Overview on requirements for manufacturing methods and dosage forms of homoeopathic medicinal products

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Overview

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    1. Structure
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    1. Homeopathic preparations (1038)
    2. The general dosage form monographs
    3. Pharmaceutical preparations (2619)

The homoeopathic section of the Ph.Eur. addresses particularities of homoeopathic medicinal products

Acidum picrinicum for homoeopathic preparations 2695
Agaricus phalloides for homoeopathic preparations 2290
Allium sativum for homoeopathic preparations 2023
Anacardium for homoeopathic preparations 2094
Apis for homoeopathic preparations 2024
Arsenicum album for homoeopathic preparations 1599
Aurum chloratum natronatum for homoeopathic preparations 2141
Barium chloratum for homoeopathic preparations 2142
Belladonna for homoeopathic preparations 2489
Cadmium sulfuricum for homoeopathic preparations 2143
Calcium iodatum for homoeopathic preparations 2144
Cocculus for homoeopathic preparations 2486
Crocus for homoeopathic preparations 1624
Cuprum aceticum for homoeopathic preparations 2146
Cuprum metallicum for homoeopathic preparations 1610
Ferrum metallicum for homoeopathic preparations 2026
Hedera helix for homoeopathic preparations 2092
Herbal drugs for homoeopathic preparations 2045
Histaminum for homoeopathic preparations 2671
Homoeopathic pillules coated 2786
Homoeopathic pillules impregnated 2079
Homoeopathic preparations 1038
Hydrastis canadensis for homoeopathic preparations 2500
Hyoscyamus for homoeopathic preparations 2091
Hypericum for homoeopathic preparations 2028
Ignatia for homoeopathic preparations 2513
Kalium bichromicum for homoeopathic preparations 2501
Magnesium fluoratum for homoeopathic preparations 2676
Magnesium phosphoricum for homoeopathic preparations 2505
Methods of preparation of homoeopathic stocks and potentisation 2371
Mother tinctures for homoeopathic preparations 2029
Nux-vomica for homoeopathic preparations 2514
Petroleum rectificatum for homoeopathic preparations 2683
Pillules for homoeopathic preparations 2153
Staphysagria for homoeopathic preparations 2289
Sulfur for homoeopathic preparations 2515
Urtica dioica for homoeopathic preparations 2030

Blue : Individual monograph
Red : General monograph

The general monograph «methods of preparation of homoeopathic stocks and potentisation» provides general aspects and specific procedures

Introduction:

- **Homoeopathic stocks are prepared, using suitable methods, from raw materials that comply with the requirements of the monograph Homoeopathic preparations (1038).** The methods described below, combined with established methods for potentisation, **are examples of methods**, but other methods described in an official national pharmacopoeia of a Member State may equally be used.
- Where material of animal or human origin is to be used, particular reference is made to the **requirements concerning the use of such raw material of zoological or human origin in the monograph Homoeopathic preparations (1038).**
- In the preparation of liquid dilutions, the ethanol of the concentration prescribed in the method may, if necessary, be replaced by ethanol (36 per cent *V/V*) or ethanol (18 per cent *V/V*).

The general monograph «methods of preparation of homoeopathic stocks and potentisation» provides general aspects and specific procedures (contin'd)

- When the individual monograph allows that the mother tincture be prepared from more than one plant species, the mother tincture can be prepared from the specified parts of an individual plant species or from any mixture thereof. If for the preparation of a mother tincture the loss on drying has to be determined, the herbal drug or mixture of herbal drug with ethanol has to be processed immediately after the value of the loss on drying has been determined.
- Unless otherwise stated, mother tinctures are prepared by **maceration lasting 10-30 days.**
- Maceration may be replaced by **long maceration (maximum 60 days)** or **very long maceration (maximum 180 days)**, provided it is demonstrated that the quality of the resulting mother tincture is the same as that of the mother tincture prepared by maceration.
- Unless otherwise stated in the individual monograph, the term 'part(s)' denotes **'mass part(s)'**. Unless otherwise stated in the method, the **maximum temperature for the preparation is 25 °C**.

