EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 01 September 2008

EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines to
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

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. Collaboration between GMDP Inspectors Working Group (formerly Ad Hoc GMP Inspection Services Working Group) and Committee of Herbal Medicinal Products (HMPC).	May 2005 – March 2006
Public consultation	May - July 2006
Date of revised version coming into operation	01 September 2009

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Principle

Because of their often complex and variable nature, 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 its 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 HMPC guidance document: "Guideline on Good Agricultural and Collection Practice for starting materials of herbal origin".

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

[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 (GACP)[4]	Part II of the GMP Guide†	Part I of the GMP Guide†
Cultivation, collection and harvesting of plants, algae, fungi and lichens, and collection of exudates			
Cutting, and drying of plants, algae, fungi, lichens and exudates *			
Expression from plants and distillation **			
Comminution, processing of exudates, extraction from plants, 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.

* Manufacturers should ensure that these steps are carried out in accordance with the marketing authorisation/registration. For those initial steps that take place in the field, as justified in the marketing authorisation/registration, the standards of Good Agricultural and Collection Practice for starting materials of herbal origin (GACP) is applicable. GMP is applicable to further cutting and drying steps.

** Regarding the expression from plants and distillation, if it is necessary for these activities to be an integral part of harvesting to maintain the quality of the product within the approved specifications, it is acceptable that they are performed in the field, provided that the cultivation is in compliance with GACP. These circumstances should be regarded as exceptional and justified in the relevant marketing authorisation/ registration documentation. For activities carried out in the field, appropriate documentation, control, and validation according to the GMP principles should be assured. Regulatory authorities may carry out GMP inspections of these activities in order to assess compliance.

Premises & Equipment

Storage areas

1. Herbal substances 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

[3] This table expands in detail the herbal section of Table 1 in part II of the GMP Guide.
[4] as published by the European Medicines Agency EMEA

micro-organisms brought in with the herbal substance, to prevent fermentation or mould growth and to prevent cross-contamination. Different enclosed areas should be used to quarantine incoming herbal substances and for the approved herbal substances.

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

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

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

Production area

5. Specific provisions should be made during sampling, weighing, mixing and processing operations of herbal substances and herbal preparations 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. 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. Audit trails for the active substance are fundamental to the quality of the starting material. The manufacturer should ensure that the suppliers of the herbal substance/preparation are in compliance with Good Agricultural and Collection Practice.

8. To fulfil the specification requirements described in the basic requirements of the Guide (chapter 4), 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.);
- which part(s) of the plant is/are used;
- when a dried plant is used, the drying system should be specified;
- a description of the herbal substance and its macro and microscopic examination;

— suitable identification tests including, where appropriate, identification tests for constituents with known therapeutic activity, or markers. Specific distinctive tests are required where an herbal substance is liable to be adulterated/ substituted. A reference authentic specimen should be available for identification purposes;
— the water content for herbal substances, determined in accordance with the European Pharmacopoeia;
— 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;
— tests to determine fungal and/or microbial contamination, including aflatoxins, other mycotoxins, pest-infestations and limits accepted, as appropriate;
— tests for toxic metals 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, as appropriate.

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

Processing instructions

9. The processing instructions should describe the different operations carried out upon the herbal substance such as cleaning, drying, crushing and sifting, and include drying time and temperatures, and methods used to control cut size or particle size.

10. 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.

11. 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.

12. For the production of an herbal preparation, instructions should include details of solvent, time and temperature of extraction, details of any concentration stages and methods used.

Quality control

Sampling

13. 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.

14. 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 unmilled plant material are required if powders are used.

15. 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.

16. 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 Ph. Eur. Monographs.