Comments on draft document

Table 1: Origin of comments

3nd List of First Safe Dilution (FSD) as released for public consultation until 07th of October 2017

Organisation or individual	Contact details (e-mail address, telephone number, name of contact person)
ECHAMP EEIG	Amandine Oset Office Manager amandine.oset@echamp.eu Tel 32 2 649 94 40

Interested parties are invited to send
comments together with a copy of the cited references.
This will facilitate the assessment of comments, suggestions and corresponding justifications.

When the reference consists of a book chapter, the copy must include
the page of the book showing the year of publication.

Comments without copies of the supporting literature will not be considered.

Comments should be sent electronically and in Word format (not pdf).

Comments and the identity of the sender will be made public
unless a justified objection is received at the time of the submission.

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Please submit comments on each document separately.

Table 2: Comments

GENERAL COMMENTS ON DRAFT DOCUMENT

Interested party	Comment and Rationale	Outcome
ECHAMP	Even if HMPWG refers to a calculation base of 10 g of a substance due to missing dosage advices, this amount is not a realistic daily dose, especially not in neonates used as the most sensitive reference group. Therefore, in case of minerals which are part of the food or are used as food additives, the comparison of the total mineral quantity in 10 g of the homeopathic medicinal product is not really compatible with tolerable daily doses of, for example "mg / day", as they are given in EFSA papers (see in specific statements below, e.g. Calcium carbonicum Hahnemanni, Calcium phosphoricum), they are to be considered as having an additional safety distance.	
ECHAMP	Mean intakes derived from nutrient requirements and dietary intakes of infants and young children are in general not the suitable basis for toxicological calculations and therefore also not for the calculation of an FSD. Papers dealing with tolerable upper intake levels of food are appropriate sources.	
ECHAMP	Secondary metabolites as e.g. naphthoquinones and pyrrolizidine alkaloids have no fundamental role in maintaining life processes of plants, but they are important for plants adaption to environment and defense processes. Therefore, content of plants secondary metabolites is often very low, with less than 1% of dry weight (1) (Ramakrishnan & Ravishankar 2011, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3329344/pdf/psb-6-1720.pdf). Thus, it reasonable to use a worst-case assumption of 10 % of these secondary metabolites in the plant for the calculation of the FSD, if no data are available.	
ECHAMP	Please provide the calculation bases, such as e.g. loss on drying, amounts of plant, dried or fresh plant, so that the calculation of FSDs is comprehensible.	

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
Calcium carbonicum Hahnemanni CaCO3 HAB	*ECHAMP*	According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. See also the general comment above regarding the calculation base of 10 g and for the suitable basis for toxicological calculations. The "Scientific Opinion on nutrient requirements and dietary intakes of infants and young children in the European Union, (EFSA Journal 2013;11(10):3408)" cited by HMPWG does not deal with safe upper limits of minerals and other food ingredients which must not be exceeded but, on the contrary, the minimum quantities of substances that children need to grow up healthy. For a safety evaluation as shown in the FSD calculation, the values indicated are not suitable for the purpose of restrictions of upper limits in homeopathic medicinal products. Papers dealing with tolerable upper intake levels of food are appropriate sources. However, values for the safety of calcium carbonate intake are found in the „Scientific Opinion on re-evaluation of calcium carbonate (E 170) as a food additive" published by EFSA on 26 July 2011 (http://www.efsa.europa.eu/en/efsajournal/pub/2318). This paper states that there are no known or anticipated toxicological risks of calcium carbonate intake in humans, which is allowed as food additive and therefore belongs to the first and basic group of the FSD decision tree. Average absorption of calcium from calcium carbonate is 20-40%, the main part is excreted as insoluble calcium carbonate via the faeces. The Scientific opinion confirms an upper limit (UL) for total Ca intake of **2,500 mg / day** as it was already proposed in 2003. The EFSA paper "Scientific opinion on the tolerable upper intake levels of Calcium" (EFSA Journal 2012, 10(7):2814)	

