Dialogue between Members of the HMA-WG HMPWG and Interested Parties AESGP, ECHAMP, EUCOPE
Vienna – 17.10.2018

Safety of Homeopathic Medicinal Products (Art. 14 and Art. 16.2) – Calculation of First Safe Dilutions (FSD)

Dossier: Adequate use of the list of FSD and PtC

- **Final dilution equal or higher than FSD** (Art. 14 & 16.2)

Column 8 (FSD) of the list of FSD is relevant as reference:

1	2	3	4	5	6	7	8	9
Stock/ raw/ starting material	Method of preparation	Toxic component concentration	Basis for FSD	Acceptable amount	Reference(s) (HMPWG)	Calculation method	FSD	Remarks (HMPWG)

No further action regarding proof of safe potency is necessary.

- **Final dilution lower than FSD** (Art. 14 & 16.2)

Column 5 (acceptable amount) of the list of FSD is relevant as reference:

1	2	3	4	5	6	7	8	9
Stock/ raw/ starting material	Method of preparation	Toxic component concentration	Basis for FSD	Acceptable amount	Reference(s) (HMPWG)	Calculation method	FSD	Remarks (HMPWG)

Further action regarding proof of safe potency is necessary, e.g. compile Module 4

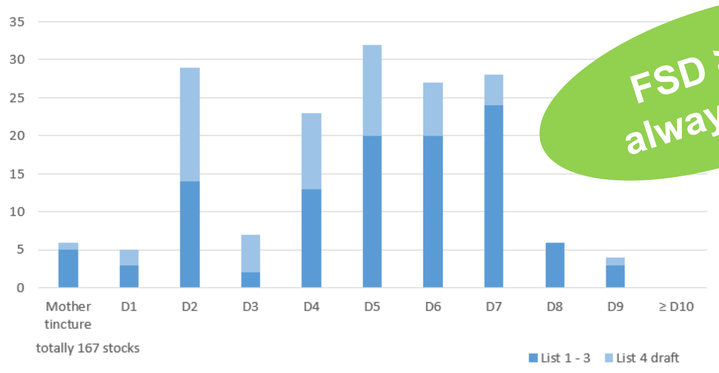
If necessary for patient safety, include *special warnings* in label
reg. patient groups, maximum daily intake, duration of use

FSD – Calculation basis

According to HMPWG PtC	daily dosage of 10 g /10 ml	**Most conservative approach**
Not required by PtC but implemented additionally	lifelong daily application	**Highly unrealistic add on**
	lifelong bodyweight of 3 kg	**Highly unrealistic add on**

All three conditions together are highly unlikely, even for chronic diseases

HMPWG FSD lists show that no FSD is > D9



FSD ≥ D9 always safe

Calculations of the worst-case-FSD show

FSD ≥ D9 always safe

Ph.Eur. Monograph 2371
(assuming the **whole plant material** is toxicologically relevant)

Method 1.1.1 (HAB 1a): 10 g D8 contain 0.1 µg plant material < TTC 0.15 µg
Method 1.1.3 (HAB 2a): 10 g D9 contain 0.0166 µg plant material < TTC 0.15 µg
Method 1.1.4 (HAB 2b): 10 g D9 contain 0.0166 µg plant material < TTC 0.15 µg
Method 1.1.5 (HAB 3a): 10 g D9 contain 0.0166 µg plant material < TTC 0.15 µg
Method 1.1.6 (HAB 3b): 10 g D9 contain 0.0166 µg plant material < TTC 0.15 µg
Method 1.1.7 (HAB 3c): 10 g D9 contain 0.0166 µg plant material < TTC 0.15 µg

Method 1.1.8 (HAB 4a): 10 g D8 contain 0.1 µg plant material < TTC 0.15 µg
Method 1.1.10 (Fr. Ph.): 10 g D7 contain 0.1 µg plant material < TTC 0.15 µg

PDE

Element pde	HMPWG Acceptable amount (FSD lists, with weight adjustment to 3 kg bw) ➢ when declared as homeopathic active substance µg/day	ICH Q3D Acceptable amount for all age groups ➢ when declared as impurity µg/day
Ag	9.9*	150*
Sb	72*	1200*
Cu	300**	3000*
Fe	300**	13000***

* **Reference:** *ICH Guideline for Elemental Impurities Q3D (EMA/CHMP/ICH/353369/2013)" for Ag, As, Hg, Sb, Cu, Pb*
** **Reference:** *Scientific Opinion on nutrient requirements and dietary intakes of infants and young children in the European Union, EFSA Journal 2013;11(10):3408*
*****Reference** *Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents (EMEA/CHMP/SWP/4446/2000)*

Fact is:

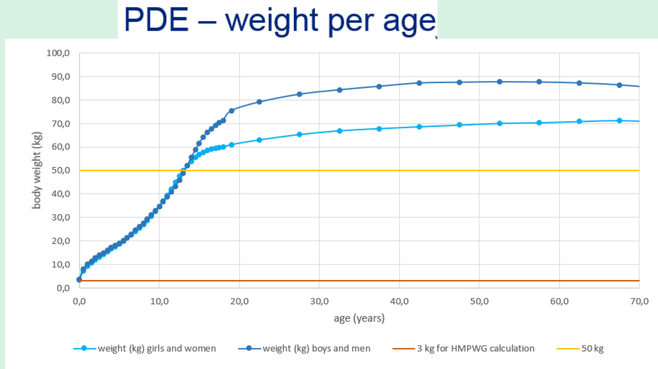
- In general: higher acceptable amounts for impurities are allowed than for hom. active substances
- Additional weight adjustment* for PDEs for hom. active substances
- Food recommendations** give no maximum toxicological limits

From a toxicological point of view, it should not matter how the toxicologically relevant component is declared in medicinal products. The acceptable amounts should be the same.

Proposals:

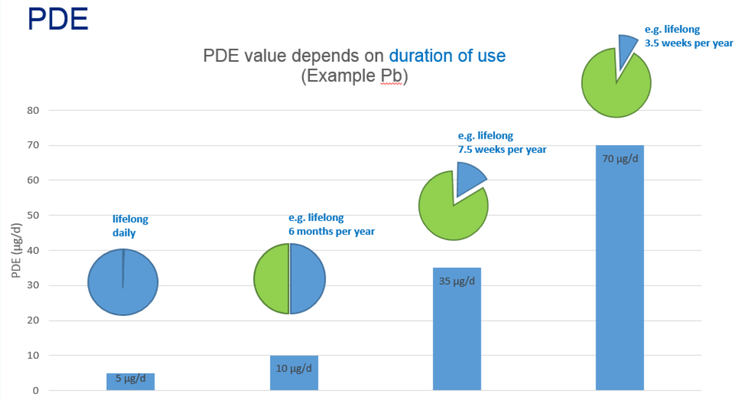
- No additional weight adjustment
- In general: Use of adequate literature references with toxicological data

PDE – weight per age



References:
0 – 18 years: Beiträge zur Gesundheitsberichterstattung des Bundes. Referenzperzentile für anthropometrische Maßzahlen und Blutdruck aus der Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (KiGGS). 2. Erweiterte Auflage, Robert Koch-Institut, Berlin 2013.
> 18 years: DeStatis – Statistisches Bundesamt. Mikrozensus – Fragen zur Gesundheit - Körpermaße der Bevölkerung. Ergebnisse des Mikrozensus 2017. 2. August 2018. Online available: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

PDE



FSD list: PDE (Pb) = 5 µg/day (**10 g per day, lifelong, 3 kg body weight**)
Calculation of PDE per duration of use is based on ICH „Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk M7".

TTC-Approach: Example Drosera

3rd List of FSD	Drosera (HAB)	Drosera (Ph.Franc.)
Method of preparation	Ph. Eur. 1.1.3	Ph. Eur. 1.1.10
Toxic component concentration	Whole plant material An assessment on the basis of naphtoquinones is possible if the content of naphtoquinones is determined by a validated method	Plumbagine: maximum of 0.01 % in MT
Basis for FSD	TTC	TTC
Acceptable amount	0.15 µg/day (neonates)	0.15 µg/day (neonates)
Calculation method	10 g MT = 8333.33 mg fresh plant material 10 g D9 = 0.0167 µg fresh plant material	10 g MT = 1 mg plumbagine 10 g D4 = 0.10 µg plumbagine
FSD HMPWG	D9	D4

Fact is:

- Whole plant material (= 100 % starting material) as calculation basis is unrealistic
- < TTC for herbal active substances

Proposals:

- **Literature data** on the amounts of ingredients in plants should be accepted as calculation basis
- **worst case** for content of secondary metabolites as basis for calculation as a result of published literature: **10 %**

What would be expected according to the statement in the PtC:

= TTC for herbal active substances

D7 would result for Drosera (HAB)

TTC-Approach: Example Chelidonium

1st List of FSD	Chelidonium majus (HAB)
Method of preparation	Ph. Eur. 1.1.5
Toxic component concentration	MT: maximum 0.20 % of alkaloids, calculated as chelidonine → 10 g MT = 20.0 mg alkaloids
Basis for FSD	TTC HMPWG rationale for TTC-approach: • toxicity concern • limited data • exclusions considerations not applicable
Acceptable amount	0.15 µg alkaloids/day
Calculation method	10 g MT = 20.0 mg alkaloids → 10 g D6 = 0.060 µg alkaloids
FSD HMPWG	D6

Fact is:

