HMA
Heads of Medicines Agencies

HOMEOPATHIC MEDICINAL PRODUCT WORKING GROUP

(HMPWG)

ASSESSMENT REPORT TEMPLATE FIRST SAFE DILUTION

DISCUSSION IN THE SUBGROUP	February - March 2009
DISCUSSION IN THE HMPWG	29 April 2009
ADOPTION FOR TRANSMISSION TO HMA for release for consultation	1 June 2009
DEADLINE FOR COMMENTS	1 October 2009
DISCUSSION IN THE SUBGROUP	October 2009
DISCUSSION IN THE HMPWG FOR ADOPTION	8 December 2009
ADOPTION BY THE HMPWG FOR TRANSMISSION TO THE HMA	January 2010
ADOPTION BY THE HMA	10 May 2010

ASSESSMENT REPORT TEMPLATE FIRST SAFE DILUTION

1. GENERAL DATA

1.1. Name of the Stock* / Raw*/Starting Material* (to be specified), and Synonyms (References) if applicable

1.2. Definition** of the Stock* /Raw*/Starting Material* (to be specified)
e.g. If Botanical :

- Name of the plant (binomial name[1] (genus, species, author) and synonyms):

[1] according to the European Pharmacopoeia
* As defined in the Ph. Eur.

** For information related to the identity, refer to “Guidance on module 3 of the homeopathic medicinal product dossier”

http://www.hma.eu/uploads/media/HMPWG_dossier_guidance_mod3.pdf

- Part(s) of the plant used:

- State of the plant (dry or fresh):

- Homeopathic Manufacturing Method/Method of preparation:

- Toxic Components (including % in the stock/starting or raw material, bibliographic reference should be provided)

1.3. Monograph European Pharmacopoeia / official national pharmacopoeias if available:

1.4. Other Specifications:

2. CRITERIA FOR THE ESTABLISHMENT OF A FIRST SAFE DILUTION

Please tick the applied criterion as defined in the PTC on Non-Clinical Safety of Homeopathic Medicinal Products of Botanical, Mineral and Chemical Origin (2007) (decision tree):

☐ Allowed as food or constituent of food *(Please proceed to 3. Allowed as food or constituent of food)*

☐ Maximum amount of raw material ≤$0.15.10^{-3}$ mg/60 kg BW/day (TTC) and phytochemical or chemical characterization available

☐ Authorised allopathic medicinal product (non-genotoxic, non-carcinogenic, non-teratogenic)

(Please proceed to 4: Authorised allopathic medicinal product)

☐ Toxicity data available (Toxicological monograph, Pharmacopoeia monograph, Scientific literature)

- o PDE
- o TTC

(Please proceed to 5. Toxicological Data)

☐ Toxicity data unavailable with sufficient phytochemical or chemical characterisation provided

- TTC

☐ Toxicity data unavailable without sufficient phytochemical or chemical characterisation provided

- CH 12/ DH 24

3. ALLOWED AS FOOD OR CONSTITUENT OF FOOD

Provide reference(s). If food extract or constituent, absence of toxicological concern has to be ascertained, otherwise maximum authorized dose should be provided (with reference) or proceed to 5 Toxicological data.

4. AUTHORISED ALLOPATHIC MEDICINAL PRODUCT (NON-GENOTOXIC, NON-CARCINOGENIC, NON-TERATOGENIC)

SPC of product used to calculate the LHRD should be provided, the reference should be justified.

5. TOXICOLOGICAL DATA

The list below is intended as guidance for bibliographical research on the toxicological properties of the raw /starting material/stock and/or its major components and components that have been shown in literature to be toxic. It is possible and understood that not all sections will be addressed due to limited published data available, however, a justification for the lack of data should be provided (see Introduction to the List of First Safe Dilutions for further information). See also ICH Q3C for list of Monographs.

Please indicate which databases *** were consulted

5.1. Acute Toxicity

For each study please specify: test substance, species, dose(s), route, major findings, LD_{50} or approximate.

Study ID/Literature Reference	Test substance	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings

5.2. Repeated Dose Toxicity

For each study please specify: test substance, species, dose(s), route, exposure time, major findings, NOAEL / NOEL / LOAEL / LOEL.

Study ID/Literature Reference/GLP	Test Substance	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL LOEL LOAEL (mg/kg/day)	Major findings

5.3. Genotoxicity

For each study please specify: test substance, test system, concentration(s)/dose(s), exposure time, outcome (positive, negative, equivocal).

