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Evaluation of Medicines for Human Use

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**COMMITTEE ON HERBAL MEDICINAL PRODUCTS
(HMPC)**

**GUIDELINE ON GOOD AGRICULTURAL AND COLLECTION PRACTICE (GACP) FOR
STARTING MATERIALS OF HERBAL ORIGIN**

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Note: the previous Herbal Medicinal Products Working Party Points to consider on GACP is now reintroduced as a HMPC Guideline. Only minor changes have been made to its contents further to the public consultation.

**GUIDELINE ON GOOD AGRICULTURAL AND COLLECTION PRACTICE FOR
STARTING MATERIALS OF HERBAL ORIGIN**

TABLE OF CONTENTS

1	Introduction
2	General
3	Quality Assurance
4	Personnel and Education
5	Buildings and Facilities
6	Equipment
7	Documentation
8	Seeds and Propagation material
9	Cultivation
10	Collection
11	Harvest
12	Primary processing
13	Packaging
14	Storage and Distribution

1. INTRODUCTION

In order to ensure appropriate and consistent quality of medicinal plant/herbal substances¹ it is necessary to establish good agricultural and collection practice for herbal starting materials (GACP). The concept of Good Manufacturing Practice for the manufacture, processing, packaging and storage of Active Pharmaceutical Ingredients (APIs) also applies to medicinal plants/herbal substances.

In the case of herbal preparations² the production and primary processing of the medicinal plant/herbal substance has a direct influence on the quality of the API. Due to the inherent complexity of naturally grown medicinal plants/herbal substances and the limited analytical techniques to characterise constituents solely by chemical or biological means, reproducible quality of starting materials of herbal origin requires an adequate quality assurance system for the collection and/or cultivation, harvest and primary processing.

Collection in wild habitats, , may present special problems, especially with regard to confusion with similar plants, environmental damage, lack of control and poorly qualified personnel.

The following Guideline on good agricultural and collection practice does not fall directly under GMP guidelines in the traditional sense. However, these considerations should be used as a basis for the establishment of such an appropriate quality assurance system.

2. GENERAL

2.1 This document is intended to address the specific concerns of growing, collecting and primary processing of medicinal plants/herbal substances that are used for medicinal purposes. It addresses specific issues associated with agricultural production and collection of medicinal plants/herbal substances in the wild. These considerations should be read in connection with GMP guidelines for APIs and should apply to all methods of production including organic production in accordance with regional and/or national regulations. These provide additional standards for the production and processing of medicinal plants/herbal substances insofar as they mainly focus on identifying those critical production steps that are needed to ensure good quality.

2.2 The main aim is to ensure consumer safety by establishing appropriate quality standards for medicinal plants/herbal substances. Especially important aspects are that medicinal plants/herbal substances:

- are produced hygienically, in order to reduce microbiological load to a minimum,
- are handled with care so that medicinal plants/herbal substances are not adversely affected during collection, cultivation, processing and storage.

During the course of the production process medicinal plants/herbal substances and their preparations are exposed to a large number of microbiological and other contaminants. This Guideline provides recommendations for producers to reduce contamination to a minimum.

¹ The term “herbal substance” should be considered as equivalent to the term “herbal drug” as defined in the European Pharmacopoeia

² The term “herbal preparation” should be considered as equivalent to the term “herbal drug preparation” as defined in the European Pharmacopoeia

- 2.3 Considerations and recommendations in this Guideline are intended for all participants from primary producers to traders and processors. Therefore, producers, traders and processors of medicinal plants/herbal substances should comply with these considerations, document all relevant activities in batch documentation and demand that their partners do likewise, unless it can be justified otherwise.

Growers and collectors of medicinal plants/herbal substances must ensure that they avoid damage to existing wildlife habitats. CITES (Convention on International Trade in Endangered species of Wild Fauna and Flora) must be adhered to.

3. QUALITY ASSURANCE

Agreements between producers and buyers of medicinal plants/herbal substances with regard to quality such as content of active principle, macroscopical and olfactory properties, limit values for microbial contamination, chemical residues and heavy metals etc., must be based on recognised regional and/or national specifications and should be laid down in written form.

