

HOMEOPATHIC MEDICINAL PRODUCT WORKING GROUP  
(HMPWG)

POINTS TO CONSIDER ON NON-CLINICAL SAFETY OF HOMEOPATHIC  
MEDICINAL PRODUCTS OF BOTANICAL, MINERAL AND CHEMICAL  
ORIGIN

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## 1 Introduction

Homeopathic medicinal products of botanical, mineral and chemical origin must be regulated according to the same non-clinical principles that are applied to other medicinal products. Specifically homeopathic medicinal products must demonstrate adequate safety.

A non-clinical assessment strategy should take the different origins of homeopathic medicinal products into account and refer to the relevant European guidelines.

This point to consider applies to homeopathic medicinal products as stated in the Directive 2001/83/EC as amended.

## 2 Scope

This point to consider describes a general framework and practical approach on how to deal with the non-clinical assessment of homeopathic medicinal products of botanical, mineral and chemical origin.

Firstly, the criteria for establishing a first safe dilution of a given homeopathic medicinal product of botanical, mineral and chemical origin are presented.

Secondly, recommendations on the requirements for non-clinical assessment (Module 4) for homeopathic medicinal products of botanical, mineral and chemical origin are formulated.

## 3 Criteria for establishment of first safe dilution

### 3.1 General remarks

The criteria for the establishment of a first safe dilution are defined in a decision-tree (see Annex 1). These are subject to updating according to the state-of-the-art of scientific knowledge. This approach enables the establishment of a first safe dilution for a homeopathic medicinal product of botanical, mineral and chemical origin. Ultimately, a validated list of first safe dilutions of homeopathic medicinal products of botanical, mineral and chemical origin can be compiled.

Homeopathic stocks are different in their degree of analytical qualification. While chemical stocks are analytically qualified, the degree of analytical qualification of botanical preparations is dependent upon the type of preparation, as is described in the Guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products (CPMP/QWP/2819/00), in the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States. Furthermore, for botanical, mineral or chemical substances that are also used in food, the assessment of the safety should consider the fact that they are allowed as food or as a constituent of food and should refer to the existing data of the food and food supplements area<sup>1</sup>.

The establishment of a first safe dilution for homeopathic medicinal products of botanical, mineral and chemical origin marks the threshold for the submission of a detailed non-clinical safety assessment (Module 4).

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<sup>1</sup> Regulation 178/2002/EC modified by 1642/2003/EC and all related directives Food supplements 2002/46/EC

For homeopathic medicinal products for which neither analytical (chemical or phytochemical) nor toxicological data are available, a justification for a given dilution will be provided within a module 4 on the basis of existing data.

### 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<sup>2</sup>) with respect to the level of the Threshold of Toxicological Concern (TTC) are applied and therefore a TTC of  $0.15 \cdot 10^{-3}$  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 (EMA/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.

### 3.3 Background on PDE

For well-described non-genotoxic carcinogenic or teratogenic homeopathic medicinal products of botanical, mineral and chemical origin, an estimate of daily human exposure at and below which there is a negligible risk to human health can be identified (Permitted Daily Exposure or PDE). Procedures for the derivation of PDE are considered in the Appendix 3 of the Note for Guidance on Impurities: Residual Solvents (CPMP/ICH/283/95). This approach requires the availability of adequate non-clinical data, which can be found in Peer-Reviewed Monographs (e.g. WHO, ECB).

### 3.4 Calculation of the first safe dilution

For the conversion of the PDE (mg/day), TTC (mg/day) or LHRD/100<sup>3</sup> (mg/day, see Annex 1) to a first safe dilution, the worst case scenario should be adopted. This implies that the proposed dose of stock is present in 10 ml of oral solution or in 10 g of trituration. This concentration, expressed as a decimal dilution ( $DH = -\log(PDE/TTC/LHRD:100)$ ) is taken as the reference for further calculations. The DH can be converted to other dilution types, including centesimal Hahnemannian (CH), Korsakovian (K) or fifty millesimal (LM) by taking into account the specific conversion factor for dilution ( $CF_{\text{dilution}}$ ) as detailed in Table 1.

