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Draft Annex 7
Manufacture of Herbal Medicinal Products

Document History	
Revision to specify application of GMP provisions for active substances used as starting materials (Part II) for the manufacture of herbal medicinal products. Additional changes are in particular related to the new Directive 2004/24/EC on traditional herbal medicinal products. Draft revision adopted for consultation at 42nd Ad Hoc Meeting of GMP Inspection Services.	07 – 09 March 2006
Public consultation to gmp@emea.eu.int and sabine.atzor@ec.europa.eu until	31 July 2006

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Principle

Because of their often complex and variable nature, and the number and small quantity of defined active constituents, control of starting materials, storage and processing assume particular importance in the manufacture of herbal medicinal products.

The "starting material" in the manufacture of a herbal medicinal product[1] can be a medicinal plant, a herbal substance[2] or a herbal preparation[1]. The herbal substance shall be of suitable quality and supporting data should be provided to the manufacturer of the herbal preparation/herbal medicinal product. Ensuring consistent quality of the herbal substance may require more detailed information on the agricultural production. The selection of seeds, cultivation and harvesting conditions represent important aspects of the quality of the herbal substance and can influence the consistency of the finished product. Recommendations on an appropriate quality assurance system for good agricultural and collection practice are provided in the document: "Guideline on Good Agricultural and Collection Practice for starting materials of herbal origin" (EMEA/HMPC/246816/2005).

[1] Throughout the annex and unless otherwise specified, the term "herbal medicinal product/ preparation" includes "traditional herbal medicinal product/ preparation".
[2] The terms herbal substance and herbal preparation as defined in Directive 2004/24/EC are considered to be equivalent to the Ph. Eur. terms herbal drug and herbal drug preparation respectively.

Table illustrating the application of Good Practices to the manufacture of herbal medicinal products[3].

Activity	Good Agricultural and Collection Practice	Part II of the GMP Guide†	Part I of the GMP Guide†
Cultivation and harvesting of plants, algae, fungi and lichens			
Cutting, comminuting and drying of plants, algae, fungi and lichens and extraction from plants			
Collection and processing of exudates			
Distillation, expression, fractionation, purification, concentration or fermentation of herbal substances			
Further processing into a dosage form including packaging as a medicinal product			

†Explanatory Note.
The GMP classification of the herbal material is dependent upon the use made of it by the Manufacturing Authorisation Holder. The material may be classified as an active substance, an intermediate or a finished product.

It is the responsibility of the manufacturer of the medicinal product to ensure that the appropriate GMP classification is applied.

Premises & Equipment

Storage areas

1. Crude (i.e. unprocessed) plants should be stored in separate areas. The storage area should 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 prevent the spread of any such animals and micro-organisms brought in with the crude plant, to prevent fermentation or moulds growth and to prevent cross-contamination. Different enclosed areas should be used to quarantine incoming plant materials and for the approved plant materials.

2. The storage area should be well ventilated and the containers should be located in such a way as to allow free circulation of air.

3. Special attention should be paid to the cleanliness and good maintenance of the storage areas particularly when dust is generated.

4. Storage of plants, extracts, tinctures and other herbal preparations may require special conditions of humidity, temperature or light protection; these conditions should be provided and monitored.

[3] This table replaces the herbal section of Table 1 in part II of GMP.

Production area

5. Specific provisions should be made during sampling, weighing, mixing and processing operations of crude plants whenever dust is generated, to facilitate cleaning and to avoid cross-contamination, as for example, dust extraction, dedicated premises, etc.

Equipment

6. The equipment, filtering materials etc. used in the manufacturing process must be compatible with the extraction solvent, in order to prevent any release or undesirable absorption of substance that could affect the product.

