Key points to recognize quality in HBEL and associated monograph

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Novartis

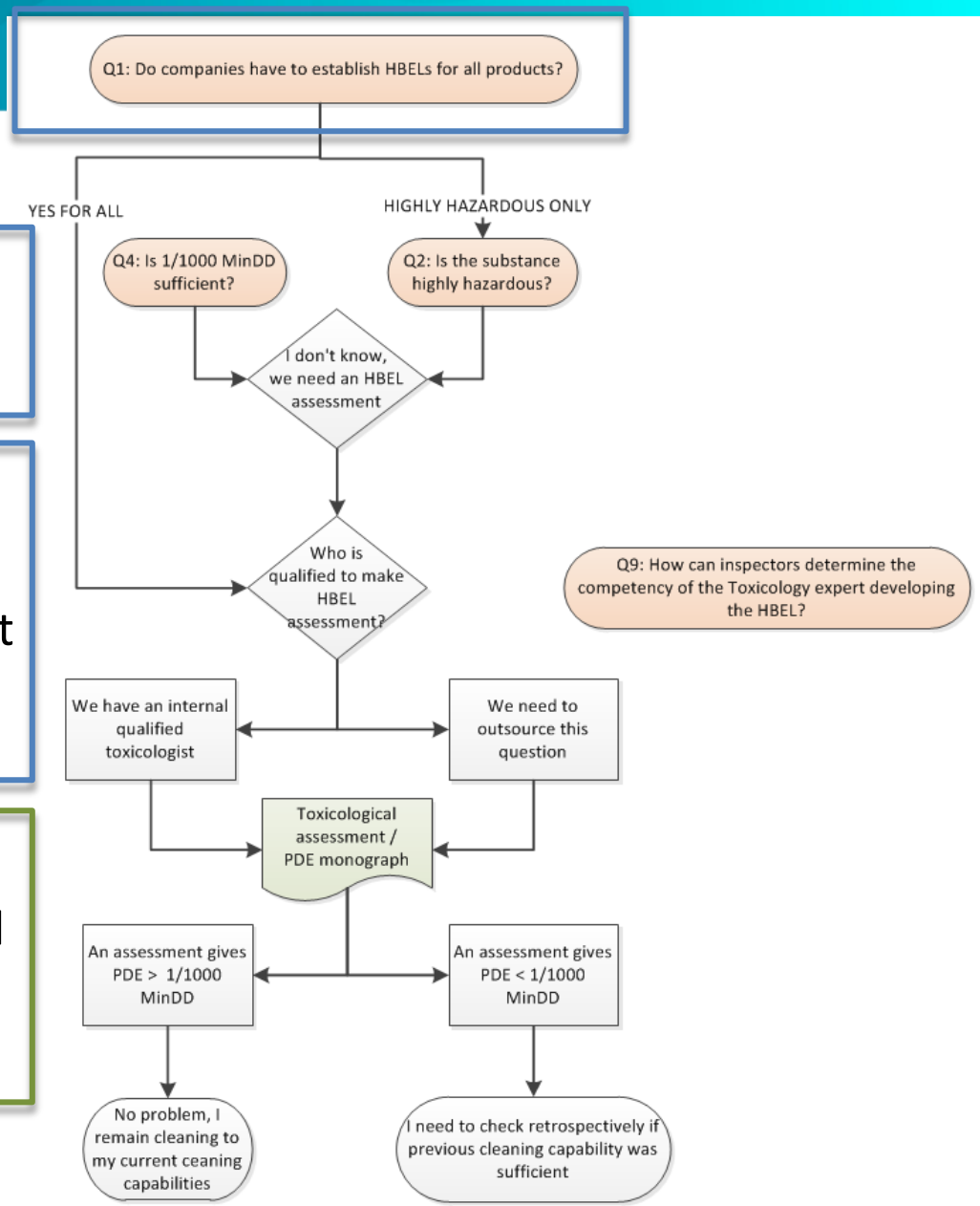
Contents

Q1: Do companies have to establish Health Based Exposure Limits (HBELs) for all products?

Thought process:

With “yes” and “only for highly hazardous” answer, the end result is that a qualified person has to make an assessment

A1: Yes. PDA fully supports the concept of HBELs that is outlined in the guidance as it advocates a risk based approach

