Authorisation and registration of Herbal medicinal products and traditional herbal medicinal products. National and Community regulation.

Steffen Bager, pharmacist, Licensing Division, Danish Medicines Agency

Member of HMPC, Committee of Herbal Medicinal Products and PCWP.

17. juni 2011
What is a medicinal product?

Section 2 of the Danish Medicines Act states that it is a medicinal product when the product:

- is presented as a suitable product for the treatment or prevention of disease in human beings or animals, or
- may be used in or administered to humans or animals to recover, change or affect physiological functions by having a pharmacological, immunological and metabolic effect, or to make a medical diagnosis.

Claims, marketing, text and marketing on the package, name, images, product form, diseases, the active substance etc. are relevant aspects in the assessment.
Borderline products

Medicinal products:

- Rx and OTC medicine, natural medicinal products, traditional medicinal products and homeopathic medicine

Not medicinal products:

- Food supplements – Danish Veterinary and Food Administration
- Feeding for animals- Danish Plant Directorate
- Biocides – Environmental Protection Agency
- Cosmetics – Environmental PA
- Medical devices – Danish Medicines Agency
Natural medicinal products –since 1976

• Natural remedies shall be understood to mean medicinal products in which the active substance exclusively comprises naturally occurring substances in concentrations that are not substantially greater than those in which they are found in nature.

• Only for oral ingestion or application to the skin or locally to mucous membranes

• Based on weu MA

• Around 100 MA (June 2011)
Well-established use

The documentation shall:

• Cover all aspects of the safety and/or efficacy assessment
• Include or refer to a review of the relevant literature
• Take pre- and post-marketing studies or epidemiological studies into account
Natural (herbal) medicinal products

Requirements for MA:

- Manufacturing according to GMP
- Wholesaling according to GDP
- Documentation of quality as medicinal products
- Documentation of safety and efficacy - based on weu and bibliography
- SmPC and Patient information - PIL
Traditional herbal medicinal products

- Herbal medicinal substances/preparations and vitamins/minerals provided an ancillary action
- Bibliographic or expert evidence that the product – or a corresponding product – has been in medicinal use for a period of at least 30 years before the application – including at least 15 years in EU
- Restrictions in indications and ways of administration:
  - Intended and designed for use without the supervision of a medical practitioner and only for oral or external use or for inhalation
- Same requirements to quality and GMP as for other medicinal products
- Simplified registration procedure
Traditional Herbal Medicinal Products in EU

Labelling and patient information in the product:

• General requirements for medicinal products in EU.

• Statement that the product is a Traditional herbal medicinal product for use in a specified indication and based on long standing use.

• Statement that the user should contact a doctor or a qualified health practitioner if the symptoms persist during the use of the product or if adverse effects not mentioned in the package leaflet occur.
Definitions in Article 1 of Dir 2001/83/EC

30. Herbal medicinal product: any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

31. Herbal substances: mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances.
32. Herbal preparations: preparations 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.

Isolated, chemically defined constituents of medicinal herbs such as Menthol, Eugenole, Digitoxine etc. are not “herbal preparations”. 
Herbal Medicinal Product (HMP):
Definitions in Article 1 of Dir 2001/83/EC 30

Herbal medicinal product

Herbal substance

Herbal preparation
Declaration of herbals – standardised extracts

1 capsule contains 140 mg - 190 mg of extract (as dry extract) from *Aesculus hippocastanum* L., semen (Horse chestnut seed) corresponding to 38 mg triterpene glycosides, calculated as anhydrous β-aescin.

Extraction solvent: Methanol 80 % V/V.
Declaration of herbals - quantified extracts

(quantified extracts / aktive markører)

1 tablet contain 480 mg extract (as a dry extract) of *Harpagophytum procumbens* D.C. and/or *Harpagophytum zeyheri* Decne, radix, corresponding to 9-15 mg harpagosid.

Extraction solvent: Ethanol 60% V/V.
Declaration of herbals

- Example of declaration of extract (other extracts)

1 capsule contains 160 mg of extract (as dry extract) from *Valeriana officinalis* L. s.l., radix (equivalent to 480 mg – 960 mg of Valerian root).

Extraction solvent: Ethanol 70 % V/V.
## Well-established use or Traditional use?

