## Homeopathic Medicinal Product Working Group (HMPWG)

### Questions and Answers on First Safe Dilutions

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Question 1
What toxicological data should be submitted in case of an application of a homeopathic medicinal product for oral administration with a dilution equivalent to 12CH or above 12CH?

Answer
In case of a dilution equivalent to 12CH or above 12CH, the reference to the present version Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin (July 2007) in Module 4 will suffice.

However, the relevant guidelines should still apply for the excipients and the impurities or degradation products detected.

Question 2
How is the First Safe Dilution elaborated by HMPWG to be applied?

Answer
The HMPWG will define one First Safe Dilution for each stock under assessment. This First Safe Dilution (FSD) can be regarded as safe (referring to a dose of stock that is present in 10 ml of oral solution or in 10 g of trituration) without presenting further data in module 4 and with reference to the FSD list. The definition of a First Safe Dilution does not exclude acceptance of applications for registration of homeopathic medicinal products containing active substances in lower potencies of the stock in question. In such cases applicants should provide adequate data in module 4 and/or calculations referring to the concentration in the finished product in order to justify other potencies. Lower potencies of stocks with appropriate concomitant warnings or contraindications as detailed in the FSD Assessment Report could be acceptable provided that the supportive FSD Assessment Report is integrated in module 4.

Question 3
Should contraindications, in particular allergies, be taken into account when determining the first safe dilution (FSD)?
**Answer**

The approach when determining the FSD should be conservative and only one FSD is applicable per stock. The FSD is the dilution of stock that is safe in all patient groups and so generally contraindications are not relevant. If an applicant wishes to have a lower potency of the stock in their finished product, they must submit a module 4 and address any relevant contraindications on the product labelling.

Contraindications with respect to allergies should be established if the allergenic properties of a substance are well-known and should be appropriately addressed on the product labelling.

**Question 4**

How is the concept of First Safe Dilutions to be applied to homeopathic medicinal products which are combination products?

**Answer**

Basically the defined First Safe Dilutions can also be applied for combination preparations. Module 4 of the applications should include reflections on possible additive and/or synergistic effects of the different active substances and consequences for calculation of product-specific safe dilutions.

**Question 5**

What is the background to use the value of TTC 0.15 μg/day?

**Answer**

According to point 3.2 of the Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin (PtC, July 2007), the TTC value has to be taken as reference for the determination of FSD of genotoxic homeopathic medicinal products (excluding aristolochia species and some structural groups as detailed in point 3.2 of the PtC, see below).

“3.2 Background information on TTC principle
For genotoxic homeopathic medicinal products of botanical, mineral and chemical origin and under the conditions as defined in Annex 1, the recommendations formulated in the Guideline on the Limits of Genotoxic impurities (CPMP/SWP/5199/02)* are chiefly followed. However, the recommendations by Kroes et al. (2004) with respect to the level of the Threshold of Toxicological Concern (TTC) are applied and therefore a TTC of $0.15 \times 10^{-3}$ mg/day is defined.

According to the recommendations by Kroes et al. (2004) the following structural groups were excluded from the TTC approach: aflatoxins, nitroso- and azoxy-compounds, heavy metals, polyhalogenated dibenzodioxin, -dibenzofuran or – biphenyl. Additionally, Aristolochia species are excluded from the TTC approach for homeopathic medicinal products of botanical origin in compliance with the Position Paper on the Risks Associated with the Use of Herbal Products containing Aristolochia species (EMEA/HMPWP/23/00). The TTC approach is not applicable for these substances and consequently the non-clinical risk assessment should be performed on a case-by-case basis and should involve the submission of a module 4.

**Threshold of Toxicological Concern (TTC) is proposed. A TTC value of 1.5 μg/day intake of a genotoxic impurity is considered to be associated with an acceptable risk (excess cancer risk of <1 in 100,000 over a lifetime) for most pharmaceuticals. From this threshold value, a permitted level in the active substance can be calculated based on the expected daily dose. Higher limits may be justified under certain conditions such as short-term exposure periods." (Guideline on the Limits of Genotoxic impurities [CPMP/SWP/5199/02]).**

Taking into account the fact that

- in the "allopathic field", children will usually get lower quantities of the medicinal product which is not systematically the case in homeopathy,
- a benefit-risk assessment is not applicable in the context of the simplified procedure and as such safety always prevails
- the FSD is considered the most conservative approach which must apply to all patients groups and all treatment durations,

it has been decided to set the TTC value at of 0.15 μg/day as recommended in the Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin (July 2007).

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.

**Question 6**

Why is a safety factor of 100 introduced when the lowest human recommended dose is used for establishing the FSD?

**Answer**

The factor 100 has its origin in two different contexts:


   “…in particular, the medicinal product may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor’s prescription.”

   The lowest human recommended dose (LHRD) of a prescription drug may hence be used for the calculation of a first safe dilution (FSD) through division by 100.

   In the Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin (PtC, July 2007) it is stated that the LHRD should be applied also for herbal medicinal products, even though the majority of herbals are non-prescription drugs.

2. The LHRD can also be used to calculate a permitted daily exposure (PDE) by applying it as a LOEL (lowest observed effect level), making the assumption that a recommended dose gives a desired effect.

   A PDE may then be calculated in accordance with appendix 3 of ICH Q3C (Impurities: Guideline for residual solvents). A number of modifying factors are used (F1-F5), but when a LHRD is used instead of a NOEL or LOEL, only factors F2 and F5 remain, where F2 = 10 to account for variability between individuals and F5 is a variable factor that may be applied if the no-effect level was not
established. When only LOEL is available, a factor up to 10 could be used for F5. In calculating the FSD, the most conservative approach is always used, so F5 = 10.

Taken together, these two modifying factors are equivalent to a factor of 100. The other modifying factors are adjusted as follows:

F1 is used for extrapolation between species, but since LHRD and FSD both relate to humans F1 = 1. F3 is used when only short term exposure studies are available. For authorized or registered medicinal products the long term use is studied and used in the benefit risk ratio so F3 = 1. F4 is used only for severe toxicity (non-genotoxic carcinogenicity, neurotoxicity, teratogenicity or reproductive toxicity). When LHRD/100 is used, F4 = 1. LHRD/100 is only suitable for non-genotoxic, non-carcinogenic, non-teratogenic material, as stated in Annex 1 of the PtC. If severe toxicity is exerted by the raw material, a more elaborate assessment of the FSD is required.

For certain starting materials, a LHRD may have limitations through e.g. known adverse effects, contraindications, special warnings, special patient groups etc. In these cases, a different method for calculation of FSD should be used or the limitation should be taken into consideration when using the LHRD for calculation of an FSD. The decision has to be made on a case by case basis.