4. PERSONNEL AND EDUCATION

- 4.1 All primary processing procedures should fully conform with regional and/or national guidelines on food hygiene and personnel entrusted with handling of medicinal plants/herbal substances should be required to have a high degree of personal hygiene (including personnel working in the field) and have received adequate training regarding their hygiene responsibilities.
- 4.2 The welfare of all staff involved in growing and processing should be ensured.
- 4.3 Personnel must be protected from contact with toxic or potentially allergenic medicinal plants/herbal substances by means of adequate protective clothes.
- 4.4 Persons suffering from known infectious diseases transmittable via food, including diarrhoea, or being transmitters of such diseases, must be suspended from areas where they are in contact with medicinal plants/herbal substances, according to regional and/or national regulations.
- 4.5 Persons with open wounds, inflammations and skin-infections should be suspended from areas where the plant processing takes place or should have to wear appropriate protective clothing/gloves until their complete recuperation.
- 4.6 Personnel should receive adequate botanical training before performing tasks that require this knowledge.
- 4.7 Collectors must have sufficient knowledge of the plant they have to collect. This includes identification, characteristics and habitat requirements. The collectors must be able to differentiate between the collected species and botanically related and/or morphologically similar species to avoid any risk to public health. Collectors should have sufficient knowledge about the best time to harvest and harvesting technique and the importance of primary processing to guarantee the best possible quality.
- 4.8 If collectors are without sufficient knowledge, a local supervisor should guarantee the education, supervision and documentation.

- 4.9 It is advisable to educate all personnel dealing with the medicinal plant/herbal substance and all those engaged in its cultivation regarding cultivation techniques including the appropriate use of herbicides and pesticides.
- 4.10 Collectors of medicinal plants/herbal substances should be instructed on all issues relevant to the protection of the environment and conservation of plant species. This will include information on regulations related to protected species.

5. BUILDING AND FACILITIES

- 5.1 Buildings used in the processing of harvested medicinal plants/herbal substances must be clean, as well as thoroughly aerated and must never be used for housing livestock.
- 5.2 Buildings must provide adequate protection for the harvested medicinal plants/herbal substances against birds, insects, rodents and domestic animals. In all storage and processing areas suitable pest control measures such as baits and electric insect killing machines must be operated and maintained by professionally qualified staff or contractors.
- 5.3 It is recommended that the packaged medicinal plant/herbal substance be stored:
- in buildings with concrete or similar easy to clean floors,
 - on pallets,
 - with a sufficient distance from the wall,
 - well separated from other herbal substances to avoid cross-contamination.
- Organic products must be stored separately.
- 5.4 Buildings where plant processing is carried out must have changing facilities as well as toilets including hand-washing facilities, according to regional and/or national regulations.

6. EQUIPMENT

Equipment used in plant cultivation and processing should:

- 6.1 Be clean, regularly serviced and oiled to ensure good working order and mounted, where applicable, in an easily accessible way. Furthermore, machinery used in fertiliser and pesticide application must be regularly calibrated.
- 6.2 Those machine parts that are in direct contact with the harvested medicinal plant/herbal substances, must be cleaned after use to ensure that remaining residue does not result in subsequent cross-contamination.
- 6.3 The equipment should be made from appropriate materials so that cross-contamination of medicinal plants/herbal substances with chemicals and other non-desirable substances is prevented.

7. DOCUMENTATION

- 7.1 All processes and procedures that could affect the quality of the product must be documented.
- 7.2 Extraordinary circumstances during the growth period that may influence the chemical composition of the medicinal plant/herbal substance such as extreme weather conditions and pests, particularly in the harvest period must be documented.
- 7.3 For cultivated medicinal plants/herbal substances all processing steps have to be documented including the location of cultivation. Field records showing previous crops and plant protect products used should be maintained by all growers.
- 7.4 For cultivated medicinal plants/herbal substances, it is essential to document the type, quantity and the date of harvest as well as the chemicals and other substances used during production such as fertilizers, pesticides, herbicides and growth promoters.
- 7.5 The application of fumigation agents must be documented.
- 7.6 The geographic location of the collection area and the harvest period should be described as precise as possible.
- 7.7 Batches of medicinal plant materials should be unambiguously and unmistakably traceable to their sources. Therefore appropriate labelling and batch assignment should take place as early as possible.. Collected and cultivated medicinal plant/herbal substance material should carry different batch numbers.
- 7.8 Batches from different geographical areas shall be mixed only if it can be guaranteed that the mixture itself will be homogenous. Such processes should be well documented.
- 7.9 All agreements (production guidelines, contracts etc.) between producer or collector and buyer should be in written form. It should be documented that cultivation, harvesting and production have been performed in accordance with these agreements. Minimum information included in the documentation should cover geographical location, country of origin and responsible producer.
- 7.10 The results of audits should be documented in an audit report (copies of all documents, audit reports, analysis reports) to be stored for a minimum of 10 years.