<table>
<thead>
<tr>
<th>Well-established</th>
<th>Traditional use</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 years medicinal use in EU</td>
<td>15/30 years use in/outside EU</td>
</tr>
<tr>
<td>Labelling as other medicinal products</td>
<td>Special labelling</td>
</tr>
<tr>
<td>Bibliographic documentation for safety and efficacy</td>
<td>Only minor indications</td>
</tr>
<tr>
<td>Pharmaceutical quality</td>
<td>Based on traditional use</td>
</tr>
<tr>
<td>GMP</td>
<td>Plausible efficacy</td>
</tr>
<tr>
<td>Marketing authorisation</td>
<td>Pharmaceutical quality</td>
</tr>
<tr>
<td></td>
<td>GMP</td>
</tr>
<tr>
<td></td>
<td>Registration</td>
</tr>
</tbody>
</table>
HMPC
27 EU Member States
2 EEA-EFTA states
5 Co-opted members

Permanent Working party

Monograph and List Working Party (MLWP)
19 MS
1 EEA-EFTA
3 co-opted members
HMPC Chairman

Temporary Working parties

Quality Drafting Group (QDG)
10 members

Organisational Matters Drafting Group (ORGAM)
10 members.
HMPC – Committee for Herbal Medicinal Products

- **Chair:** Dr. Werner Knöss (DE) since November 2010
- **Vice-Chair:** Dr Ioanna Chinou (EL)
- **27 Members + 24 Alternates**
- **5 Co-opted members (clinical pharmacology, paediatrics, non-clinical pharmacology, toxicology, GP**
- **EEA Members:** Norway, Iceland
- **Observers:** EDQM/European Pharmacopoeia,
- **Bosnia, Croatia, Turkey, FYROM, Serbia, Montenegro, Kosovo**
- **European Commission representative**
HMPC tasks

- To establish Community herbal monographs relevant for the **registration** as well as the **authorisation** of herbal medicinal products

- Prepare a draft list of herbal substances/preparations and combinations thereof for use in traditional herbal medicinal products (Community List)

- To give an opinion where other medicinal products containing herbal substances are referred to the Agency and to perform the tasks in relevant referral procedures

- Establish guidelines on quality, safety and efficacy on herbal medicinal products
Monographs and monographs

- EDQM –Ph.Eur. monographs
- Quality specifications
- EMA monographs
- Clinical data
- Pre-clinical data
- Posology etc.
- Traditional use in EU
Community Monograph

A scientific summary of all data available on the safety and efficacy of a herbal substance/preparation intended for medicinal use.

Based on an assessment report (published together with the monograph and the list of References)

Contains:

**WEU** “A systematic review of all relevant clinical data available for the herbal medicinal product/substance

**TU** “Data” on historical use and to demonstrate "plausibility" and to exclude direct and indirect risks.

**Not legally binding**: Shall be taken into account by the MS when assessing an application for authorisation or for registration.
# Community herbal monograph on *Arctostaphylos uva-ursi* (L.) Spreng, folium

**Draft**

**13 July 2000**

**14 July 2009**

**Committees on Herbal Medicinal Products (HMPC)**

**Discussion in Working Party on Community monographs and Community list (MLWP)**

**Adoption by Committees on Herbal Medicinal Products (HMPC) for release for assessment**

<table>
<thead>
<tr>
<th>Keywords</th>
<th>Herbal medicinal products (HMPC); Community herbal monographs; traditional use; <em>Arctostaphylos uva-ursi</em> (L.) Spreng; Uva ursi; Folium; bearberry leaf</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG (bulgarian); CS (czech); EN (english); ES (spanish); FI (finnish); FR (french); HE (hebrew); IT (italian); NL (dutch); NO (norwegian); PT (portuguese); SV (swedish); TR (turkish)</td>
<td></td>
</tr>
</tbody>
</table>
Community herbal monograph on *equisetum arvense* L., Herba (horsetail)

4.1 Indication

- **Well-established use**
  
- **Traditional use**
  - Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.
  
- The product is a traditional herbal medicinal product for use in specified indication exclusively based upon long-standing use.
Community herbal monograph on *Pimpinella anisum* L., Fructus (anis)

4.1. Therapeutic indications

- **Well-established use**
  - (none)

- **Traditional use**
  - Traditional herbal medicinal product for symptomatic treatment of mild, spasmodic gastro-intestinal complaints including bloating and flatulence.
  - Traditional herbal medicinal product used as an expectorant in cough associated with cold.
  - The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.
## Key documents

<table>
<thead>
<tr>
<th>Name</th>
<th>Language</th>
<th>First published</th>
<th>Last updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final community herbal monograph on <em>Foeniculum vulgare</em> Miller subsp. vulgare var. dulce (Miller) Thellung, fructus</td>
<td>(English only)</td>
<td>06/08/2007</td>
<td></td>
</tr>
<tr>
<td>Opinion of the Committee on Herbal Medicinal Products on a community herbal monograph on <em>Foeniculum vulgare</em> Miller subsp. vulgare var. dulce (Miller) Thellung, fructus</td>
<td>(English only)</td>
<td>05/07/2007</td>
<td></td>
</tr>
<tr>
<td>List of references supporting the assessment report on: <em>Foeniculum vulgare</em> Miller subsp. vulgare var. dulce</td>
<td>(English only)</td>
<td>20/02/2003</td>
<td></td>
</tr>
<tr>
<td>Assessment report on <em>Foeniculum vulgare</em> Miller</td>
<td>(English only)</td>
<td>20/02/2003</td>
<td></td>
</tr>
<tr>
<td>Overview of comments received on community herbal monograph and community list entry on <em>Foeniculum vulgare</em> Miller subsp. vulgare var. dulce, fructus and on a community herbal monograph and</td>
<td>(English only)</td>
<td>20/02/2003</td>
<td></td>
</tr>
</tbody>
</table>
Impact of the List – Article 16 f

2. If an application for traditional-use registration relates to a herbal substance, preparation or a combination thereof contained in the list referred to in paragraph 1, the data specified in Article 16c(1)(b)(c) and (d) do not need to be provided.

