

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

### Mother tincture (*homeopathic stock of herbal origin*) and specific data related to dilutions of the stock lower than the No-Assay-Threshold (NAT)

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Disclaimer:

1. This guidance is based on HMPWG guidance on module 3. It is completed with some [examples or clarifications](#) in order to facilitate the compilation of the module 3 for a homeopathic stock of herbal origin. 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**

#### **3.2.S.1.1 Nomenclature**

"A definition of the homeopathic stock of herbal origin and the homeopathic name (s) should be provided.

- *Binominal scientific name of plant (genus, species, variety and author) and chemotype (where applicable)*
- *State (fresh or dried) and part(s) of the plant*
- *Other names (synonyms)/ **homeopathic names** /Latin names*
- *Reference of the homeopathic manufacturing procedure*
- *Description of vehicles used"*

A monograph of an official Pharmacopoeia of a Member State exists:  
this information is included in the monograph.

A monograph of an official Pharmacopoeia of a Member State does not exist:  
this information including some references has to be provided

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### **3.2.S.1.2 Structure**

Not applicable

### **3.2.S.1.1 General properties**

5 This information is included in the monograph or otherwise has to be provided.

### **3.2.S.2 Manufacture**

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- Intermediate and final dilutions: see the document "dilution".
  - Mother tincture:

#### **3.2.S.2.1 Manufacturer**

15 *"The name, address, and responsibility of each supplier of the raw material, each manufacturer of the mother tincture, and each proposed production site or facility involved in manufacturing/collection and testing should be provided".*

20 Concerning each supplier of the raw material: a document that the supplier respects the good agricultural and collection practice (GACP) should be provided.

If the exhaustive list of the raw material suppliers cannot be mentioned, justification is needed and a Risk Management/Risk Assessment plan should be provided:

25 Concerning the quality of the raw material, the applicant should always ensure that:

- the raw material complies with the Ph.Eur monograph 2045 (Herbal drugs for homoeopathic preparations).
- the risk of possible contaminants is assessed and that this risk is appropriately managed (and eventually adapted in function of the individual suppliers) = RA/RM
  - \* On which level are the tests done? Why?
  - \* Which tests are done? Why?
  - \* What is the testing frequency? Why?

35 Depending on the case, e.g. when the origin of the raw material is not well known or e.g. if the cultivation/collection/storage/... are insufficiently documented, this risk assessment and risk management have to be done based on other criteria.

All these variable factors should be covered in the data provided to the FAMHP within the framework of this dossier.

40 If, taking into account the variability in availability of the herbal drug, the Applicant needs to have several suppliers thereof and he wishes to get a supplier authorized - within the framework of a medicinal product dossier for authorization or registration - for which not all information is readily available, all RA/RM data – as described above - have to be submitted for evaluation. The Applicant should, when providing these data, take into account the quality guidelines relating to herbal drugs as published on the EMA-website:

45 <http://www.ema.europa.eu/htms/human/humanguidelines/quality.htm#herbal>

50 Concerning each manufacturer of the mother tincture: GMP certificate(s) should be provided.

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

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

"The description of the homeopathic stock represents the applicant's commitment for the manufacture of the homeopathic stock. Information should be provided to adequately describe the manufacturing process and process controls. For example:

5 A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents/vehicles, reagents (if applicable), critical steps and the controls that are intended to result in the routine and consistent production of the mother tincture. A flow chart of the manufacturing process should be included. Reference should be made to the appropriate section of a European Pharmacopoeia, or in absence thereof, to a homeopathic manufacturing procedure described in an official Pharmacopoeia of a Member State of the European Union.

10 The different stages of the preparation of the mother tincture must be sufficiently described to allow the assessment of the consistency of the quality. The material, processes and specific precautions (light, moisture, miscellaneous contamination, and temperatures) must be described".

Reference to a monograph is not enough. Manufacturing procedure has to be provided.

20 Maceration time:

The applicant has to follow the prescriptions of the Ph. Eur. monographs but also has to detail the different stages of the preparation of the homeopathic stocks. In order to guarantee the reproducibility of the quality as asked by the Ph Eur, the applicant is asked to specify the maceration time taking into account the specific nature of the raw material/ the stock or if not possible a larger range has to be justified mentioning the factors on which the maceration time depends and as reflected by appropriate IPC (e.g. when maceration of 10 days is carried out, when maceration of 20 days is carried out and when maceration of 30 days is carried out).

