Gesellschaft für Toxikologie

Advanced Course / Workshop
„Risikobewertungskonzepte für verschiedene regulatorische Bereiche

Login

Bewertung von Verunreinigungen in Humanarzneimitteln

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SANOFI
Empowering Life

Types of impurities in drugs for human use

Synthesis impurities

- **Organic impurities**
  (e.g. starting materials, by-products, intermediates, degradation products, reagents) → ICH Q3A und Q3B, ICH M7 (for mutagenic impurities)
- **Inorganic impurities** → ICHQ3D, USP <232>
  (e.g. metals from catalysts, ligands, salts)
- **Residual solvents** → ICH Q3C

Cross-contamination

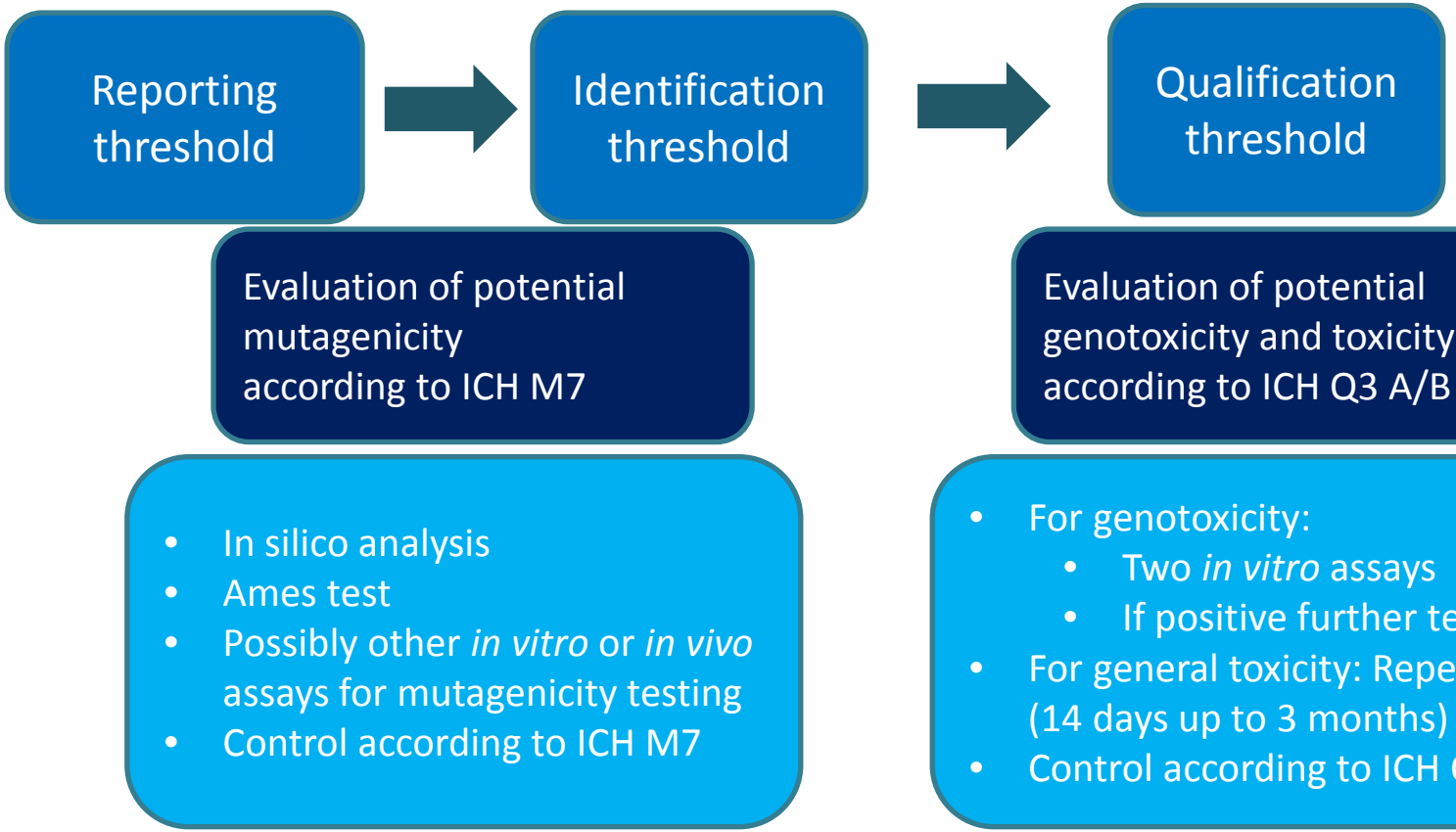
(e.g. with other drug substances)