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		(https://www.efsa.europa.eu/de/efsajournal/pub/2814), published in 2012, also confirms an upper limit (UL) for total Ca intake of **2,500 mg / day.** As is shown in the calculation in the 3rd list the **Ca amount** in **10 g D1** of Calcium carbonicum Hahnemanni is **420.42 mg**, which is clearly below given UL of 2,500 mg/day. Therefore a **FSD of D1 is sufficient**.	
Calcium phosphoricum CaHPO4·2H2O HAB	*ECHAMP*	According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. See also the general comment above regarding the calculation base of 10 g. The "Scientific Opinion on nutrient requirements and dietary intakes of infants and young children in the European Union, (EFSA Journal 2013;11(10):3408)" (https://www.efsa.europa.eu/de/efsajournal/pub/3408) cited by HMPWG does not deal with safe upper limits of minerals and other food ingredients which must not be exceeded but, on the contrary, the minimum quantities of substances that children need to grow up healthy. For a safety evaluation as shown in the FSD calculation, the values indicated are not suitable for the purpose of restrictions of upper limits in homeopathic medicinal products. Papers dealing with tolerable upper intake levels of food are appropriate sources. **Assessment of Calcium**: However, values for the safety of calcium intake are found in the „Scientific Opinion on re-evaluation of calcium carbonate (E 170) as a food additive" published by EFSA on 26 July 2011 (http://www.efsa.europa.eu/en/efsajournal/pub/2318). This paper specifically states that there are no known or anticipated toxicological risks of the food additive calcium carbonate intake in humans. But the paper in general gives information about the safety of calcium. It confirms an upper limit (UL) for total Ca intake of **2,500 mg / day** as it was already proposed in 2003.	

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		The EFSA paper "Scientific opinion on the tolerable upper intake levels of Calcium" (EFSA Journal 2012, 10(7):2814) (https://www.efsa.europa.eu/de/efsajournal/pub/2814), published in 2012, also confirms an upper limit (UL) for total Ca intake of **2,500 mg / day.** As is shown in the calculation in the 3rd list the **Ca amount** in **10 g D1** of Calcium phosphoricum is **256.2 mg**, which is clearly below given UL of 2,500 mg/day. Therefore **concerning** the **Ca content** a **FSD of D1 is sufficient**. **Assessment of Phosphate**: According to the "Scientific opinion: Ferrous phosphate added for nutritional purposes to food supplements 1. Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food", published 2009 by EFSA (https://www.efsa.europa.eu/de/efsajournal/pub/951), Phosphorus (as phosphate) is on the list of vitamin and mineral substances which may be used in the manufacture of food supplements in Annex I of Directive 2002/46/EC and a number of phosphorous salts are listed in Annex II of this Directive as approved mineral substances which may be used in the manufacture of food supplements. For phosphorus, the SCF established in 1993 Population Reference Intakes of 300 mg for children, 775 and 625 mg in males and females aged 11-17 years and 550 mg/day in adults (SCF, 1993). More recently higher recommendations were established by IOM (1997) and D-A-CH (2000) as follows: 700 mg/day for adults and **up to 1250 mg/day for adolescents. For the younger age groups a factorial approach was used.** Regarding phosphorus, the NDA Panel could not derive an Upper level (UL) but indicated that **normal healthy individuals can tolerate phosphorus (as phosphate) intakes up to at least 3000 mg/day** without adverse systemic effects (EFSA, 2005) (http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/233.pdf).	

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		As is shown in the calculation in the 3rd list the **phosphate amount** in **10 g D1** of Calcium phosphoricum is **607.2 mg**, which is clearly below the tolerated phosphorus amount of 3,000 mg/day. Therefore **concerning** the **phosphorus content** a **FSD of D1 is sufficient**.	
Chimaphila umbellate HAB	*ECHAMP*	Why is the D1 used in the calculation method? According to the given preparation methods, Ph. Eur. 1.1.5 (HAB 3a), one has to calculate up from the mother tincture, as it is done for Symphytum (HAB V3a) and also Drosera (HAB 2a), with even lower amount of fresh plant material as in case of Drosera. How was the exact amount of fresh material calculated in the current table? According to our understanding this is not possible in general, only case by case if one knows the respective loss on drying. From our point of view there is no general need to calculate with the total plant material, even if there would be no validated data concerning content of the secondary metabolites Naphthochinone (NCs) (please refer to the relevant general comment). Specifically it is not justified to use the whole plant as the toxicological relevant component since it is known that the toxicological relevant components of Chimaphila are the naphthoquinones (NQ). Literature data are available and had been already used in the assessment carried out by HMPWG according to the safety of NQ-containing drugs, relevant for Drosera, Juglans, Chimaphila and Plumbago. (HMPWG 2012). Michelitsch and Co-Workers (1997) analysed different Chimaphila mother tinctures and showed NC contents between about 0.017 – 0.027%, which is about 10% of the content in plant material given in (HagerROM 2016). Therefore in this assessment the following calculation bases are used: 0.2% Naphthochinone in the dried plant material (HagerROM 2016) TTC: 0.15 µg/day (neonate)	

