GUIDELINE ON QUALITY OF HERBAL MEDICINAL PRODUCTS¹/TRADITIONAL HERBAL MEDICINAL PRODUCTS

<table>
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<tr>
<th>DISCUSSION AT THE HMPC</th>
<th>January – July 2005</th>
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<tr>
<td>DRAFT AGREED BY QUALITY WORKING PARTY</td>
<td>June 2005</td>
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<td>ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION</td>
<td>27 July 2005</td>
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<td>ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION</td>
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<td>END OF CONSULTATION (DEADLINE FOR COMMENTS)</td>
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Comments should be provided to QWP@emea.eu.int

This guideline updates the CPMP/CVMP/QWP ‘Note for guidance 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.

¹ Throughout the guideline and unless otherwise specified, the term “herbal medicinal product” includes “traditional herbal medicinal product”.
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\(^2\) The term “herbal substance” should be considered as equivalent to the term “herbal drug” as defined in the European Pharmacopoeia

\(^3\) The term “herbal preparation” should be considered as equivalent to the term “herbal drug preparation” as defined in the European Pharmacopoeia
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’ (EMEA/CPMP/QWP/2820/00 and EMEA/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 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 Notice to Applicants, in the relevant volumes of the Rules governing medicinal products in the European Union.

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 guidance ‘Points to Consider on Good Agricultural and Collection Practice for starting materials of herbal origin’ (EMEA/HMPWP/31/99) should also be considered.

3. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCE(S) OF A HERBAL MEDICINAL PRODUCT

There are a number of herbal preparations described in the European Pharmacopoeia. ‘Standardised Extracts’ are herbal preparations adjusted within an acceptable tolerance to a given content of constituents with known therapeutic activity; standardisation is achieved by adjustment of the herbal preparations with inert material or by blending batches of herbal preparations. ‘Quantified Extracts’ are herbal preparations adjusted to a defined range of constituents; adjustments are made by blending batches of herbal preparations. ‘Other Extracts’ are herbal preparations essentially defined by their production process and their specifications.

1. In the case of a herbal substance or a herbal preparation consisting of comminuted or powdered herbal substances

   (i) The quantity of the herbal substance or the herbal preparation shall be given as a range corresponding to a defined quantity of constituents with known therapeutic activity
or (ii) the quantity of the herbal substance or the quantity of the native herbal preparation shall be stated if constituents with known therapeutic activity are unknown.

Examples:

i)  
**Active substance**
Name: Sennae folium  
Quantity: 415-500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as Sennoside B.

Other substance(s)
Name

ii)  
**Active substance**
Name: Valerianae radix  
Quantity: 900 mg

Other substance(s)
Name

2. **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: If the constituents with known therapeutic activity are known, the equivalent quantity $x - y^*$, or the ratio $(a - b): 1^*$ of the herbal substance to the herbal preparation shall be stated and the quantity of the herbal preparation may be given as a range corresponding to a defined quantity of these constituents (see example).

   or  
   (iia) Quantified extracts: In the case of quantified extracts the equivalent quantity $x - y^{**}$, or the ratio $(a - b): 1^{**}$ of the herbal substance to the herbal preparation shall be stated. Furthermore content of the quantified substance(s) shall be specified in a range.

   or  
   (iib) Other extracts: The equivalent quantity $x - y^*$, or the ratio $(a - b): 1^*$ of the herbal substance to the herbal preparation shall be stated if constituents with known therapeutic activity are unknown.

The composition of any solvent or 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.

**EXAMPLE**

i)  
**Active substance**
Name: Sennae folium  
Quantity: 50-65 mg, corresponding to 12.5 mg of dry extract ethanolic 60% (V/V) hydroxyanthracene glycosides, calculated as Sennoside B

Excipient (s)
Name: “Diluent”
Quantity

(*) ‘a’ and ‘b’ or ‘x’ and ‘y’ have to be justified by the applicant

(**) The quantity indicated refers to the specifications provided in the documentation.
or

**ii a) Active substance**

<table>
<thead>
<tr>
<th>Name</th>
<th>Quantity</th>
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<tr>
<td><em>Ginkgo biloba</em> L. folium</td>
<td>60 mg, containing 13.2-16.2 mg flavanoids expressed as flavone glycosides,</td>
</tr>
<tr>
<td>dry extract acetonic 60% (v/v)</td>
<td>1.68 - 2.04 mg ginkgolides A, B &amp; C</td>
</tr>
<tr>
<td>((a – b): 1)</td>
<td>1.56 - 1.92 mg bilobalide.</td>
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**Excipient(s)**

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<th>Name</th>
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or

