General concepts in the Ph. Eur.: theory and rationale

General Notices, General Chapters and General Monographs

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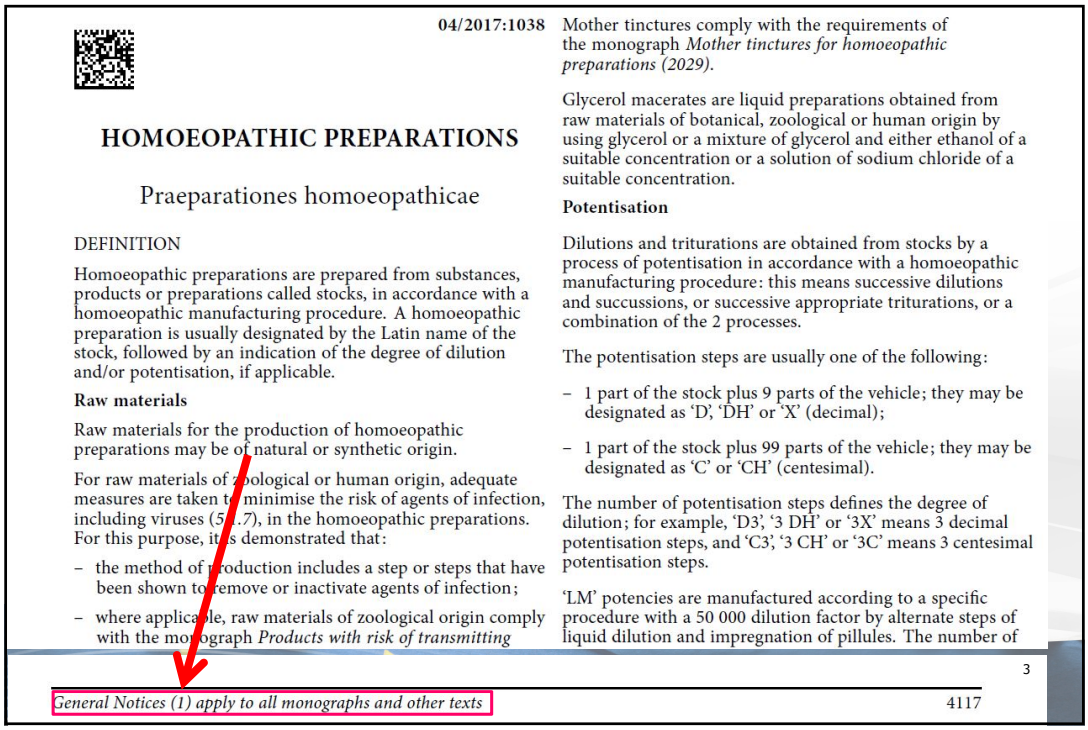
General Notices: Chapter 1 of the Ph. Eur.



04/2017:1038

HOMOEOPATHIC PREPARATIONS

Praeparationes homoeopathicae

DEFINITION

Homoeopathic preparations are prepared from substances, products or preparations called stocks, in accordance with a homoeopathic manufacturing procedure. A homoeopathic preparation is usually designated by the Latin name of the stock, followed by an indication of the degree of dilution and/or potentisation, if applicable.

Raw materials

Raw materials for the production of homoeopathic preparations may be of natural or synthetic origin.

For raw materials of zoological or human origin, adequate measures are taken to minimise the risk of agents of infection, including viruses (5.1.7), in the homoeopathic preparations. For this purpose, it is demonstrated that:

- the method of production includes a step or steps that have been shown to remove or inactivate agents of infection;
- where applicable, raw materials of zoological origin comply with the monograph *Products with risk of transmitting*

Mother tinctures comply with the requirements of the monograph *Mother tinctures for homoeopathic preparations (2029)*.

Glycerol macerates are liquid preparations obtained from raw materials of botanical, zoological or human origin by using glycerol or a mixture of glycerol and either ethanol of a suitable concentration or a solution of sodium chloride of a suitable concentration.

Potentisation

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.

The potentisation steps are usually one of the following:

- 1 part of the stock plus 9 parts of the vehicle; they may be designated as 'D', 'DH' or 'X' (decimal);
- 1 part of the stock plus 99 parts of the vehicle; they may be designated as 'C' or 'CH' (centesimal).