Structure of 2371

Introduction

1. MOTHER TINCTURES AND LIQUID POTENTISATIONS
   - METHOD 1.1. HYDROALCOHOLIC MOTHER TINCTURES PREPARED **WITHOUT HEATING**
   - METHOD 1.2. HYDROALCOHOLIC MOTHER TINCTURES PREPARED **WITH HEATING**
2. GLYCEROL MACERATES
3. LIQUID DILUTIONS
4. TRITURATIONS
5. OTHER PREPARATIONS

The differences between the methods in (2371) arise from the different traditions: Comparison of methods 1.1.3 and 1.1.10

METHOD 1.1.3 (HAB 2a: MOTHER TINCTURES AND LIQUID DILUTIONS)	METHOD 1.1.10 (FRENCH PHARMACOPOEIA)
• used for fresh herbal drugs containing generally less than 70 per cent of expressed juice and more than 60 per cent moisture (loss on drying) and no essential oil or resin.	• Generally used for herbal drugs: Fresh or dried, as specified in the individual monograph
• Mother tinctures (approximate ethanol content of 50 per cent *V/V)* prepared by maceration	• Mother tinctures prepared by maceration
• Herbal drug is comminuted.	• Herbal drug is comminuted
• Loss on drying (2.2.32) is determined. Unless otherwise prescribed, determine the loss on drying on 2.00-5.00 g of the comminuted herbal drug and dry at 105 °C for 2 h.	• Loss on drying (2.2.32) at 105 °C for 2h or water content is determined (2.2.13).

Comparison of methods 1.1.3 and 1.1.10 (contin'd)

METHOD 1.1.3 (HAB 2a: MOTHER TINCTURES AND LIQUID DILUTIONS)	METHOD 1.1.10 (FRENCH PHARMACOPOEIA)
• To the comminuted herbal drug immediately add not less than half the mass of ethanol (90 per cent *V/V*) and allow to stand in well-closed containers. • Use the following expression to calculate the amount (A_2), in kilograms, of ethanol (90 per cent *V/V*) required for the mass (*m*) of raw material, then subtract the amount of ethanol (90 per cent *V/V*) already added and add the difference to the mixture. A_2=m x T/ 100 m=mass of raw material, in kilograms; T=percentage loss on drying of the sample. • Allow to stand for not less than 10 days, swirling from time to time, then express the mixture and filter the resulting liquid.	• This value is taken into account to calculate and produce a 1 in 10 mother tincture (1:10 mother tincture) with a suitable ethanol content, using comminuted herbal drug and ethanol of the appropriate concentration. Other ratios than 1 in 10 may be prescribed in the individual monographs. • Allow to macerate for at least 10 days, with sufficient shaking. • Separate the residue from the ethanol and strain under pressure if necessary. Allow the combined liquids to stand for 48 h and filter.

Comparison of methods 1.1.3 and 1.1.10 (contin'd)

METHOD 1.1.3 (HAB 2a: MOTHER TINCTURES AND LIQUID DILUTIONS)	METHOD 1.1.10 (FRENCH PHARMACOPOEIA)
• Adjustment to any value specified in the individual monograph: Determine the percentage dry residue (2.8.16) or, where prescribed, the percentage assay content of the above-mentioned filtrate. Calculate the amount (A_1), in kilograms, of ethanol (50 per cent V/V) required, using the following expression: $A_1 = m \times (N_x - N_0)/N_0$ m =mass of filtrate, in kilograms; N_0 = percentage dry residue or percentage assay content as required in the individual monograph; N_x = percentage dry residue or percentage assay content of the filtrate. • Mix the filtrate with the calculated amount of ethanol (50 per cent V/V). Allow to stand for not less than 5 days, then filter if necessary.	• For mother tinctures with a required assay content, adjustment may be carried out, if necessary, by adding ethanol of the same concentration as used for the preparation of the tincture.

Comparison of methods 1.1.3 and 1.1.10 (contin'd)

METHOD 1.1.3 (HAB 2a: MOTHER TINCTURES AND LIQUID DILUTIONS)	METHOD 1.1.10 (FRENCH PHARMACOPOEIA)
Potentisation • The 1st 'decimal' dilution (D1) is made from: 2 parts of the mother tincture; 8 parts of ethanol (50 per cent *V/V*). • The 2nd decimal dilution (D2) is made from: 1 part of the 1st 'decimal' dilution; 9 parts of ethanol (50 per cent *V/V*). (…)	Potentisation • The 1st decimal dilution (D1) is made from: 1 part of the mother tincture; 9 parts of ethanol of the appropriate concentration. (…)
• The 1st 'centesimal' dilution (C1) is made from: 2 parts of the mother tincture; 98 parts of ethanol (50 per cent *V/V*). • The 2nd centesimal dilution (C2) is made from: 1 part of the 1st 'centesimal' dilution; 99 parts of ethanol (50 per cent *V/V*). (…)	• The 1st centesimal dilution (C1) is made from: 1 part of the mother tincture; 99 parts of ethanol of the appropriate concentration. (…)

«Homeopathic preparations» (1038) describes some homoeopathic dosage forms

Dosage forms

A dosage form of a homoeopathic preparation **complies with any relevant dosage form** monograph in the European Pharmacopoeia, **and with the following**:

- for the purpose of dosage forms for homoeopathic use, 'active substances' are considered to be 'dilutions or triturations of homoeopathic stocks' or 'homoeopathic stocks' (in case of a mother tincture or a glycerol macerate);
- these dosage forms can contain one or more 'active substances';
- they are prepared using appropriate excipients.