Type of test/study ID/ Literature Reference/GLP	Test Substance	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria		Salmonella strains	+/- S9	
Gene mutations in mammalian cells		CHO-cells, HGPRT-locus	+/- S9	
Chromosomal aberrations in vivo		Mouse, micronuclei in bone marrow	+/- S9	
…		...		

If the compound is identified as a genotoxicant without sufficient evidence for a threshold-related mechanism, apply the TTC (max. amount of raw material ≤$0.15.10^{-3}$ mg/day)

5.4. Carcinogenicity

For each study please specify: test substance, species, dose(s), route, exposure time, major tumour findings, NOAEL / NOEL.

Study ID/Literature Reference/GLP	Test Substance	Dose/Route	Species/N° Animals	Major Findings	Tumour findings	Comments

5.5. Reproductive Toxicity

For each study please specify: test substance, species, dose(s), route, exposure time, major findings, NOAEL / NOEL / LOAEL / LOEL.

Study ID/Literature Reference/GLP	Test Substance	Species; Number Female/ group	Route & Dose	Dosing Period	Major Findings	NOEL, NOAEL , LOEL, LOAEL (mg/kg/day)

5.6. Other

Any other non-clinical relevant findings can be mentioned here (in vitro and in vivo).

For each study please specify: test substance, species/cell type, dose(s) / concentration(s), route, exposure time, major findings, NOAEL / NOEL / LOAEL / LOEL.

5.7. Toxicokinetic Data

Information on the absorption, distribution, metabolisation and excretion can be mentioned here.

For each study please specify: test substance, test system (in vivo/ in vitro), dose(s)/concentration(s), exposure time, pharmacokinetic parameters (C-max, T-max, AUC, volume of distribution), metabolite, … .

5.8. Human Safety Data

Human safety data of the stock/raw/starting material and/or of the major components and components that have been shown in literature to be toxic
All published human safety data should be reported.

For each study please specify: test substance, dose(s), duration of administration, route of administration, major findings.

5.9. Conclusion

Calculation of Permitted Daily Exposure (PDE, mg/ kg/day) with justification of the factors used;

If applicable :

$$PDE = \frac{n \times 50}{F_1 \times 10 \times F_3 \times F_4 \times F_5}$$

F1=

F2 = 10

F3=

F4=

F5=

n = NOEL or LOEL (if no NOEL available)

F1 to F5 as defined in the ICH Q3C Note for guidance on impurities: Residual solvents (CHMP/ICH/283/95)

The reference of the study selected should be provided

If the compound is identified as a genotoxicant without sufficient evidence for a threshold-related mechanism, apply the TTC (max. amount of raw material $\leq 0.15.10^{-3}$ mg/day)

6. INTEGRATED RISK ASSESSMENT OF THE STOCK/RAW/STARTING MATERIAL AND/OR OF THE MAJOR COMPONENTS AND COMPONENTS THAT HAVE BEEN SHOWN IN LITERATURE TO BE TOXIC

Information as put forward in points 3, 4 and 5 should be discussed.
Non-clinical and human findings will be assessed with consideration for special age- and patient groups: children (0-12 years), pregnant and lactating women, women of childbearing potential, elderly, … .

7. ACCEPTABLE AMOUNT (MG/KG/DAY) BASED ON STOCK/RAW /STARTING MATERIAL/COMPOUND (TO BE SPECIFIED)

- Food legislation:
- LHRD/100:
- PDE mg /day:
- TTC:
- "CH 12"/"DH 24"

8. FIRST SAFE DILUTION

Calculation of the first safe dilution as defined in the PTC on Non-Clinical Safety of Homeopathic Medicinal Products of Botanical, Mineral and Chemical Origin (2007).

***** Recommended databases (Non exhaustive list)**

TOXNET (http://toxnet.nlm.nih.gov/)

PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Search&db=pubmed)

INCHEM (Chemical Safety Information from Intergovernmental organisations http://www.inchem.org/)

National Toxicology Program (http://ntp.niehs.nih.gov/)

LIST OF ABBREVIATIONS

CH: Centesimal Hahnemannian dilution

DH: Centesimal Hahnemannian dilution

Eur. Ph.: European pharmacopoeia

LHRD: Lowest Human Recommended Dose

LM: fifty millesimal dilution

LOAEL: Lowest Observed Adverse Effect Level

LOEL: Lowest Observable Effect Level

NOAEL: No Observable Adverse Effect Level

NOEL: No observable effect level

PDE: Permitted Daily Exposure

TTC: Threshold of Toxicological Concern

SPC: Summary of the Product Characteristics

GLP: Good Laboratory Practice

F1…F5: as defined in the ICH Q3C Note for guidance on impurities: Residual solvents (CHMP/ICH/283/95)