

**HOMEOPATHIC MEDICINAL PRODUCT WORKING GROUP
(HMPWG)**

INTRODUCTION TO THE LIST OF FIRST SAFE DILUTIONS

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INTRODUCTION TO THE LIST OF FIRST SAFE DILUTIONS

The List of First Safe Dilutions is compiled following the recommendations of the “Points to Consider on Non-Clinical Safety of Homeopathic Medicinal Products of Botanical, Mineral and Chemical Origin” (2007). Consequently, the general framework and practical approach on how to deal with the non-clinical assessment and the criteria for establishing a first safe dilution of a given homeopathic preparation as delineated in this document apply.

Additional clarifications beyond the recommendations of the “Points to Consider on Non-Clinical Safety of Homeopathic Medicinal Products of Botanical, Mineral and Chemical Origin” (2007) ensure a harmonized approach towards the use, limitations and interpretation of the List of First Safe Dilutions.

These include the following:

General Considerations:

- The list of first safe dilutions applies to homeopathic preparations of botanical, mineral and chemical origin for human use only.
- The nomenclature of the intended list position references the respective name of the official pharmacopoeia monograph. In case no pharmacopoeia monograph exists, the substance should be adequately defined by its scientific name with a reference to published literature. In addition national homeopathic synonyms (Member state in brackets) can be added, if applicable.
- Identifying the raw/starting material, plant parts are to be added in case of stocks derived from herbal origin.
- If applicable the original condition of the raw/starting material (fresh or dried) is to be added.
- The homeopathic manufacturing method should be referenced.
- The list of first safe dilutions applies to monopreparations only. Toxicological data provided (e.g. PDE/TTC/LHRD, target organs) could be of use when assessing safety of combinations.
- The first safe dilution is basically related to a PDE, LHRD or TTC and therefore is independent of a specific finished product.
- 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.
- The toxicological assessment of externally used preparations needs to be addressed within the frame of a registration dossier because additional aspects need to be specifically addressed (e.g. possible excipients, local tolerance).

Toxicological Considerations:

A first safe dilution of a homeopathic preparation of botanical, mineral and chemical origin should be safe for all age- and patient groups in all Member States (cfr. article 14 of Directive 2001/83/EC). This has a direct impact on estimation of Permitted Daily Exposures (PDE) based on toxicological data. In this context, a conservative approach is proposed with strict requirements with respect to toxicological data for calculation of a PDE (cfr. decision tree in "Points to Consider on Non-Clinical Safety of Homeopathic Medicinal Products of Botanical, Mineral and Chemical Origin" (2007)).

- In this respect, sufficient non-clinical data (including reproductive toxicity studies) should be obtained from peer-reviewed monographs (see also ICH Q3C for recommendations on monographs used), or other scientific literature. Safety factors for the calculation of a PDE as detailed in ICH Q3C can be applied for all patient groups. In order to avoid exclusion of age- or patient groups in the case of absence of essential toxicity data precluding the calculation of a PDE; the TTC, the LHRD or CH12/DH 24 (for compounds excluded from TTC) are applicable as a basis for calculation of the first safe dilution (cfr. "Points to Consider on Non-Clinical Safety of Homeopathic Medicinal Products of Botanical, Mineral and Chemical Origin" (2007)).
- If the use in children is intended the calculation of PDE can be adapted to the average body weight of the intended age group. This is only possible if no toxicological effects on developing organ systems have been detected. As the used methodology is not applicable for preterm babies, first safe dilutions of homeopathic preparations of botanical, mineral and chemical origin are not applicable for this age-group.
- If there is sufficient toxicological evidence for the effects of a specific component within the raw/starting material, the relevant component can be used to refine the PDE.
- National initiatives regarding labelling and exclusion of certain age- or patient groups and thus possible acceptance of lower dilutions at a national level remain possible.

If the applicant uses the limit referred to in the list of FSD, a toxicological assessment is only necessary on additional aspects related to the finished product. If a registration of a more concentrated preparation is intended, safety has to be justified via an expert report in the application.

List of used abbreviations

FSD: First Safe Dilution
LHRD: Lowest Human Recommended Dose
PDE: Permitted Daily Exposure
TTC: Threshold of Toxicological Concern