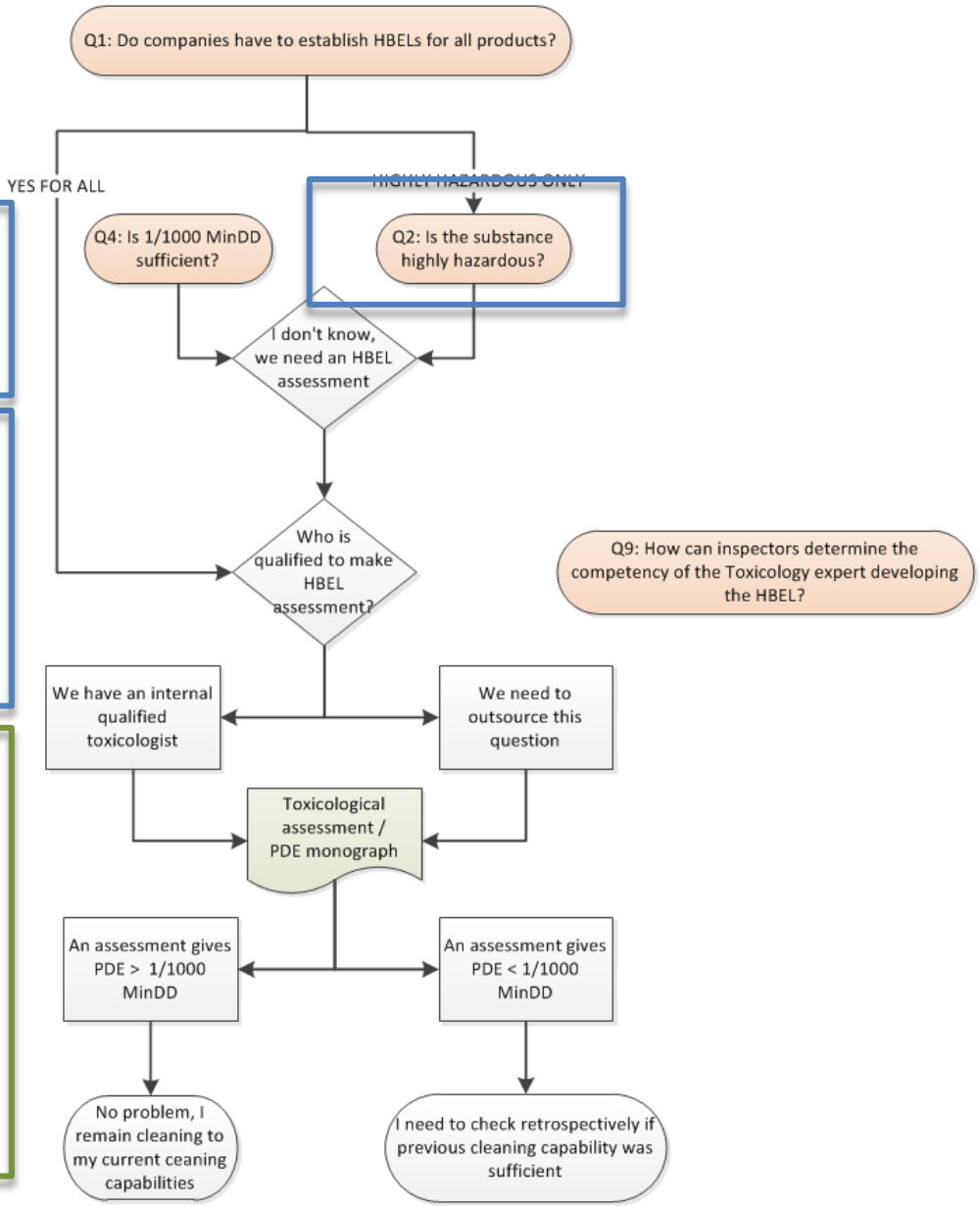


Q2: What products/active substances are considered to be highly hazardous?

Thought process:

Is the substance highly hazardous? With “yes” and “only for highly hazardous” answer, the end result is that a qualified person has to make an assessment

A2: The distinction of compounds into two categories, “highly hazardous” and “not highly hazardous” goes against the principle of assigning a HBEL to each compound based on all available data. The HBEL is the unique descriptor of the level of hazard that a compound constitutes

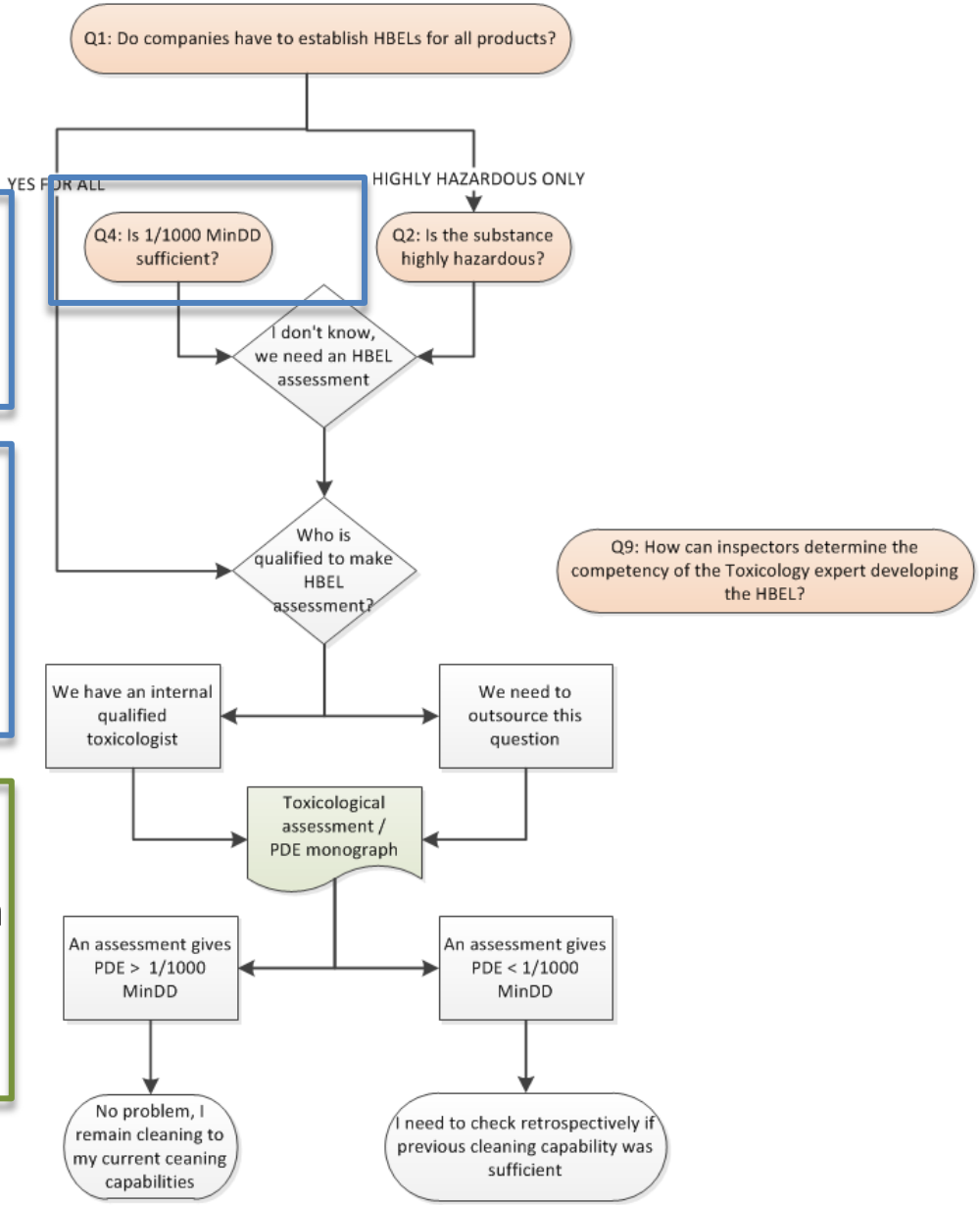


Q4: Can calculation of HBELs be based on clinical data only (e.g. to establish the HBEL on 1/1000th of the minimum therapeutic dose)?