The PDE, TTC or LHRD/100, as referred to in Table 1, should be interpreted as a dose of stock. When considering a stock of botanical origin, the manufacturing method of the mother tincture and of 1DH (D1) should be taken into account by applying the specific conversion factor for the manufacturing method ( $CF_{\text{manufacturing method}}$ ) as detailed in Table 2.  $CF_{\text{manufacturing method}}$  is related to the equivalent quantity of dried plant in the mother tincture and/or in 1DH (D1) manufactured by the methods described in the European Pharmacopoeia.

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<sup>2</sup> Kroes et al. 2004 "Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet" Food and chemical toxicology 42, 65-83.

<sup>3</sup> For herbal medicinal products the LHRD as recommended in recognised EU monographs should be applied.

**Table 1. Calculation of the First Safe Dilution and the Conversion Factor for Dilution (CF<sub>dilution</sub>) taking into account the pharmaceutical form and the type of dilution**

FIRST SAFE DILUTION nDH n=-log (concentration of PDE, LHRD/100 or TTC in 10ml solution or 10g trituration)*	CF <sub>dilution</sub> for trituration or solution			CF <sub>dilution</sub> for 1% impregnated pharmaceutical forms by a dilution quantitatively equivalent to the first safe dilution (nDH)			CF <sub>dilution</sub> for pharmaceutical forms containing 10% or less than 10% of a dilution or trituration quantitatively equivalent to the first safe dilution (nDH)		
	nDH	xDH	xCH/K	xLM	xDH	xCH/K	xLM	xDH	xCH/K
n = even	x=n	x=n/2	x=(n-6)/5*	x=n-2	x=(n-2)/2	x=(n-8)/5*	x=n-1	x=n/2	x=(n-7)/5*
n = uneven	x=n	x=(n+1)/2	x=(n-6)/5*	x=n-2	x=(n-1)/2	x=(n-8)/5*	x=n-1	x=(n-1)/2	x=(n-7)/5*
In case of application of the TTC criteria, n=9	valid for			valid for			valid for		
	<ul style="list-style-type: none"> <li>oral preparations- liquid forms</li> <li>oral preparations - solid forms (triturations)</li> </ul>			<ul style="list-style-type: none"> <li>impregnated oral preparations &amp; solids forms</li> </ul>			<ul style="list-style-type: none"> <li>cutaneous and transcutaneous preparations</li> <li>ear preparations</li> <li>eye preparations</li> <li>vaginal preparations</li> <li>rectal preparations</li> </ul>		

\* round up to the higher whole number

DH: Decimal Hahnemannian (D, X); CH (C): Centesimal Hahnemannian; K: Korsakovian

**Table 2. Calculation of Conversion Factor for Different Manufacturing Methods**

(CF<sub>manufacturing method</sub>)