The number of potentisation steps defines the degree of dilution; for example, 'D3', '3 DH' or '3X' means 3 decimal potentisation steps, and 'C3', '3 CH' or '3C' means 3 centesimal potentisation steps.

'LM' potencies are manufactured according to a specific procedure with a 50 000 dilution factor by alternate steps of liquid dilution and impregnation of pillules. The number of

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General Notices (1) apply to all monographs and other texts 4117

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- the method of production includes a step or steps that have been shown to remove or inactivate agents of infection;
- where applicable, raw materials of zoological origin comply with the monograph Products with risk of transmitting agents of animal spongiform encepha
- where applicable, the animals and the tissues used to obtain the raw materials comply with the health requirements of the competent authorities for ani
  consumption;

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General Notices: Knowledge Database

Detailed view of .

Status	In use
Monograph Number	10000
English Name	General notices (1.)
French Name	Prescriptions générales (1.)
Latin Name	
Pinyin Name	
Chinese Name	
Pharmeuropa	
Published in English Supplement	9.2
Published in French Supplement	9.2
On-going	Revision
State of work	0
Pharmeuropa	
Description	Definition of the term "freshly prepared"
Chromatogram	Not available
Additional information	Not available
History	View history
Interchangeable (ICH_Q4B)	NO
International Harmonisation chapter 5.8	NO
Reference standards	
Practical Information	**Test(s)** **Brand Name/Information**
CEP	

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General Notices: View History

SUPPLEMENT 8.2
Chapter revised in order to address the consistency of production approach in the context of reduction of animal testing; and address the utilisation of process analytical technology and/or real-time release testing.

SUPPLEMENT 7.6
Implementation of pharmacopoeial methods: user's responsibility clarified in this respect.
Calculation: provisions for residual solvents introduced in assay calculations (already given in general monograph *Substances for pharmaceutical use (2034)*) for better visibility.

SUPPLEMENT 7.5
Potential adulteration: new section added under *1.4. Monographs*.

SUPPLEMENT 7.4
Indication of permitted limit of impurities: paragraph modified to reflect new way of expressing acceptance criteria.

EDITION 7.0: corrected

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SUPPLEMENT 6.8
Limits: the text has been modified to clarify the interpretation of limits in relation to the rounding rules applied to the values stated in Pharmacopoeial monographs. The new statement clarifies that trailing zeros are considered significant when stated in compendia limits, which is in line with USP and JP practices.
SUPPLEMENT 6.7
Following the creation of the new general chapter *5.1.8. Microbiological quality of herbal medicinal products for oral use*, a definition for 'herbal medicinal product' has been added. The definition is based on Directive 2001/83/ EC of the European Parliament and of the Council of the European Union.
SUPPLEMENT 6.5
1.1. General statements (conventional terms): definitions of a number of terms commonly used in monographs and general chapters are included. These definitions are useful additions to aid interpretation of Ph. Eur. texts.
Medicinal product: the definition is that stated in Directives 2001/82/EC (as amended by Directive 2004/28/EC) and 2001/83/EC (as amended by Directive 2004/27/EC).
Excipient: the term "auxiliary substance" is still mentioned because it is often used in Ph. Eur. monographs.
The definitions have been included in the section Conventional terms. In this context the definitions refer only to terms used in the Ph. Eur. and do not contradict the same terms already defined in national legislation. The definitions will be useful in other fields of activity, for example in anti-counterfeiting documents, since the Council of Europe is wider in geographic scope than the European Union.
Monographs (identification): certain monographs give 2 or more equivalent sets of tests for identification. This concept has been defined and an example is given for illustration. The current system of 1st and 2nd identifications remains. The 2nd identification is for use by pharmacies, and this has been specified.

PUBLICATION 6.0
Quality systems: the statement formerly included under Production has been placed in a slightly modified form as a separate paragraph to give it more prominence.
General monographs: in response to many comments and queries, a paragraph indicating the complementary nature of general and individual monographs has been added.
Validation of pharmacopoeial methods: in response to many comments and queries, a statement has been added on validation of test methods; the methods are accepted by European regulatory authorities as validated so that a simple reference to the monograph is sufficient; there is no explicit statement for users, although it is implicit in regulatory documents; a clear statement has been added; validation by the analyst is not required, unless otherwise stated in the monograph (including any general method referred to).
References to regulatory documents: monographs and general chapters may contain references to regulatory documents (for example EMEA Notes for Guidance - see for example *5.14. Gene transfer medicinal products for human use*); inclusion of these references does not change the status of the documents referred to, nor their scope; an explicit statement to this effect has been added.
Chemical Abstracts Service (CAS) Registry Number: CAS numbers are included in monographs for information in the 6th Edition; the statement included in the General Notices is a condition of use of CAS numbers from the American Chemical Society.
Production: 'Instructions' has been replaced by 'mandatory requirements', since this corresponds better to the contents of the Production sections in monographs and clarifies the status.
Powdered herbal drugs: a statement has been added to cover this new feature of monographs on herbal drugs.
Functionality-related characteristics of excipients: this paragraph has been revised in the light of developments in excipient monographs.
Reference standards: this section has been abbreviated and a reference to the new general chapter *5.12 Reference standards* added.

