Good Agricultural and Wild Collection Practice (GACP) of Medicinal Plants in Europe

Johannes Novak and Renato Iguera
European Herb Growers Association (EUROPAM), c/o Institute for Animal Nutrition and Functional Plant Compounds, Veterinaerplatz 1, A-1210 Wien, Austria
Medicinal plant production in the EU – the European players

- European Medicines Agency (EMA, formerly EMEA)

- European Herb Growers Association (EUROPAM)
  - founded December 1994 at the “Nyons International Herb Conference” (France)
  - members:
    - national organizations of medicinal and aromatic plant growers (12 European countries)
    - industry members
    - individual members
EUROPAM – main mission

- To act as a representative of European producers with regard to the political institutions and organizations of the European Union and their Member states.
- To back the interests of the majority of producers of perfumery, aromatic and medicinal plants.
- To partake in the policies of standardizing products and of defining their quality criteria.
- To encourage contact and collaboration between members.
- To encourage cooperation research. To disseminate useful information to members.
Criticism on plant raw materials before the times of GACP

- Insufficient of changeable qualities
- Lack of information and control concerning the use of plant protection products
- Risk of pesticide residues
- Risk of contaminations
  - Heavy metals
  - Polycyclic aromatic hydrocarbons (PAH)
  - Toxins (mycotoxins, pyrrolizidine alkaloids, tropane alkaloids, etc.)
  - Microbes
- Lack of traceability
- Lack of quality assurance systems
- Over-harvesting, uncontrolled collection, over-exploitation
What can be done to counter this criticism?

- To be conscious of
  - The critical steps
  - The risks to produce insufficient quality
  - The risk of residue and contamination
  - The risk of unsustainable wild collection
- Ensure constant high quality and safety standard level
- Ensure the full traceability of the production and record keeping
- To establish a quality assurance system
The GMP pyramide

GMP

(Product)
Processing,
Packaging

extraction, isolation, purification
The GMP pyramid grows

- (product) processing, packaging
- extraction, isolation, purification
- production of basic raw materials
  - (wild collection / cultivation / primary processing)
'Good Agricultural Practices' (GAP) is not an invention by EUROPAM
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>first draft EUROPAM GAP (Good Agricultural Practices)</td>
</tr>
<tr>
<td>1999</td>
<td>EMA comments to EUROPAM GAP</td>
</tr>
<tr>
<td>2000</td>
<td>first draft EUROPAM GWP (Good Wild Crafting Practices)</td>
</tr>
<tr>
<td>2002</td>
<td>Integration of GAP and GWP into GACP</td>
</tr>
<tr>
<td>2002</td>
<td>EMA publication „Points to Consider on GACP for Starting Materials of Herbal Origin“ EMEA/HMPWP/31/99/Rev.3)</td>
</tr>
<tr>
<td>2003</td>
<td>WHO „GACP for medicinal plants“</td>
</tr>
<tr>
<td>2006</td>
<td>EMA „Guideline on Good Agricultural and Collection Practice (GACP) for Starting Materials of Herbal Origin“ EMEA/HMPC/246816/2005</td>
</tr>
</tbody>
</table>

latest version of the EUROPAM GACP: www.europam.net
GACP worldwide

- China
- EMA
- EUROPAM
- Japan
- Korea
- WHO
- USA
Differences between EMA and WHO GACP

- Ethical and legal consideration
- Intellectual property right and benefit-sharing
- Threatened and endangered species
- Environmental aspects
- Ecological environment and social impact for cultivation
- Technical planning for wild collection
Guideline on Good Agricultural and Collection Practice (GACP) for Starting materials of Herbal Origin
EMEA/HMPC/246816/2005

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
4. Personnel and Education

- ... 
- 4.7 Personnel should receive adequate botanical training before performing tasks that require this knowledge.
- 4.8 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 ...
5. Buildings and Facilities

- ... 

- 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.

- ...
7. Documentation

- 7.1 All processes and procedures that could affect the quality of the product must be documented.
- ...
- 7.7 Batches of medicinal plant materials should be unambiguously and unmistakeably traceable to their sources. Therefore appropriate labelling and batch assignment should take place as early as possible. …
9. Cultivation

9.1 Soil and fertilisation

9.1.1 Medicinal plants should not be grown in soil contaminated with ludge, 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.

...
10. Collection

- ... 
- 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. 
  - ...

11. Harvesting

- ... 
- 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.
- ...
12. Primary Processing

- 12.1 Primary processing includes washing, cutting before drying, fumigation, freezing, distillation, drying, etc. …

- …

- 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.

- …
Where stops GACP, where starts GMP?

- 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
Where stops GACP, where starts GMP?

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

<table>
<thead>
<tr>
<th>Activity</th>
<th>Good Agricultural and Collection Practice (GACP)</th>
<th>Part II of the GMP Guide</th>
<th>Part I of the GMP Guide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cultivation, collection and harvesting of plants, algae, fungi and lichens, and collection of exudates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutting, and drying of plants, algae, fungi, lichens and exudates *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expression from plants and distillation **</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commination, processing of exudates, extraction from plants, fractionation, purification, concentration or fermentation of herbal substances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Further processing into a dosage form including packaging as a medicinal product</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Where stops GACP, where starts GMP?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Good Agricultural and Collection Practice (GACP)</th>
<th>Part II of the GMP Guide†</th>
<th>Part I of the GMP Guide†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cultivation, collection and harvesting of plants, algae, fungi and lichens, and collection of exudates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutting, and drying of plants, algae, fungi, lichens and exudates *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expression from plants and distillation **</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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, GACP is applicable. GMP is applicable to further cutting and drying steps.
**Where stops GACP, where starts GMP?**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Good Agricultural and Collection Practice (GACP)</th>
<th>Part II of the GMP Guide</th>
<th>Part I of the GMP Guide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cultivation, collection and harvesting of plants, algae, fungi and lichens, and collection of exudates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutting, and drying of plants, algae, fungi, lichens and exudates *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expression from plants and distillation **</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** 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.**
= systematic and independent examinations of a system to determine whether safety, quality and related management activities are undertaken in accordance with the documentation, to determine compliance with the requirements and very that these arrangements are implemented effectively