25 The applicant is reminded that the Ph. Eur. monograph "Methods of preparation of homeopathic stocks and potentisation" mentions that "Maceration may be replaced by long maceration (maximum 60 days) or very long maceration (maximum 180 days), provided it is demonstrated by appropriate data that the quality of the resulting mother tincture is the same as that of the mother tincture prepared by maceration".

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

"The information on the raw material and the solvents/reagents or vehicles used for the homeopathic stock and final dilutions preparation should be presented".

40 Solvents/reagents:

The certificates of analysis of ethanol and purified water used for the preparation of the mother tincture should be provided in this section.

45 Raw materials:

"The state (e.g. fresh, dried) of the material used and, where applicable, information on pharmacological active, toxic constituents or marker compound(s)<sup>1</sup>, if applicable, should be provided. Additionally a macroscopic and microscopic description<sup>2</sup> of the raw material should be presented".

50 <sup>1</sup> "information on pharmacological active, toxic constituents or marker compound(s)": this information should be provided when the raw material is not described in a monograph or when the raw material contains toxic constituents.

55 <sup>2</sup> "a macroscopic and microscopic description": this information should be provided when the raw material is not described in a monograph or when the monograph is not enough to detect a falsification of the supplied raw material.

Supportive data should be provided:

- 5 • "Name and address of the supplier and supplier commitment and/or manufacturer and manufacturer's commitment , if different from the applicant
- Data on the origin/source of the material
- Synthetic or manufacturing route
- Production:
  - 10 - Natural state of plant (wild or cultivated)
  - Harvesting location, time of harvesting and, if possible, stage of vegetation
  - Conditions of cultivation
  - Information on pre or post harvest treatment
  - Processing, where applicable
  - Duration and conditions of storage"

#### 15 **3.2.S.2.4 Control of critical steps and intermediates**

The applicant is asked to provide the acceptance criteria of all manufacturing parameters with a range of numerical values, when applicable.

20 Manufacturing parameters concerning the maceration process: size of cut raw material, manufacturing formula, mixing conditions, maceration time, filter size...

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

To be completed if any reference to an official monograph cannot be made.

#### 25 **3.2.S.2.6 Manufacturing process development**

To be completed if any reference to an official monograph cannot be made.

### **3.2.S.3 Characterisation**

#### 30 **3.2.S.3.1 Elucidation of structure and other characteristics**

To be completed with relevant information.

#### **3.2.S.3.2 Impurities**

To be completed.

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

#### **3.2.S.4.1 Specifications**

1) **Raw material:**

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**\*If a monograph exists:**

Specifications	Acceptance criteria
<b>IDENTIFICATION</b>	
<b>Macroscopic descriptions</b>	See individual monograph
Microscopic descriptions	See individual monograph
Further tests can be required (ex: thin-layer chromatography)	See individual monograph
<b>TESTS</b>	
<b>Foreign matter</b> (2.8.2)	See individual monograph
<b>Loss on drying</b> (2.2.32)	See individual monograph
Adulteration	See individual monograph
Pesticides (2.8.13)	compliance with the requirements for pesticide residues
Heavy metals (2.4.27)	<i>cadmium</i> : maximum 1.0 ppm; <i>lead</i> : maximum 5.0 ppm; <i>mercury</i> : maximum 0.1 ppm (unless otherwise indicated in the monograph)
Aflatoxins (2.8.18)	not more than 2 µg/kg of aflatoxin B <sub>1</sub> 4 µg/kg for the sum of aflatoxins B <sub>1</sub> , B <sub>2</sub> , G <sub>1</sub> and G <sub>2</sub> (unless otherwise indicated in the monograph)
Radioactive contamination	compliance with the requirements for radioactive contamination
Microbiological quality	TAMC: ≤ 10 <sup>7</sup> CFU/g TYMC: ≤ 10 <sup>5</sup> CFU/g Escherichia coli: ≤ 10 <sup>3</sup> CFU/g Salmonella: absence (25g)
<b>ASSAY</b>	See individual monograph

10 This table is an example. According to the monograph of the raw material, all these specifications are not retaken or other specifications can be required (water (2.2.13), total ash (2.4.16), bitterness value (2.8.15), ochratoxin A(2.8.22),...)

15 Foreign matter: The maximum content of foreign matter is indicated in the individual monograph.

20 Loss on drying: This test is carried out on dried herbal drugs.  
If a fresh plant is processed more than 24 h after harvesting, a test for loss on drying should be carried out.  
The minimum limit is indicated in the individual monograph.

