10/11/2016
Preamble to the 1st List of First Safe Dilutions (FSD)
1st List of First Safe Dilutions

Overview of comments received on draft document

"Preamble to the 1st List of First Safe Dilutions (FSD)" and "1st List of First Safe Dilutions"

as released for public consultation on the HMA website until 27 August 2016

Deadline for public consultation	27 August 2016
Discussion in the FSD-Subgroup	4 October 2016
Adoption by the FSD-Subgroup	24 October 2016
Discussion and Adoption by HMPWG for publication on HMA-website	10 November 2016

Overview of Comments received

Table 1: Organisations and/or individuals that commented on the draft document

"Preamble to the 1st List of First Safe Dilutions (FSD)" and "1st List of First Safe Dilutions" on May 2016 until 27 August 2016

	Organisation and/or individuals
1	Association of the European Self-Medication Industry (AESGP)
2	German Pharmaceutical Industry Association (BPI e. V.)
3	European Committee for Homeopathy (ECH)
4	European Coalition on Homeopathic and Anthroposophic Medicinal Products (ECHAMP)
5	Laboratoires Lehning

Table 2: Discussion of comments

GENERAL COMMENTS		
Interested party	**Comment and Rationale**	**Outcome**
ECHAMP **BPI** (hint to TTC and item 4 both are missing in the comment of BPI) **AESGP** (additional text → + AESGP in grey letters)	1) The provisions in the document "Structure of the list of first safe dilutions" have not been adhered in the following points: First column – Starting material: - No reference to monograph - No reference to other published literature - No synonyms - No plant part - No information about fresh/dried No column "toxicological comments" Please complete the list according to the document "Structure of the list of first safe dilutions" 2) We do not agree with the body weight adjustment in the PDE calculation. Indeed PDE approach already includes safety factors (F1, F2, F3, F4, F5). Additionally the FSD calculation proposed here is based on the worst case scenario that one whole unit (10 ml or 10 g) is taken daily by a newborn child with 3 kg body weight, which is highly unrealistic. It is important to say that the dosage of homeopathic medicinal products is proportional to the age groups. Therefore the dosage is adapted to the age, and is reduced in younger patient. Such a calculation leads to a disproportionate accumulation of safety factors, and finally to very high FSD. ECHAMP: This approach was already accepted by HMPWG in its decision to set a TTC value of 0.15 µg/day (without body weight adjustment).	1) An improvement of the existing process has been developed in HMPWG. As a pragmatic approach, a modified and condensed procedure evolved. In the first column, the link to the pharmacopoeial monograph (Ph. Franç., HAB, Ph. Eur.) of the stock - if available - will be added. The respective monograph provides all relevant information about the starting material. Entries regarded to toxicological comments as well as additional references to published literature are possible in the column "Remarks". 2) The FSD should be safe for all patient groups, therefore, the most conservative approach has to be chosen considering every possible user of a homeopathic medicinal product. As outlined in the documents "Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin" (PtC) and in the "Introduction of the List of First Safe Dilutions", the first safe dilution refers to a 10 ml solution/10 g trituration. Pharmaceutical form, posology, excipients and vehicles are not within the framework of FSD list. In cases of deviations from the FSD list entry, the applicant shall be free to submit a module 4 with an own assessment. TTC and PDE are two different approaches that cannot be compared. For derivation of PDE, the PtC refers to the "Note for Guidance on Impurities: Residual Solvents" (CPMP/ICH/283/95). In the current version

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	AESGP: If one adds that the TTC approach considers the limit for genotoxic risk of 0.15 mcg/day instead of 1.5 mcg, for substances lacking scientific evidence of risk, an extra safety factor of 10x is included too. In fact, in ICH Q3D it is clearly stated that the "PDEs established in this guideline are considered to be protective of public health for all patient populations". As the PDEs are given in µg/day, a body weight-adjusted calculation is explicitly not necessary to establish the FSD. In the following specific comments, take in account the FSD calculated with 50 kg (and not with 3 kg). 3) Some methods of preparation are missing: Berberis vulgaris 1.1.10, Sanguinaria 1.1.8, Strychnos nux vomica (= Nux vomica) 1.1.10 and Veratrum album 1.1.10. 4) We welcome the decision of HMPWG to improve the process of establishing FSD. However, we do not understand why the released "First List of FSDs" ignores the work that was put in establishing FSDs already in 2014. 5) We strongly suggest providing the assessment reports further on to make the calculation of the FSD easier to follow. The current 1st List of First Safe Dilutions (FSD) unfortunately seems arbitrary and not very scientific-based, as it lacks transparency, for example on the criteria for the establishment of an FSD. + AESGP: As a general remark we would like to suggest that the documents on FSD (assessment reports) and Q&A are available permanently on the HMA website, and not only during the consultation phase. Moreover, we would appreciate if the Q&As were provided on the HMA website as consolidated whole version and not only the Q&A under consultation. A further level of transparency and the availability of meeting reports, working documents and details on the adopted entries would definitely be of advantage.	of the guideline (EMA/CHMP/ICH/82260/2006), a body weight (bw) adaptation for children is proposed. Usually, the PDE is calculated by dividing the point of departure (POD), e.g. NOAEL mg/kg/day, by the product of the uncertainty factors F1- F5 and subsequently multiplying with 50 (kg body weight). This calculation finally results in a limit value given as mg/day. Unless otherwise indicated, the PDE is related to the body weight considered in the calculation/derivation. The calculation of FSD should refer to the primary literature/POD, usually expressed as a value in mg/kg/day. Dividing by uncertainty factors F1-F5 would lead to a limit value in mg/kg/day, which is reasonably multiplied by 3 (kg bw neonate) to result in a FSD. For examples where for FSD derivation a weight-related value is still advised based on respective POD (point of departure), and examples where NO further weight adjustment to PDE ICH Q3D value is deemed necessary, see footnote [i]. In summary, posology cannot be considered in FSD assessment. In contrast to the TTC approach, for regulatory and toxicological reasons weight adjustment is required for the calculation of FSDs based on PDE. 3) These will be added in the current list. 4) The HMPWG will take up this point and will include former data as far as possible. 5) Due to the new condensed procedure in the FSD

