# Impurities

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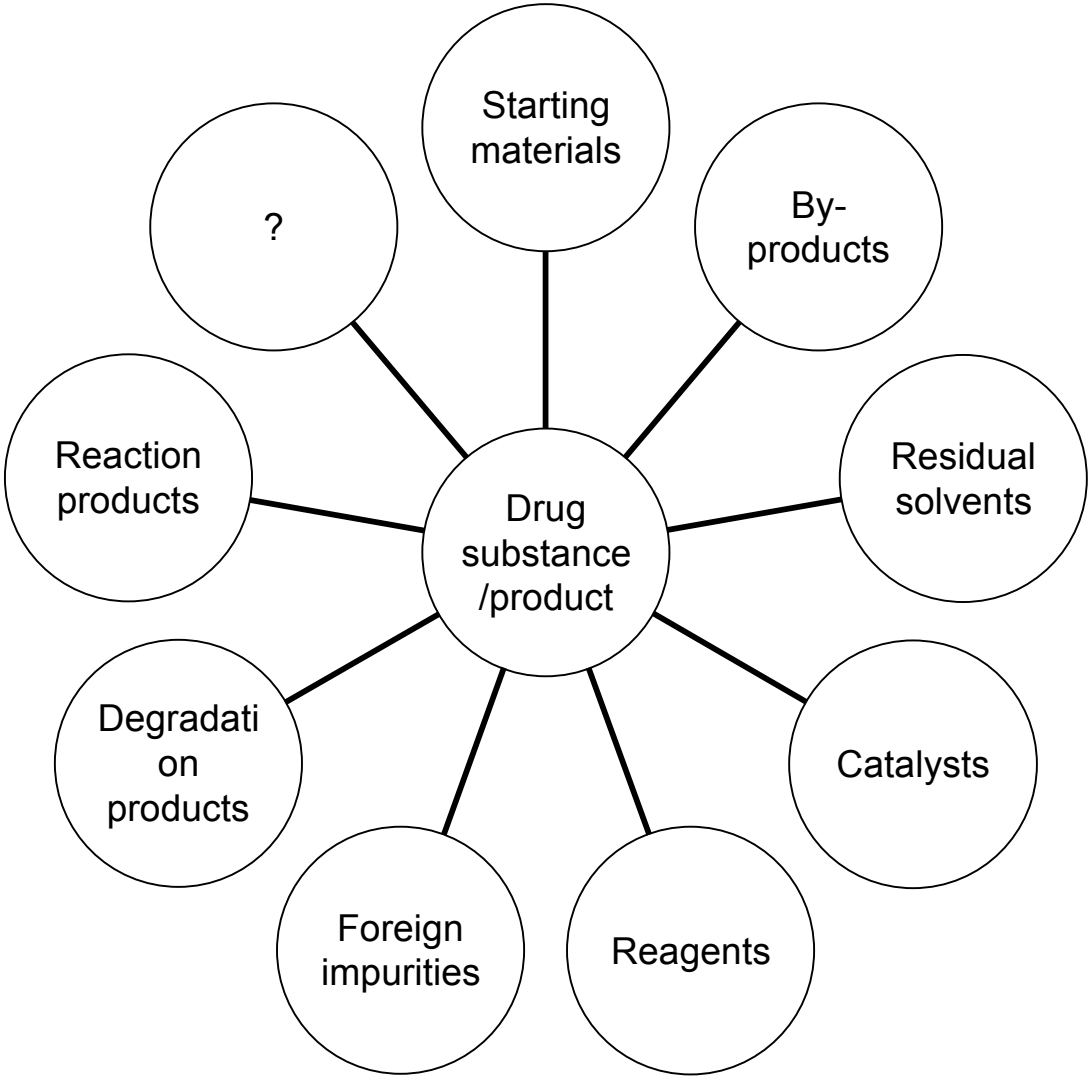
# Impurities


Starting materials
?
By-products
Reaction products
Drug substance /product
Residual solvents
Degradation products
Catalysts
Foreign impurities
Reagents

# Possible classification of impurities

| | |
|---|---|
| • Classification | Legal basics |
| • Organic impurities | ICH Q3A/ICH Q3B |
| • Anorganic impurities | |
| • Residual solvents | ICH Q3C |
| • Metal catalysts | Specific limits for residues of metal catalysts |
| • Genotoxic impurities | Limits of genotoxic impurities |

