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**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS  
(CPMP)  
COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS  
(CVMP)**

**NOTE FOR GUIDANCE ON QUALITY OF HERBAL MEDICINAL  
PRODUCTS  
(formerly EMEA/HMPWP/9/99)**

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**Note:**

This is a revision of the *Note for guidance on Quality of herbal remedies* (November 1997) in Volume 3A of the Rules Governing Medicinal Products in the European Union.

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**NOTE FOR GUIDANCE ON QUALITY OF HERBAL MEDICINAL  
PRODUCTS**

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## INTRODUCTION

This Note for guidance concerns the application of Part 2 of the Annex to Directive 75/318/EEC and 81/852/EEC, as amended<sup>(\*)</sup>. The special problems of herbal medicinal products and the differences between medicinal products containing chemically defined active substances are described in this document

The Note for guidance should be read in conjunction with Annex 7 “Manufacture of Herbal Medicinal Products” 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 including 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 drug is obtained to ensure material of consistent quality.

Reference substances used in the control of all stages of the manufacturing process should be specified.

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

#### 1. *In the case of a herbal drug or a herbal drug preparation consisting of comminuted or powdered herbal drugs*

either (i) the quantity of the herbal drug or the quantity of the native herbal drug preparation shall be stated if constituents with known therapeutic activity are unknown

or (ii) the quantity of the herbal drug or the herbal drug preparation shall be given as a range corresponding to a defined quantity of constituents with known therapeutic activity.

#### EXAMPLE

i)	<u>Active substance</u>	
	<u>Name</u>	<u>Quantity</u> <sup>(**)</sup>
	Valerianae radix	900 mg
	<u>Other substance(s)</u>	
	<u>Name</u>	
	...	
ii)	<u>Active substance</u>	
	<u>Name</u>	<u>Quantity</u>
	Sennae folium	415-500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as Sennoside B.
	<u>Other substance(s)</u>	
	<u>Name</u>	

(\*) In this Note for guidance, the sequence used is designed to relate directly to Part 2 of the Annex to Directive 75/318/EEC and 81/852/EEC as amended.

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

2. In the case of a herbal drug 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:

either (i) the equivalent quantity  $x - y^{(*)}$ , or the ratio  $(a - b) : 1^{(*)}$  of the herbal drug to the herbal drug preparation shall be stated if constituents with known therapeutic activity are unknown (this does not apply to fatty or essential oils).

or (ii) if the constituents with known therapeutic activity are known, the quantity of the herbal drug preparation may be given as a range corresponding to a defined quantity of these constituents (see example).

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 drug 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

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

or

<i>Valerianae radix</i> dry extract ethanolic 60% (V/V)	125 mg equivalent to $x - y$ mg <i>Valerianae radix</i>
<u>Excipient(s)</u>	
<u>Name</u>	
<u>"Diluent"</u>	

or

ii) Active substance

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

Excipient (s)

<u>Name</u>	<u>Quantity</u>
<u>"Diluent"...</u>	

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

## **B. DESCRIPTION OF THE METHOD OF PREPARATION**

The manufacturing process within the meaning of this section is the preparation of the finished product from herbal drug(s) or herbal drug preparation(s). 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” Volume 3A Rules Governing Medicinal Products in the European Union) If herbal drug preparations are the starting material, the manufacture of the herbal drug preparations and their controls do not belong under this section but under section C.

Information on process validation should also be provided in accordance with the Notes for Guidance on Development Pharmaceuticals and Process Validation.

## **C. CONTROL OF STARTING MATERIALS**

### *1. Control of the herbal drug and of herbal drug preparations*

- Control of the herbal drug

A comprehensive specification for each herbal drug must be submitted, even if the starting material is a herbal drug 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 drug 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 drug is given in a Pharmacopoeia referred to in Directive 75/318/EEC and 81/852/EEC, Annex 1, a comprehensive specification on the herbal drug must be supplied and should be set out in the same way where practicable, as the monographs on herbal drugs 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 drugs with constituents of known therapeutic activity, assays of their content (with test procedure) 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 drugs where constituents of known therapeutic activity are not known, assays of marker substances (with test procedure) are required. The choice of markers should be justified.

As a general rule, herbal drugs must be tested for microbiological quality and for residues of pesticides and fumigation agents, toxic metals, likely contaminants and adulterants, etc., unless otherwise justified. 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) and VICH guideline (CVMP/VICH/591/98).

