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Committee on Herbal Medicinal Products (HMPC)

Guideline on quality of herbal medicinal products¹/traditional herbal medicinal products

Final

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¹ Throughout the guideline and unless otherwise specified, the term “herbal medicinal product” includes “traditional herbal medicinal product”.



Explanatory note: This guideline updates the CPMP/CVMP/QWP 'Guideline on quality of herbal medicinal products'. Further to the adoption of Directive 2004/24/EC for traditional herbal medicinal products for human use, the guideline was updated to take account of the newly introduced definitions and responsibilities. In addition, other clarifications and corrections to the existing text were introduced.

There is no expectation that existing herbal medicinal products on the market will be affected by this guideline, with the exception of traditional herbal medicinal products for human use that were already on the market on the entry into force of Directive 2004/24/EC (30 April 2004) for which the competent authorities shall apply the provisions of Directive 2004/24/EC within seven years of its entry into force. For any new marketing authorisation application, this guideline is applicable.

This guideline is also applicable to any traditional use (human) registration application submitted after 30 October 2005, by when Member States shall comply with Directive 2004/24/EC.

Explanatory note on revision 2: Minor corrections updating the CPMP/CVMP/QWP 'Guideline on quality of herbal medicinal products' were introduced, which take into account new and revised guidelines, the European Pharmacopoeia revised general monograph 'Herbals Drugs', as well as new requirements for impurities. Given the nature of this update, a concept paper or public consultation was not required.

Guideline on quality of herbal medicinal products/traditional herbal medicinal products

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1. Introduction

This guideline concerns the application of Module 3 of Annex I to Directive 2001/83/EC as amended for human herbal medicinal products and Part 2 of Annex I to Directive 2001/82/EC as amended for veterinary herbal medicinal products. The special problems of herbal medicinal products and the differences between medicinal products containing chemically defined active substances are described in this document. It should be read in conjunction with the 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products' (EMA/CPMP/QWP/2820/00 and EMA/CVMP/815/00 as revised).

A simplified registration procedure was established for traditional herbal medicinal products for human use under Directive 2004/24/EC. The quality of a herbal medicinal product is independent of its traditional use, therefore all general principles of quality also apply to traditional herbal medicinal products for human use. Traditional herbal medicinal products for human use may additionally contain vitamins or minerals. Concerning these products, this guideline describes specific aspects linked to mixtures of herbal substances/preparations with vitamins and/or minerals. In addition, the quality, specifications and documentation for each vitamin and mineral have to comply with all relevant legislation and guidelines.

Applications should be submitted in the format referred to in the relevant Notice to Applicants, in the relevant volumes of the Rules Governing Medicinal Products in the European Union and the 'Guideline on the use of the CTD format in the preparation of a registration application for Traditional Herbal Medicinal Products' (EMA/HMPC/71049/2007).

2. Scope

This guideline intends to cover the general quality aspects of herbal medicinal products (for human and veterinary use), including traditional herbal medicinal products for human use. Products containing chemically defined isolated constituents or a mixture thereof are not herbal medicinal products.

The guideline should also be read in conjunction with Annex 7 "Manufacture of Herbal Medicinal Products" of Good Manufacturing Practice (GMP) for Medicinal Products, Volume 4, Rules Governing Medicinal Products in the European Union; GMP recommendations should be respected.

Consistent quality for products of herbal origin can only be assured if the starting materials are defined in a rigorous and detailed manner, particularly the specific botanical identification of the plant material used. It is also important to know the geographical source and the conditions under which the herbal substance is obtained to ensure material of consistent quality. The 'Guideline on Good Agricultural and Collection Practice for Starting Materials of Herbal Origin (GACP)' (EMA/HMPC/246816/2005) should also be considered.

3. Qualitative and quantitative particulars of the active substance(s) of a herbal medicinal product

All herbal substances/herbal preparations are essentially defined by their production process and their specifications.

- Standardised herbal substances/herbal preparations are adjusted to a given content of constituents with known therapeutic activity within an acceptable tolerance; standardisation is achieved by adjustment of the herbal substances/herbal preparations with excipients or by blending batches of herbal substances and/or herbal preparations.
- Quantified herbal substances/herbal preparations are adjusted to a defined range of constituents (active markers); adjustment is exclusively achieved by blending batches of herbal substances and/or herbal preparations.
- Other herbal substances/herbal preparations are active substances for which neither constituents with known therapeutic activity nor active markers are known. These herbal substances/herbal preparations are not adjusted to a defined content of analytical marker.