# ICH Q3A

"Impurities Testing:
Impurities in New Drug Substances"

- Scope:
  - for content/qualification of „chemical substances"
  - not for peptides, biological/biotechnological, oligonucleotide, radiopharmaceutical, fermentation products and semi-synthetic products derived therefrom, herbal products, and crude products of animal or plant origin
  - not intended to apply to new drug substances used during the clinical research stage of development
  - not for extraneous contaminants, polymorphic forms and enantiomeric impurities

# ICH Q3A

Principles of this guideline:

- Reporting
- Identification
- Qualification

of impurities at defined limits

# ICH Q3A - Vocabulary

- Reporting of impurities: for example by their relative retention time (RRT)
- Identified impurities: known by their chemical structure
- Qualification: the process of acquiring and evaluating data that establishes the biological safety of an individual impurity
- Specified impurities: identified or unidentified impurities, selected by their specifications

# ICH Q3A

- Example for a drug substance:
  - Imp. A (Ph.Eur. Monograph) <0.20%
  - Imp. B (Ph.Eur. Monograph) <0.10%
  - Imp. C <0.15%
  - Imp (RRT 0.9) <0.10%
  - Any unknown imp. <0.10%
  - Total imp. <0.20%

# ICH Q3A - Thresholds

| Maximum daily dose | Reporting threshold | Identification threshold | Qualification threshold |
|---|---|---|---|
| ≤ 2 g/day | 0.05% | 0.10% | 0.15% |
| > 2 g/day | 0.03% | 0.05% | 0.05% |

# ICH Q3A - Thresholds

| Maximum daily dose | Reporting threshold | Identification threshold | Qualification threshold |
|---|---|---|---|
| ≤ 2 g/day | 0.05% | 0.10% or 1.0 mg per day intake (whichever is lower) | 0.15% or 1.0 mg per day intake (whichever is lower) |
| > 2 g/day | 0.03% | 0.05% | 0.05% |

# vs. European Pharmacopoeia

- Ph.Eur. - general monograph 07/2007:**2034**, Substances for pharmaceutical use

- Ph.Eur. – general text 07/2006:51000, **5.10**. Control of impurities in substances for pharmaceutical use

  - for new and existing drug substances
  - Ph.Eur. is implemented in national law (AMG)
  - limits identical to those provided in guideline Q3A

# ICH Q3B

"Impurities in New Drug Products"

- Scope:
  - for content/qualification of "degradation products"
  - not for peptides, biological/biotechnological, oligonucleotide, radiopharmaceutical, fermentation products and semi-synthetic products derived therefrom, herbal products, and crude products of animal or plant origin
  - not intended to apply to new drug substances used during the clinical research stage of development
  - not for extraneous contaminants, polymorphic forms and enantiomeric impurities
  - not for impurities arising from excipients or extractables/leachabels of the container closure system

# ICH Q3B

Principles of this guideline:

- Reporting
- Identification
- Qualification

of degradation products at defined limits

# ICH Q3B - Thresholds

**Reporting Thresholds**

| Maximum Daily Dose[1] | Threshold[2,3] |
|---|---|
| ≤ 1 g | 0.1% |
| > 1 g | 0.05% |

**Identification Thresholds**

| Maximum Daily Dose[1] | Threshold[2, 3] |
|---|---|
| < 1 mg | 1.0% or 5 µg TDI, whichever is lower |
| 1 mg - 10 mg | 0.5% or 20 µg TDI, whichever is lower |
| >10 mg - 2 g | 0.2% or 2 mg TDI, whichever is lower |
| > 2 g | 0.10% |

**Qualification Thresholds**

| Maximum Daily Dose[1] | Threshold[2,3] |
|---|---|
| < 10 mg | 1.0% or 50 µg TDI, whichever is lower |
| 10 mg - 100 mg | 0.5% or 200 µg TDI, whichever is lower |
| >100 mg - 2 g | 0.2% or 3 mg TDI, whichever is lower |
| > 2 g | 0.15% |

# Pharmacopoeia?

- Ph.Eur. only applicable for drug substances
- BP and USP comprise relevant monographs for drug products
- Q3B is a generally accepted guideline for setting limits in drug products