Thought process:

With “yes” and “only for highly hazardous” answer, the end result is that a qualified person has to make an assessment

A4: Remove references to 1/1000th of the minimum therapeutic dose based on the approach described in the EMA/CHMP/SWP/598303/2011 as the two documents are contradicting



BOTTOM LINE

PDA reminds that in EMA/CHMP/SWP/598303/2011 EMA had stated, - "In some cases arbitrary limits such as 1/1000th of the lowest clinical dose or 10ppm are used as limits for cleaning validation. These limits do not take account of the available pharmacological/ toxicological data and possible duration of exposure and may be too restrictive or not restrictive enough

PDA recommends that a scientifically justified, toxicological, risk based approach with a documented rationale should be used

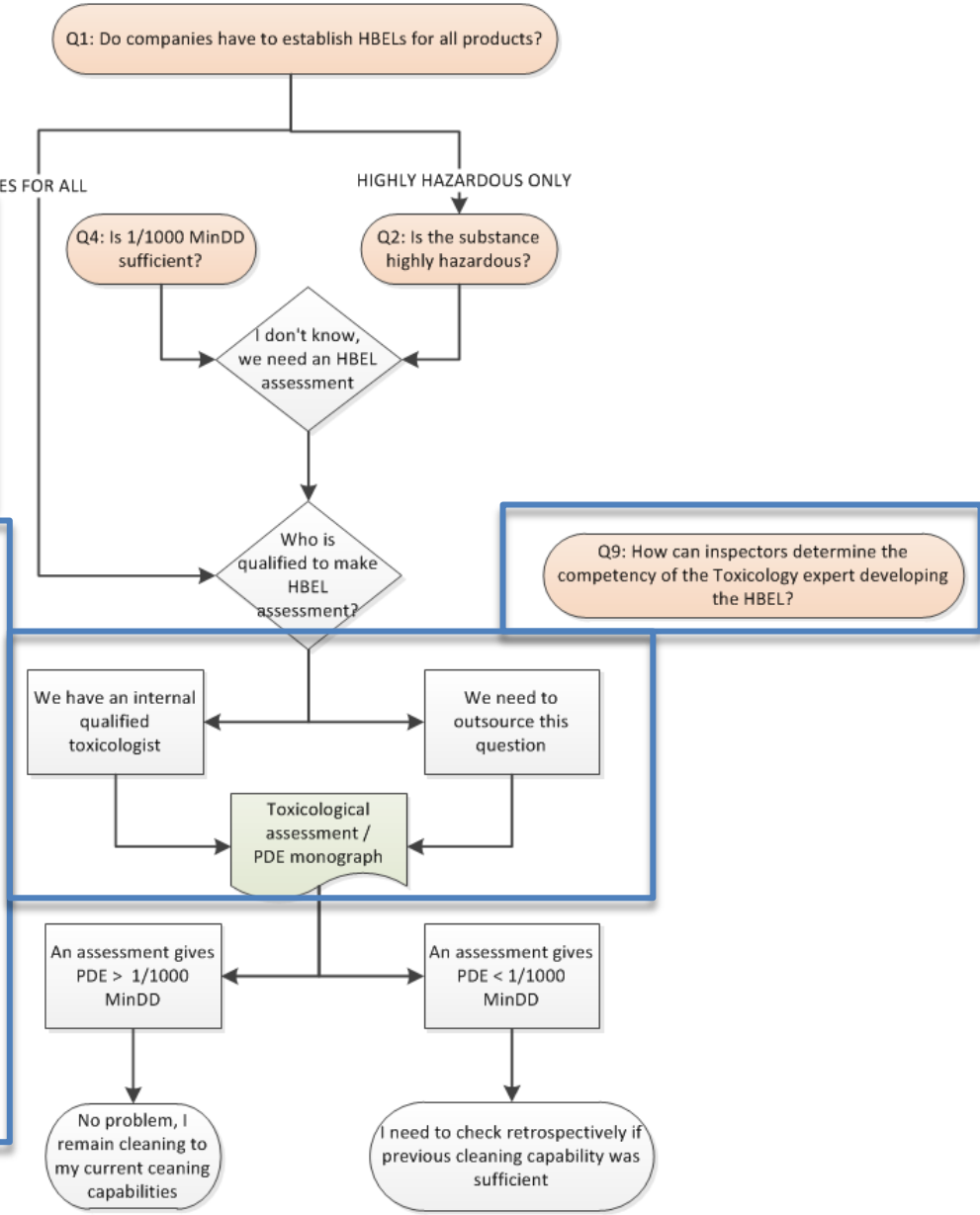
Investment in appropriate toxicological expertise is required.

Q9: How can inspectors determine the competency of the toxicology expert developing the HBEL?

Thought process:

A. We have internal expert(s) that has experience in calculation of limits (eg. OELs) – we are good

B. We have no internal expert – we need to outsource, find a qualified toxicologist and take responsibility for quality of this work



Olson et al. (2016), Issues and approaches for ensuring effective communication on ADE values applied to pharmaceutical cleaning, *Regul. Toxicol. Pharmacol.* 79, S19-S27
DOI: 10.1016/j.yrtph.2016.05.024

Risk assessment requires expertise to reduce uncertainties

Who is a competent/qualified toxicologist?

