia

Permitted Daily Exposure (PDE) Calculation

$$\text{PDE (mg/day)} = \frac{\text{NOEL or LOEL (mg / kg)} \times \text{Weight adjustment (50 kg)}}{\text{Modifying factors: F1} \times \text{F2} \times \text{F3} \times \text{F4} \times \text{F5}}$$

F1: Interspecies differences (surface area : body weight ratio for man compared to testing species; rat = 5, mouse = 12)

F2: Inter-individual differences (10)

F3: Duration of exposure (1-10)

F4: Nature of toxicity, for a threshold genotoxic comp.:>10??

F5: Quality of data (1-10)

Genotoxic compound <u>without</u> evidence of threshold

- In general, pharmaceutical measurements should be guided by a policy of controlling levels to

  "as low as reasonably practicable"

  (ALARP principle),

  where avoiding is not possible.

Threshold of Toxicological Concern (TTC)

- TTC value higher than 1.5 microgram/day may be accepted :
  - Short-term use
  - Patient popolation very small
  - Life-threatening condition (safer alternatives not available)
  - Human exposure from other sources (e.g. food) much greather

IMPURITIES

Notes on Attachment 1

a) If considered desirable, a minimum screen for genotoxic potential should be conducted. A Study to detect point mutations and one to detect chromosomal aberrations, both in vitro,
are seen as an acceptable minimum screen.

IMPURITIES

New Drug Substances

Notes on Attachment 1

b) If general toxicity studies are desirable, study(ies) should be designed to allow comparison of unqualified material. The study duration should be based on available relevant information and performed in the species most likely to maximise the potential to detect the toxicity of an impurity. In general, a minimum duration of 14 days and a maximum duration of 90 days will be acceptable.