# ICH Q3C

"Impurities: Residual Solvents"

- Scope:
  - for drug substance, drug product and excipients
  - Independent of single monographs
  - For new and old drug substances/products
  - All solvents have to be present to the authorities
  - not for solvents used as excipients
  - not for clinical trials

# ICH Q3C

- Categorisation
  - class 1 toxic/carcinogen, should be avoided:
    benzene, carbon tetrachloride, 1,2-Dichloroethane, 1,1-Dichloroethene, 1,1,1-Trichloroethane
  - class 2 inherent toxic, should be limited:
    e.g. Methanol, Toluene, THF
  - class 3 less toxic, should be limited ≤ 0.5%
    e.g. Ethanol, Acetone
  - Residual solvents without toxicological data, limits should be justified e.g. isopropyl ether

# ICH Q3C

- setting limits for class 2 solvents:
  - conc (ppm) = 1000 x PDE / Dose

    PDE = "permitted daily exposure"
    dose = maximum daily dose

- Option 1: assuming Dose 10 g
- Option 2: real dose if option 1 is not possible for calculation of the sum of residuals in drug substances and excipients

# vs. European Pharmacopoeia

- EP – general text 01/2005:50400,
  5.4. Residual solvents, limiting residual solvent levels in active substances, excipients and medicinal products

  - Ph.Eur. is implemented in national law (AMG)
  - limits identical to those provided in guideline Q3C; including THF and NMP

# Metal catalysts

"Specification limits for residues of metal catalysts or metal reagents"

- Scope:
  - used in the synthetic route of the drug substance or any excipient
  - for new and old market products, but 5 years for implementation possible (Sep. 2013)
  - not for clinical research (higher limits are acceptable)
  - not for counter ions of a salt, or an excipient like pigments
  - not for extraneous contaminants (GMP issue)

# Metal catalysts

- Categorisation
  - class 1A, 1B and 1C are metals of significant safety concern
    e.g. Pt, Ni
  - class 2 are metals with low safety concern
    e.g. Mn
  - class 3 are metals with minimum safety concern
    e.g. Fe
- Limits depend on route of administration like oral, parenteral and/or inhalation
- Sum parameter of class 1B metals < 10ppm/< 1ppm

# Metal catalysts

| Classification | Oral Exposure | | Parenteral Exposure | | Inhalation exposure * |
|---|---|---|---|---|---|
| | PDE ($\mu$g/day) | Concentration (ppm) | PDE ($\mu$g/day) | Concentration (ppm) | PDE (ng/day) |
| **Class 1A:**<br>**Pt, Pd** | 100 | 10 | 10 | 1 | Pt: 70 * |
| **Class 1B:**<br>**Ir, Rh, Ru, Os** | 100** | 10** | 10** | 1** | |
| **Class 1C:**<br>**Mo, Ni, Cr, V**<br>Metals of significant safety concern | 250 | 25 | 25 | 2.5 | Ni: 100<br>Cr (VI): 10 |
| **Class 2:**<br>**Cu, Mn**<br>Metals with low safety concern | 2500 | 250 | 250 | 25 | |
| **Class 3:**<br>**Fe, Zn**<br>Metals with minimal safety concern | 13000 | 1300 | 1300 | 130 | |

# Metal catalysts

Calculation

$$\text{concentration (ppm)} = \frac{\text{PDE}}{\text{MDD}}$$

PDE: permitted daily exposure (µg/day)
MDD: maximum daily dose (g/day):
Option 1: 10 g,
Option 2: real MDD, 1 - 10 g

# Genotoxic impurities

"Limits of genotoxic impurities"

- Scope:
  - for new active substances
  - for existing active substance for new applications
  - for variations pertaining the synthetic route
  - not retrospective to authorized products, unless there is no specific cause for concern

# Genotoxic impurities

- Definition of genotoxicity:

"Positive finding in an in-vitro (in-vivo) test."