Expertise comes with appropriate education and experience in the field of risk assessment and calculation of health based limits

Example of appropriate expertise:

- Formal training in toxicology or related field (e.g., pharmacology), preferably with higher degree (MSc, PhD) or demonstrated by Certification in Toxicology (e.g., ERT, DABT)
- Hands on experience deriving health-based exposure limits (e.g., PDEs/ADEs, OELs) – multiple years desirable

Important is to benchmark the expertise, connect with peers to assure consistency as well as mentor the next generation of toxicologists

Who would you trust with the limits for your loved ones?

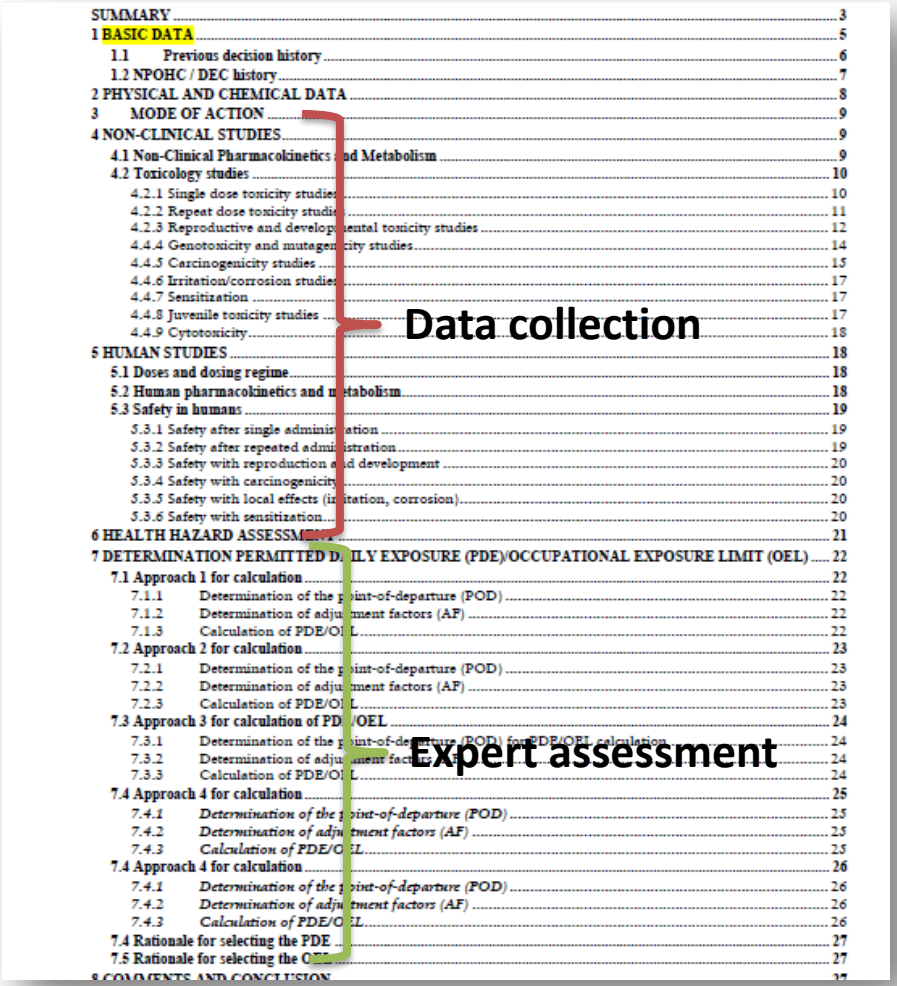
Olson et al. (2016), Issues and approaches for ensuring effective communication on ADE values applied to pharmaceutical cleaning, *Regul. Toxicol. Pharmacol.* 79, S19-S27
DOI: 10.1016/j.yrtph.2016.05.024

How do I identify good HBEL monograph?

Derivation of HBEL should be the result of a structured scientific evaluation of all relevant, available pharmacological and toxicological data including both non-clinical and clinical data

The format of the documentation of the HBEL is not standardized. It should contain:

- **Data Collection**
  - Chemical Identity
  - Mode of Action
  - Pre-clinical Studies
  - Clinical Studies
  - Pharmacokinetics and pharmacodynamics
- **Expert assessment**
  - Identification of the critical effect
  - Assigment of adjustment factors (AF)
  - If data allows, several calculations of may be proposed
  - Argumentation for the selected HBEL



Example of Health Hazard Assessment Monograph from Novartis

How do I identify good HBEL monograph?