Homoeopathic dosage form 'pillule'

Pillules for homoeopathic use are solid preparations obtained from sucrose, lactose or other suitable excipients. (…)

- Existing monographs in the homoeopathic section: Pillules for homoeopathic preparations (2153), Homoeopathic pillules, impregnated (2079), Homoeopathic pillules, coated (2786).

«Homeopathic preparations» (1038) describes some homoeopathic dosage forms *(contin'd)*

- ***Homoeopathic dosage form 'tablet'***

  Tablets for homoeopathic use are solid preparations obtained from sucrose, lactose or other suitable excipients according to the monograph Tablets (0478). They may be prepared either by **compressing one or more 'active substances' with the excipients or by impregnating preformed tablets** with one or more liquid 'active substances'. The preformed tablets for impregnation are obtained from sucrose, lactose or other suitable excipients according to the monograph Tablets (0478). Tablets for homoeopathic use are intended for **sublingual or oral use**.

- ***Homoeopathic dosage forms 'parenteral preparation', 'eye preparation', 'nasal preparation'***

  For the last potentisation step(s), an ethanol-free vehicle is used to minimise the content of ethanol in the final preparation. The residual ethanol content (2.9.10) is not greater than 1 per cent *V/V* unless otherwise justified and authorised.

- There are some fix combinations of manufacturing methods and corresponding dosage forms (see table 1038.-1). The competent authority has the right to accept or reject particular combinations of manufacturing method and substance.

General monographs for different types of Pillules are covered in the homoeopathic section

Source:www.kidsgo.de

Pillules for homoeopathic preparations (2153):

- «Plain» Pillules which are intended for impregnation or coating
- Quality requirements comprising identification of excipients, tests for uniformity of mass or fineness, Uniformity of impregnation and Microbiological contamination

Impregnated pillules (2079):

- Production section specifies that impregnation takes place in proportions of 1 mass or 1 volume part of liquid to 100 mass parts of pillules
- Tests section requires microbial contamination test

Coated pillules (2786):

- Production section provides methods for coating of «plain» pillules
- Tests section requires Uniformity of mass and microbial contamination test.

Ph. Eur. Dosage form monographs apply to the respective homoeopathic dosage forms: example Liquid preparations for oral use (0672)

DEFINITION

Liquid preparations for oral use are usually solutions, emulsions or suspensions containing one or more active substances in a suitable vehicle; they may, however, consist of liquid active substances used as such (oral liquids). (…)

The vehicle for any preparations for oral use is chosen having regard to the nature of the active substance(s) and to provide organoleptic characteristics appropriate to the intended use of the preparation.

Liquid preparations for oral use may contain suitable antimicrobial preservatives, antioxidants and other excipients such as dispersing, suspending, thickening, emulsifying, buffering, wetting, solubilising, stabilising, flavouring and sweetening agents and colouring matter, authorised by the competent authority. (…)

Where applicable, containers for liquid preparations for oral use comply with the requirements of *Materials used for the manufacture of containers* (3.1 and subsections) and *Containers* (3.2 and subsections). (...)

Ph. Eur. Dosage form monographs apply to the respective homoeopathic dosage forms: example Liquid preparations for oral use (0672) (contin'd)

PRODUCTION

During development of a preparation for oral use whose formulation contains an antimicrobial preservative, the need for and the efficacy of the chosen preservative shall be demonstrated to the satisfaction of the competent authority. A suitable test method together with criteria for judging the preservative properties of the formulation are provided in the text on *Efficacy of antimicrobial preservation* (5.1.3).

During development, it must be demonstrated that the nominal content can be withdrawn from the container, for liquid preparations for oral use presented in single-dose containers.

In the manufacturing, packaging, storage and distribution of liquid preparations for oral use, suitable measures are taken to ensure their microbial quality; recommendations on this aspect are provided in the text on 5.1.4. *Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use*.

In the manufacture of liquid preparations for oral use containing dispersed particles, measures are taken to ensure a suitable and controlled particle size with regard to the intended use.