# Genotoxic impurities

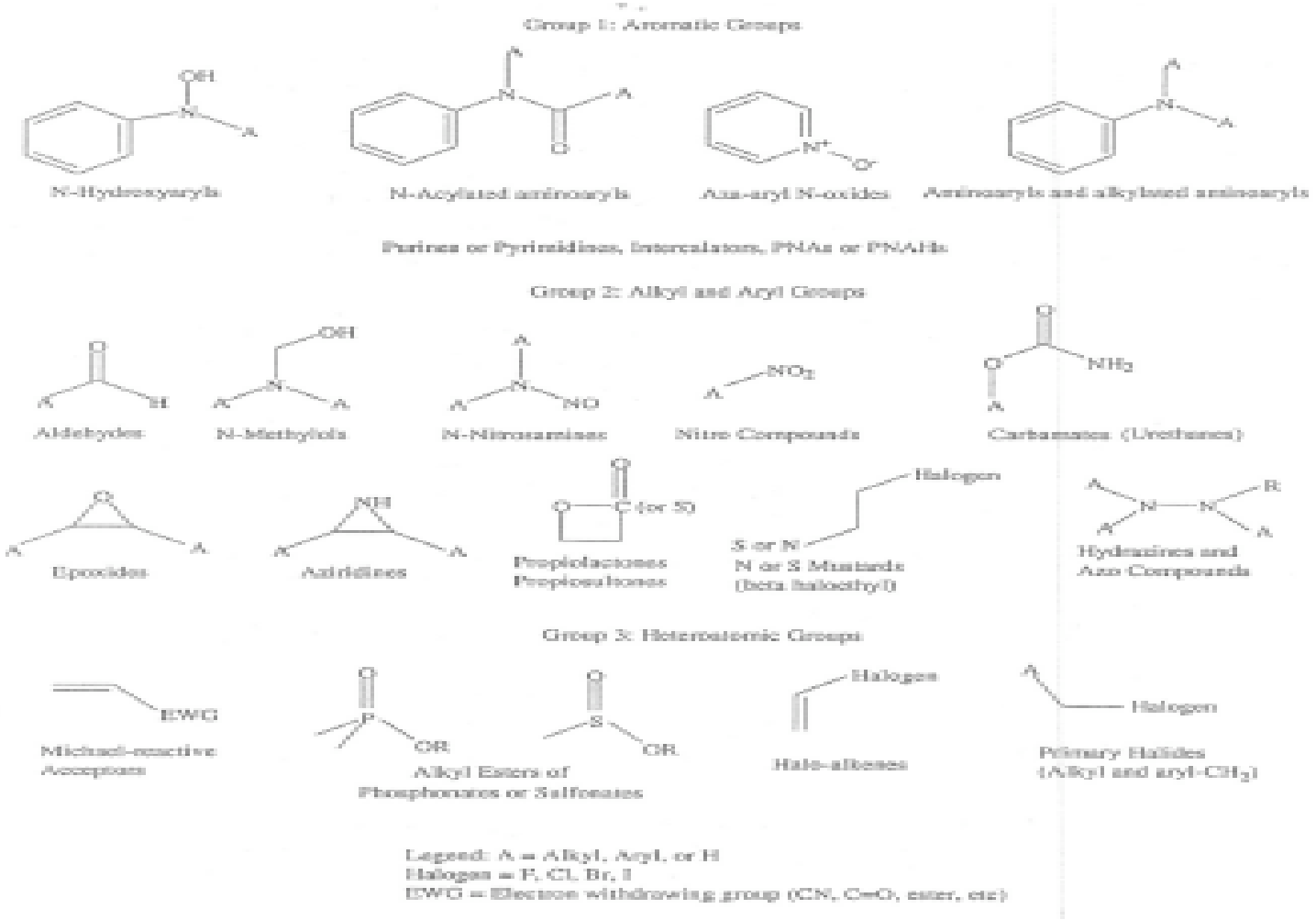
AMES-Test:

- Bacteria with a Mutation, couldn‘t produce a special amino acid
- if a chemical substance reverse the mutation it is genotoxic
- test is fast (1 week) and cheap

# Genotoxic impurities

- Detailed discussion and justification of genotoxic substances used in the drug substance
- **TTC = threshold for toxicological concern = 1.5 µg/person/day**
- concentration (ppm) = TTC / dose
- Higher / Lower Limits possible

# Genotoxic impurities



# Genotoxic impurities – Q/A

- **What might constitute "a cause-for-concern" in terms of application to currently marketed products?**
  - new knowledge may indicate a previously unknown cause for concern (e.g. alkyl mesylate)

- **What happend with drug substances, which do not have pharmacopoeial monographs and are implemented before the CHMP guideline?**
  - Action is needed only where there is study data demonstrating genotoxicity of the impurity. The existence of structural alerts alone is considered insufficient to trigger follow-up measures unless it is a structure of very high concern, e.g. N-nitroso, aflatoxins-like and azoxy-compounds. If a new synthetic route is used that may give rise to different potentially genotoxic impurities or to higher levels of previously recognized potentially genotoxic impurities then the situation should be discussed with the competent authority.

