## HOMEOPATHIC MEDICINAL PRODUCT WORKING GROUP (HMPWG)

### ASSESSMENT REPORT TEMPLATE FIRST SAFE DILUTION

<table>
<thead>
<tr>
<th>DISCUSSION IN THE SUBGROUP</th>
<th>February - March 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISCUSSION IN THE HMPWG</td>
<td>29 April 2009</td>
</tr>
<tr>
<td>ADOPTION FOR TRANSMISSION TO HMA</td>
<td>1 June 2009</td>
</tr>
<tr>
<td>for release for consultation</td>
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<tr>
<td>DEADLINE FOR COMMENTS</td>
<td>1 October 2009</td>
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<tr>
<td>DISCUSSION IN THE SUBGROUP</td>
<td>October 2009</td>
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<td>DISCUSSION IN THE HMPWG FOR ADOPTION</td>
<td>8 December 2009</td>
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<tr>
<td>ADOPTION BY THE HMPWG FOR TRANSMISSION TO THE HMA</td>
<td>January 2010</td>
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<tr>
<td>ADOPTION BY THE HMA</td>
<td>10 May 2010</td>
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</tbody>
</table>
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”

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)
  - [ ] PDE
  - [ ] TTC
(Please proceed to 5. Toxicological Data)

☐  Toxicity data unavailable with sufficient phytochemical or chemical characterisation provided
   o  TTC

☐  Toxicity data unavailable without sufficient phytochemical or chemical characterisation provided
   o  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.

<table>
<thead>
<tr>
<th>Study ID/Literature Reference</th>
<th>Test substance</th>
<th>Species/ Sex/Number/ Group</th>
<th>Dose/Route</th>
<th>Approx. lethal dose / observed max non-lethal dose</th>
<th>Major findings</th>
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### 5.2. Repeated Dose Toxicity

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

<table>
<thead>
<tr>
<th>Study ID/Literature Reference/GLP</th>
<th>Test Substance</th>
<th>Species/Sex/ Number/Group</th>
<th>Dose/Route</th>
<th>Duration</th>
<th>NOEL/ NOAEL</th>
<th>LOEL</th>
<th>LOAEL</th>
<th>Major findings</th>
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5
### 5.3. Genotoxicity

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

<table>
<thead>
<tr>
<th>Type of test/study ID/Literature Reference/GLP</th>
<th>Test Substance</th>
<th>Test system</th>
<th>Concentrations/Concentration range/Metabolising system</th>
<th>Results Positive/negative/equivocal</th>
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<tbody>
<tr>
<td>Gene mutations in bacteria</td>
<td>Salmonella strains +/- S9</td>
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<tr>
<td>Gene mutations in mammalian cells</td>
<td>CHO-cells, HGPRT-locus +/- S9</td>
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<tr>
<td>Chromosomal aberrations in vivo</td>
<td>Mouse, micronuclei in bone marrow +/- S9</td>
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If the compound is identified as a genotoxicant without sufficient evidence for a threshold-related mechanism, apply the TTC (max. amount of raw material \( \leq 0.15 \times 10^{-3} \) mg/day)

### 5.4. Carcinogenicity

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

<table>
<thead>
<tr>
<th>Study ID/Literature Reference/GLP</th>
<th>Test Substance</th>
<th>Dose/Route</th>
<th>Species/N° Animals</th>
<th>Major Findings</th>
<th>Tumour findings</th>
<th>Comments</th>
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5.5. Reproductive Toxicity

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

<table>
<thead>
<tr>
<th>Study ID/Literature Reference/GLP</th>
<th>Test Substance</th>
<th>Species; Number Female/group</th>
<th>Route &amp; Dose</th>
<th>Dosing Period</th>
<th>Major Findings</th>
<th>NOEL, NOAEL, LOEL, LOAEL (mg/kg/day)</th>
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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:

\[
PDE = \frac{n \times 50}{F_1 \times 10 \times F_2 \times F_3 \times F_4}
\]

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 ≤0.15 \times 10^{-3} \text{ 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/)


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)