→ EMA Guideline on setting health based exposure limits…

Leachables and Extractables

→ PQRI–OINDP (2006) and PODP (2014), USP <661>, <1663>, <1664>, …; EMA GL plastic packaging material

General process for observed/actual impurities ICH Q3 versus ICH M7



Qualification of impurities (ICH Q3A / B)

General Threshold principle:

ICH Q3A: No toxicological qualification if below 0,15 % or 1 mg for daily dose up to 2 g

Attachment 1: Thresholds

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/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)
> 2g/day	0.03%	0.05%	0.05%

ICH Q3B: More staggered approach for degradants

Attachment 1: Thresholds for Degradation Products in New Drug Products

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%

→ Exception for those Thresholds:
In silico alert for Mutagenicity!!

Qualification of impurities (ICH Q3C)

- Evaluated for possible risk to human health and placed into three classes:
  - **Class 1 solvents: Solvents to be avoided**
    - Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.
  - **Class 2 solvents: Solvents to be limited**
    - Non-genotoxic animal carcinogens
    - possible causative agents of other irreversible toxicity such as neurotoxicity/teratogenicity.
    - Solvents suspected of other significant but reversible toxicities.
  - **Class 3 solvents: Solvents with low toxic potential**
    - Solvents with low toxic potential to man; no health-based exposure limit is needed
    - Class 3 solvents have PDEs of 50 mg or more per day.

PDE is derived from the no-observed-effect level (NOEL), or the lowest-observed effect level (LOEL) in the most relevant animal study as follows:

$$PDE = \frac{NOEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5} \qquad (1)$$

TABLE 1. Class 1 solvents in pharmaceutical products (solvents that should be avoided).

Solvent	*Concentration limit (ppm)*	*Concern*
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard

TABLE 2. Class 2 solvents in pharmaceutical products.

Solvent	*PDE (mg/day)*	*Concentration limit (ppm)*
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60

Qualification of impurities (ICH Q3D)

- **Class 1**: Elements are human toxicants, limited/no use in the manufacture of drugs.
- **Class 2**: Elements generally considered as route-dependent human toxicants. Divided in 2 sub-classes based on their relative likelihood of occurrence in the drug product.
  - **Class 2A** elements have relatively high probability of occurrence in the drug product and thus require risk assessment The class 2A elements are: Co, Ni and V.
  - **Class 2B** elements with reduced probability of occurrence in the DP related to their low abundance . As a result, they may be excluded from the risk assessment Elemental impurities includes: Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl.
- **Class 3: E**lements with relatively low toxicities by oral route (high PDEs, generally > 500 µg/day) but may require consideration in the risk assessment for inhalation/parenteral routes. Elements in this class include: Ba, Cr, Cu, Li, Mo, Sb, and Sn.

Table A.2.1: Permitted Daily Exposures for Elemental Impurities[1]

Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1

Scope of ICH M7	
• **Focussing on DNA reactive impurties (Mutagenic Impurities), clastogenicity not in scope!!** • **New drug substances (DS) and new drug products (DP) in clinical development and subsequent application for marketing.** • **Marketed products (e.g changes in DS/DP manufacturing process) and changes in clinical Use**	
Not in the scope of ICH M7	
If API itself is mutagenic via direct interaction with DNA	At therapeutic concentrations, increased cancer risk expected, Impurities would not significantly add to cancer risk. Apply ICH Q3A/B
Biologics	Biotherapeutics, peptide, oligonucleotide, radio pharma-ceuticals, fermentation products, herbal products and crude products of animal/plant origin**, Except if chemically modified**
Oncology compounds	Advanced cancer indications (ICH S9). Apply ICH Q3 A/B
Residual solvents	Apply ICH Q3 C
Residues of metal catalysts	Apply ICH Q3 D
Leachables	Associated with drug product packaging
Excipients Moreover, simple salts (Cl-, NO3, H2SO4, PO4) and the corresponding acids	If used in existing marketed products, flavoring agents, colorants, perfumes But for excipients chemically synthesized and used for the first time in a drug product: risk assessment outlined in ICH M7 can be used for limiting potential carcinogenic risk.