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		assessment, the respective list entry provides all relevant information and key references which are generally accessible to the public. If the chosen way of assessment is not self-explaining, an explanation is included in the column "Remarks". To achieve more transparency for the stocks assessed via PDE under "Acceptable amount" the PDE is presented in [mass unit]/**kg** instead of [mass unit]/**50 kg** and the derivation of the respective PDE was added in the column "Remarks". Under the heading "First Safety Dilutions (FSD) subgroup" on the HMA website, a consolidated version of Q&A, adopted October 2015, is available; meeting reports are published on the website too.
Lehning	The formulation depicted in the HMPWG Point to Consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin is never used in the point 7. Calculation method. –log (PDE or LHRD/100 or TTC) Documents should be harmonized.	The chosen way of showing the calculation is more transparent than the formula given in the "Points to Consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin" (PtC). A HMPWG document for calculation of FSD and a proposal for revision of PtC is under development.
Lehning	FSD is determined for 10g of trituration, i.e on a theoretical value for a single substance. Nevertheless this theoretical value of "10 g" is not appropriate for medicinal products containing 2 and more active substances, and intended to be administered following a recommended posology Therefore the determination of a safety margin would be more appropriate in the case of combination of active substances since it will be determined on a case by case approach based on recommended daily intake of the medicinal product. It must be recognized by Health Authorities that safety margin may be determined for homeopathic medicinal product composed of various active substances with	Concerning the application of FSD in combination products, see Question 4 in the document "Questions and Answers on First Safe Dilutions" on the HMA website. It is more precise to adjust the content of an active substance in a combination preparation to the acceptable amount given in column 5 of the FSD list than using safety margins.

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	excipients and used as per recommended posology – for compounds at a final dilution lower than the one mentioned in the list of first safe dilutions (instead of a detailed Module 4). Safety margin for such product is determined by comparing the acceptable amount (point 5) with the real quantity of toxicological marker in the daily dose. e.g. homeopathic medicinal product (tablet of 500mg) composed of various active substances including 20mg of Belladonna 3DH (Eu. Ph). For a maximum posology of 2 tablets 3 times per day. Maximal amount of Belladonna 3DH = 120mg/day-> the real quantity of toxicological marker (0.05%) in the daily dose = 0.06µg alkaloids/day. Quantity below the acceptable amount => safety margin is guaranteed while the FSD depicted in the proposed document is 4DH.	
Lehning	Add the calculation for stocks as per the French Pharmacopeia and not only HAB, where monographs and values are available.	This will be taken into account for the current and for the following FSD lists.
AESGP	AESGP welcomes the intention of the 1st list of first safe dilutions (FSD) to provide harmonised guidance in order to facilitate consistent assessment by the competent authorities. However, we would like to express our concerns that calculations from safety assessments of non-homeopathic medicines are 1:1 transposed to homeopathic medicinal products. This results in an increasing limitation of safe dilutions beyond or far beyond D4. We therefore strongly plead for taking sufficiently into account the particularities of homeopathic medicinal products, in particular the safety criterion of D4 laid down in Directive 2001/83/EC as well as the fact that homeopathic preparations of D4 and above did not show any relevant safety problems during their long presence in the market.	DH4 is not a safe dilution for every active substance, that is used in homeopathy; a substance-specific assessment is always necessary. Otherwise it would not be necessary to establish a list of first safe dilutions. In article 14 subparagraph 1, third bullet point of the Directive 2001/83/EC it is outlined, that *"Only homeopathic medicinal products which satisfy all of the following conditions may be subject to a special, simplified registration procedure: …**a sufficient degree of dilution to guarantee the safety** of the medicinal product; in particular, the medicinal product may not contain either more than one part per 10 000 of the mother tincture …"*. This possibly requires derivations from the dilution DH4.
AESGP	Please reconsider the situation having one FSD per stock (as for Atropa and Chimaphila). The safety, e.g. the FSD, has to be determined in relation to the manufacturing method, as the amount of toxicologically relevant substances in fact depends on the manufacturing method. Furthermore, concerning the evaluation of	HMPWG agrees to the proposal to consider the different methods of preparation in FSD assessment. The French and German manufacturing methods had already been taken into account for Atropa belladonna and Chelidoni-

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	the safety, the FSD can be different depending on the manufacturing method. For example, for Chimaphila, the calculation of FSD gives D8 for method 1.1.5, and D7 for method 1.1.10. We therefore suggest, as proposed earlier, to have different FSDs taking into account the manufacturing method and to include the different manufacturing methods in the same assessment report.	um majus in the 1st List of First Safe Dilutions.
ECH	No Assessments Reports are available anymore; therefore fully understanding of the data is not possible anymore.	See answers to comments from ECHAMP, BPI and AESGP in the first row.
ECH	Please complete the list according to the document “Structure of the list of first safe dilutions”; Data are missing for: -reference to a monograph -part of the plant (e.g. Berberis vulgaris) -fresh or dried plant -synonyms	
ECH	There is an urgent need to have a “consolidated list of all FSDs” including the work on the list of FSDs during 2012-2014	