Conventional terms

Definitions (introduced in supplement 6.5)

- ✓Medicinal product: the definition is that stated in Directives 2001/82/EC (as amended by Directive 2004/28/EC) and 2001/83/EC (as amended by Directive 2004/27/EC).
- ✓Herbal medicinal product
- ✓Active substance
- ✓Excipient (auxiliary substance)

Meanings of terms employed in the pharmacopoeia

- ✓"competent authority"
- ✓"unless otherwise justified and authorised"

➢ **the definitions refer only to terms used in the Ph. Eur. and do not contradict the same terms already defined in national legislation.**

Flexibility in the Ph.Eur. -Alternative methods

- ➢ Ph. Eur. tests are reference methods, essential in cases of dispute.
- ➢ Compliance is required, but alternative methods may be used as long as they lead to the same pass/fail result.
- ➢ It is the responsibility of the user to demonstrate their suitability. Approval of the competent authority is necessary in many cases.

Flexibility in the Ph.Eur. – Waiving of tests

- Compliance to the Ph. Eur. is a prerequisite
- Testing might be omitted based on
  - product design
  - control strategy
  - process validation

As a consequence: Tests for process-specific impurities may be omitted if it is demonstrated that they will not occur with the particular process used.

Identification

- For pharmaceutical industry (excipients, API, medicinal products), tests as described under First identification section shall be performed.
- Community and hospital pharmacies may only perform the tests as described under 2nd identification if all other tests (under Assay and Tests section) have been performed by the manufacturer of the excipient/API (and a respective CoA is available).

Human and veterinary use

- Unless otherwise stated, monographs cover human **and** veterinary use.
- Where a substance is used in both human and veterinary products, the same quality specification is applied.
- When the monograph title bears "for veterinary use" the substance is intended only for veterinary products.

Validation of Pharmacopoeial methods

*"The **test methods** given in monographs and general chapters have been validated in accordance with accepted scientific practice and current recommendations on analytical validation. Unless otherwise stated in the monograph or general chapter, validation of the test methods by the analyst is not required."*

Validation of Pharmacopoeial methods (cont.)

Implementation of pharmacopoeial methods. *When implementing a pharmacopoeial method, the user must assess if and to what extent the suitability of the method under the actual conditions of use needs to be demonstrated according to relevant monographs, general chapters and quality systems.*

Position of the Ph. Eur. with regard to adulteration of drugs

The Ph. Eur. cannot prevent any criminal activity in the field of medicines

However: several incidents have occurred within a short period of time (heparins, melamine, adulteration of glycerol with diethylene glycol) which has lead Ph. Eur. Commission to take a position on this issue

Decision to include a Potential adulteration section in the General Notices

Section: "Potential Adulteration"

- Scope: to help Ph. Eur. users to detect adulterated material
- Method given in "Potential adulteration" section
- Suitable quality systems at all stages of production
- Testing based on risk assessment
- The absence of such section does not imply that attention is not required!

Potential adulteration section in individual monographs

So far, no monograph includes such section (no incident has occured following the introduction of the section in the General Notices)

In case of a future incident, the Ph. Eur. can provide the structure to host such section

General Chapters

Why general chapters?

Chapter 2. Methods of analysis

Editorial convenience: to avoid repeating standard methods in each monograph

Chapter 5. General texts

- ✓ Guidance or recommendations (examples: 5.1.10: Guidelines for using the test for bacterial endotoxins; 5.17: recommendations on methods for dosage forms testing)
- ✓ Non-mandatory quality considerations on classes of products (examples: 5.14: Gene transfer medicinal products for human use)

General chapters

- Not mandatory **"*per se*"**
- When referred to in a monograph, they become part of the standard
- Can be used for substances not covered by monographs, may need validation
- Some general chapters are not referred to in any monograph (2.4.48 Raman spectrometry, Chapter 5.20 Metal catalysts or metal reagent residues): they provide useful guidance and can be referred to in applications

General chapters (cont.)