Assessment of mutagenicity hazard and classification

Step 2 : LISTING OF POTENTIAL IMPURITIES and Step 3: ASSESSMENT OF GENOTOXICITY			
Project Code:	CD/PD Site:	Chemical Process Code:	Clinical Development Phase:

Step 2		Step 3		
	Date:		Date:	

#	Origin of Potential Chemical Impurity	Compound Name and/or Code	Chemical Structure, CAS #, MW, mol file	Preclinical Safety Assessment							CMC Action
				Classification ICH-M7	Mutagen	Clastogen	Genotoxicity results from public and internal data	Date of analysis and program versions	in-silico prediction DEREK: Results and alert location	in-silico prediction Leadscope Results (location)	GTI # given
Section A: SYNTHESIS COMPOUNDS. Compounds that are part of the chemical process (intermediates, starting materials, reagents)											
Section B: KNOWN AND OBSERVED PROCESS IMPURITIES. Compounds that, as a result of side reactions, reactions of impurities, and/or degradation, are confirmed to be formed and present in potentially significant levels											
Section C: REASONABLY PREDICTABLE IMPURITIES. Compounds that, as a result of side reactions, reactions of impurities, and/or degradation, could predictably be formed and present in potentially significant levels											

Class 1 and according to ICH M7

Class	Actions
Class 1 Known mutagenic carcinogens Carcinogens with positive in bacterial mutagenicity test (i.e., Ames test) or other relevant mutagenicity tests (i.e., gene mutation tests indicative of DNA-reactivity, such as in vivo gene mutation studies)	Control at or below compound specific acceptable limit based on carcinogenicity TD_{50} or PDE In case no robust carcinogenicity data can be found: Control at or below TTC-based acceptable intakes
Class 2 Known mutagens, but without carcinogenicity data Positive in bacterial mutagenicity test (i.e., Ames test) or other relevant mutagenicity tests (see above)	Control at or below TTC-based acceptable intakes

Class 1 Compound-specific acceptable intakes

- Class 1 compounds (mutagenic carcinogens)
  - Compound-specific acceptable intake (µg/person/day) is linear extrapolation to a probability of 1 in 100 000 cancer risk (accepted lifetime risk level) derived from robust rodent carcinogenicity data
    - Could be based on the TD_{50}* :
      - **TD_{50} in (mg/kg)/50000 x 50 kg body weight**
    - Could alternatively be based on the BMDL10**:
      - **BMDL10 (mg/kg) / 10000 x 50 kg body weight**
    - Or derived from published recommended values from internationally recognized bodies (e.g., WHO).

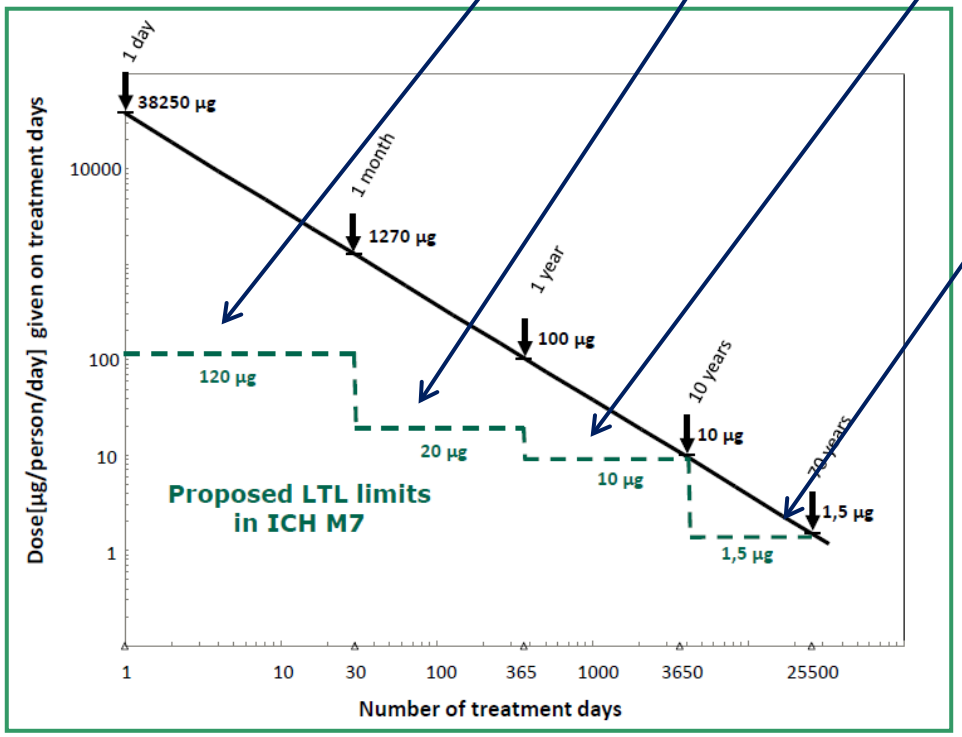
*TD_{50} = value giving a 50% tumor incidence equivalent to a cancer risk probability level of 1:2, can be found in the Carcinogenic Potency Database (TOXNET http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CPDB.htm#jumpc)