SPECIFIC COMMENTS ON TEXT – Preamble to the 1st List of First Safe Dilutions (FSD)			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Preamble	**ECHAMP** **BPI** **AESGP** (additional text → + AESGP in grey letters)	*Toxic component concentration: component, on which the calculation of FSD is based* - *Toxicologically relevant component of the raw material if it is specified with an upper content threshold in a pharmacopoeial monograph* - *Whole starting material in cases where the relevant toxicological principle is not known or an upper limit is not defined in a pharmacopoeial monograph* What if in literature an upper limit for the toxicological relevant component is available, but not included in the respective monograph? In these cases, shall the whole starting material be assessed? That does not seem appropriate. We suggest the following formulation: *Toxic component concentration: component, on which the calculation of FSD is based* - *Toxicologically relevant component of the raw material if it is specified with an upper content threshold in a pharmacopoeial monograph or in other relevant literature* - *Whole starting material in cases where the relevant toxicological principle is not known or an upper limit is not defined in a pharmacopoeial monograph or in other relevant literature* + AESGP: In the HMPWG document 'Preamble to the 1st List of FSD' it is said that FSD are valid only for oral dosage form. However in the draft version of the '1st List of FSD' of 2016, the parenteral PDE for Chrome and derivatives are considered.	Not agreed: The reference to published data in literature in general cannot be accepted as they do not fulfil the standard of quality that a pharmacopoeial monograph provides. Only information supplied by an official regulatory authority document may be used. Use of the parenteral PDE for hexavalent chromium: the explanation is included under the column "Remarks": "…Due to the toxicity of hexavalent chromium and a possible high bioavailability of the active substance in the case of a sublingual application, as a conservative approach the parenteral PDE was chosen."

SPECIFIC COMMENTS ON TEXT – 1st List of First Safe Dilutions			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Acidum arsenicosum	**ECHAMP** **BPI** **AESGP**	No weight adjustment necessary. PDE = 15 µg As/day (for all patient populations according to the reference ICH Q3D). 10 g D6 = 8.031 µg As > **FSD = D6**	See under "GENERAL COMMENTS ON DRAFT DOCUMENT", answer 2) on page 2. No change of FSD.
Arsenum iodatum	**ECHAMP** **BPI** **AESGP**	No weight adjustment necessary. PDE = 15 µg As/day (for all patient populations). 10 g D6 = 1.726 µg As > **FSD = D6**	See under "GENERAL COMMENTS ON DRAFT DOCUMENT", answer 2) on page 2. No change of FSD.
Berberis vulgaris	**ECHAMP** **BPI** **AESGP**	*The plant part concerned is not mentioned as intended in the document "Structure of the list of first safe dilutions"* Probably the plant part concerned here is the bark of Berberis vulgaris. If the fruits are used, this FSD is not valid, as fruits do not or only in traces contain berberine, depending on the degree of ripeness. Therefore, it is important to mention the part of the plant part as intended in the document "Structure of the list of first safe dilutions". Please complete the list according to the document "Structure of the list of first safe dilutions" and add a clarification that preparations containing Berberis fructus are not concerned. Safety factors F4 and F5 have been omitted for Berberis 1.1.8. Furthemore, FSD calculation has not been described for Berberis (bark) 1.1.10. Considering a maximum of 0.30% alkaloids in the stock (1.1.10):	- Plant part: As outlined in the outcome to the comments in table 1, the reference to the relevant pharmacopoeia was inserted in the first column for each entry. Hence, the information about the plant part used is available. - The FSD calculation for Berberis vulgaris PPH, Ph. Eur. 1.1.10 (Ph. Franç.) will be added to the current list. - For the purpose of consistency, the uncertainty factors will be completed by adding F4 equal to 1 as well as F5 equal to 1 to the entry in the column "Remarks".

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		- 10 g TM → 30 mg alkaloids - 10 g D1 → 3 mg alkaloids - 10 g D2 → 0.3 mg alkaloids. With a PDE of respectively 22.3 mg/day (50 kg) and 1.34 mg/day (neonate), we obtain a **FSD of D1 (50 kg) or D2 (if including neonates).**	
Berberis vulgaris	**Lehning**	Berberis vulgaris as per the French Pharmacopeia: 10g MT = 60 mg berberine 10g D2 = 0.6 mg Berberine => FSD = 2DH	The FSD calculation for Berberis vulgaris PPH, Ph. Eur. 1.1.10 (Ph. Franç.) will be added to the current list.
Berberis vulgaris	**ECH**	Part of the plant is missing! (probable bark, due to the reference to HAB 4a ?) There are 2 different HAB monographs; Berberis vulgaris bark and Berberis vulgaris e fructibus There are differences in Berberine content in bark and fruits. It is important to mention the part of the plant, see general comments Please ad, that the FSD is not valid for Berberis vulgaris e fructibus!	See answer to comment from ECHAMP, BPI, AESGP to Berberis vulgaris.
Chelidonium majus	**ECHAMP** **BPI** **AESGP**	The following comments are for both 1.1.5 and 1.1.10. *"Basis for FSD: TTC: 0.15 µg/day"* We do not agree with the TTC of 0.15 µg/day as basis for FSD calculation. In the EMA Assessment report on *Chelidonium majus* L., herba several studies concerning **genotoxicity** are mentioned. Recent and in vivo studies indicate no genotoxic potential.	For the assessment of Chelidonium majus, TTC wasn´t chosen as a suitable approach because of genotoxicity concerns but due to the not convincing non-clinical data in conjunction with clinical concerns. In the "Assessment report on Chelidonium majus L., herba" of HMPC (EMA/HMPC/369801/2009) on page 39 is stated: "The evidence to support a safe oral daily dose limit of not more than 2.5 mg alkaloids could be considered. However, the