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		Loss on Drying 60% 10 g MT: 4.4 mg Naphthochinone 10 g D5: 0.133 µg Naphthochinone (< TTC) FSD = D5	
Chimaphila umbellata Ph. Fr.	*ECHAMP*	We do not agree with the principle to use the TTC based on the whole plant, and we suggest to use the TTC value (0.15 µg/day) with naphtoquinone derivatives content (see Juglans for which the FSD is calculated with TTC based on juglone). According to HagerROM 2008, the aerial part of the dried plant contains 0.2% naphtoquinone derivatives (0.02% in MT), giving the following calculation: . 10 g stock → 2 mg naphtoquinone derivatives . 10 g D1 → 200 µg naphtoquinone derivatives . 10 g D2 → 20 µg naphtoquinone derivatives . 10 g D3 → 2 µg naphtoquinone derivatives . 10 g D4 → 0.2 µg naphtoquinone derivatives . 10 g D5 → 0.02 µg naphtoquinone derivatives (< TTC) → FSD = D5. In addition, we agree with the possibility of an individual assessment on the basis of naphthoquinones (NQ) if the content of NQ is determined by a validated method.	
Drosera HAB	*ECHAMP*	How was the exact amount of fresh material calculated? See also the corresponding comment for Chimaphila as well as the general comment on secondary metabolites It is not justified to use the whole plant as the toxicological relevant component since it is known that the toxicological relevant components of Drosera are the naphthoquinones (NQ). Literature data are available and had been already used in the assessment carried out by HMPWG according to the safety of NQ-containing drugs, relevant for Drosera, Juglans, Chimaphila and Plumbago. (HMPWG 2012). In this report the following was stated: “Naphthoquinonederivates max. 0,5% in the whole dried plant (HagerROM 2008)”. For the calculation in this report a loss by drying of 60 % was used and due to the lack of data the TTC-concept, including weight adaption. With these data an	

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		acceptable amount of 0.0333 µg NQ and an FSD of D6 was calculated for adults and due to the weight adaption an acceptable amount of 0.00333 µg NQ corresponding to an FSD of D7 for all patient groups derived. However, in the Overview of Comments Received from Public Consultation (2012) on FSD Assessment Reports (HMPWG 2014) was stated by HMPWG: "In the Q&A-document is stated, that a bodyweight adaption of TTC 0,15 µg/d is not necessary due to the conservatism of the approach." In the Question and Answer Document on First Safe Dilution (HMA 2015) the following is stated: "This TTC threshold is also applied by EFSA, however expressed here on a µg/day basis. With respect to the use of the TTC for the determination of an FSD it is considered that there is no need for further adjustment for body weight taking into account both the conservatism in the TTC approach (0.15 µg/day instead of 1.5 µg/day as recommended in the Guideline on the Limits of Genotoxic impurities [CPMP/SWP/5199/02] and Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, M7 [June 2014]) and the anticipated benefit of the medicinal product." Taking into account this information, the following calculation seems appropriate: - Use of the literature value of 0.5 % NQ in the whole dried plant - A loss by drying of 60 % - TTC-concept without weight adaption as justified by HMPWG In 2011, for Drosera data on the NQ content of 27 different HAB mother tinctures were submitted to BfArM by German companies via BAH. The NQ content in mother tincture varied between 0.00008 and 0.001%. These data show that the actual contents of NQ are still well below the literature data of 0.5 %. Based on these data the following results: 10 g D6, corresponding to 10 µg whole fresh plant and 0.02 µg NQ →	

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		safe for all age groups In addition, we agree with the possibility of an individual assessment on the basis of naphthoquinones (NQ) if the content of NQ is determined by a validated method.	
Drosera (Ph. Fr)	*ECHAMP*	We do not agree with the principle to use the TTC based on the whole plant, and we suggest to use the TTC value (0.15 µg/day) with plumbagin content (see Juglans for which the FSD is calculated with TTC based on juglone). According to analytical data on Drosera 1.1.10 (on 3 batches), concentration in plumbagin could be estimated to max 0.010% in MT, giving the following calculation: . 10 g stock → 1 mg plumbagin . 10 g D1 → 100 µg plumbagin . 10 g D2 → 10 µg plumbagin . 10 g D3 → 1 µg plumbagin . 10 g D4 → 0.1 µg plumbagin (< TTC) → FSD = D4.	
Galenit Ph. Fr.	*ECHAMP*	Method 4.1.2 Galenit 1.1.10 does not exist Put in the same box method of preparation Ph. Eur 4.1.1 and 4.1.2.	
Petroleum rectificatum HAB/Ph. Eur.	*ECHAMP*	A request to EDQM concerning the information given in the Ph.Eur. monograph of Petroleum rectificatum resulted in the following response: The background of the purity test “Aromatic hydrocarbons” in the Ph. Eur. monograph Petroleum rectificatum for homoeopathic preparations” (also described in the French Pharmacopoeia and in the GHP) is to assure that the production (distillation and further rectification of petroleum) is performed correctly, i.e. to verify the good quality of the distillation of petroleum by checking the absence (or presence of traces) of Aromatic hydrocarbons. Crude mineral oil contains as aromatic hydrocarbons mainly alkylbenzols such as benzene, o-, m-, p-xylenol and toluene and in low amounts polycyclic aromatic hydrocarbons such as naphthalene, anthracene and benzo(a)pyrene. However, as Petroleum rectificatum is a fraction of petroleum (= fraction	