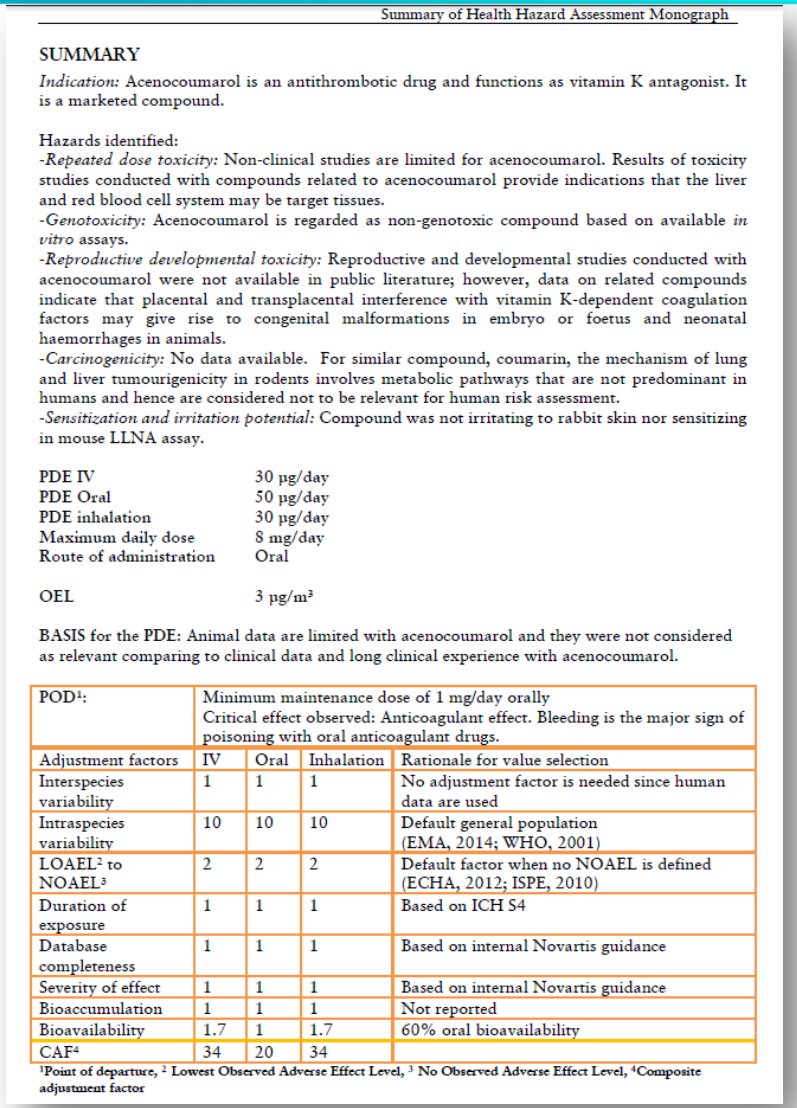
- Summary in line with EMA expectations to facilitate review by stakeholders. The basis for the HBEL should be clearly described
  - Calculated HBELs for several routes of administration

Default are usually oral, IV, inhalation; depends on the expected route of administration of drugs produced in shared facilities

  - Point of Departure (PoD)

Based on what value was HBEL calculated

  - Rationale for selection of critical effect at the PoD
  - Adjustment factors explained/referenced



Summary of Health Hazard Assessment Monograph

SUMMARY

Indication: Acenocoumarol is an antithrombotic drug and functions as vitamin K antagonist. It is a marketed compound.

Hazards identified:
-*Repeated dose toxicity:* Non-clinical studies are limited for acenocoumarol. Results of toxicity studies conducted with compounds related to acenocoumarol provide indications that the liver and red blood cell system may be target tissues.
-*Genotoxicity:* Acenocoumarol is regarded as non-genotoxic compound based on available *in vitro* assays.
-*Reproductive developmental toxicity:* Reproductive and developmental studies conducted with acenocoumarol were not available in public literature; however, data on related compounds indicate that placental and transplacental interference with vitamin K-dependent coagulation factors may give rise to congenital malformations in embryo or foetus and neonatal haemorrhages in animals.
-*Carcinogenicity:* No data available. For similar compound, coumarin, the mechanism of lung and liver tumourigenicity in rodents involves metabolic pathways that are not predominant in humans and hence are considered not to be relevant for human risk assessment.
-*Sensitization and irritation potential:* Compound was not irritating to rabbit skin nor sensitizing in mouse LLNA assay.

PDE IV	30 µg/day
PDE Oral	50 µg/day
PDE inhalation	30 µg/day
Maximum daily dose	8 mg/day
Route of administration	Oral
OEL	3 µg/m³

BASIS for the PDE: Animal data are limited with acenocoumarol and they were not considered as relevant comparing to clinical data and long clinical experience with acenocoumarol.

POD[1]:	Minimum maintenance dose of 1 mg/day orally Critical effect observed: Anticoagulant effect. Bleeding is the major sign of poisoning with oral anticoagulant drugs.			
Adjustment factors	IV	Oral	Inhalation	Rationale for value selection
Interspecies variability	1	1	1	No adjustment factor is needed since human data are used
Intraspecies variability	10	10	10	Default general population (EMA, 2014; WHO, 2001)
LOAEL[2] to NOAEL[3]	2	2	2	Default factor when no NOAEL is defined (ECHA, 2012; ISPE, 2010)
Duration of exposure	1	1	1	Based on ICH S4
Database completeness	1	1	1	Based on internal Novartis guidance
Severity of effect	1	1	1	Based on internal Novartis guidance
Bioaccumulation	1	1	1	Not reported
Bioavailability	1.7	1	1.7	60% oral bioavailability
CAF[4]	34	20	34	

[1]Point of departure, [2] Lowest Observed Adverse Effect Level, [3] No Observed Adverse Effect Level, [4]Composite adjustment factor

Example of Health Hazard Assessment Monograph from Novartis

Hot to identify good HBEL?

A system should exist of review of HBELs. Consistent expert work when calculating the limits can be identified by:

- Having a company wide written document that describes the concurrent scientifically justified process for collecting, assessing the data and assigning appropriate safety/adjustment factors throughout the development process (from defaults pre-FIH through commercialization), and the provision for peer review

Limits for the same substance may vary between the experts up to 10x (ref. Olson et al., 2016). Having a consistent approach for the company is essential

- Having HBEL monograph reviewed periodically to keep up with the latest dataset, scientifically justified method and industry standards for HBEL calculation

As drug candidates move through development, the amount and types of available data increase, reducing the uncertainty, so the HBELs should be reviewed and, if necessary, changed based on the new information

Hayes et al. (2016), A harmonization effort for acceptable daily exposure application to pharmaceutical manufacturing – Operational considerations, *Regul. Toxicol. Pharmacol.* 79, S39-S47
https://doi.org/10.1016/j.yrtph.2016.06.001

Hot to identify poor HBEL?