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		Older and in vitro tests with single components (e.g. sanguinarine) showed DNA damage. An Ames-Test was carried out with the mother tincture according to the German Homeopathic pharmacopoeia (HAB) (Haddouk 2001). The Chelidonium extract tested had no mutagenic properties in the test. In the 'Points to Consider on non-clinical Safety of Homeopathic Medicinal Products of Botanical, Mineral and Chemical Origin' is stated that "the recommendations formulated in the 'Guideline on the Limits of Genotoxic impurities … are chiefly followed". As clarified in the Q&A Document on the 'Guideline on the limits of genotoxic impurities', Question 3.i): Question: "If an impurity triggers a mutagenic structural alert, will a negative result in an Ames test on the impuritiy (conducted to regulatory acceptable standards) be sufficient to conclude that the compound is of no concern with respect to genotoxicity and no further 'qualification' studies will be required?" Answer: "Yes, a negative Ames test (conducted to regulatory acceptable standards) will overrule a structural alert and no further studies would be required…" Hence, it is proved that the mother tincture prepared according to the German Homeopathic pharmacopoeia (HAB) is not genotoxic. According to **toxicity** in the EMA assessment report is stated, that the acute toxicity of the total extract is low. Therefore, the rationale for TTC-approach "toxicity concern" can not be accepted. Thus the TTC approach is not applicable. + BPI and AESGP: Furthermore, TTC should only be applied for compounds of unknown toxicity in the absence of specific thresholds or effect levels such as NOELs. In the same Assessment report, a NOEL is mentioned. Therefore, a PDE can be calculated. We suggest as basis for the calculation of the FSD a PDE. The study mentioned in the EMA assessment report (Mheddhbi 2002) reveals an NOEL of 1,820 mg/kg/day for rats (4 weeks duration). The following	scientific rationale or the information available is not reassuring." In the "Public statement on Chelidonium majus L., herba" of HMPC (MA/HMPC/743927/2010) the benefit-risk assessment therefore was considered negative. In the "German graduated plan for medicinal products for internal use containing celandine" the intake of less than the lower threshold value of 2.5 µg chelidonine/day is deemed as safe (no limitations/warnings necessary in the package leaflet). In the graduated plan, a body weight adaptation of the threshold values for children is claimed: 2.5 µg divided through 70 kg (weight proposed in the graduated plan) = 0.0357 µg/kg x 3 kg = 0,107 µg chelidonine/day for a neonate/3 kg (when dividing through 50 kg → 0.15 µg/3 kg neonate/day). This value lies in the same range as TTC. Hence, the rationale for applying TTC is based on the principle of conservatism and the supporting aspect that the outcome of both approaches lies in the same range. No change of FSD.

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		PDE calculation can be performed: PDE = 1,820 x 50 / 5 x 10 x 10 x 1 x 1 = 182 mg/day. The amount of 182 mg of the homoeopathic stock corresponds to 0.273 mg (= 273 µg) of total alkaloids expressed as chelidonine. The acceptable amount in chelidonine is therefore 273 µg/day (for 50 kg) and 16.38 µg/day (neonate). <u>FSD calculation for 1.1.5</u>: Considering a maximum of 0.20% alkaloids in the stock prepared according to 1.1.5: - 10 g D3 → 60 µg alkaloids - 10 g D4 → 6 µg alkaloids This results in a FSD of **D3 (50 kg) or D4 (if including neonates).** <u>FSD calculation for 1.1.10</u>: Considering a maximum of 0.050% alkaloids in the stock prepared according to **1.1.10**: - 10 g D2 → 50 µg alkaloids - 10 g D3 → 5 µg alkaloids This results in a FSD of **D2 (50 kg) or D3 (if including neonates).**	
Chelidonium majus	**Lehning**	4. Basis for FSD: documents from French Agency	The threshold values in the French document correspond to those of the German graduated plan for Chelidonium majus. As outlined in the comment above, the calculation in the graduated plan refers to the body weight of an adult person with the recommendation for a body weight adjustment for

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		- les médicaments apportant quotidiennement plus de 2,5 mg d'alcaloïdes totaux de la chélidoine doivent être retirés du marché, en raison d'un rapport bénéfice / risque défavorable. En effet, il est apparu qu'à partir de cette dose, des cas d'hépatique aiguë pouvaient survenir. - pour les médicaments apportant quotidiennement entre 2,5 µg et 2,5 mg d'alcaloïdes totaux de la chélidoine, intervalle de doses pour lequel des modifications des tests hépatiques (comme les transaminases) peuvent être observés, le résumé des caractéristiques du produit doit être complété par les mentions suivantes : ✓ une contre-indication pour les patients souffrant de pathologies hépatiques, et en cas de grossesse ou allaitement, ✓ un arrêt du traitement dès apparition des premiers signes d'hépatotoxicité, ✓ une surveillance de la fonction hépatique pour les traitements de plus de 4 semaines. - Les médicaments apportant quotidiennement moins de 2,5 µg d'alcaloïdes totaux de la chélidoine ne semblent avoir provoqué d'effets hépatotoxiques. 5. Acceptable amount: 2.5 µg/day of alkaloids 10g D4 = 0.5µg alkaloids 5. Acceptable amount with safety mentions and contra-indication: 2.5mg/day of alkaloids 10g D1 = 0.5mg alkaloids	children. As the FSD should be safe for all patients that possibly may be treated with a homeopathic medicinal product, the body weight of a new-born child has to be considered. Safety information are not foreseen for homeopathic medicinal products using the simplified procedure as according to article 14 of Directive 2001/83/EC their safety has to be guaranteed by a sufficient degree of dilution.
Cr^{6+}/Kalium bichromicum	**ECHAMP** **BPI** **AESGP**	According to an official French Journal (Journal Officiel de la République française du 2 juillet 2015), the homeopathic dilutions below D5 are forbidden for Kalium bichromicum. Thus, **the dilution D6 is accepted** (see attached document). The French Authorities (ANSM) agree with this. Moreover, use of the parenteral PDE is not justified, as it assumes that the sublingual bioavailability of Cr^{6+} is 100% (as the parenteral bioavailability by definition is 100%). There are no scientific data to support this assumption. Moreover, 100% sublingual absorption can be assumed at best only for very lipophilic substances. The use of the parenteral PDE therefore overestimates the risk considerably. Moreover, as multiple uncertainty factors were used for the derivation of the oral PDE, the use of the oral PDE can be considered sufficiently protective.	1st List of FSD states: D7 based on 25 µg $Cr^{6+/}$day (50 kg; parenteral PDE) > 1.5 µg $Cr^{6+/}$day (neonate)" Rationale: The proposed oral PDE for chromium is 250 µg/day for a 50 kg individual (derived value). The estimated parenteral PDE is 25 µg/day (theoretically assumed value based on a bioavailability of 10%). The hexavalent chromium FSD has been determined on the basis of worst-case assumptions considering the substance-specific toxicological profile in conjunction with the particularities of the application of homeopathic globuli/tablets, namely, dissolving them under the tongue. Hexavalent chromium could be absorbed by sublingual route, hence, the more conservative and tenfold lower parenteral PDE was deemed the appropriate reference/point of departure (POD). Furthermore, the reader is referred to several efforts of establishing limit values for Cr^{6+} by other bodies/organisations: The values lie in