Documentation

Specifications for starting materials

7. This Annex applies to all herbal starting materials: medicinal plants, herbal substances or herbal preparations.

8. The herbal medicinal product manufacturers must ensure that they use only herbal starting materials manufactured in accordance with GMP and the Marketing Authorisation dossier. Comprehensive documentation on audits of the herbal starting material suppliers carried out by, or on behalf of the herbal medicinal product manufacturer should be made available. The audit trail of the API is fundamental to the quality of starting material. The manufacturer should ensure that the suppliers of the herbal substance/preparation are in compliance with Good Agricultural and Collection Practice[4].

9. To fulfil the specification requirements described in the basic requirements of the Guide (chapter 4, point 4.11), documentation for herbal substances/preparations should include:

- the binomial scientific name of plant (genus, species, subspecies/variety and author (e.g. Linnaeus); other relevant information such as the cultivar name and the chemotype should also be provided, as appropriate;
- details of the source of the plant (country or region of origin, and where applicable, cultivation, time of harvesting, collection procedures, possible pesticides used, possible radioactive contamination etc.);
- whether the whole plant or only a part is used;
- when a dried plant is used, the drying system should be specified;
- a description of the plant and its macro and microscopical examination;
- suitable identification tests including, where appropriate, identification tests for known active ingredients, or markers. Specific distinctive tests are required where a herbal substance is liable to be adulterated/substituted. A reference authentic specimen should be available for identification purposes;
- the water content for herbal substances;
- assay of constituents of known therapeutic activity or, where appropriate, of markers; the methods suitable to determine possible pesticide contamination and limits accepted, in accordance with European Pharmacopoeia methods or, in absence thereof, with an appropriate validated method, unless otherwise justified;

[4] See current version of the Guideline on Good Agricultural and Collection Practice for Starting Materials of Herbal Origin (EMEA/HMPC/246816/2005)

— tests to determine fungal and/or microbial contamination, including aflatoxins, other mycotoxins, pest-infestations and limits accepted, as appropriate;
— tests for toxic metals[5] and for likely contaminants and adulterants, as appropriate;
— tests for foreign materials, as appropriate;
— any other additional test according to the European Pharmacopoeia general monograph on herbal substances or to the specific monograph of the herbal substance.

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

Processing instructions

10. The processing instructions should describe the different operations carried out upon the crude plant such as cleaning, drying, crushing and sifting, and include drying time and temperatures, and methods used to control fragment or particle size.

11. In particular, there should be written instructions and records, which ensure that each container of herbal substance is carefully examined to detect any adulteration/substitution or presence of foreign matter, such as metal or glass pieces, animal parts or excrement, stones, sand, etc., or rot and signs of decay.

12. The processing instructions should also describe security sieving or other methods of removing foreign materials and appropriate procedures for cleaning/selection of plant material before the storage of the approved herbal substance or before the start of manufacturing.

13. For the production of a herbal preparation, instructions should include details of solvent, time and temperature of extraction, details of any concentration stages and methods used[6].

Sampling

14. Due to the fact that medicinal plant/herbal substances are heterogeneous in nature, their sampling should be carried out with special care by personnel with particular expertise. Each batch should be identified by its own documentation.

15. A reference sample of the plant material is necessary, especially in those cases where the herbal substance is not described in the European Pharmacopoeia or in another Pharmacopoeia of a Member State. Samples of plant material are required if powders are used.

Quality control

16. Quality Control personnel should have particular expertise and experience in herbal substances, herbal preparations and/or herbal medicinal products in order to be able to carry out identification tests and recognise adulteration, the presence of fungal growth, infestations, non-uniformity within a delivery of crude material, etc.

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[5] See the current version of Guideline on specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products (CPMP/QWP/2820/00 EMEA/CVMP/815/00).

[6] See the current version of the Guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products (CPMP/QWP/2819/00 EMEA/CVMP/814/00).

17. The identity and quality of herbal substances, herbal preparations and of herbal medicinal products should be determined in accordance with the relevant current European guidance on quality and specifications of herbal medicinal products and traditional herbal medicinal products and, where relevant, to the specific Monographs of the European Pharmacopoeia.