# Genotoxic impurity – staged TTC?

Available online at www.sciencedirect.com
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Regulatory Toxicology and Pharmacology 44 (2006) 198–211
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Regulatory Toxicology and Pharmacology
www.elsevier.com/locate/yrtph

## A rationale for determining, testing, and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity

Lutz Müller [a,*], Robert J. Mauthe [b], Christopher M. Riley [c], Marta M. Andino [d], David De Antonis [d], Chris Beels [e], Joseph DeGeorge [f], Alfons G.M. De Knaep [g], Dean Ellison [f], Jane A. Fagerland [h], Rebecca Frank [i], Betsy Fritschel [j], Sheila Galloway [f], Ernie Harpur [k], Charles D.N. Humfrey [l], Alexander S. Jacks [i], Nirdosh Jagota [m], John Mackinnon [e], Ganapathy Mohan [k], Daniel K. Ness [n], Michael R. O'Donovan [l], Mark D. Smith [o], Gopi Vudathala [k], Larry Yotti [p]

1 x 10E6

Table 1
Proposed allowable daily intake (μg/day) for genotoxic impurities of unknown carcinogenic potential during clinical development, a staged TTC approach depending on duration of exposure (ADIs for shorter durations than 12 months are based on linear extrapolation (Bos et al., 2004) from TTC value of 0.15 μg/day (Cheeseman et al., 1999; Kroes et al., 2004))

| | Duration of exposure | | | | |
|---|---|---|---|---|---|
| | ≤1 month | >1–3 month | >3–6 month | >6–12 month | >12 month |
| Allowable Daily Intake (μg/day) for different duration of exposure (as normally used in clinical development) | 120[a] or 0.5%[c] whichever is lower | 40[a] or 0.5%[c] whichever is lower | 20[a] or 0.5%[c] whichever is lower | 10[a] or 0.5%[c] whichever is lower | 1.5[b] [c] |

Known carcinogens should have compound-specific risk calculated (see text and Fig. 1).
[a] Probability of not exceeding a $10^{-6}$ risk is 93%.
[b] Probability of not exceeding a $10^{-5}$ risk is 93%, which considers a 70-year exposure.
[c] Other limits (higher or lower) may be appropriate and the approaches used to identify, qualify, and control ordinary impurities during developed should be applied. In particular, approaches that foresee a very low dose of the API ("microdoses") may facilitate higher limits than 0.5%.

# Thanks!

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# Relevant Guidelines I

- Impurities Testing: Impurities in New Drug Substances, CPMP/ICH/ 2737/99-ICH Q3A (R2)
- Impurities in New Medicinal Products, CPMP/ICH/ 2738/99-ICH Q3B (R2)
- Impurities: residual solvents, CPMP/ICH/ 283/95-ICH Q3C (R3)
- Application of NfG on residual solvents to marketed products, CPMP/QWP/8567/99
- Maintenance document for NfG on impurities: residual solvents. Type of maintenance: updating based on new information (Q3C (M)), CPMP/ICH/1507/02
- Maintenance of NfG on impurities: residual solvents. PDE for tetrahydrofuran (THF) and N-methylpyrrolidone (NMP) (Q3C (M)), CPMP/ICH/1940/00 corr.

# Relevant Guidelines II

- Specification Limits for Residues of Metal Catalysts, CPMP/SWP/QWP/4446/00
- Limits of genotoxic impurities, CPMP/SWP/5199/02 EMEA/CHMP/QWP/251344/2006

# Relevant Ph.Eur.-Monograph/Text

- Ph.Eur. - general monograph 07/2007: 2034, Substances for pharmaceutical use
- Ph.Eur. – general text 07/2006:51000, 5.10. Control of impurities in substances for pharmaceutical use
- EP – general text 01/2005:50400, 5.4. Residual solvents, limiting residual solvent levels in active substances, excipients and medicinal products