

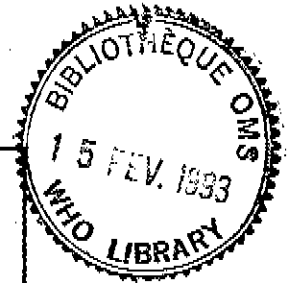


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This document was discussed and provisionally adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations during its meeting, 30 November-4 December 1992. Comments are now invited from experts, as well as from interested institutions and specialists in view of finalization of the text. Kindly address your comments to Dr A. Mechkovski, Drug Quality Assurance, World Health Organization 1211 Geneva 27, Switzerland, before the end of April 1993.



## GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS

### Supplementary guidelines for the manufacture of herbal medicinal products

#### GLOSSARY

##### CONSTITUENTS WITH KNOWN THERAPEUTIC ACTIVITY

Substances or groups of substances which are chemically defined and known to contribute to the therapeutic activity of a plant material or of a preparation.

##### HERBAL MEDICINAL PRODUCT

Medicinal product containing, as active ingredients, exclusively plant material and/or preparations. This term is generally applied to a finished product. If it refers to unfinished product, it should be indicated as such.

##### MARKERS

Constituents of a medicinal plant material which are chemically defined and of interest for control purposes. Markers are generally used when constituents with known therapeutic activity are not found or are uncertain and may serve to calculate the quantity of plant material or preparation in the finished product. However, the marker has to be quantitatively determined in the plant material or preparation when the starting materials are tested.

##### MEDICINAL PLANT

A plant (wild or cultivated) used for medicinal purposes.

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## **MEDICINAL PLANT MATERIAL (crude plant material, vegetable drug)**

Medicinal plants or parts thereof collected for medicinal purposes.

## **PLANT PREPARATIONS**

Comminuted or powdered plant material, extracts, tinctures, fatty or essential oils, resins, gums, balsams, expressed juices, etc. prepared from plant material, and preparations whose production involves a fractionation, purification or concentration process, excluding chemically defined isolated constituents. A plant preparation can be regarded as the active ingredient whether or not the constituents with therapeutic activities are known.

## **GENERAL**

Unlike conventional pharmaceutical products, which are usually prepared from synthetic materials using reproducible manufacturing techniques and procedures, the production of herbal medicinal products utilizes material of plant origin which may be prone to contamination, deterioration and variation in quality. Furthermore, the manufacture and quality control of herbal medicinal products often utilizes procedures and techniques which are substantially different from those used for conventional pharmaceutical products.

The control of the starting materials, storage and processing assumes particular importance because of the often complex and variable nature, the number and the small quantity of defined active ingredients in many herbal medicinal products.

## **PREMISES**

### **Storage areas**

1. Medicinal plant materials should be stored in separate areas. The storage area should be well ventilated and be equipped in such a way as to give protection against the entry of insects or other animals, especially rodents. Effective measures should be taken to limit the spread of animals and microorganisms introduced with the plant material and to prevent cross-contamination. Containers should be located in such a way as to allow free air circulation.
2. Special attention should be paid to the cleanliness and good maintenance of the storage areas particularly when dust is generated.
3. Storage of plants, extracts, tinctures and other preparations may require special conditions of humidity, temperature or light protection; these conditions should be provided and monitored.

### **Production area**

4. To facilitate cleaning and to avoid cross-contamination whenever dust is generated, specific provisions should be taken during sampling, weighing, mixing and processing operations of medicinal plants; for example, dust extraction, dedicated premises, etc.

## **DOCUMENTATION**

### **Specifications for starting materials**

5. In addition to the data described in the "Good manufacturing practices for pharmaceutical products" (sections 14, 18),\* the specifications for medicinal plant materials should as far as possible include the following:

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\* WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-second report, World Health Organization, Geneva, 1992 (TRS 823)

- botanical name; with reference to the authors;
- details of the source of the plant (country or region of origin, and where applicable, cultivation, time of harvesting, collection procedures, possible pesticides used, etc.);
- whether the whole plant or only a part is used;
- when dried plant is purchased, drying system should be specified;
- description of plant material, macro- and/or microscopical visual inspection;
- suitable identification tests including, where appropriate, identification tests for known active ingredients, or markers;
- assay, where appropriate, of constituents of known therapeutic activity or markers;
- methods suitable to determine possible pesticide contamination and limits accepted;
- tests for toxic metals and for likely contaminants, foreign materials and adulterants.
- test for radioactivity, aflatoxins, microbial contamination.