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

- Control of herbal drug preparations

If the herbal medicinal product contains not the herbal drug itself but a preparation, the comprehensive specification on the herbal drug must be followed by a description and validation of the manufacturing process for the herbal drug preparation. The information may be supplied either as part of the marketing authorisation application or using the European Drug Master File procedure. If the latter is chosen the documentation should be submitted in accordance with the Note for Guidance “European Drug Master File Procedure for Active Substances” Volume 3A – Rules Governing Medicinal Products in the European Union).

Where the preparation is the subject of a European Pharmacopoeia monograph the procedure for Certification of suitability to the monographs of the European Pharmacopoeia can be used when the procedure becomes operational.

For each herbal drug preparation, a comprehensive specification must be submitted. This must be established on the basis of recent scientific data and must give particulars of the characteristics, identification tests and purity tests. This has to be done e.g. by different appropriate chromatographic methods. If deemed necessary by the results of the analysis of the starting material, tests on microbiological quality, residues of pesticides, fumigation agents, solvents and toxic metals have to be carried out. Radioactivity should be tested if there are reasons for concerns. Quantitative determination (assay) of markers or of substances with known therapeutic activity is required. The content must be indicated with the lowest possible tolerance. The test methods must be described in detail.

If preparations from herbal drugs with constituents of known therapeutic activity are standardised (i.e. adjusted to a defined content of constituents with known therapeutic activity) it must 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.

#### *1. Control of excipients*

Excipients including those added during the manufacture of the herbal drug preparations should be described according to the “Note for guidance on Excipients in the dossier for application for marketing authorisation of a medicinal product” (Volume 3A – Rules Governing Medicinal Products in the European Union for Human Medicinal Products, EMEA/CVMP/004/98 for Veterinary Medicinal Products )

### **D. 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 done in the finished product.

### **E. 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” and the analytical procedures should be validated according to the ICH guideline “Validation of analytical procedures: methodology” (CPMP/ICH/281/95) and VICH guideline (CVMP/VICH/591/98)

The control tests on the finished product must be such as to allow the qualitative and quantitative determination of the composition of the active substances and a specification has to be given which may be done by using markers if constituents with known therapeutic activity are

unknown. In the case of herbal drugs or herbal drug preparations with constituents of known therapeutic activity, these constituents must also be specified and quantitatively determined.

If a herbal medicinal product contains several herbal drugs or preparations of several herbal drugs 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 must 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.

## **F. STABILITY TESTS**

This section should be in accordance with the "Note for guidance on Stability testing of new active substances and medicinal products" (CPMP/ICH/380/95 and CVMP/VICH/899/99) and the "Note for guidance on stability testing of existing active substances and related finished products" (CPMP/QWP/556/96 and EMEA/CVMP/846/99).

Since the herbal drug or herbal drug 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. It must also be shown, as far as possible e.g. by means of appropriate fingerprint chromatograms, that other substances present in the herbal drug or in the herbal drug preparation are likewise stable and that their proportional content remains constant.

If a herbal medicinal product contains several herbal drugs or preparations of several herbal drugs 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 drug or herbal drug preparation with constituents of known therapeutic activity, the variation in content during the proposed shelf-life should not exceed  $\pm 5\%$  of the initial assay value, unless justified. In the case of a herbal medicinal product containing a herbal drug or herbal drug preparation where constituents with known therapeutic activity are unknown, a variation in content during the proposed shelf-life of  $\pm 10\%$  of the initial assay value can be accepted if justified by the applicant. These criteria shall apply to the stability testing of active substances in like manner.

## ANNEX - GLOSSARY

**Herbal medicinal products:** are medicinal products containing as active substances exclusively herbal drugs or herbal drug preparations.

**Herbal drugs:** 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 drugs. Herbal drugs are precisely defined by the botanical scientific name according to the binominal system (genus, species, variety and author).

Herbal drug preparations: are obtained by subjecting herbal drugs to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal drugs, tinctures, extracts, essential oils, expressed juices and processed exudates.

Native herbal drug preparation: refers to the preparation without excipients.

**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 drug or of a preparation.

**Markers:** are chemically defined constituents of a herbal drug 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 drug or preparation in the finished product if that marker has been quantitatively determined in the herbal drug or preparation when the starting materials were tested.

**Standardisation**<sup>(\*\*)</sup>: means adjusting the herbal drug 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 drugs or herbal drug preparations (e.g. standardised extract from the European Pharmacopoeia).

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(\*\*) In some Member States the expression "standardisation" is used on a national level to describe all measures which are taken during the manufacturing process and quality control leading to a reproducible quality