In cases where excipients for the manufacture of active substances are used (e.g. for technological reasons or for adjustment of standardised herbal substances/preparations), the name and the quantity of these excipients have to be stated.

3.1. Herbal substances and herbal preparations consisting of comminuted or powdered herbal substances

For herbal substances and herbal preparations consisting of comminuted or powdered herbal substances the grade of comminution has to be given. Furthermore the following has to be indicated:

(i) in the case of standardisation: the quantity of the herbal substance/preparation shall be given as a range corresponding to a defined quantity of constituents with known therapeutic activity.

(iia) in the case of quantification: the quantity of the herbal substance/preparation shall be stated as a distinct content and the content of the quantified substance(s) shall be specified in a range.

(iib) for all other cases: the quantity of the herbal substance or the quantity of the genuine herbal preparation shall be stated as a distinct content.

Examples

i) Active substance

<u>Name</u>	<u>Quantity</u>
Sennae folium	415-500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as sennoside B

ii) Active substance

<u>Name</u>	<u>Quantity</u>
Salicis cortex	4 g, corresponding to 40 to 48 mg of total phenolic glycosides, expressed as salicin

iib) Active substance

<u>Name</u>	<u>Quantity</u>
Valerianae radix	900 mg

3.2. Herbal preparations produced by steps, which exceed comminution

In the case of a herbal preparation produced by steps which exceed comminution, the nature and concentration of the solvent and the physical state of the extract have to be given. Furthermore the following has to be indicated:

(i) Standardised extracts: the equivalent quantity of the herbal substance x - y (*), or the ratio (a - b): 1 (*) of the herbal substance to the genuine herbal preparation shall be stated and the quantity of the genuine herbal preparation may be given as a range corresponding to a defined quantity of these constituents (see example).

(iia) Quantified extracts: the equivalent quantity of the herbal substance x - y (*), or the ratio (a - b): 1 (*) of the herbal substance to the genuine herbal preparation shall be stated and the quantity of the genuine herbal preparation has to be given as a distinct content. Furthermore content of the quantified substance(s) shall be specified in a range.

(iib) Other extracts: the equivalent quantity of the herbal substance x - y (*), or the ratio (a - b): 1 (*) of the herbal substance to the genuine herbal preparation shall be stated and the quantity of the genuine herbal preparation has to be given as a distinct content.

*) 'a' and 'b' or 'x' and 'y' have to be justified by the applicant

The composition of any extraction solvent or extraction solvent mixture and the physical state of the extract must be indicated. If any other substance is added during the manufacture of the herbal preparation to adjust the preparation to a defined content of constituents with known therapeutic activity, or for any other purpose, the added substance must be mentioned as an "other substance" and the genuine extract as the "active substance".

However, where different batches of the same extract are used to adjust constituents with known therapeutic activity to a defined content, or, for any other purpose, the final mixture shall be regarded as the genuine extract and listed as the "active substance" in the unit formula. Full details of production and control must however be provided in the dossier.

Examples

i) Active substance

<u>Name</u>	<u>Quantity</u>
Sennae folium dry extract ethanolic 60% (V/V) ((a - b): 1)	50-65 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as sennoside B

or

Active substance

<u>Name</u>	<u>Quantity</u>
Sennae folium dry extract ethanolic 60% (V/V) (equivalent to x - y mg Sennae folium)	50-65 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as sennoside B

ii) Active substance

<u>Name</u>	<u>Quantity</u>
Ginkgo folium dry extract acetonetic 60% (V/V) ((a - b): 1)	60 mg, containing 13.2-16.2 mg of flavonoids expressed as flavone glycosides, 1.68 - 2.04 mg of ginkgolides A, B & C,

and 1.56 - 1.92 mg of bilobalide

or

Active substance

<u>Name</u>	<u>Quantity</u>
Ginkgo folium dry extract acetonic 60% (V/V) (equivalent to x - y mg Ginkgo folium)	60 mg, containing 13.2-16.2 mg of flavonoids expressed as flavone glycosides, 1.68 - 2.04 mg of ginkgolides A, B & C, and 1.56 - 1.92 mg of bilobalide

iib) Active substance

<u>Name</u>	<u>Quantity</u>
Valerianae radix dry extract ethanolic 60% (V/V) ((a - b) : 1)	125 mg

or

<u>Name</u>	<u>Quantity</u>
Valerianae radix dry extract ethanolic 60% (V/V) equivalent to x - y mg Valerianae radix	125 mg

4. Description of the method of preparation of the herbal medicinal product

The manufacturing process, within the meaning of this section, is the preparation of the herbal medicinal product from herbal substance(s) and/or herbal preparation(s). In the case of traditional herbal medicinal products for human use, the manufacturing process, within the meaning of this section, is the preparation of the herbal medicinal product from herbal substance(s) and/or herbal preparations and/or vitamins and/or minerals.