To avoid poor quality HBEL work, the company has to take responsibility for the limits and efficiently communicate them to all stakeholders

- The company that produces medicines should have a senior expert toxicologist or a qualified company representative that takes the responsibility for the HBELs on behalf of the company

Experience shows that poor quality monographs may be obtained from unreliable sources because they are cheap and fast. This practice needs to be discouraged

Good communication between clients and contract manufacturers (CM) is essential when the CM produces various substances for various clients on the same equipment (adapted from Hayes et al., 2016)

Check the date of the monograph, especially for drugs in development; review needs to be done when new data is generated.

Examples of poor HBEL derivation

HBEL based on an OEL from a Safety Data Sheet

- *Having no detailed rationale for deriving limits is not appropriate*

HBEL based on LD50

- *LD50 may not protect from all effects (eg. genotoxicity, teratogenicity) (ref. Lovsin Barle et al., 2014)*

HBEL based on *in silico* assessment

- *In silico tools are not sufficient to calculate limits; default limits may be applied based on mutagenicity alerts (example ref. Araya et al., 2015)*

HBELs referring to mixtures

- *As a general rule mixtures shuld to be assessed separately for each constituent (note: Salt forms can be addressed in the same monograph)*

Preclinical or clinical data missing or not taken into account in the gap analysis

- *Assessment of ALL relevant data is mandatory*

Having no rationale if HBELs are protective of sensitive subpopulations

- *Certain drugs require dose adjustments or have different pharmakokinetics in certain conditions; PoD and AFs must be selected and explained appropriately*

Lovsin Barle E, Cudd AM, Looser R, Bechter R, Winkler GC (2014). Carryover and occupational exposure limits: can they be correlated? Chimica Oggi 32:18-23 http://www.teknoscienze.com/tks_article/carryover-and-occupational-exposure-limits-can-they-be-correlated/

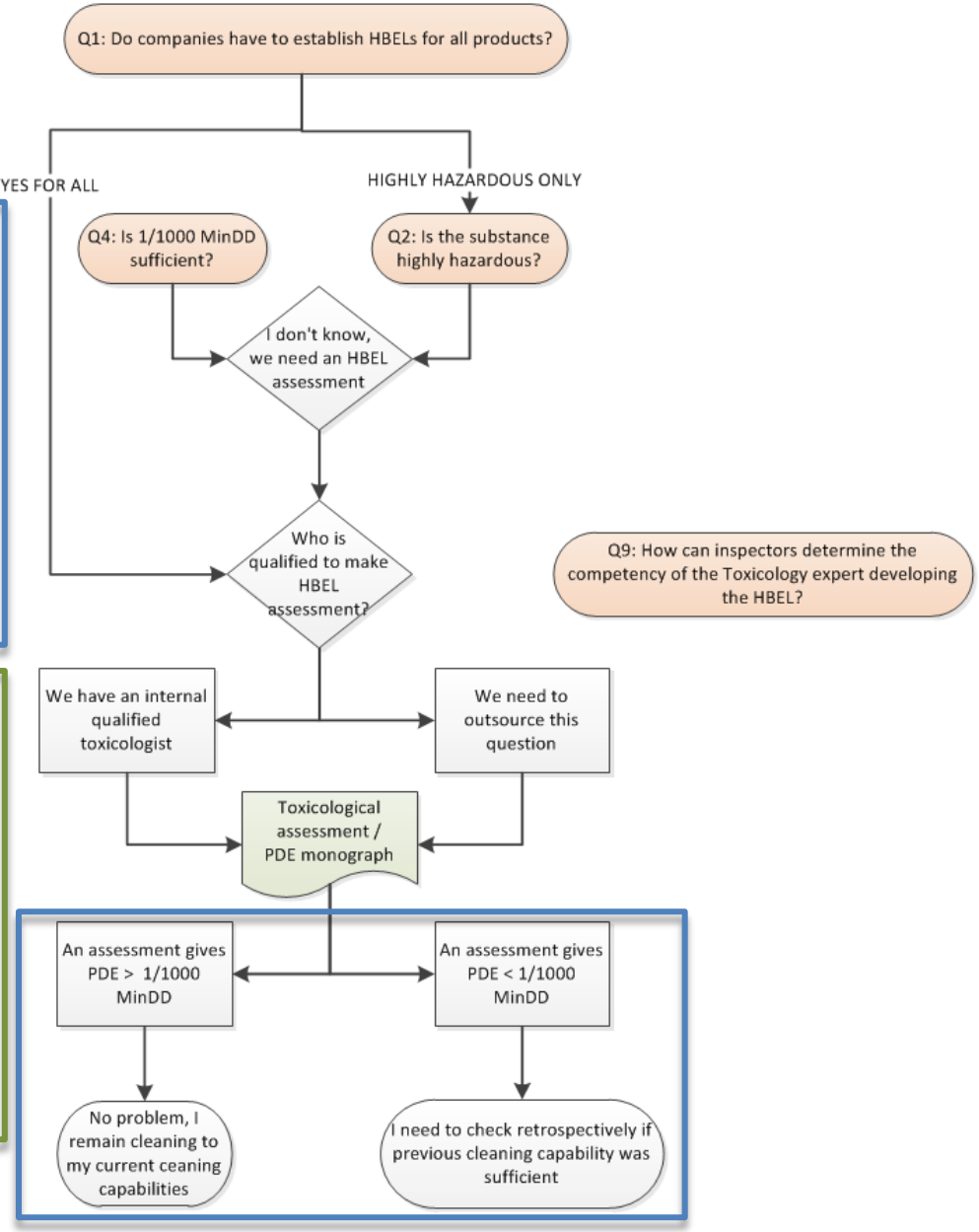
Araya S, Lovsin Barle E, Glowienke S (2015), Mutagenicity assessment strategy for pharmaceutical intermediates to aid limit setting for occupational exposure. Regul Toxicol Pharmacol. 73: 515-520 DOI: 10.1016/j.yrtph.2015.10.001

Question:

Now that I have a high quality HBEL, I can compare it to the previously used method for deriving maximal safe carry-over, presumably based on 1/1000 MinDD