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		Using the oral PDE: **FSD = D6**	the medium two-digit nanogram to mid two-figure microgram range and provide supporting evidence for using the more conservative reference value 25 µg/day [U.S. EPA. IRIS Toxicological Review of Hexavalent Chromium (External Review Draft, 2015 IN PROCESS; Toxicological Profile for Chromium. Wilbur S, Abadin H, Fay M, et al. Atlanta (GA): Agency for Toxic Substances and Disease Registry (US); 2012 Sep.; OEHHA Office of Environmental Health Hazard Assessment PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER HEXAVALENT CHROMIUM (Cr VI) 2011; ECHA, European Chemical Agency, Committee for Risk Assessment (RAC) RAC/27/2013/06 Rev.1, APPLICATION FOR AUTHORISATION: ESTABLISHING A REFERENCE DOSE RESPONSE RELATIONSHIP FOR CARCINOGENICITY OF HEXAVALENT CHROMIUM, December 2013]. No change of FSD.
Kalium bichromicum	**Lehning**	As per the French Agency: 5DH En conséquence, je vous informe de mon intention de modifier, pour des raisons de santé publique, les autorisations des spécialités homéopathiques préparées à partir de **kalium bichromicum** en les limitant aux dilutions supérieures ou égales à **5DH (**soit **3CH)**.	See above (remarks regarding hexavalent chromium) . No change of FSD.
Cr6+/Kalium bichromicum	**ECH**	The use of parenteral PDE is not reasonable justified	See above (remarks regarding hexavalent chromium) No change of FSD.
Hydrargyrum biiodatum	**ECHAMP** **BPI** **AESGP**	No weight adjustment necessary. PDE = 30 µg Hg/day (for all patient populations). 10 g D6 = 4.86 µg Hg > **FSD = D6**	See under “GENERAL COMMENTS ON DRAFT DOCUMENT”, answer 2) on page 2. No change of FSD.
Kalium stibyltar-	**ECHAMP**	No weight adjustment necessary. PDE = 1.200 µg Sb/day (for	See under “GENERAL COMMENTS ON DRAFT DOCU-

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taricum	**BPI** **AESGP**	all patient populations). 10 g D4 = 382.2 µg Sb > **FSD = D4**	MENT", answer 2) on page 2. No change of FSD.
Plumbum metallicum	**ECHAMP** **BPI** **AESGP**	No weight adjustment necessary. PDE = 5 µg Pb/day (for all patient populations). For lead in particular, data from the pediatric population (0-7 years) were used to set the PDE that was the basis for FSD calculation! Therefore, further weight adjustment is not only unnecessary, but also unscientific. 10 g D7 = 1.0 µg Pb > **FSD = D7**	ICH Q3D (Lead): "…PDE – Oral Exposure … According to the US EPA model (Integrated Exposure Uptake Biokinetic (IEUBK) Model, 1994) (100% absorption, no other sources of lead), oral intake of 5 µg/day translates into a blood level of 1-2 µg/dL for children age 0-7 years (0-82 months) (US EPA, 2007, 2009). PDE = 5.0 µg/day" See above under GENERAL COMMENTS ON DRAFT DOCUMENT point 2.) - remarks regarding weight adjustment (example Lead: In this case, the POD, point of departure, represents a value established for children, hence, an adjustment is deemed dispensable). Agreed to request, FSD value has been changed.
Plumbum metallicum	**ECH**	Oral PDE of ICH Q3D for Pb of 5 µg/day is also valid for newborns, but HMPWG sets this value for 50 kg adults and a much lower value of 0.3 µg Pb/day for neonate. Contradiction to ICH Q3D and wrong FSD	See above.
Sanguinaria canadensis	**ECHAMP** **BPI** **AESGP**	1.1.10 We don't agree with the calculation of the PDE. According to the study from Keller, the oral intake of Sanguinaria extract has no selective effect on fertility, reproduction or fetal and neonatal development in rats at dosage levels of 5-60 mg/kg/day. Thus, the PDE is the following, using a NOEL of 60 mg/kg/day:	PDE-derivation: According to the safety factor F3 statement (ICH Q3D) "F 1 for reproductive studies in which the whole period of organogenesis is covered", the additional factor is indeed dispensable, however, the calculation based on the second study (monkey) leads to a more conservative outcome and overrides the previous.