The description should include details of the process together with the controls exercised. This section should be in accordance with the 'Note for guidance on manufacture of the finished dosage form' (CPMP/QWP/486/95)/'Note for guidance: manufacture of the finished dosage form' (EMA/CVMP/126/95). If herbal preparations are the starting material, the manufacture of the herbal preparations and their controls should not be located under this section but under the section entitled "Control of starting materials".

Information on development pharmaceuticals and process validation should also be provided in accordance with the 'Note for guidance on development pharmaceuticals' (EMA/CPMP/QWP/155/96), the 'Note for guidance on Pharmaceutical Development (EMA/CHMP/167068/2004), the 'Note for guidance: development pharmaceuticals for veterinary medicinal products' (EMA/CVMP/315/98) and the 'Note for guidance on process validation' (EMA/CPMP/QWP/848/96 and EMA/CVMP/598/99).

5. Control of starting materials

5.1. Control of herbal substances and of herbal preparations

This section should be in accordance with the 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products' (EMA/CPMP/QWP/2820/00 and EMA/CVMP/815/00 as revised).

Control of herbal substances

A comprehensive specification for each herbal substance must be submitted. This also applies if the applicant is not the manufacturer of the herbal substance. If the starting material is a herbal preparation, e.g., in the case of fatty or essential oils used as active substances of herbal medicinal products, a specification for the herbal substance is required, unless fully justified. The binomial scientific name of the plant (genus, species, variety and author), chemotype (where applicable) and name of its parts, have to be stated.

If no monograph for the herbal substance is given in a Pharmacopoeia referred to in Annex I of Directives 2001/83/EC or 2001/82/EC as amended, a comprehensive specification for the herbal substance must be supplied and should be set out in the same way where practicable, as the monographs on herbal substance in the European Pharmacopoeia. Information on the site of collection, the time of harvesting and stage of growth, treatment during growth with pesticides etc, and drying and storage conditions should be included, if possible. The comprehensive specification should be established on the basis of recent scientific data. In the case of herbal substances with constituents of known therapeutic activity, assays of their content (with the test procedures) are required. The content must be included as a range, so as to ensure reproducibility of the quality of the herbal medicinal product. In the case of herbal substances where constituents of known therapeutic activity are not known, assays of marker substances (with the test procedures) are required. The choice of markers should be justified.

As a general rule, herbal substances must be tested, unless otherwise justified, for microbiological quality, for mycotoxins (aflatoxins, ochratoxin A), and for residues of pesticides and fumigation agents, toxic metals, likely contaminants and adulterants, etc. The use of ethylene oxide is prohibited for the decontamination of herbal substances². Radioactive contamination should be tested for if there are reasons for concerns. Specifications and descriptions of the analytical procedures must be submitted, together with the limits applied. Analytical procedures not given in a Pharmacopoeia should be validated in accordance with the ICH 'Note for guidance on Validation of analytical procedures: text and methodology' (CPMP/ICH/381/95) or the corresponding VICH guidelines (CVMP/VICH/590/98 and CVMP/VICH/591/98), unless otherwise justified.

Reference samples of the herbal substances must be available for use in comparative tests e.g. macro- and microscopic examination, chromatography etc.

Control of herbal preparations

If the herbal medicinal product contains a preparation, rather than merely the herbal substance itself, the comprehensive specification for the herbal substance must be followed by a description and validation of the manufacturing process for the herbal preparation. This also applies if the applicant is not the manufacturer of the herbal preparation. The information may be supplied either as part of the marketing authorisation application or by using the European Active Substance Master File procedure. If the latter route is chosen, the documentation should be submitted in accordance with the 'Guideline on active substance master file procedure' (EMA/CPMP/QWP/227/02 and EMA/CVMP/134/02 as revised).

Where the preparation is the subject of a European Pharmacopoeia monograph, the EDQM Certification procedure (for Certificates of Suitability, CEPs) can be used to demonstrate compliance with the relevant Ph. Eur. monograph.