Any treatment used to reduce fungal/microbial contamination or other infestation should be documented. Instruments for such procedures should be available and should include details of process, tests and limits for residues.

#### Qualitative and quantitative requirements

6. They should be expressed in the following ways:

6.1 In the case of medicinal plant material: either

- (a) the quantity of plant material must be stated or
- (b) the quantity of plant material may be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity.

#### EXAMPLE

	<u>Name</u>	<u>Quantity</u>
(a)	Active ingredient Sennae folium	900 mg
(b)	Active ingredient Sennae folium	830-1000 mg, corresponding to 25 mg of hydroxyanthracene glycosides, calculated as Sennoside B
	Other ingredients .....	0-170 mg, corresponding to the quantity of Sennae folium

6.2 In the case of a plant preparation, either

- (a) the equivalent quantity or the ratio, for example, 8:1 of the plant material to the plant preparation, must be stated (this does not apply to fatty or essential oils), or
- (b) the quantity of the plant preparation may be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity (*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 plant preparation to adjust the preparation to a certain level of constituents with known therapeutic activity, or for any other purpose, the added substance must be mentioned as "other ingredients" and the genuine extract as the "active ingredient".

**EXAMPLE**

	<u>Name</u>	<u>Quantity</u>
(a) Active ingredient	Sennae folium dry 60%	125 mg ethanolic extract (8:1)
	Sennae Folium dry 60%	125 mg equivalent to 1000 mg Sennae folium ethanolic extract
(b) Active ingredient	Sennae folium dry 60%	100-130 mg, corresponding to 25 mg of hydroxyanthracene ethanolic extract (8:1) glycosides, calculated as Sennoside B
	Other ingredients	
	Dextrin	20-50 mg

**Specifications for the finished product**

7. The control tests for the finished product must be such as to allow the qualitative and quantitative determination of the composition of the active ingredients. If the therapeutic activity of constituents is known, they must be specified and quantitatively determined. When this is not feasible, specifications have to be based on the determination of markers.
8. If either the final product or preparation contain several plant materials and a quantitative determination of each active ingredient is not feasible, a joint determination may be carried out for several active ingredients. The need for such procedure must be justified.

**Processing instructions**

9. The processing instructions should give the different operations to be performed with the plant material, such as drying, crushing and sifting, and also include the temperatures for the drying process, and the methods to be used to control fragments or the particle size. Sieving instructions or other methods to remove foreign materials should be given as well. Details of any process, such as fumigation used to reduce the levels of microbial contamination together with their determination should also be given.
10. For the production of plant preparations, the instructions should include details concerning any vehicle or solvent, time and temperatures to be observed during extraction, details of any concentration methods used.

**QUALITY CONTROL**

11. Personnel of Quality Control units should have particular expertise in herbal medicinal products in order to carry out identification tests, recognition of adulteration, presence of fungal growth, infestations, non-uniformity within a consignment of medicinal plant materials, etc.
12. Reference samples of plant materials must be available for use in comparative tests e.g. macro- and microscopic examination, chromatography etc.

**Sampling**

13. Sampling has to be carried out with special care by personnel with particular expertise since medicinal plant materials are composed of individual plants or plants thereof and present some heterogeneity.

For additional advice see document "Quality Control Methods for Medicinal Plant Materials", Section 1, "General advice on sampling".\*\*

#### STABILITY TESTS

14. It will not be sufficient to determine only the stability of the constituents with known therapeutic activity, since plant materials or plant preparations in their entirety are regarded as the active ingredient. It also must be shown, as far as possible e.g. by chromatography in the finger-print region, that other substances present are stable and that their proportional content remains constant.
15. If a herbal medicinal product contains several plant materials or preparations of several plant materials, and the determination of the stability of each active ingredient is not feasible, the stability of the product should be determined by appropriate methods such as chromatography (fingerprint region), overall methods of assay and physical and sensory tests or other appropriate tests.

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\*\* WHO/PHARM/92.559 (draft document)