**ii b) Active substance**

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<tr>
<th>Name</th>
<th>Quantity</th>
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<tbody>
<tr>
<td><em>Valeriana</em>ae radix</td>
<td>125 mg</td>
</tr>
<tr>
<td>dry extract ethanolic 60% (V/V)</td>
<td>equivalent to x - y mg <em>Valeriana</em>ae radix</td>
</tr>
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or

*Valeriana*ae radix  125 mg  
dry extract ethanolic 60% (V/V) equivalent to x - y mg *Valeriana*ae radix

**Excipient(s)**

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4. **DESCRIPTION OF THE METHOD OF PREPARATION**

The manufacturing process, within the meaning of this section, is the preparation of the finished 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 finished 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’ (Eudralex 3AQ 2A)/’Note for guidance: manufacture of the finished dosage form’ (EMEA/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 process validation should also be provided in accordance with the ‘Note for guidance on development pharmaceutics’ (EMEA/CPMP/QWP/155/96), the ‘Note for guidance: development pharmaceutics for veterinary medicinal products’ (EMEA/CVMP/315/98) and the ‘Note for guidance on process validation’ (EMEA/CPMP/QWP/848/96 and EMEA/CVMP/598/99).

5. **CONTROL OF STARTING MATERIALS**

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’ (EMEA/CPMP/QWP/2820/00 and EMEA/CVMP/815/00 as revised).

- Control of herbal substances
A comprehensive specification for each herbal substance must be submitted, even if the starting material is a herbal preparation. This also applies if the applicant is not the manufacturer of the preparation. 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 scientific name of the parent plant and its part(s) have to be stated.

If no monograph for the herbal substance is given in a Pharmacopoeia referred to in Annex I of Directive 2001/83/EC or 2001/82/EC, 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. This should include the botanical name and authority and the common name, if used, for labelling purposes. 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 finished 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 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 substances4. 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 guideline ‘Validation of analytical procedures: methodology’ (CPMP/ICH/281/95) or the corresponding VICH guideline (CVMP/VICH/591/98).

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. 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’ (EMEA/CPMP/QWP/227/02 and EMEA/CVMP/134/02).

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.

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, residues of pesticides, fumigation agents, solvents and toxic metals should be performed. Radioactivity should be tested if there are reasons for concern. A quantitative determination (assay) of markers or of substances with known therapeutic activity is also required. The content should be indicated with the lowest possible tolerance (the narrowest possible tolerance with both upper and lower limits stated). 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.

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4 European Pharmacopoeia monograph on herbal drugs (1433)
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 Rev. 1 corr).

3. Control of excipients

Excipients, including those added during the manufacture of the herbal preparations, should be described according to the ‘Note for guidance on excipients in the dossier for application for marketing authorisation of a medicinal product’ (Eudralex 3AQ 9A) or the ‘Note for guidance on excipients in the dossier for application for marketing authorisation of veterinary medicinal products’ (EMEA/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 FINISHED 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 finished product.

7. CONTROL TESTS ON THE FINISHED PRODUCT

This section should be in accordance with the ‘Note for guidance 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’ (EMEA/CPMP/QWP/2820/00 and EMEA/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/281/95 and CVMP/VICH/591/98).

The control tests on the finished product should allow the qualitative and quantitative determination of the composition 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.

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 Rev. 2 and ‘Guideline on stability testing of new veterinary drug substances and medicinal products’ CVMP/VICH/899/99), the ‘Note for guidance on stability testing of existing active substances and related finished products’ (CPMP/QWP/122/02 Rev. 1 and EMEA/CVMP/846/99), 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)’ (EMEA/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 constant.

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 ±5% of the initial 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 ±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.
ANNEX – GLOSSARY

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.

Genuine (Native) herbal preparation: refers to the preparation without excipients.

Herbal medicinal products: are medicinal products, 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: are mainly whole, fragmented or cut, plants, parts of plants, algae, fungi, lichen in an unprocessed state, usually in 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 binominal system (genus, species, variety and author).

Markers: are chemically defined constituents of a herbal substance which are of interest for control purposes independent of whether they have any therapeutic activity or not. Markers may serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the finished product if that marker has been quantitatively determined in the herbal substance(s) or herbal preparation(s) when the starting materials were tested.

Solvent: An inorganic or an organic liquid used as a vehicle 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 preparation to a defined content of a constituent or a group of substances with known therapeutic activity respectively by adding excipients or by mixing herbal substances or herbal preparations (e.g. standardised extract from the European Pharmacopoeia).

Traditional herbal medicinal products: are medicinal products for human use that fulfil the conditions laid down in article 16a (1) of Directive 2001/83/EC, as amended.