² European Pharmacopoeia monograph on Herbal Drugs (1433)

For each herbal preparation, a comprehensive specification is required. This should be established on the basis of recent scientific data and should give particulars of the characteristics, identification tests and purity tests. Appropriate chromatographic methods should be used. If deemed necessary by analysis of the starting material, tests on microbiological quality, mycotoxins (aflatoxins, ochratoxin A), residues of pesticides and fumigation agents, toxic metals and solvents should be performed. Radioactivity should be tested if there are reasons for concern. A quantitative determination (assay) of substances with known therapeutic activity or of markers is also required. For standardised herbal preparation, the content of constituents with known therapeutic activity must be indicated with the lowest possible tolerance (with both upper and lower limits). In the case of active markers used for quantified extracts the content of the markers has to be given as a defined range. In the case of an analytical marker of an extract for which neither constituents of known therapeutic activity, nor active markers are known, the specified minimum and maximum content is related to the validated analytical range as a base for analytical suitability within the frame of batch related control. The test methods should be described in detail.

If preparations from herbal substances with constituents of known therapeutic activity are standardised (i.e. adjusted to a defined content of constituents with known therapeutic activity) it should be stated how such standardisation is achieved. If another substance is used for these purposes, it is necessary to specify as a range the quantity that can be added.

5.2. Control of vitamins and minerals (if applicable)

Vitamin(s) and mineral(s), which could be ancillary substances in traditional herbal medicinal products for human use, should fulfil the requirements of the 'Guideline on summary of requirements for active substances in the quality part of the dossier' (CHMP/QWP/297/97 as revised).

5.3. Control of excipients

Excipients, including those added during the manufacture of the herbal preparations, should be described according to the 'Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product' (Eudralex 3AQ 9A), the 'Guideline on excipients in the dossier for application for marketing authorisation of medicinal products' (CHMP/QWP/396951/06), or the 'Note for guidance on excipients in the dossier for application for marketing authorisation of veterinary medicinal products' (EMA/CVMP/004/98), as appropriate. For novel excipients, the dossier requirements for active substances apply (refer to Directive 2001/83/EC as amended for human medicinal products and Directive 2001/82/EC as amended for veterinary medicinal products).

6. Control tests carried out at an intermediate stage of the manufacturing process of the herbal medicinal product

Details of all control tests, with details of test procedures and limits applied at any intermediate stages of the manufacturing processes, are required especially if these tests cannot be performed on the herbal medicinal product.

7. Control tests on the herbal medicinal product

This section should be in accordance with the 'Guideline on specifications and control tests on the finished product' (Eudralex 3AQ 11A), the 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal

products/traditional herbal medicinal products' (EMA/CPMP/QWP/2820/00 and EMA/CVMP/815/00 as revised) and the analytical procedures should be validated according to the ICH/VICH guidelines 'Validation of analytical procedures: methodology' (CPMP/ICH/381/95 and CVMP/VICH/591/98).

The control tests on the finished product should allow the qualitative and quantitative determination of the active substance(s). A specification should be provided and this may include the use of markers where constituents with known therapeutic activity are unknown. In the case of herbal substances or herbal preparations with constituents of known therapeutic activity, these constituents should be specified and quantitatively determined. For traditional herbal medicinal products for human use containing vitamins and/or minerals, the vitamins and/or minerals should also be specified and quantitatively determined.

If a herbal medicinal product contains a combination of several herbal substances or preparations of several herbal substances, and if it is not possible to perform a quantitative determination of each active substance, the determination may be carried out jointly for several active substances. The need for this procedure should be justified.

The criteria given by the European Pharmacopoeia to ensure the microbiological quality should be applied unless justified. The frequency of testing for microbial contamination should be justified, according to the (V)ICH Notes for guidance on Specifications: (Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, (CPMP/ICH/367/96, and Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances, EMA/CVMP/VICH/10/04).

8. Stability tests

This section should be in accordance with the 'Note for guidance on stability testing of new active substances and products' (CPMP/ICH/2736/99 as revised) and 'Guideline on stability testing of new veterinary drug substances and medicinal products' (CVMP/VICH/899/99 as revised), the 'Guideline on stability testing of existing active substances and related finished products' (CPMP/QWP/122/02 and EMA/CVMP/846/99 as revised), the 'Note for guidance on in-use stability testing of human medicinal products' (CPMP/QWP/2934/99) and the 'Note for guidance on in-use stability testing of veterinary medicinal products (excluding immunological veterinary medicinal products) (EMA/CVMP/424/01).

