federal agency for medicines and health products

# FAMHP GUIDANCE ON MODULE 3 OF THE HOMEOPATHIC MEDICINAL PRODUCT DOSSIER:

# REFERENCE DOSSIER "DILUTION"

**Version:** 19/09/2013
**Reference of the document:** FAMHP/Homeo/M3/DL
**Division:** Unit Homeo/Phyto
**Total number of pages:** 4

Disclaimer:

1. This guidance is based on HMPWG guidance on module 3. It is completed with some examples or explanations in order to facilitate the compilation of the module 3 for a reference dossier "dilution". All possible cases are not presented.
2. The words "dilution" and "trituration" have to be understood according to the definition of "potentisation" retaken in the Ph. Eur. monograph "Homoeopathic preparations (1038*)": Dilutions and triturations are obtained from stocks by a process of potentisation in accordance with a homoeopathic manufacturing procedure: this means successive dilutions and succussions, or successive appropriate triturations, or a combination of the 2 processes*.

## 3.2.S.1 General information

All possible kinds of dilutions and their manufacturer should be mentioned in this section.

*For example:* dilutions in water, dilutions in x % alcohol, dilution in water/ethanol/glycerol, dilutions D, dilutions CH, dilutions K, dilutions LM…

Reference to all the different preparation and potentisation methods used should be made.
*For example*, the ones described in a Ph. Eur. monograph (2371: Methods of preparation of homoeopathic stocks and potentisation, 1038: Homoeopathic preparations).

## 3.2.S.2 Manufacture

### 3.2.S.2.1 Manufacturer

The name, address, and responsibility of each dilution manufacturer, and each proposed production site or facility involved in manufacturing and testing should be provided.
GMP certificate(s) should be provided.

Federal agency for medicines and health products
Eurostation II – place Victor Horta 40/40 – 1060 Brussels
Phone +32 2 5248000 fax +32 2 5248001
E-mail welcome@fagg-afmps.be website www.afmps.be

**3.2.S.2.2 Description of manufacturing process and process controls**

In this section information should be provided to adequately describe the manufacturing process and process controls.

Each potentisation method quoted in the section 3.2.S.1 general information should be described. This remark concerns only the potentisation method. The method of preparation of the homoeopathic stock should be only described in the specific dossier of the stock.

For each potentisation method, a composition table and a sequential procedure narrative should be provided. The narrative should include quantities of stocks, dilutions and solvents/vehicles reflecting a representative batch scale for commercial manufacture (including intermediate steps, e.g. dilution library, bulks if applicable…).
The different stages of the preparation of the intermediate and final dilutions must be sufficiently described to allow the assessment of the consistency of the quality.

All the equipment (LAF and potentisation machine included) and operating conditions (e.g. potentisation time, potentisation speed, …) should be described in details.

**3.2.S.2.3 Control of materials**

The information on the solvents/reagents or vehicles used for intermediate and final dilutions preparation should be presented.

The information on the raw material(s) and the solvents/reagents or vehicles used for the homeopathic stock(s) should be only described in the specific dossier of the stock.

The certificates of analysis of all vehicles (e.g. ethanol and purified water) used for the preparation of the dilutions should be provided in this section.

**3.2.S.2.4 Control of critical steps and intermediates**

To be completed if applicable (according to the manufacturing process).

**3.2.S.2.5 Process validation and/or evaluation**

To be completed.

**3.2.S.2.6 Manufacturing process development**

Reference to the manufacturing method of an official pharmacopoeia shall be made.

**3.2.S.3 Characterisation**

Information on impurities originating from the raw material(s): see the specific dossier of the stock.

Information on impurities arising from the manufacturing process: to be provided if applicable.

**3.2.S.4 Control of drug substance**

**3.2.S.4.1 Specifications**

The specifications, for each kind of dilution as referred in the section 3.2.S.1, should be provided. Information provided should comply with relevant quality guidelines.

Remark:
Dilutions above the NAT (No-Assay Threshold): all information should be detailed in this dossier

Dilutions below the NAT: Specific information (for example: the assay of a compound) should be detailed in the specific dossier of the stock.

**3.2.S.4.2 Analytical procedures**

Analytical procedures used for testing each kind of dilution should be provided.

**3.2.S.4.3 Validation of analytical procedures**

Analytical validation information, including experimental data for the analytical procedures used for testing each kind of dilutions should be provided.

**3.2.S.4.4 Batch analysis**

For each kind of dilution, description of batches and results of batch analysis should be provided.

**3.2.S.4.5 Justification of specification**

Justification for each kind of dilution specifications should be provided.

**3.2.S.5 Reference standards or materials**

Information on the reference standards or reference materials used for testing each kind of dilution should be provided if applicable.

**3.2.S.6 Container closure system**

Description of container closure system(s) used for storage of each kind of dilution should be provided. The combination of the container closure specifications and the dilutions stability data may be sufficient to demonstrate suitability of the container closure system for storage of the dilutions.

Certificate of analysis should be provided. The container closure system should comply with Ph. Eur. monographs concerning materials and containers.

**3.2.S.7 Stability**

Stability data of each kind dilution should be provided.

*Dilutions above the NAT*:

If stability is demonstrated for a dilution above the NAT, these data can be used as reference for all dilutions, whatever the origin of the stock, as long as the vehicle and the container closure system are the same ones.

Whatever the stock, for dilutions/triturations above the No-Assay-Threshold (NAT), common stability studies (focusing on e.g. ethanol content, microbiological quality,…) can be performed as far as the storage conditions (container closure system…) and the vehicle composition are the same.

Dilutions/triturations higher than the No-Assay-Threshold cannot have an expiry date higher than the one of the stock.

*Dilutions below the NAT*:

Stability study should be provided in the specific dossier of the stock.

Stability data from homeopathic stocks can be transferable to dilutions / triturations obtained thereof as far as it was demonstrated/justified that the stock is stable in its new dilution/trituration medium (e.g. when alcohol % is similar to alcohol % of the mother tincture, when there is absence of interaction with lactose of trituration) and in their container closure system during the shelf-life fixed for the stock. That is why:

- a table containing the stored intermediate dilutions with their solvents of dilution and their container closure system should be provided,
- a rationale with the stability relevant parameters concerning the stock should be provided.

**References and related documents**

HMPWG - GUIDANCE ON MODULE 3 OF THE HOMEOPATHIC MEDICINAL PRODUCT DOSSIER
(HMA-website http://www.hma.eu/uploads/media/HMPWG_dossier_guidance_mod3.pdf)

**History**

| Version | Date of application | Reason for change |
|---|---|---|
| 1 | 4/12/2012 | Initial version |
| 2 | 18/02/2013 | Correction of editing error and clarification |
| 3 | 19/09/2013 | Clarification, disclaimer |
| | | |