- Literature used for assessment not given
- TTC approach used although for this tincture negative Ames test and NOEL exist (HMPC)

Proposals:

- In general: assessment reports should be published and literature references should be given
- Existing NOEL should be used for the calculation of a PDE

TTC-Approach

Year	Publication	Category	limit value for substance with structural alert for genotoxicity	limit value for substance without structural alert for genotoxicity
2007	HMWPG PTC on Non-clinical Safety of Homeopathic Medicinal Products of Botanical, Mineral and Chemical Origin	Homeopathic medicinal products, active substances	0.15 µg/day	0.15 µg/day if PDE derivation is not possible
2008	EMEA Guideline on the assessment of genotoxicity of herbal substances/preparations	Herbal medicinal products, active substances	1.5 µg/day	-
2012	EFSA Scientific Opinion on Exploring Options for providing advice about possible human health risks based on the concept of TTC	Food	0.15 µg/day	depending on substance class: 18-1800 µg/d
2014	EMA/CHMP/ CVMP/ SWP/169430/2012 Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities (2014)	Medicinal products, residues	1.5 µg/person/day	Result of a structured scientific evaluation of all available pharmacological and toxicological data

Fact is:

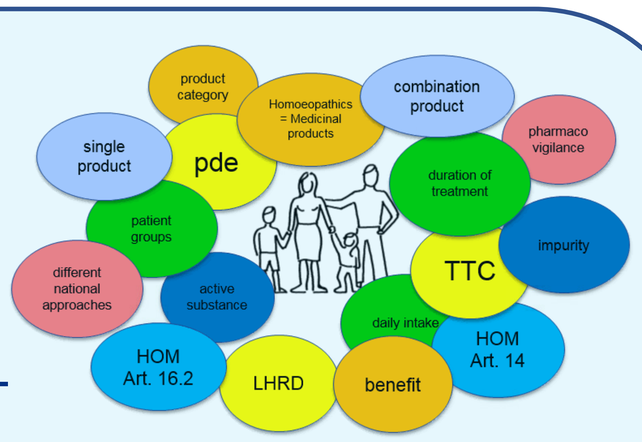
The TTC for genotoxic and non-genotoxic hom. active substances is

- the same
- < TTC for herbal active substances
- ≤ impurities in the food sector
- < impurities in medicinal products

What would be expected according to the statement in the PtC:

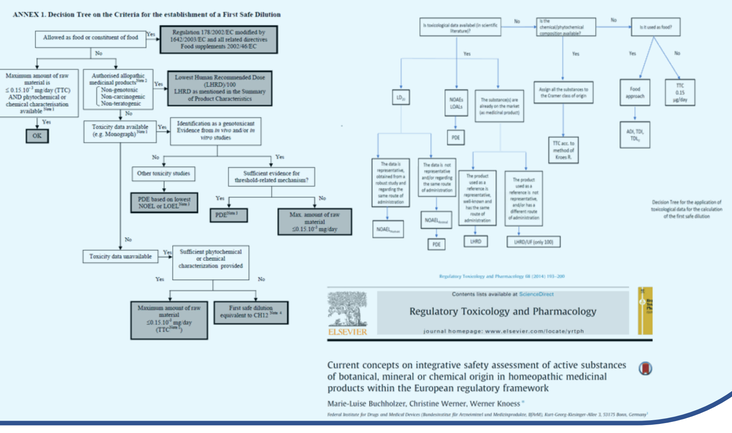
The TTC for genotoxic and non-genotoxic hom. active substances is

- not the same
- = TTC for herbal active substances
- ≥ impurities in the food sector (e.g. Cramer classes for non-genotox)
- ≥ impurities in medicinal products (**Cramer classes**)



Patient Safety – A matter of declaration?

Decision trees:
Fact is: Different national approaches have been established, e.g.



Proposals and points of discussion

- Acceptable amount (concentration) should be reference basis for product specific calculations instead of FSD expressed as D- or C-potency
- Different acceptable amounts depending on product category scientifically not adequate
- Same evaluation criteria for homeopathic medicinal products as for other medicinal products
- At least same evaluation criteria for homeopathic active substances as for impurities in homeopathic medicinal products
- FSD ≥ D9 is always safe (instead of C12 / D24)
- Discuss inclusion of special warning in the label of Art. 14 (patient groups, max. daily intake, duration of use), if necessary
- Discuss PDE calculation without further weight adjustment
- TTC approach: same as for herbal medicinal products, application of Cramer classes
- Define consequences for registration acc. to Art. 14 in case FSD results below 1/10,000 (Ø - D3)

➔ One European standard is appreciated.

➔ Transparent and comprehensible assessment of scientific data (incl. Assessment Reports, also updating, Cramer classes).

➔ No discrimination in categories by legal definition, same criteria for homeopathic medicinal products.