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		of mineral oil with a distillation range between 130 and 280 °C) with a distillation range between 180 °C and 220 °C the polycyclic aromatic hydrocarbons which have boiling points in the range of 300 °C to 500 °C (e. g. benzo(a)pyrene: 495 °C, anthracene: 340 °) are not contained in Petroleum rectificatum. That means with the test the above mentioned alkylphenols and napthalene (boiling point 218 °C) are detected. Regarding quantitative values corresponding to the absorption of ≤ 0.100: **The absorbance of 0.100 between 250 nm and 400 nm corresponds to about 0.5 % aromatic hydrocarbons (calculated as naphthalene).** (EDQM 2017) The maximum content of aromatic hydrocarbons is therefore limited by Ph. Eur. to 0.5 %. 10 g D6 correspond to 0.05 µg aromatic hydrocarbons → safe for all age groups	
Petroleum rectificatum Ph.Franc	*ECHAMP*	Erase the entry of Petroleum rectificatum Pharmacopoiea Française, it does not exist.	
Rauwolfia serpentina; Rauwolfia serpentina, ethanolic decoctum; Reserpinum	*ECHAMP*	It is not clear which product is used as reference product for LHRD. Please name the reference product concretely.	
Symphytum officinale HAB	*ECHAMP*	How was the exact amount of fresh material calculated? See also the corresponding general comment as well as the general comment on secondary metabolites. From our point of view there is no need to calculate with the total plant material, even if there are no validated data concerning content of Pyrrolizidinalkaloids (PAs).	

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		As it is said in the HMPC "Assessment report on *Symphytum* L., radix", Comfrey roots contain 0.2-0.4% PAs, whereby the content in roots is about 100fold higher than in leaves (EMA-HMPC 2015, http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2015/06/WC500187600.pdf). Therefore, we can calculate with 0.4% PA in dried comfrey root. Loss on drying: 60% In fresh plant are 40% * 0.4% = 0.16% PAs 10 g MT contains 5.3 mg PAs 10 g D1 (3 parts MT + 7 parts Ethanol) contains 1.60 mg PAs 10 g D4 contains 1.60 µg PAs 10 g D5 contains 0.160 µg PAs Acceptable amount 0.021 µg PA/day 10 g D6 contains 0.016 µg PAs Therefore a FSD of D6 is sufficient.	
Symphytum officinale Ph. Fr.	*ECHAMP*	We suggest to make the calculation using the toxic components (PA) and not the whole plant. With an estimated concentration of 0.01% PA in MT and an acceptable amount of 0.021 µg PA/day, we obtained the following FSD: . 10 g TM → 1 mg PA . 10 g D1 → 100 µg . 10 g D2 → 10 µg PA . 10 g D3 → 1 µg PA . 10 g D4 → 0.1 µg PA . 10 g D5 → 0.01 µg PA → FSD = D5.	

Literature References:

1. Barnes J, Anderson LA, Phillipson JD. Herbal Medicines. Drosera. London: Pharmaceutical Press. Electronic version, 2014.

2. EDQM onlinesupport. Q107795. 16 August 2017

3. EFSA 2012. Scientific opinion on the tolerable upper intake level of calcium. EFSA J 2012; 10(7):2814.

4. HMA 2015. Questions and Answers on First Safe Dilutions. October 2015.

5. HMPWG 2012. Assessment Report First Safe Dilution
   - Drosera Rotundifolia L.
   - Juglans Regia L.
   - Chimaphila Umbellata L.
   - Plumbago Europaea L.

6. HMPWG 2014. Overview of Comments Received from Public Consultation (2012) on FSD Assessment Reports / List Entries of the following Stocks:
   - Atropa belladonna
   - Atropa belladonna Rh
   - Atropinum sulfuricum
   - Aurum iodatum
   - Naphthoquinones (Chimaphila umbellata, Drosera rotundifolia, Juglans regia, Plumbago europaea)
   - Kalium iodatum
   - Rauwolfia serpentina
   - Rauwolfia serpentina, ethanol. Decoctum
   - Reserpinum
   - Silybum marianum

7. Michelitsch A, Zellnig K, Baumeister A, Schubert-Zsilavecz M, Likussar W. Gehaltsbestimmung von Chimaphilin in Chimaphila umbellata Urtinktur mittels differentieller Pulspolarographie. Pharmazie 1997;52(6):451-3. German

8. Ramakrishnan A, Ravishankar GA. Influence of abiotic stress signals on secondary metabolites in plants. Plant Signal Behav 2011;6(11):1720-31.