**BMDL10=estimate (benchmark) of the lowest dose which is 95% certain to cause no more than a 10% cancer incidence in rodents.

Class 2: Acceptable intakes based on threshold of toxicological concern

Table 1: TTC-based acceptable intake for less than life time exposure for an individual impurity

Duration of treatment	≤ 1 month	>1-12 months	>1-10 years	>10 years to lifetime
Daily intake (µg/day)	120	20	10	1.5



Calculated daily dose as a function of treatment days for 10^{-5} risk of cancer

Extrapolation from the most potent rodents carcinogens

Gold database

ICH M7 Monographs and Acceptable Intakes (AIs) for Mutagenic Chemicals: examples

Compound	AI/PDE (µg/day)
Acrylonitrile	5
1-Chloro-4-nitrobenzene	430
p-Cresidine	45
Dimethylcarbamyl chloride	5 0.6 (inhalation)*
Ethyl chloride	1,810
Ethyl methane sulfonate	100
Formaldehyde	10,000 (oral)*
Glycidol	4
Hydrazine	42 (oral)*
Methyl Iodide	Not calculated

- **Monographs prepared by industry & acceptable intakes suggested**

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Potential impurities in drug substances: Compound-specific toxicology limits for 20 synthetic reagents and by-products, and a class-specific toxicology limit for alkyl bromides

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Class 3 according to ICH M7

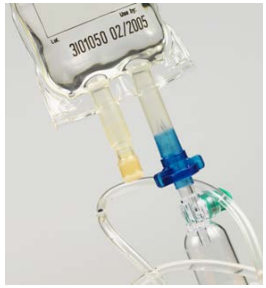
Classes	Actions
Class 3: Alerting structure, unrelated to the structure of the drug substance, no mutagenicity data Structural alerts for mutagenicity in a knowledge-based system (DEREK) and/or a statistical-based system (Leadscope) (not applicable if out of domain)	Control at or below TTC-based acceptable intakes or Conduct a bacterial mutagenicity test (Ames test) • If positive in Ames test: Re-classified as Class 2 impurity Control at or below TTC-based acceptable intakes • If negative in Ames test: Re-classified as Class 5 impurity Treat as non-mutagenic impurity (ICH Q3A/B).

Class 4 and 5 according to ICH M7

Classes		Actions
Class 4 Alerting structure, same structure 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 (ICH Q3A/B).
Class 5 1) No structural alerts or 2) Alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity		Treat as non-mutagenic impurity (ICH Q3A/B), but 1) and 2) to be handled differently in documentation

Leachables und Extractables

Drug containers and packaging meant to protect a drug from environmental contamination but are themselves a source of contamination:





Polymeric packaging components (monomers, oligomers, polymeric initiators, stabilizers, …)

Chemical substances migrating from or staying on the surfaces of components of fabrication machinery, containers etc. (metals, silicon, oils, degreasing agents, ...)