- Example: Chromatographic separation techniques, 2.2.46
  - ➢ Provides definitions and calculations of common parameters (peak, retention time, resolution etc)
  - ➢ Defines permitted deviations to adjust chromatographic conditions, e. g. composition of mobile phase, column length, particle size etc. without re-validation
  - ➢ Provides general system suitability parameter, not given in the individual monograph, symmetry factor 0.8 to 1.5

General chapters (cont.)

- Recent revisions:
  - Water: micro determination 2.5.32
  - Potentiometric titration 2.2.20
  - Approximate pH of solutions 2.2.4
  - Amperometric titration 2.2.19
  - Potentiometric determination of ionic concentration using ion-selective electrodes 2.2.36
- New (9th edition):
  - **2.8.25 HIGH-PERFORMANCE THIN-LAYER CHROMATOGRAPHY OF HERBAL DRUGS AND HERBAL DRUG PREPARATIONS**

General Monographs

General monographs

- General monographs on classes of substances
  - Quality aspects that cannot be treated in each individual monograph (e.g. residual solvents)
  - Quality aspects that are common to a class of products (e.g. vaccines for human use)
  - Classes defined by different criteria: production method, origin, risk factors (e.g. fermentation, TSE risk)
- General monographs on dosage forms

  General monographs apply to all substances and preparations within the scope of the Definition section of the general monograph

No cross-reference in individual monographs: *Check which monograph applies!*

Substances for pharmaceutical use (2034)

- Definition: *Substances for pharmaceutical use are any organic or inorganic substances that are used as active substances or excipients for the production of medicinal products for human or veterinary use.*
- Requirements laid down in this general monograph apply to all substances for pharmaceutical use whether or not the substance is covered by an individual monograph.
- Consists of the following sections: production, characters, identification, tests, assay, labelling.

Pharmaceutical Preparations (2619)

- 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.
- does not cover investigational medicinal products, but competent authorities may refer to pharmacopoeial standards when authorising clinical trials using investigational medicinal products.

Examples of general monographs of relevance to homoeopathic products

- Pharmaceutical preparations (2619)
- Homoeopathic preparations (1038)
- Herbal drugs for homoeopathic preparations (2045)
- Mother tinctures for homoeopathic preparations (2029)
- Pillules for homoeopathic preparations (2045)
- Homoeopathic pillules, impregnated (2079)
- Homoeopathic pillules, coated (2786)
- Etc…

Relation between General Monographs and General Chapters

Which has priority, a general monograph or an individual monograph?

- Basic principle is that general and individual monographs are complementary and one does not overrule the other.
- Exceptions are clearly indicated either in the general monograph or in the individual one.

Complementarity of general & individual monographs

"General monographs and individual monographs are complementary. If the provisions of a general monograph do not apply to a particular product, this is expressly stated in the individual monograph."

General notices

5.20 Elemental impurities

- will reproduce the essentials of ICH Q3D guideline,
- will be cross-referenced in general monograph 2034,
- will be cross-referenced in general monograph 2619,
- and will become mandatory as from 1st January 2018 (supplement 9.3)

5.1.7 Viral Safety

- Emphasises the importance of carrying out a risk assessment on viral safety of materials of human or animal origin
- Cross reference to 5.1.7 in general monographs on preparations, i.e. homoeopathic preparations, allergens, extracts, immunosera, monoclonal antibodies, products of recombinant DNA technology, vaccines and substances for pharmaceutical use

5.2.8. Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products

- Identical with the EMA Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products –
- 5.2.8 is referred to in General monograph 1483 Products with risk of transmitting agents of animal spongiform encephalopathies

1483 Products with TSE risk

- Implements chapter 5.2.8, which is a transcription of the CPMP/CVMP Note for Guidance (NfG)
- Chapter 5.2.8 is revised when NfG updated
- Compliance with NfG is mandatory via EU directive
- Certification via monograph can be used to demonstrate compliance
- Applies to complete production chain

Take home messages

Before using the Ph. Eur., **please**:

- read the General Notices
- check which general text applies


Thank you for your attention!
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