- 5 Pesticides and heavy metals: Where justified\*\*, these tests may be performed on the mother tincture according to the requirements of the general monograph "Mother tinctures for homoeopathic preparations (2029)".
- 10 Radioactive contamination: In some specific circumstances, the risk of radioactive contamination is to be considered. Where justified\*\*, this test may be performed on the mother tincture
- 15 Microbiological quality, Aflatoxins: these tests can be required in some cases (dried raw material,..)
- 15 Assay: Where applicable, herbal drugs for homoeopathic preparations are assayed by an appropriate method. An assay is required for all raw materials containing a toxic substance, and in this case a maximal limit should be fixed (link with module 4).
- 20 \*\*for example: fresh raw material having to be processed less than 24 h after harvesting.
- 25 Pesticides, heavy metals and radioactive contamination:
  - it is acceptable not to perform tests if raw material from biological agriculture (organic certification has to be provided).
  - Without the precise information concerning the place of origin of the raw material, it is impossible to know if the soil is not contaminated by (persistent) pesticides, heavy metals or radioactivity. Therefore if the needed information cannot be provided, pesticides, heavy metals and radioactivity tests should be retaken in the specifications of the raw material and should be carried out in routine (see risk assessment/risk management plan).
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- 35 **\*If a monograph does not exist:**  
To be completed on the basis of bibliographic references and laboratory data, and taking into account Ph. Eur. requirements (see monograph Herbal drugs for homoeopathic preparations, 2045).
- 40

2) **Mother tincture:**

**\*If a monograph exists:**

Specifications	Acceptance criteria
IDENTIFICATION Where applicable, at least 1 chromatographic identification test is carried out.	See individual monograph
TESTS <b>Relative density</b> (2.2.5)	See individual monograph
<b>Ethanol</b> (2.9.10)	See individual monograph
<b>Methanol and 2-propanol</b> (2.9.11)	See individual monograph
<b>Dry residue</b> (2.8.16)	See individual monograph
Pesticides* (2.8.13) and Heavy metals* (2.4.27)	Limits will be set, taking into consideration the nature and the origin of the herbal drug. The dilution factor of the mother tincture and the limit of detection of the method are also taken into account when fixing these limits.
Radioactive contamination*	compliance with the requirements for radioactive contamination
Microbiological quality (5.1.4/5.1.8)	compliance with the requirements for microbiological quality
ASSAY	See individual monograph

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This table is an example.

\*when not performed on the raw material

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Methanol and 2-propanol: tests have to be performed because maceration process can be responsible for the formation thereof.

Relative density and ethanol: If the test for relative density is carried out, the test for ethanol need not be carried out, and vice versa.

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Assay: Where applicable, an assay with quantitative limits is performed.

An assay should be required for all mother tinctures containing a toxic substance, and in this case a maximal limit should be fixed (link with module 4).

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Microbiological quality:

The no routine testing for microbiological quality has to be justified by use the suitable decision tree of the note for guidance specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances (CHMP/ICH/367/96).

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\* Ethanol is scientifically accepted to be bactericidal in aqueous mixtures at concentrations between 60-95% v/v and the optimum concentration

is generally considered to be 70 % v/v. Ethanol is however ineffective against bacterial spores and has a poor penetration of organic matter (see Ref. EMEA/531300/2008 and EMA/HMPC/41500/2010) ⇒ no routine test is justified.

- 5 \* For mother tincture with ethanol content between > 20 % (v/v) and < 60 % (v/v): perform the test for efficacy of antimicrobial preservation and use the suitable decision tree in order to justify a skip testing.

**\*If a monograph does not exist:**

- 10 To be completed on the basis of bibliographic references and laboratory data, and taking into account Ph. Eur. requirements (see monograph Mother tinctures for homoeopathic preparations, 2029).

3) **Dilutions:**

- 15 Dilutions below the NAT:  
See the section 3.2.S.7 Stability

- Dilutions above the NAT:  
See the generic dossier "dilution".

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**3.2.S.4.2 Analytical procedures**

To be completed if any reference to an official monograph cannot be made.

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

- 25 To be completed if any reference to an official monograph cannot be made.

**3.2.S.4.4 Batch analysis**

Description of batches and results of batch analysis should be provided for raw material and mother tincture.