Migrants from secondary and tertiary packaging components (inks, label adhesives, …)

Leachables und Extractables

Definitions:

Extractables: Organic and inorganic compounds that are released from the container/closure system into an extraction solvent under laboratory conditions.

- Have the potential to leach into a drug product under normal conditions of storage and use and thus become leachables.

Leachables: Compounds that are present in a drug product formulation because they have leached from the container/closure system under normal conditions of storage or in accelerated stability studies

Leachables are of concern due

- to their potential safety risk to patients and
- potential compatibility risks for the drug product (e.g., drug substance interaction/ degradation, pH change, particle formation, protein aggregation/structure change, etc.)

Leachables und Extractables

Drug products of main concern:

- Ophthalmic drug products
- Parenteral drug products
- Inhalation drug products

Guidelines: e.g.

- FDA Guidances:
  - Container closure systems for packaging human drugs and biologics (1999),
  - Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation (2002)
- EMA Guideline on plastic immediate packaging materials (2005)
- PQRI–Recommendations for OINDP (2006) and PODP (2014)
- USP <661>, <1663>, <1664>, <1664.1>, Draft <1665>, …

Leachables und Extractables

PQRI (Product Quality Research Institute) Leachables and Extractable Working Group

- is a working group established to developed regulatory guidance for Extractable/Leachable analysis, which is also recognized by the FDA

PQRI issued guidances:

- Safety thresholds and best practices for extractables and leachables in Orally Inhaled and Nasal Drug Products (OINDP), 2006
- PQRI Leachables and Extractables Working Group Initiatives for Parenteral and Ophthalmic Drug Product (PODP), 2014

Include:

- Justification of analytical testing and safety evaluation thresholds for leachables
- Best practices for extractables and leachables studies

Leachables und Extractables

PQRI proposed safety thresholds for leachables in PODP (2013):

Threshold	Safety Concern Threshold (SCT) (genotoxicant)#	SCT (sensitizers/irritants)	Qualification Threshold (QT) (general toxicity)
OINDP	0.15 µg/day	-	5 µg/day
PODP	1.5 µg/day	5 µg/day	150 µg/day (50 µg/day*)

Lower thresholds may be required for e.g. PAH's, nitrosamines, and 2-mercaptobenzothiazole

* 3rd PQRI/FDA Conference, 2017, http://pqri.org/wp-content/uploads/2017/02/CombinedPQRI-PODPSlides_PQRI-FDA_22Mar2017.pdf

If level > SCT / QT:

Consider patient population and duration of use and consider conducting:

- Literature-based risk assessments
- Genotoxicity studies (e.g., point mutation)
- General toxicity studies (one species, usually 14 to 90 days)
- Other specific toxicity endpoints, as appropriate

Cross-contamination / PDEs

EMA Guideline on setting health based exposure limits …

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2014
EMA/CHMP/ CVMP/ SWP/169430/2012
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities

Cross-contamination / PDEs

EMA Guideline on setting health based exposure limits …

Main focus:

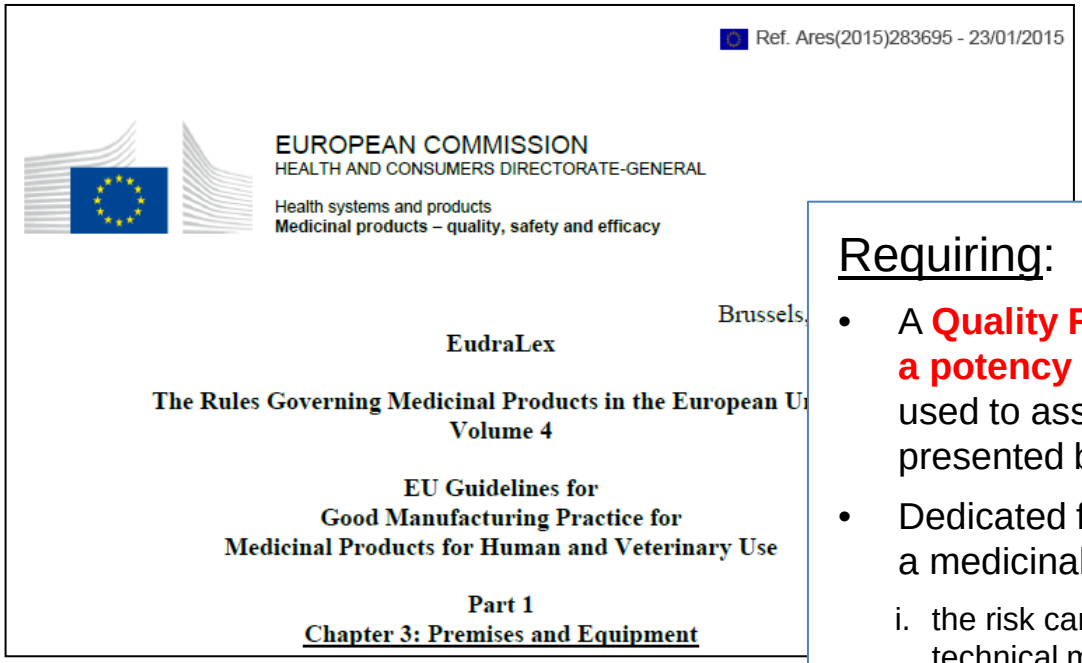
- Concern: **Cross-contamination**, when different medicinal products are produced in shared facilities.
- Therefore: The presence of contaminants should be managed according to the **risk** posed.
- **Health based limits** through the derivation of a safe threshold value should be employed to identify risk.
- Derivation of such a threshold value (e.g. **permitted daily exposure (PDE)** or threshold of toxicological concern (TTC) should be the result of a structured scientific evaluation of all available pharmacological and toxicological data including both non-clinical and clinical data.

→ The PDE represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.

Synonyms: Acceptable Daily Exposure (ADE)
Health-Based Exposure Limit (HBEL)

Cross-contamination / PDEs

… in conjunction with Chapters 3 and 5 of the GMP guideline



Ref. Ares(2015)283695 - 23/01/2015

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products – quality, safety and efficacy

Brussels,

EudraLex

The Rules Governing Medicinal Products in the European U
Volume 4

EU Guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Part 1
Chapter 3: Premises and Equipment

Requiring:

- A **Quality Risk Management process, which includes a potency and toxicological evaluation**, should be used to assess and control the cross-contamination risks presented by the products manufactured.
- Dedicated facilities are required for manufacturing when a medicinal product presents a risk because:
  i. the risk cannot be adequately controlled by operational and/ or technical measures,
  ii. scientific data from the toxicological evaluation does not support a controllable risk (e.g. allergenic potential from highly sensitising materials such as beta lactams) or
  iii. relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method.

Calculation of PDEs

What should be the contents of a PDE monograph?

Data requirements for hazard identification

Hazard identification is the qualitative appraisal of the inherent property of a substance to produce adverse effects. For hazard identification, a review of all available animal and human data should be performed for each compound. Data for hazard identification would include non-clinical pharmacodynamic data, repeat-dose toxicity studies, carcinogenicity studies, *in vitro* and *in vivo* genotoxicity studies, reproductive and developmental toxicity studies as well as clinical data (therapeutic and adverse effects). The availability of data for an active substance will vary depending

4.2 Use of clinical data

The aim of determining a health-based exposure limit is to ensure human safety, and consequently it is considered that good quality human clinical data is highly relevant. Unintended pharmacodynamic effects in patients caused by contaminating active substances may constitute a hazard thus clinical pharmacological data should be considered when identifying the critical effect. Consideration should be given to what extent the active substance in question has been associated with critical adverse effects in the clinical setting.

Calculation of PDEs

What should be the contents of a PDE monograph?

- **Summary**
- **General information on the substance** (chemical identity: compound name, CAS No. etc.; for APIs: mode of action, indication)
- **Pharmacology / Mechanism of action**
- **Pharmacokinetics and metabolism**
- **Toxicity data**:
  - Single-dose toxicity
  - Repeat-dose toxicity
  - Developmental and reproductive toxicity
  - Local tolerance / (skin) sensitisation
  - Genotoxicity
  - Carcinogenicity
- **Human data**:
  - Human therapeutic doses (all indications, routes and patient populations, lowest pharm. active dose)
  - Pharmacokinetics and drug-drug interactions
  - Adverse effects in clinical trials / at therapeutic use
  - Pregnancy and Lactation
- **Calculation of the PDEs**:
  1) Identification of critical non-clinical and clinical effects;
  2) Dose-response / NO(A)EL for these effects;
  3) Calculation of PDEs for these effects;
  4) Decision which PDE is used; route-specific PDEs as needed (e.g. PDE parenteral, oral, inhalation)
- **References**