Manufacturing method	CF <sub>manufacturing method</sub> of mother tincture (MT) and D1 (1DH) (European pharmacopoeia) <sup>4</sup> calculated with reference to the dried plant material	
	Ratio raw material (stated in dried plant)/MT	Ratio raw material (stated in dried plant)/D1
Eur. Ph.method 4c . (1/10)	1 part dried plant + 9 parts ethanol, equivalent to <b>1/10</b> part dried plant/part MT	1 part MT + 9 parts ethanol = 1/10MT, equivalent to <b>1/100</b> part dried plant/part D1
Eur. Ph method. 4d . (1/20)	1 part dried plant+ 19 parts ethanol, equivalent to <b>1/20</b> part dried plant/ part MT	1 part MT + 9 parts ethanol = 1/10 MT, equivalent to <b>1/200</b> part dried plant/part D1
Eur. Ph. , method 1 1a	1 part expressed juice + 1 part ethanol = 1/2 part juice/part MT, equivalent to <b>((100-T)/2T)</b> part dried plant/part MT	2 parts MT + 8 parts ethanol = 2/10 MT, equivalent to <b>2/10*((100-T)/2T)</b> part dried plant/ part D1
1b	1 part fresh plant latex + 2 parts ethanol = 1/3 part juice/part MT, equivalent to <b>((100-T)/3T)</b> part dried plant/part MT	3 parts MT + 7 parts ethanol=3/10 part MT/part D1, equivalent to <b>3/10*((100-T)/3T)</b> part dried plant/part D1
Eur. Ph. , method. 2a,2b	1 part of fresh plant + (1*T/100) parts ethanol = (100/100+T) part fresh plant part /MT, equivalent to <b>[(100-T)/(100+T)]</b> part dried plant/part MT	2 parts of MT + 8 parts ethanol = 2/10 MT, equivalent to <b>2/10 * [(100-T)/(100+T)]</b> part dried plant/part D1
Eur. Ph. , method 3a,3b	1 part of fresh plant + (2*1*T/100) parts ethanol = [100/(100+2T)] part fresh plant / part MT, equivalent to <b>[(100-T)/(100+2T)]</b> part dried plant/part MT	3 parts of MT + 7 parts ethanol = 3/10 MT, equivalent to <b>3/10 * [(100-T)/(100+2T)]</b> part dried plant/part D1
Eur. Ph. , method 4a,4b	1 part of dried plant+ 10 parts ethanol = <b>1/11</b> part dried plant/part MT mentioned as D1	D1 equivalent to MT

T: loss on drying (%); D1: first decimal dilution (1DH)

Working hypothesis for Eur. Ph., methods 1: the % of juice/latex is equivalent to T

Note: CF<sub>manufacturing method</sub> is only valid if the same part(s) of the plant and similar alcohol strength are used for the manufacturing of MT.

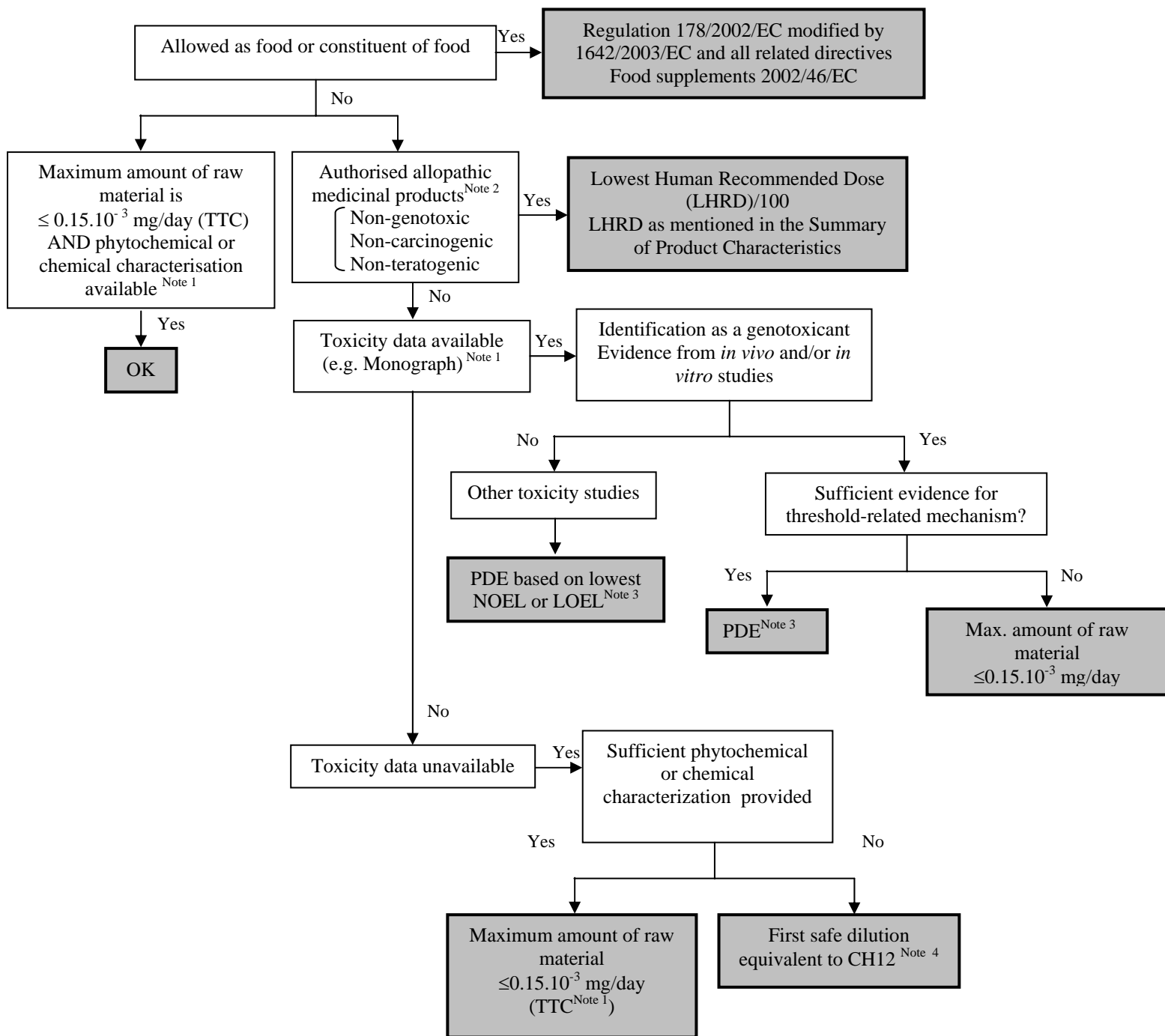
<sup>4</sup> Methods of preparation of homeopathic stocks and potentisation Eur. Ph. 2371