Article 16e(1)(c) and (d) shall not apply.

**Applicant** does not need to submit:

1. information on previous authorisations/registrations
2. evidence on traditional use
3. bibliographic / expert evidence on safety
Impact of the List –Article 16 f –cont.

**Competent authority** cannot refuse the application:

- because the product could be harmful
- because of lack of plausibility / sufficient traditional use
## Fees for applications

(AESGP survey 2011)

<table>
<thead>
<tr>
<th>Country</th>
<th>THMP new</th>
<th>THMP re-reg.</th>
<th>WEU/Biblio (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUSTRIA</strong></td>
<td>€ 2,800  to € 3,000</td>
<td>€ 2,500 to € 2,761</td>
<td>€ 5,600</td>
</tr>
<tr>
<td><strong>BELGIUM</strong></td>
<td>€ 2,500</td>
<td>€ 4,000 to € 4,239.81</td>
<td></td>
</tr>
<tr>
<td><strong>BULGARIA</strong></td>
<td>€ 1,790 + € 441</td>
<td>€ 7,670 + € 3,580 (additional dosage form as line ext.) + € 767 (additional pack size)</td>
<td></td>
</tr>
<tr>
<td><strong>CZECH REP.</strong></td>
<td>€ 3,995</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DENMARK</strong></td>
<td>€ 1,015</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FRANCE</strong></td>
<td>€ 10,110 to € 10,600</td>
<td>€ 5,055</td>
<td>€ 10,110</td>
</tr>
<tr>
<td><strong>GERMANY</strong></td>
<td>€ 17,000</td>
<td>€ 15,700</td>
<td>no fees indicated yet as applications were still pending</td>
</tr>
<tr>
<td><strong>GREECE</strong></td>
<td>€ 500</td>
<td>€ 2,048</td>
<td></td>
</tr>
</tbody>
</table>
So what is the difference? (1)

<table>
<thead>
<tr>
<th>Natural medicinal products/ herbal medicinal products</th>
<th>Traditional herbal medicinal products</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Well-established use&quot;, i.e. min. 10 years of medicinal use within EU</td>
<td>Traditional use, i.e. min. 30 years, including at least 15 years within the Community</td>
</tr>
<tr>
<td>Vegetable, animal, mineral drugs/preparations</td>
<td>Only vegetable drugs/preparations</td>
</tr>
<tr>
<td>Not isolated substances (not e.g. vitamins as active substances)</td>
<td>Vitamins-minerals – provided an ancillary action</td>
</tr>
<tr>
<td>Oral, external use, local use on mucous membranes</td>
<td>Oral use, external use or inhalation</td>
</tr>
</tbody>
</table>
So what is the difference? (2)

<table>
<thead>
<tr>
<th>Natural medicinal products/herbal medicinal products</th>
<th>Traditional herbal medicinal products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor diseases</td>
<td>Exclusively “traditional” indications, intended and designed for use without the supervision of a medical practitioner</td>
</tr>
<tr>
<td>Bibliografic documentation for efficacy and safety</td>
<td>Efficacy is plausible</td>
</tr>
<tr>
<td>Labeled “naturlægemiddel”</td>
<td>Special labelling</td>
</tr>
</tbody>
</table>
Ginger community monograph

- Assessment report on Zingiber officinale Roscoe, rhizome
- Based on Article 10a of Directive 2001/83/EC as amended (well-established use)
- Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)
- Discussed in MLWP January and March 2011
- First draft for public consultation exp. July 2011
Ginger – indications to be discussed

- Nausea and vomiting
- Postoperative nausea and vomiting
- Pregnancy-induced nausea and vomiting
- Chemotherapy-induced nausea and vomiting
- Motion sickness
- Musculoskeletal disorders
- Primary dysmenorrhoea
- Asthma
- Tolerance to tube feeding
• **Ginger - efficacy**

  • **Design:** Double-blind, placebo-controlled study on the Naval education ship Danmark
  
  • **Number of persons:** 79 students
  
  • **Dosage:** Ginger 1000 mg powder or placebo
  
  • **Parameter:** Number of vomiting and cold sweating
  
  • **Result:** Significantly (P < 0.05) better than placebo
  
  • **Reference:** Acta Otolaryngol 1988, 105, 45-49