GENERAL COMMENTS			
Interested party	**Comment and Rationale**		**Outcome**
		PDE = 60x50 / 5x10x1x1x1 = 60 mg/day for Sanguinaria extract containing 68% total benzophenanthridine alkaloid, corresponding to 40.8 mg/day, if expressed in total benzophenanthridine alkaloid. Considering a maximum of 0.30% alkaloids in the stock (1.1.10): - 10 g stock → 30 mg alkaloids - 10 g D1 → 3 mg alkaloids - 10 g D2 → 0.3 mg alkaloids. With a PDE of respectively 40.8 mg/day (50 kg) and 2.5 mg/day (neonate), we obtain a **FSD of TM (stock) (50 kg) or D2 (if including neonates).** This FSD is not valid for preparations prepared according to Ph. Eur. 1.1.8 (HAB V.4a). Different reference substances are used: In Ph. Franc. The content of alkaloids is calculated as sanguinarine chloride, in HAB it is calculated as chelidonine. Furthermore, the designations of the individual dilutions differ in both methods. In other cases both methods of preparation have been presented (e.g. for Atropa belladonna). Why not in this case? Please add the calculation of a FSD for preparations prepared according to Ph. Eur. 1.1.8 (HAB V.4a) and confirm that they are also valid for preparations according to HAB V.19f.	Conclusive remark: FSD value will be calculated on the basis of the NOAEL determined in the thirteen-week oral toxicity study in cynomolgus monkey (1988) of 10 mg Sanguinarine chloride/kg bw and addressing the uncertainty with an uncertainty factor (UF) of 600 as indicated in the column “Remarks”. Both analytical methods are suitable to determine the toxicological relevant constituents. HAB-monograph: the content of alkaloids is determined as total alkaloids “calculated as chelidonine”. This includes the determination of sanguinarine. The FSD calculation for Sanguinaria canadensis HAB 4a and Sanguinaria canadensis, ethanol. Decoctum HAB 19f will be added to the current list.
Strychnos nux-vomica	**ECHAMP** **BPI** **AESGP**	*“Indole alkaloids: 0.15 – 0.30 % in MT” (specifications Ph Eur.)* This specification refers to the sum of brucine and strychnine. Only 43 – 67 % thereof is strychnine. This fact was not taken into account in the calculation of the FSD.	Brucine has a similar mechanism of action as strychnine in acting as an antagonist at glycine receptors. In the literature (Hagers Enzyklopädie der Arzneistoffe und Drogen, Hager-ROM 2014, entry Strychni semen) brucine is described as less toxic than strychnine. Animal data support this state-

GENERAL COMMENTS			
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		FSD calculation for 1.1.8: Considering a maximum of 0.30% alkaloids brucine and strychnine (including 43-67% strychnine) in the stock (1.1.8): - 10 g stock (= D1) → 30 mg alkaloids / 20 mg strychnine - 10 g D2 → 3 mg alkaloids / 2 mg strychnine - 10 g D3 → 0.3 mg alkaloids / 0.2 mg strychnine - 10 g D4 → 30 µg alkaloids / 20 µg strychnine - 10 g D5 → 3 µg alkaloids / 2 µg strychnine - 10 g D6 → 0.3 µg alkaloids / 0.2 µg strychnine. Using the toxicological value from HMPWG of 300 ng/kg/day for strychnine, corresponding to 15 µg/day (50 kg) and 0.9 µg/day (neonate), and taking in account the content of strychnine in the dilution, we obtain a **FSD of D5 (50 kg) or D6 (if including neonates).** Furthermore, FSD calculation has not been described for Nux vomica 1.1.10. FSD calculation for 1.1.10: Considering a maximum of 0.30% alkaloids brucine and strychnine (including 43-67% strychnine) in the stock (1.1.10): - 10 g stock → 30 mg alkaloids / 20 mg strychnine - 10 g D1 → 3 mg alkaloids / 2 mg strychnine - 10 g D2 → 0.3 mg alkaloids / 0.2 mg strychnine - 10 g D3 → 30 µg alkaloids / 20 µg strychnine - 10 g D4 → 3 µg alkaloids / 2 µg strychnine	ment (www.inchem.org). The HMPWG therefore agrees to refer to the content of strychnine only. No change of FSD. Calculation for 1.1.10: The FSD calculation for 1.1.10 will be added to the current list.

GENERAL COMMENTS			
Interested party	**Comment and Rationale**		**Outcome**
		- 10 g D5 → 0.3 µg alkaloids / 0.2 µg strychnine. Using the toxicological value from HMPWG of 300 ng/kg/day for strychnine, corresponding to 15 µg/day (50 kg) and 0.9 µg/day (neonate), and taking in account the content of strychnine in the dilution, we obtain a **FSD of D4 (50 kg) or D5 (if including neonates).**	
Strychnos nux vomica	**Lehning**	*Strychnos nux vomica as per Eu. Ph. 1.1.10:* *10g MT = 30mg alkaloids* *10g D5 = 0.3µg alkaloids = >FSD = 5DH*	The FSD calculation for 1.1.10 will be added to the current list.
Veratrum album	**ECHAMP** **BPI** **AESGP**	*Remarks: "20% resorption in case of oral intake"* The scientific justification is missing. This statement is not comprehensible. Please make the scientific justification for the factor of 20 % resorption for oral use available. *"Acceptable amount: 3 µg protoveratrine/day (50 kg) → 0.18 µg protoveratrine/day(neonate)"* We do not agree with the calculation of the PDE. The reference used for the calculation of the FSD is based on i.v.-human data. The FSD is only valid for oral intake. The PDE-concept has been developed and is scientifically accepted primarily for the transfer of results from animal studies to humans, not for transmission of results from studies with different routes of administration in humans as the modifying factors show. Furthermore, in the ICH document Q3C (CPMP/ICH/283/95) is stated that "the PDE is derived preferably from a NOEL. If no NOEL is obtained, the LOEL may be used.", and as stated in the Points to Consider on non-clinical	20 % resorption in case of oral intake: This information was taken from Goodman LS, Gilman A, 1965, The pharmacological basis of therapeutics, 3. edition, MacMillan Publishing Co., Toronto London, 716–720. It is strengthened by data from Doyle AE and Smirk FH, Br Heart J. 1953 Oct; 15(4): 439–449, which compared the effectiveness of the veratrum alkaloids neogermitrine and protoveratrine in hypertension in different dosage forms (oral and parenteral). The effective intravenous dose for protoveratrine was from 0.19-0.30 mg/patient. The usual effective dose for oral application was about 1.0-1.25 mg/patient. To achieve the same effectiveness, the oral dose has to be about 4-5fold as high as the intravenous posology, this corresponds to an oral resorption of 20-24%. An oral dosage of about 1.0-1.15 mg protoveratrine/day is confirmed in Alimurung MM and Grajo MZ, Am J Cardiol. 1958 Sep;2(3):361-71. Human data suitability for PDE-concept:

GENERAL COMMENTS			
Interested party	**Comment and Rationale**		**Outcome**
		safety on homeopathic medicinal products of botanical, mineral and chemical origin the PDE shall be calculated according to this (CPMP/ICH/283/95). Therefore, it is more suitable to take an animal study with oral intake and a NOEL as reference. *Veratrum album* L. contains several steroidal alkaloids such as protoveratrine A and B, germerine, jervine and veratridine. There are no oral studies available from which a PDE can be calculated for protoveratrine A. Therefore, in the following, studies are considered in which jervine has been investigated for its toxicity. Due to the fact that jervine is the most toxic ingredient in *Veratrum album* L., these studies appear to be appropriate for the assessment of the toxicity of extract under investigation. The toxicity is evaluated based also on the assumption that the alkaloids present in the extract under investigation are all jervine: *Keeler (1975)*: Rats, mice and hamsters were treated with jervine in oral dosages of up to 360 mg/kg (n = up to 8; up to 5 days of gestation), 360 mg/kg (n = up to 9; up to 4 days of gestation) and 250 mg/kg (n = up to 8; up to 4 days of gestation), respectively: Rats: No malformations, but deaths in dams have been observed; NOEL 360 mg/kg: PDE = 360 x 50 / 5 x 10 x 10 x 1 x 1 = 36 mg/day. Mice: Exencephalics in treated animals, but these might be fortuitous due to the strain used; furthermore, deaths in dams have been observed; nevertheless, the assumed PDE calculation is as follows with a LOEL of 180 mg/kg: PDE = 180 x 50 / 12 x 10 x 10 x 5 x 10 = 0.15 mg/day. Hamster: Teratogenic effects at 170 mg/kg; furthermore, deaths in dams have been observed; the assumed PDE calculation is as follows with a LOEL of 170 mg/kg: PDE = 170 x 50 / 10 x 10 x 10 x 5 x 10 = 0.17 mg/day. Following the principles for calculation of a First Safe Dilution the study of Keeler with the NOEL of 360 mg/kg and the PDE	As outlined in Question 6 of the document "Questions and Answers on First Safe Dilutions" the lowest human recommended dose can also be used to calculate a permitted daily exposure by applying it as a LOEL and using the uncertainty factors F2 = 10 (variability between individuals) and F5 = 10 (NOEL not established). The same approach is used in ICH Q3D for establishing a PDE for lithium (ICH guideline Q3D on elemental impurities, Step 5; EMA/CHMP/ICH/353369/2013; 25 July 2016, p. 51). For calculating a parenteral PDE for lithium a reference to oral data considering the bioavailability was made. This procedure supports the derivation of an oral PDE for protoveratrine based on parenteral data. Calculation of PDE/FSD: As protoveratrine has a very narrow therapeutic range, a reference was taken, that describes the lowest reported effective dosage of protoveratrine in humans (1.2 µg/kg i. v., Krayer O, Meilmann E, 1977, Veratrum Alkaloids with Antihypertensive Activity. In: Gross F (Hrsg.) Handbook of Experimental Pharmacology, Antihypertensive Agents, Springer-Verlag, Berlin Heidelberg, Bd. 39, S. 547–570). No data are provided for proving the statement, that jervine is the most toxic alkaloid in Veratrum album. For toxicological profile data see footnote [ii]. In view of these data, it is not imaginable that the suggested acceptable amount of 36 mg protoveratrine/day (50 kg) and 2.16 mg protoveratrine/day (neonate) may be a safe dose. Furthermore, the basis for PDE-calculation (360 mg/kg in rats) obviously was not a NOEL, as deaths in dams had been observed.

GENERAL COMMENTS			
Interested party	**Comment and Rationale**		**Outcome**
		of 36 mg/day is the most suitable one. The acceptable amount is therefore 36 mg jervine/day (50 kg) → 2.16 mg jervine/day (neonate). Since jervine is more toxic than protoveratrine, it seems appropriate to transfer the values to protoveratrine. This results in an additional safety margin. This means an acceptable daily amount of 36 mg protoveratrine/day (50 kg) → 2.16 mg protoveratrine/day (neonate). This results in a FSD of D3. - 10 g stock (= D1) → 30 mg protoveratrine - 10 g D2 → 3 mg protoveratrine - 10 g D3 → 0.3 mg protoveratrine Furthermore, FSD calculation has not been described for Veratrum album 1.1.10.	Monograph Veratrum album in Ph. Franç.: - different starting material (fresh underground parts) - no information about the amount of protoveratrine A in the mother tincture Hence, the FSD for Veratrum album, Ph. Franç. has to be calculated considering the whole amount of plant material as toxicologically relevant. No change of FSD.
Veratrum album	**ECH**	The use of parenteral PDE is not reasonable justified. The scientific justification of the calculation with "20% resorption in case of oral intake" compared with PDE based on i.v. data is missing.	See answer in the table row above.
Zincum isovalerianicum	**ECHAMP** **BPI** **AESGP**	The acceptable amount of 6.12 mg/day for valeric acid has not been found in EFSA Journal (2013). According FDA requirements, isovaleric acid is a food additive permitted for direct addition to food for human consumption as a synthetic flavouring substance and adjuvant. There is no safety concern at current levels of intake when isovaleric acid is used as a flavouring agent. The ADI is considered as acceptable, according to the Committee JECFA. We suggest to make the toxicological evaluation of the stock using zinc as the toxicological marker.	The toxicological assessment of HMPWG was based on the content of zinc in Zincum isovalerianicum. The UL of 25 mg/day for zinc of the Scientific Committee on Food (SCF) is valid for adults only. For children the SCF recommends 7 mg/day for the age of 1-3; recommendations for children beneath the age of one are missing. In EFSA Journal 2013;11(10):3408, the daily intake of zinc via breast milk is specified with 2 mg for the early month of life. This value is deemed adequate for the majority of healthy term breast-fed infants up to six months of life and lies in a similar range as the UL of 4 mg zinc/day for infants aged 0-6