8. SEEDS AND PROPAGATION MATERIAL

- 8.1 Seeds should originate from plants that have been accurately identified in terms of genus, species, variety/cultivar/chemotype and origin and should be traceable. The same applies to vegetatively propagated medicinal plants. Seeds and/or vegetatively propagated medicinal plants used in organic production have to be certified as organic. The starting material should be as free as possible from pests and diseases in order to guarantee healthy plant growth. Where possible, species naturally resistant or tolerant to disease should preferably be used.
- 8.2 The presence of different species, varieties or different plant parts has to be controlled during the entire production process, and such adulteration should be avoided. The use of genetically modified medicinal plants or seeds must comply with regional and/or national regulation

9. CULTIVATION

Different Standing Operating Procedures may be acceptable depending on whether conventional or organic methods of cultivation are employed. However, care should be taken to avoid any environmental impact. The principles of good crop husbandry must be followed including appropriate rotation of crops.

9.1 Soil and fertilisation

- 9.1.1 Medicinal plants should not be grown in soil contaminated with sludge, heavy metals, residues, plant protection products or other chemicals etc. Any chemicals used in the growth or protection of the crop should be kept to a minimum.
- 9.1.2 Manure applied should be thoroughly composted and should be void of human faeces.
- 9.1.3 All other fertilising agents should be applied sparingly and in accordance with the needs of the particular species. Fertilisers should be applied in such a manner as to minimise leaching.

9.2 Irrigation

- 9.2.1 Irrigation should be controlled and carried out according to the needs of the medicinal plant.
- 9.2.2 Water used in irrigation should comply with regional/national quality standards.

9.3 Crop maintenance and plant protection.

- 9.3.1 Tillage should be adapted to plant growth and requirements.
- 9.3.2 Pesticide and herbicide applications should be avoided as far as possible. When necessary approved plant protection products should be applied at the minimum effective level in accordance with the recommendations from the manufacturer and authorities. The application should be carried out only by qualified staff using approved equipment. The minimum interval between such treatment and harvest time must be stipulated by the buyer or be consistent with recommendations from the manufacturer of the plant protection product. Regional and/or national regulations on maximum residue limits in the European Pharmacopoeia, European Directives, Codex Alimentarius etc should be complied with.

10. COLLECTION

- 10.1 Individuals should be designated to identify and verify collected medicinal plants/herbal substances and to supervise collectors. (see 4.7 and 4.8)
- 10.2 Collection must be carried out in compliance with existing regional and national and/or national species conservation legislation. Collection methods must not damage the growth environment ensuring optimum conditions for regeneration of the medicinal plant/herbal substance harvested.
- 10.3 Medicinal plants/herbal substances from species that are listed as endangered (CITES, Convention on International Trade in Endangered Species of Wild Fauna and Flora) must not be collected unless the relevant competent authority has given its authorisation. (see 4.10)
- 10.4 The recommendations in sections 3, 5, 6, 7, 11, 12, 13 and 14 have to be followed.