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If the exhaustive list of suppliers cannot be provided (see 3.2.S.2.1), the applicant is asked to annex to each certificate of analysis of the raw material, the supportive data concerning the supplier, the geographical origin and the risk analysis/risk management plan.

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

To be completed if any reference to an official monograph cannot be made.

40 **3.2.S.5 Reference standards or materials**

Information (supplier and supplier reference) on the reference standards or materials used for example the TLC and the assay of the raw material and the mother tincture should be provided.

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

Description of container closure system(s) used for storage of the raw material and the mother tincture should be provided. The combination of the container closure specifications and the raw material/mother tincture stability data may be sufficient to demonstrate suitability of the container closure system for storage of the raw material/mother tincture.

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

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The relation between the provided data and the bottles used for storage and stability studies has to be established.



### **3.2.S.7 Stability**

For each batch used for the stability study, the batch size and the type of container closure system including its size have to be mentioned.

#### **1) Raw material:**

Stability data or re-testing may also be required for the raw material that is not processed immediately after testing. This is the case for dried raw material that is stored before use.

#### **2) Mother tincture:**

Stability data of the mother tincture and the final dilution should be provided. For the final dilution, see the document "dilution".

#### **General requirements:**

- According to the guideline on stability testing: stability testing of existing active substances and related finished products (CPMP/QWP/122/02), the stability studies should be conducted on the active substance packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.
- According to the note for guidance on bracketing and matrixing designs for stability testing of drug substances and drug products (CPMP/ICH/4104/00), the various characteristics of the container closure system may affect product stability. These characteristics include especially surface area to volume ratio and headspace to volume ratio.

Usually if different sizes of bottles are used for the storage, the note for guidance on bracketing and matrixing designs for stability testing of drug substances and drug products (CPMP/ICH/4104/00) should be followed.

According to this note: "*Bracketing can be applied to studies of the same container closure system where either container size or fill varies while the other remains constant. However, if a bracketing design is considered where both container size and fill vary, it should not be assumed that the largest and smallest containers represent the extremes of all packaging configurations. Care should be taken to select the extremes by comparing the various characteristics of the container closure system that may affect product stability. These characteristics include container wall thickness, closure geometry, surface area to volume ratio, headspace to volume ratio, water vapour permeation rate or oxygen permeation rate per dosage unit or unit fill volume, as appropriate*".

Concerning glass bottles and screw caps of the same supplier, the same type, the same colour, the same range but of different volume:

According to the previous documents, a long term stability study (and an accelerated stability study) should be performed on the smallest and the biggest bottles in order to accept as storage container closure system all documented glass bottles of this range with a volume included in the studied volume range.

Nevertheless a stability study concerning only the worst-case scenario (usually the smallest bottle used for storage of the mother tincture including, if applicable, the bottle used for storage of the mother tincture in the dilution library) could be accepted if characteristics of each container closure systems used in the stability study are provided. Concerning the mother tincture stored in glass bottles, two characteristics have to be taken into account: the surface area to volume ratio and the headspace to volume ratio. These two characteristics are also the ones to take into account and to be compared if it is envisaged to change the bottle brand.

Concerning stainless steel container:

Use of additional stripes of stainless steel in glass bottles cannot be accepted as such as a method to simulate the storage in stainless steel containers but can be performed to demonstrate the compatibility of stainless steel with the mother tincture.

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After it has been demonstrated that glass and stainless steel could be considered both as inert materials for the storage of a particular MT, these stainless steel containers could be accepted if their characteristics (surface area to volume ratio and headspace to volume ratio) are provided and if the worst-case scenario for glass bottle is also applicable to the stainless steel containers.

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Results of the retests performed on different batches of different mother tinctures stored in stainless steel containers can also be considered as suitable data proving the stability of the mother tincture in these containers.

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**3) Dilutions:**

Dilutions below the NAT:

Stability data or a relevant rationale should be provided:

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:

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- 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.

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Dilutions above the NAT:

See the generic dossier "dilution".

the dilutions/triturations higher than the No-Assay-Threshold cannot have an expiry date that exceeds the expiry date of the stock.

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**35 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](http://www.hma.eu/uploads/media/HMPWG_dossier_guidance_mod3.pdf))

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**History**

Version	Date of application	Reason for change
1	4/12/2012	Initial version
2	18/02/2013	Correction of editing error (tables)
3	19/09/2013	Disclaimer, clarification, correction reference guideline EMEA/531300/2008

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