Since the herbal substance or herbal preparation in its entirety is regarded as the active substance, a mere determination of the stability of the constituents with known therapeutic activity will not suffice. The stability of other substances present in the herbal substance or in the herbal preparation, should, as far as possible, also be demonstrated, e.g., by means of appropriate fingerprint chromatograms. It should also be demonstrated that their proportional content remains comparable to the initial fingerprint.

If a herbal medicinal product contains combinations of several herbal substances or herbal preparations, and if it is not possible to determine the stability of each active substance, the stability of the medicinal product should be determined by appropriate fingerprint chromatograms, appropriate overall methods of assay and physical and sensory tests or other appropriate tests. The appropriateness of the tests shall be justified by the applicant.

In the case of a herbal medicinal product containing a herbal substance or herbal preparation with constituents of known therapeutic activity, the variation in content during the proposed shelf-life should not exceed $\pm 5\%$ of the declared assay value, unless justified. In the case of a herbal

medicinal product containing a herbal substance or herbal preparation where constituents with known therapeutic activity are unknown, a variation in marker content during the proposed shelf-life of \pm 10% of the initial assay value can be accepted if justified by the applicant.

In the case of traditional herbal medicinal products for human use containing vitamins and/or minerals, the stability of the vitamins and/or minerals should be demonstrated.

9. Definitions

- **Acceptance criteria:** Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.
- **Constituents with known therapeutic activity:** are chemically defined substances or groups of substances which are generally accepted to contribute substantially to the therapeutic activity of a herbal substance, a herbal preparation or a herbal medicinal product.
- **Drug extract ratio (DER):** means the ratio between the quantity of herbal substance used in the manufacture of a herbal preparation and the quantity of the herbal preparation obtained. The number (given as the actual range) written before the colon is the relative quantity of the herbal substance; the number written after the colon is the relative quantity of the herbal preparation obtained.
- **Extraction solvents:** are solvents which are used for the extraction process.
- **Genuine (Native) herbal preparation:** refers to the preparation without excipients, even if for technological reasons the genuine herbal preparation is not available. However, for soft and liquid herbal preparations the genuine herbal preparation may contain variable amounts of (extraction) solvent.
- **Ratio of herbal substance to genuine herbal preparation (DER genuine):** is the ratio of the quantity of the herbal substance to the quantity of the resulting genuine herbal preparation. The number (given as the actual range) written before the colon is the relative quantity of the herbal substance; the number written after the colon is the relative quantity of the genuine herbal preparation obtained.
- **Herbal medicinal products:** any medicinal product, exclusively containing as active substances one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.
- **Herbal preparations:** are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.
- **Herbal substances:** all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).
- **Herbal teas:** consist exclusively of one or more herbal substance(s) intended for oral aqueous preparations by means of decoction, infusion or maceration. The preparation is prepared immediately before use. Herbal teas are usually supplied in bulk form or in sachets.

- **Markers:** are chemically defined constituents or groups of constituents of a herbal substance, a herbal preparation or a herbal medicinal product which are of interest for control purposes independent of whether they have any therapeutic activity. Markers serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the Herbal Medicinal Product if the marker has been quantitatively determined in the herbal substance or herbal preparations.

There are two categories of markers:

- **Active markers:** are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.
 - **Analytical markers:** are constituents or groups of constituents that serve for analytical purposes.
- **Quantification:** means adjusting the herbal preparation to a defined range of constituents exclusively achieved by blending different batches of herbal substances and/or herbal preparations (e.g. quantified extracts).
 - **Solvent:** An inorganic or an organic liquid used for the preparation of solutions or suspensions in the manufacture of a herbal preparation or the manufacture of a herbal medicinal product.
 - **Specification:** A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a herbal preparation / herbal substance or herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal preparation / herbal substance and / or herbal medicinal product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant.
 - **Standardisation:** means adjusting the herbal substance / herbal preparation to a defined content of a constituent or a group of constituents with known therapeutic activity respectively either by adding excipients or by blending batches of the herbal substance and/or herbal preparation (e.g. standardised extracts).
 - **Traditional herbal medicinal products:** Medicinal Products for human use that fulfil the conditions laid down in article 16a (1) of Directive 2001/83/EC, as amended.