Answer:

1. **HBEL > 1/1000 MinDD -> cleaning was sufficient**
2. **HBEL < 1/1000 MinDD -> retrospective check if previous cleaning was sufficient**

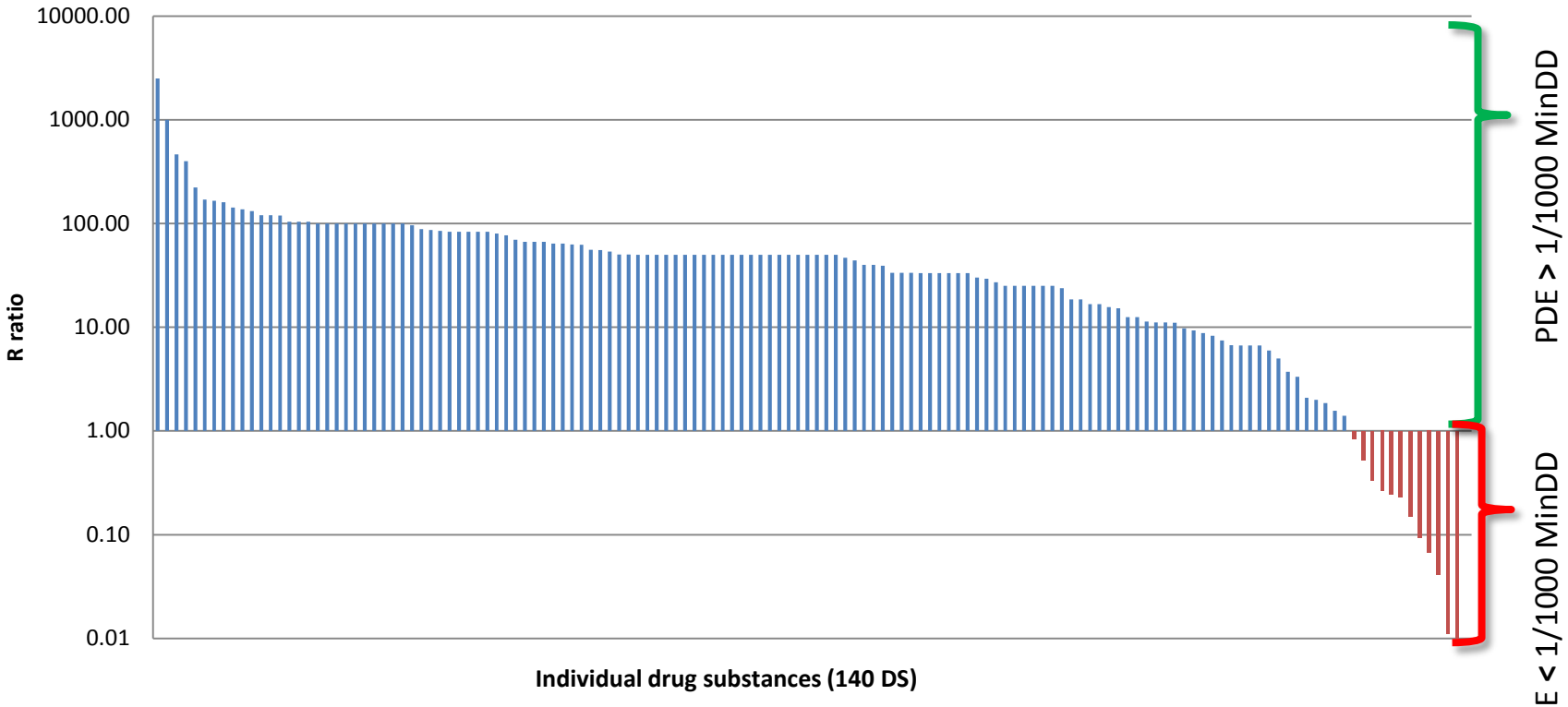


How do I identify high risks based on toxicological information?

Comparison of PDE with 0.001 Minimal Daily Dose (MinDD) for Cleaning Validation

Lovsin Barle et al. (2017), Comparison of Permitted Daily Exposure with 0.001 Minimal Daily Dose for Cleaning Validation, PharmTech 41, 42–53 http://www.pharmtech.com/comparison-permitted-daily-exposure-0001-minimal-daily-dose-cleaning-validation

PDE by the route/ 0.001 MinDD (R ratio)