<table>
<thead>
<tr>
<th>Type</th>
<th>Applied?</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal Audit (self inspection)</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Buyer audits (external audits)</td>
<td>yes</td>
<td>FAH: SOP for inspecting cultivated and wild crafted medicinal plants.</td>
</tr>
<tr>
<td>Independent third parties audits</td>
<td>upcoming</td>
<td></td>
</tr>
<tr>
<td>(external audits)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
How to transfer GACP guidelines into practice?
How to transfer GACP guidelines into practice?

- The EUROPAM Code of Practice (work in progress!)
  - Introduction
  - SOP 1: Standard Operating Procedure (SOP)
  - SOP 2: Training
  - SOP 3: Contracts
  - SOP 4: Hygiene
  - SOP 5: Batch Identification (‘BATCH-ID’) / Traceability
  - SOP 6: Wild Collection
  - SOP 7: Cultivation
  - SOP 8: Post-Harvest Processing
  - SOP 9: Quality Control /Specification
  - SOP 10: Sampling
  - ANNEX A: Glossary of Terms
  - ANNEX B: Examples
Sales Contract Between

_______________________________________________
based in ________________________________
represented by ________________________________
hereinafter called the BUYER

and

The cooperative or farm ________________________________
based in ________________________________
represented by ________________________________
hereinafter called the VENDOR

It has been agreed as follows:

**Article 1: Object**
The object of this contract is the sale of

.........................................................
GACP – Code of Conduct
Example for the content of a field record

- Farmer
- Name of the field
- Area
- Localisation of the field (only province, country)
- Main crops in neighbourhood
- Species
- Variety/cultivar/accession of propagation material
- Pre-crop
- Description of the vegetative development:
  - Date
  - Stage of plant development/cultivation
  - Observations/pictures
- Use of fertilizer:
  - Date of application
  - Type (organic/mineral)
  - Composition
  - Concentration
  - Amount
  - Development stage
  - ...
Example 10: SOP organic field production of coriander seeds

- **Definitions**

- **Plant material sources:** *Coriandrum sativum* L. var. *microcarpum*; coriander;
- **Plant material harvested:** Coriander fruits (often referred to as coriander seeds)
- **Description of the plant:** Annual, up to 50 cm high. The leaves are variable in shape, broadly lobed at the base of the plant, slender shape higher on the flowering stems. The flowers in small umbels, white or very pale pink, asymmetrical, with the petals pointing away from the centre of the umbel longer (5–6 mm) than those pointing toward it (only 1–3 mm). The fruit is a globular, dry schizocarp of 1.5 - 3 mm (*C. sativum* var. *microcarpum*). TSW: 4-10g, Composition: 0.5% - 1% essential oil.

- **Figure 1:** left: drawing of the coriander plant; right: coriander dried coriander fruits (often called coriander seeds)
What should be the content of a batch certificate?

- general information about the product
- guarantee traceability
- should enable a first risk assessment
- confirmation of (e.g.) GACP compliance
Letter to the editor

EUROPAM statement on requirements for a batch certification of medicinal and aromatic plants (MAPs)

quantity transferred). Besides the commercial trade name, the scientific name is essential for MAPs. Additionally, it is important to know about the mode of production and origin of the product (cultivation or wild...
<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed content of a batch certificate for medicinal and aromatic plants.</td>
</tr>
</tbody>
</table>

1. General information
   1.01. Product (commercial name)
   1.02. Species (scientific name)
   1.03. Plant part
   1.04. Supplier
   1.05. Batch number
   1.06. Quantity
   1.07. Cultivation or wild collection (if wild collection: permit required?)
   1.08. Conventional or organic production
   1.09. Origin (country and district)
   1.10. Harvest year and harvest period

2. Cultivation
   2.01. Irrigation (yes/no)
   2.02. Fertilization (none/mineral/organic)
   2.03. Plant protection products used (trade name/active substance)

3. Post-harvest processing
   3.01. Washing (yes/no)
   3.02. Freezing (yes/no)
   3.03. Cutting (yes/no)
   3.04. Distillation (yes/no)
   3.05. Steam treatment (yes/no)
   3.06. Irradiation (yes/no)
   3.07. Drying (natural/artificial), if artificial name of combustible (direct heating only)
   3.08. Fumigation (yes/no), if yes fumigant used
   3.09. Separation procedures
   3.10. Other post-harvest procedures
   3.11. Packaging material
   3.12. Storage conditions

4. Other comments

5. Compliance
   5.1. Production in compliance with GACP according to EMEA/HMPC/246816/2005? (yes/no/not applicable)
   5.2. Name and position/title of person authorizing the batch release
   5.3. Signature of person authorizing the batch release
   5.4. Date of signature
General Assembly 1996 – Potsdam, Germany
...the Association is Growing...