11. HARVEST

- 11.1 Medicinal plants/herbal substances should be harvested when they are at the best possible quality for the proposed use.
- 11.2 Damaged plants or plant parts need to be excluded or limited in accordance with a specific pharmacopoeial monograph, where relevant.
- 11.3 Medicinal plants/herbal substances should be harvested under the best possible conditions avoiding wet soil, dew, rain or exceptionally high air humidity. If harvesting occurs in wet conditions possible adverse effects on the medicinal plant/herbal substance due to increased moisture levels should be counteracted.
- 11.4 Cutting devices or harvesters must be adjusted such that contamination from soil particles is reduced to a minimum.
- 11.5 The harvested medicinal plant/herbal substance should not come into direct contact with the soil. It must be promptly collected and transported in dry, clean conditions.
- 11.6 During harvesting, care should be taken to ensure that no toxic weeds mix with harvested medicinal plants/herbal substances.
- 11.7 All containers used during harvesting must be clean and free of contamination from previous harvests. When containers are not in use, they must be kept in dry conditions free of pests and inaccessible to mice/rodents, livestock and domestic animals.
- 11.8 Mechanical damage and compacting of the harvested medicinal plant/herbal substance that would result in undesirable quality changes must be avoided. In this respect, attention must be paid to
 - overfilling of the sacks,
 - stacking up of sacks.
- 11.9 Freshly harvested medicinal plants/herbal substances must be delivered as quickly as possible to the processing facility in order to prevent thermal degradation.
- 11.10 The harvested crop must be protected from pests, mice/rodents, livestock and domestic animals. Any pest control measures taken should be documented.

12. PRIMARY PROCESSING

- 12.1 Primary processing includes washing, cutting before drying, fumigation, freezing, distillation, drying, etc. Where applicable, all of these processes must conform to regional and/or national regulations and should be carried out as soon after harvesting as possible.
- 12.2 On arrival at the processing facility the harvested medicinal plant/herbal substance has to be promptly unloaded and unpacked. Prior to processing the material should not be exposed directly to the sun, except in cases where there is a specific need, and must be protected from rainfall, insect infestation etc.
- 12.3 In the case of natural open air drying, the medicinal plant/herbal substance must be spread out in a thin layer. In order to secure adequate air circulation, the drying frames must be located at a sufficient distance from the ground. Drying directly on the ground or under direct exposure to the sunlight should be avoided unless specifically required. Attempts must be made to achieve uniform drying of the medicinal plant/herbal substance and thus avoid mould formation.
- 12.4 Except in the case of open air drying, the drying conditions such as temperature, duration, air circulation etc must be selected taking into consideration the medicinal plant part such as root, leaf or flower and the nature of its active constituent, such as essential oils. Individual conditions must be recorded in detail.
- 12.5 All materials must be inspected and where necessary sieved in order to eliminate sub-standard product and foreign bodies. Sieves must be maintained in a clean state and should be serviced regularly.
- 12.6 Clearly marked waste-bins should be available, emptied daily and cleaned.

13. PACKAGING

- 13.1 In order to protect the product and to reduce the risk of pest attacks, early packaging is advisable.
- 13.2 Following processing monitored by in-process controls, the product should be packaged in clean and dry, preferably new sacks, bags or cases. The label must be clear, permanently fixed and made from non-toxic material. Information must conform with regional and/or national labelling regulations.
- 13.3 Reusable packaging material should be well cleaned and properly dried prior to use. No contamination should occur through reusing of bags.
- 13.4 Packaging materials must be stored in a clean and dry place that is free of pests and inaccessible to livestock and domestic animals. It must be guaranteed that no contamination of the product occurs by the use of packaging materials, particularly in the case of fibre bags.

14 STORAGE AND DISTRIBUTION

- 14.1 Packaged dried medicinal plants/herbal substances, including essential oils, should be stored in a dry, well-aerated building, in which daily temperature fluctuations are limited and good aeration is ensured.

Fresh products should be stored between 1°C and 5°C while frozen products should be stored below -18°C (or below -20°C for long term storage).

- 14.2 In the case of bulk transport, it is important to secure dry conditions. Furthermore, in order to reduce the risk of mould formation or fermentation it is advisable to use aerated containers. As a substitute, the use of sufficiently aerated transport vehicles and other aerated facilities is recommended. Essential oil transport must conform with appropriate regulations. Regional and/or national regulations on transport have to be respected.
- 14.3 Fumigation against pest attack should be carried out only where necessary and must be carried out exclusively by licensed personnel. Only registered chemicals must be used. Any fumigation against pest attack should be reported in the documentation.
- 14.4 For fumigation of warehouses, only substances permitted by the regional and/or national regulations should be used.
- 14.5 When frozen storage or saturated steam is used for pest control, the humidity of the material must be controlled after treatment.

GLOSSARY

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).

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.