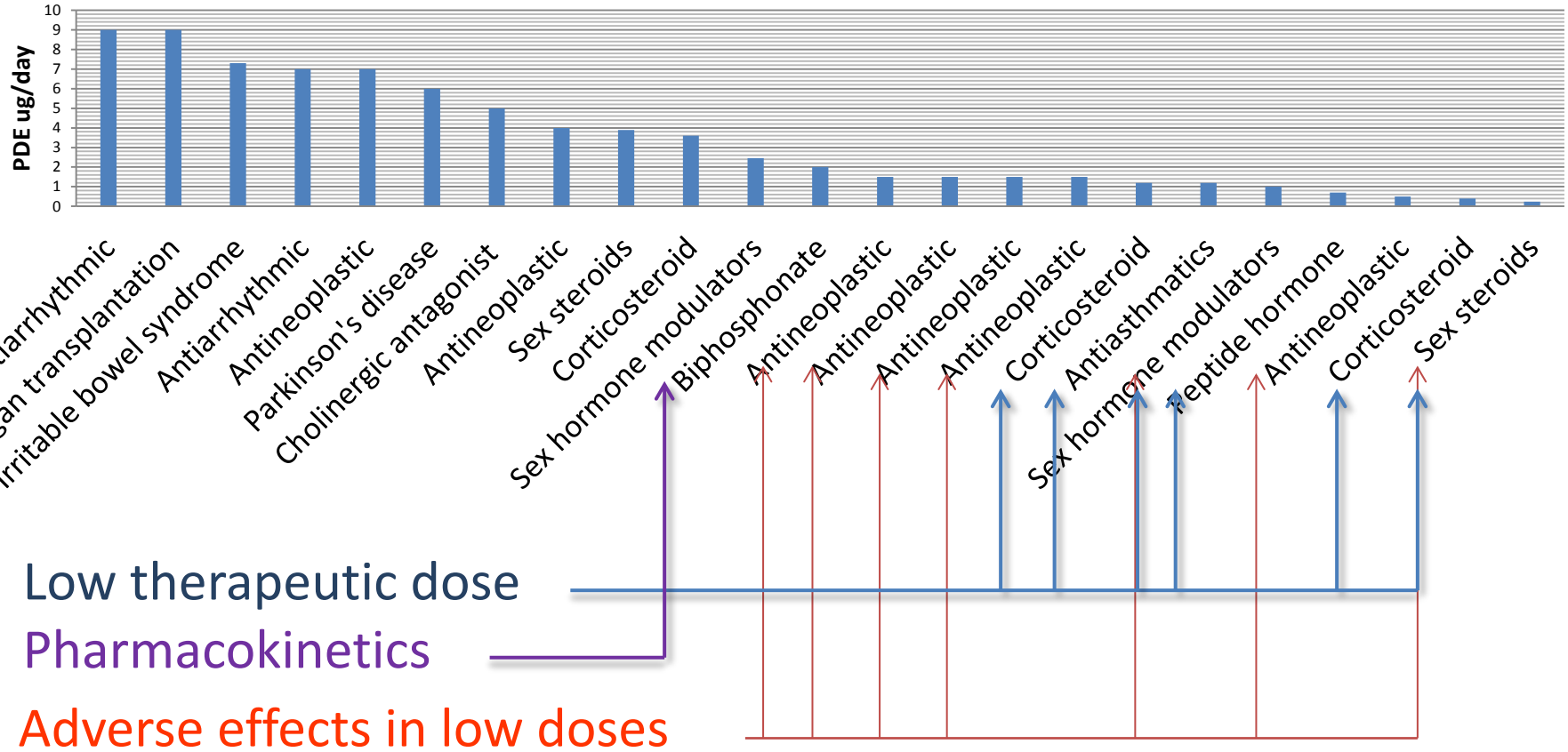
- Approximately 10% of substances had PDE< 1/1000 MinDD, presenting to be potential risk for patients if 1/1000 MinDD was used previously
- However there may be medicines with high daily doses included , that may not be issue for cleaning

Reasons for PDE lower than 1/1000 MinDD

- Drug not dosed daily or only for short treatment duration
- Drug accumulates or has a long elimination half life
- Drug not indicated for certain route of administration
- Drug not indicated for certain population (eg. pregnant women)
- Drug with severe toxicity (eg. teratogenic at therapeutic dose, genotoxic, with serious target organ toxicity)

Indication	Mode of Action	R ratio
Antibiotic	Chloramphenicol	0.70
Antineoplastic	Cyclin-dependent kinase (CDK) inhibitor	0.52
Antiviral	Multiple: against both RNA and DNA viruses	0.33
Antineoplastic	Histone deacetylase inhibitor (HDAC)	0.26
Antineoplastic	Sex hormone modulator : Estrogen receptor antagonists	0.25
Organ transplantation	Antimetabolite: purine synthesis inhibitor	0.23
Antineoplastic	Arsenic substance	0.19
Organ transplantation	Antimetabolite: purine synthesis inhibitor	0.15
Antineoplastic	DNA replication inhibitor: DNA precursor / antimetabolite	0.09
Antineoplastic	DNA replication inhibitor: DNA precursor / antimetabolite	0.07
Antineoplastic	DNA replication inhibitor: DNA precursor / antimetabolite	0.01
Antineoplastic	Hedgehog signaling pathway inhibitor	0.01

Reasons for "low" PDE (under 10 ug/day)



- Low PDE may be a high risk for achieving cleaning limits; other criteria that are included in determining risk is batch size, maximal daily dose of the next product, as well as other criteria associated with cleaning that are not related to toxicology

Application of the HBELs to pediatric formulations

There are three "safety nets" when it comes to pediatric drugs:

1. during MSC calculation
2. when prescribing medicines to pediatric patients
3. when calculating HBEL

1. Maximal Safe Carry-Over (MSC) calculation

$$MSC_{pedi} = \frac{PDE_{50kg} \times BS_{pedi}}{MaxDD_{50kg}}$$

- Typically the MaxDD of the aduts are used in the calculation

2. Prescription of medicines to pediatric patients

- Children will normally receive a lower dose of the contaminant than adults because they would also receive a proportionally lower dose of a potentially contaminated product

Application of the HBELs to pediatric formulations

3. HBEL derivation

- If pediatric consideration is taken into account when selecting critical effect in pediatric population, and potentially lowering the value with additional adjustment factor, there is no need to have different PDEs for adults and children
- Overall, the HBEL are based conservatively enough to cover all age groups (adult, paediatric, geriatric)

Based on the presented reasosns, additional safety factors for pediatric populations are not required

Sussman et al. (2016), A Harmonization Effort for Exposure Methodology – Considerations for Application of Adjustment Factors, *Regul. Toxicol. Pharmacol.* 79, S57-S66 DOI: 10.1016/j.yrtph.2016.05.023

SUMMARY

The basic concept that the HBEL approach employs to assure redundancy of terminology such as “highly hazardous” and the use of 1/1000 MinDD:

-a rigorous methodology completed by a trained and knowledgeable individual(s) to accurately determine a safe/acceptable exposure for a given substance and

-a solid implementation plan to ensure the consistent application of practices is employed by cross-functional users in complex quality risk management systems (ref. Olson et al., 2016)

-there are many factors in controlling carry-over risks beyond the HBEL which also need to be done consistently and by qualified experts

The dose makes the poison

Acknowledgements

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