Ph. Eur. Dosage form monographs apply to the respective homoeopathic dosage forms: example Liquid preparations for oral use (0672) (contin'd)

TESTS

Uniformity of dosage units. Solutions, suspensions and emulsions in single-dose containers comply with the test for uniformity of dosage units (2.9.40) or, where justified and authorised, with the test for uniformity of content or ur g preparations present in the dosage for

"For homoeopathic preparations, the provisions of general chapters 2.9.6 and 2.9.40 are normally not appropriate, however in certain circumstances compliance with these chapters may be required by the competent authority;

Uniformity of content (2.9.6). Unles ose preparations that are suspensions com container as completely as possible an with test B for uniformity of content of single-dose preparations.

Uniformity of mass. Single-dose preparations that are solutions or emulsions comply with the following test: weigh individually the contents of 20 containers, emptied as completely as possible, and determine the average mass. Not more than 2 of the individual masses deviate by more than 10 per cent from the average mass and none deviate by more than 20 per cent.

Ph. Eur. Dosage form monographs apply to the respective homoeopathic dosage forms: example Liquid preparations for oral use (0672) (contin'd)

Dose and uniformity of dose of oral drops. Into a suitable graduated cylinder, introduce by means of the dropping device the number of drops usually prescribed for one dose, or introduce by means of the measuring device the usually prescribed quantity. The dropping speed does not exceed 2 drops per second. Weigh the liquid, repeat the addition, weigh again and carry on repeating the addition and weighing until a total of 10 masses are obtained. No single mass deviates by more than 10 per cent from the average mass. The total of 10 masses does not differ by more than 15 per cent from the nominal mass of 10 doses. If necessary, measure the total volume of 10 doses. The volume does not differ by more than 15 per cent from the nominal volume of 10 doses.

Uniformity of mass of delivered doses from multidose containers (2.9.27). Liquid preparations for oral use supplied in multidose containers comply with the test. Oral drops are not subject to the provisions of this test.

LABELLING

The label states the name of any added antimicrobial preservative.

(...)

Ph. Eur. Dosage form monographs apply to the respective homoeopathic dosage forms: example Liquid preparations for oral use (0672) (contin'd)

Oral drops

DEFINITION

Oral drops are solutions, emulsions or suspensions that are administered in small volumes such as drops by the means of a suitable device.

LABELLING

The label states the number of drops per millilitre of preparation or per gram of preparation if the dose is measured in drops.

(...)

«Overarching» requirements for all pharmaceutical preparations are given in general monograph 2619

INTRODUCTION

"This monograph is intended to be a reference source of standards in the European Pharmacopoeia on active substances, excipients and dosage forms, which are to be applied in the manufacture/preparation of pharmaceuticals, but not a guide on how to manufacture as there is specific guidance available covering methods of manufacture and associated controls. (…)"

Definition section provices the scope:

-licensed preparations

-unlicensed: extemporaneous and stock preparations

Section «ethical considerations and guidance in the preparation of unlicensed pharmaceutical preparations: addresses that a suitable level of risk assessment is undertaken in considering the preparation of an unlicensed pharmaceutical preparation.

«overarching» requirements for all pharmaceutical preparations are given in general monograph 2619 (contin'd)

- PRODUCTION section covers important aspects for Formulation, Active substances and excipients, Microbiological quality, Containers and Stability.
- TESTS section comprises general considerations for pharmaceutical preparations, appearance, identity and purity tests, uniformity requirements and reference standards.

  "re-grouped" uniformity requirements cover important aspect for homoeopathic preparations:

  Uniformity (2.9.40 or 2.9.5/2.9.6). (…) for homoeopathic preparations, the provisions of general chapters 2.9.6 and 2.9.40 are normally not appropriate, however in certain circumstances compliance with these chapters may be required by the competent authority; (…)
- Further sections: ASSAY, LABELLING AND STORAGE, GLOSSARY

Summary

- Quality aspects that are unique for homoeopathic medicinal products are covered in the homoeopathic section of the Ph.Eur. Above this all relevant general Ph.Eur. texts apply.
- The homoeopathic section comprises methods for preparations of homoeopathic stocks and potentisation
  - These methods address the different traditions in Europe. They have been adapted based on the French Pharmacopoeia (Ph. F.) and the German Homoeopathic Pharmacopoeia (HAB)
- In terms of dosage forms, both requirements of the homoeopathic section and the general section of the Ph.Eur. apply, e.g. «Liquid preparations for oral use»
- The general monograph «Pharmaceutical preparations» is a reference sources of standards in the Ph.Eur. on active substances, excipients and dosage forms in the manufacture/preparation of licensed and unlicensed pharmaceutical preparations, comprising homoeopathic medicinal products.

Thank you for your attention.

Source: www.edqm.eu