Calculation of PDEs

Generally, the following equation is applied:

$$\textbf{PDE}\ (\mu g/day) = \frac{\text{Point of Departure (POD) x Body Weight (50 kg)}}{\text{F1 x F2 x F3 x F4 x F5 x } \alpha\text{-Factor}}$$

where:

POD: NOAEL (No observed adverse effect level) or e.g. human dose
F1: Extrapolation between species (1-12)
F2: Variability between individuals (default: 10)
F3: Extrapolation to chronic exposure (1-10)
F4: Severe toxicity (e.g. teratogenicity without maternal tox: 10)
F5: Extrapolation to a no effect level (1-10)
α-Factor: Route-to-route extrapolation (as needed)

Calculation of PDEs

Genotoxic (mutagenic) substances

…without sufficient carcinogenicity data and/or threshold related mechanism:

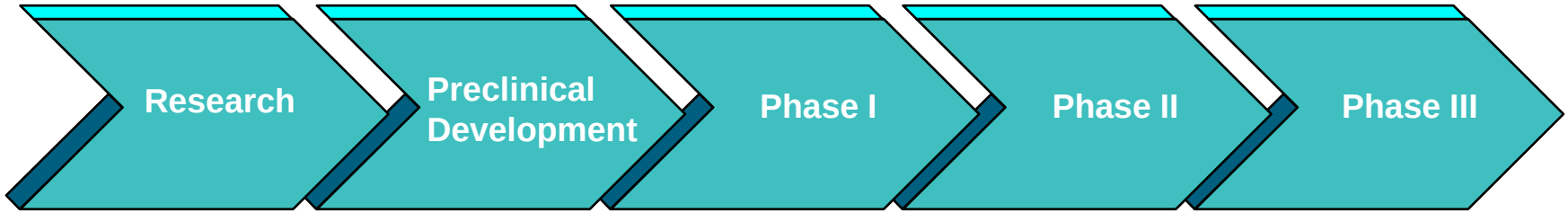
→ Threshold of Toxicological Concern (TTC) of **1.5 µg/person/day**

PDEs for Investigational Medicinal Products (IMPs/APIs in early development):

Categorisation into default values (or categories) based on mode of action, first pharmacological and toxicological data, as proposed e.g. by Dolan *et al.* 2005, EMA Guideline etc. (adapted):

Compounds …	PDE / TTC
… not likely to have a high pharmacological activity or toxicity	100 µg/day
… that may have a high pharmacological activity or toxicity	10 µg/day
… that may have a very high pharmacological activity or toxicity	1 µg/day
… known/expected to have an extremely high pharm. activity or toxicity	0.1 µg/day

Calculation of PDEs



Start of development (SoD):
Categorized PDE

Start of Phase I:
Setting of preliminary PDE values

Regular Updates of PDE assessments
(change of values if indicated)

Final PDEs at Submission

Potentially further updates, if new information about the API shows higher than previously known hazard or pharmacological activity

Use of PDEs in Cleaning Validation

➔ Calculation of Maximum Allowable Carry Over (MACO), Maximum Allowable Residue (MAR) etc., e.g.

$$\text{MACO} = \frac{\text{PDE} \times \text{Minimum Batch Size}_{\text{Following product}}}{\text{Largest Daily Dose}_{\text{Following product}}}$$

↓

Highest Acceptance Limit

- Further criteria:
  - Visual clean
  - Process Control Limit → cleaning target based on statistical analysis of the process

Any questions?

Synthesis impurities

- **Organic impurities**
  (e.g. starting materials, by-products, intermediates, degradation products, reagents) → ICH Q3A und Q3B, ICH M7 (for mutagenic impurities)
- **Inorganic impurities** → ICHQ3D, USP <232>
  (e.g. metals from catalysts, ligands, salts)
- **Residual solvents** → ICH Q3C

Cross-contamination

(e.g. with other drug substances)

→ EMA Guideline on setting health based exposure limits…

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