## 4 Requirements for Non-Clinical Data Submission (Module 4)

For compounds at a final dilution equal to or higher than the one mentioned in the list of first safe dilutions, a reference to the list of first safe dilutions in Module 4 will suffice. However, the relevant guidelines should still apply for the excipient(s) used and the impurities or degradation products detected (e.g. CPMP/ICH/2737/99, CPMP/ICH/2738/99, CPMP/ICH/283/95).

For compounds at a final dilution lower than the one mentioned in the list of first safe dilutions and for compounds not included in the list of first safe dilutions, a detailed Module 4 should be compiled. This should be based upon the specificity of the raw material and taking into account the requirements detailed in the Annex 1 of the Directive 2001/83/EC as amended . Any missing data should be justified; e.g. justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking.

## ANNEX 1. Decision Tree on the Criteria for the establishment of a First Safe Dilution



### Note 1

Excl. aflatoxins, nitroso- and azoxy-compounds, heavy metals, polyhalogenated dibenzodioxin, -dibenzofuran or -biphenyl. For herbal products, *Aristolochia* species are excluded.

### Note 2

Including authorised and registered herbal medicinal products (2004/24/EC).

### Note 3

PDE calculation according CPMP/ICH/283/95

### Note 4

Or justify in a module 4 for lower dilutions

## Abbreviations

**C:** Centesimal Hahnemannian dilution  
**CH:** Centesimal Hahnemannian dilution  
**Cfdilution:** conversion factor for dilution  
**CFmanufacturing method:** conversion factor for manufacturing method  
**D:** Decimal Hahnemannian dilution  
**DH:** Decimal Hahnemannian dilution  
**D1:** First decimal dilution (1DH)  
**ECB:** European chemicals bureau  
**Eur. Ph.:** European pharmacopoeia  
**HMA :** Heads of medicines agencies  
**HMPWG :** Homeopathic medicinal products working group  
**K:** Korsakovian dilution  
**LHRD:** Lowest Human Recommended Dose  
**LM:** fifty millesimal dilution  
**LOEL:** Lowest Observable Effect Level  
**log:** logarithm  
**MT:** mother tincture  
**NOEL:** No observable effect level  
**PDE :** Permitted Daily Exposure  
**T: :** loss on drying (%);  
**TTC :** Threshold of Toxicological Concern  
**WHO:** World Health Organisation  
**X:** Decimal Hahnemannian dilution