GENERAL COMMENTS			
Interested party	**Comment and Rationale**		**Outcome**
		The Scientific Committee on Food from European Commission has set a UL (tolerable upper intake level) of 25 mg/day of zinc for adults, including pregnant and lactating women. Considering an UL of 25 mg/day of zinc from all sources (food and medicinal products) and assuming that 10% may be provided by medicinal products only, the toxicological reference value is estimated at 2.5 mg/day of zinc. Taking into consideration a proportion of 21.5% zinc in zinc isovalerate and a content of 103.0% zinc isovalerate in the stock, it can be calculated that: - 10 g stock → 2.2 g zinc - 10 g D1 → 0.22 g zinc - 10 g D2 → 22 mg zinc - 10 g D3 → 2.2 mg zinc. Using the toxicological value of 2.5 mg for zinc, we obtain a **FSD of D3.** Moreover, according to the Food and Nutrition Board (FNB) of the National Academy of Sciences, the Tolerable Upper Intake Level (UL, defined as "the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the specified life stage group") is 4 mg zinc/day for infants aged 0-6 months (see: http://www.ncbi.nlm.nih.gov/books/NBK222317/#ddd00653. 10 g D3 = 2.3 mg zinc > **FSD = D3**	months from the FNB (Food and Nutrition Board). If 10% of the UL for zinc for children at the age of 1-3 years (= 0.7 mg/day) or the age of 0-6 months (= 0.4 mg/day) is taken as basis of assessment, the FSD would be the same (DH4) as if using the recommended value of EFSA of 2 mg. Thus, the second approach strengthens the evaluation based on data from EFSA. The respective reference for valeric acid will be added to the table in the First List of FSD. The acceptable amount of valeric acid is calculated on the basis of information given in the document "KONINKLIJK BESLUIT van 29 AUGUSTUS 1997 betreffende de fabricage van en de handel in voedingsmiddelen die uit planten of uit plantenbereidingen samengesteld zijn of deze bevatten". On page 66 of the document, the intake of the dried root of Valeriana officinalis or equivalents to it via food is restricted to 3.6 g/day. According to the Ph. Eur. monograph Valerianae radix and the given content of valerianic acid in the monograph (0.17 %) a most conservative acceptable amount is calculated as 6.12 mg. No change of FSD.

[i] Examples:

Arsenic

Excerpt: “PDE– Oral Exposure: The oral PDE is based on the chronic effects of As to skin and sets the limit at 15 µg/day based on ATSDR MRL and EPA IRIS limit of 0.0003 mg/kg/d. 0.0003 mg/kg/d x 50 kg human = 0.015 mg/d = 15 µg/d”.

In this case, the MRL as the POD (point of departure) is given in mg/kg/d and, for FSD calculation, this value is to be multiplied by 3 (kg bw neonate) to ensure a first safe dilution for all population groups.

Lead

In the case of Lead, for instance, the POD (point of departure) represents a value established for children, hence, an adjustment is deemed dispensable.

Mercury

POD (point of departure) = BMDL10 of 0.06 mg Hg/kg/day (JECFA, 2011; referenced in ICHQ3D document); uncertainty factors F1-F5 = 5 x 10 x 2 x 1 x 1; 0,0006 mg/kg/d x 3 kg bw neonate = 0,0018 mg/d

Antimony

POD (point of departure) = NOAEL 50 ppm equivalent to 6000 µg Sb/kg/day (Lynch BS, Capen CC, Nestmann ER, Veenstra G, Deyo JA. Review of subchronic/chronic toxicity of antimony potassium tartrate. Reg Toxicol Pharmacol 1999;30(1):9-17; referenced in ICHQ3D document); uncertainty factors F1-F5 = 5 x 10 x 5 x 1 x 1; 24 µg/kg/d x 3 kg bw neonate = 72 µg/d

Overview

►weight-related value still advised, based on respective POD (point of departure):
Antimony
Arsenic
Cadmium
Cobalt
Copper
Gold
Lithium
Mercury
Platinum
Selenium
Silver
Thallium
Tin

► NO further weight adjustment of the PDE ICH Q3D value deemed necessary for FSD derivation
Barium
Lead

[ii] **Comparison of protoveratrine and jervine** - LD50 data from mice:

- protoveratrine: LD50 (mice, i. v.) 0,048 mg/kg
- jervine: LD50 (mice, i. v.) 9,3 mg/kg

(HagerROM 2014, entry Veratri rhizome) suggest a more than 100fold higher toxicity of protoveratrine. The proposed PDE of 36 mg protoveratrine/day/50 kg is considerably inconsistent to the clinical experience with protoveratrine as an antihypertensive drug:

- Hoobler SW et al.: Treatment of Hypertension with oral protoveratrine, Ann Intern Med. 1952;37(3):465-481
  A dose of 0.75-1.5 mg protoveratrine is recommended, the authors state that “a dose slightly larger than the effective one generally produced marked hypotension with nausea and vomiting …”
- Doyle AE and Smirk FH, Br Heart J. 1953 Oct; 15(4): 439–449
  “The doses of protoveratrine used ranged between 0.5 mg and 2.0 mg, the usual effective dose being between 1.0 and 1.25 mg. … In 5 out of the 17 patients the same dose caused hypotensive effects and toxic effects; in 6 of the 17 patients a small difference of 0.25 mg occurred, while in the remaining 6 patients the therapeutic and toxic doses differed by more than 0.25 mg.”

This citations show the narrow therapeutic range of protoveratrine.
The lethal dose in humans for the structural related substance veratrine is 20 mg (Forth/Henschler: Allgemeine und spezielle Pharmakologie und Toxikologie). In Grobosch T et al. 2008; J Anal Toxicol. Nov-Dec;32(9):768-73 an accidental intoxication with Veratrum album is described with an intake of approximately 2 × 20 mL of a beverage (self-made alcoholic root beverage from Veratrum album) containing 20.4 mg/L protoveratrine A, and 13.7 mg/L protoveratrine B, corresponding to an intake of about 1.364 mg protoveratrine A+B. The person developed nausea, vomiting and oral paraesthesia, severe bradycardia (35 beats/min) and hypotension (50/30 mm Hg).