New Frontiers in the Quality of Medicines

Workshop
Herbals: Implementation of the new legislative framework

Moderators:
Dr Konstantin Keller
Prof Dr Arnold Vlietinck

EDQM International Conference
13-15 June 2007
Strasbourg, France
European Union Legislation

Review 2004

Directive 2001/83/EC
Community code relating to medicinal products for human use.
Amended by Directive 2004/24/EC of 31 March 2004, as regards traditional herbal medicinal products for human use

Implementation by 30 October 2005

Regulation 726/2004/EC

Specific Committee on Herbal Medicinal Products
European Union Legislation

Review 2004

February 2007

European Commission refers

Czech Republic, France, Ireland, and The Netherlands

to the European Court of Justice


EMEA Committee on Herbal Medicinal Products

Chair / Vice-Chair: Dr. Konstantin Keller/ Dr. Heribert Pittner AU

<table>
<thead>
<tr>
<th>Austria</th>
<th>Finland</th>
<th>Latvia</th>
<th>Romania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estonia</td>
<td>France</td>
<td>Lithuania</td>
<td>Slovak Republic</td>
</tr>
<tr>
<td>Belgium</td>
<td>Germany</td>
<td>Luxembourg</td>
<td>Slovenia</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>Greece</td>
<td>Malta</td>
<td>Spain</td>
</tr>
<tr>
<td>Cyprus</td>
<td>Hungary</td>
<td>Netherlands</td>
<td>Sweden</td>
</tr>
<tr>
<td>Czech Rep.</td>
<td>Ireland</td>
<td>Poland</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Denmark</td>
<td>Italy</td>
<td>Portugal</td>
<td></td>
</tr>
</tbody>
</table>

4 co-opted Members:
Clinical Pharmacology, Pharmacology, Toxicology, Pediatrics

EEA Members: Norway, Iceland

Observer: EDQM/Europ. Pharm.
Croatia, Turkey
### Herbal Medicinal Products in the EU

#### Access to the market

**Marketing Authorization**

1. Full documentation with new tests and trials

2. Full bibliographic documentation  
   (well-established use)

3. Mixed Applications

   Centralized or (mainly) national procedure with full access to mutual recognition or decentralized procedures

---

**New option** for access to the market:

Directive 2001/83 EC, Chapter 2a, Articles 16 a – 16 i

**Registration**

4. “Simplified dossier” for traditional herbal medicinal products

   National procedure with limited access to mutual recognition procedure (monograph or list from the HMPC required)
The simplified registration procedure

Registration of traditional herbal medicinal products applicable to traditional herbal medicinal products

Article 16c 1 (c)
medicinal use within the EU throughout > 30 years
or
> 15 years in and > 15 years outside the EU

Opportunity for THMPs with a long tradition in one EU Member state, but less known in other Member states; “innovative”

The simplified registration procedure

The Committee for Herbal Medicinal Products shall

• at the request of a MS draw up an opinion on the adequacy of the evidence of the long-standing use
• after referral of a MS draw up a Community Herbal Monograph on traditional herbal products used < 15 years within the Community

Opportunity for THMPs with a long tradition outside the EU and a suitable dossier on quality and safety (e.g. Ayurveda)
The simplified registration procedure

Details relating to the period of traditional use

**Article 16 c**

(3) The requirement to show medicinal use throughout the period of 30 years, referred to in paragraph 1(c), is satisfied even where the marketing of the product has not been based on a specific authorisation. It is likewise satisfied if the number or quantity of ingredients of the medicinal product has been reduced during that period.

Opportunity for simplifying and modernizing complex combination products; “sharing history” for different products; moving from trad. food supplements to medicinal products

The new simplified registration procedure

Combinations with vitamins and minerals may be registered if their action is ancillary to the herbal constituent(s)

**Article 16 a (2)**

2. Notwithstanding Article 1(30), the presence in the herbal medicinal product of vitamins or minerals for the safety of which there is well-documented evidence shall not prevent the product from being eligible for registration in accordance with paragraph 1, provided that the action of the vitamins or minerals is ancillary to that of the herbal active ingredients regarding the specified claimed indication(s).
The new simplified registration procedure

Article 16c
Dossier requirements

• Administrative and Pharmaceutical dossier identical to “full” marketing authorisation

• Bibliographical or expert evidence on traditional use of the product or a corresponding product

• Expert report on safety. All safety-studies that are necessary may be requested by the Agency

Facilitating access to the market

Directive 2001/83/EC

The Committee for Herbal Medicinal Products will prepare:

Article 16f
A list of traditional herbal drugs/-preparations/combinations

Article 16h
Community herbal monographs on herbal drugs or herbal drug preparations that may be used for full marketing authorisations of well-established herbal medicinal products or simplified registrations
Transparency on HMPC activities

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)
Meeting report, 8 May 2007

The Committee on Herbal Medicinal Products met for the 17th time at the EMEA on 8 May 2007.

The Committee adopted revised rules of procedure, which can be found at:
http://www.emea.eu.int/hmps/general/contacts/HMPC/HMPC.html

Report from the Working Party on Community Monographs and Community List
(MLWP)

The 34th meeting of the permanent HMPC Working Party on Community Monographs and Community List (MLWP) took place on 7 May 2007.

On recommendation of the MLWP, the HMPC adopted the following draft Community herbal

Detailed report after each meeting on www.emea.eu.int

---

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)
Overview of status of HMPC assessment work - MAY 2007

9 Final opinions adopted (Community Monographs)

Aloe (various species, mainly Aloe ferox MILLER and hybrids) (W)
Cassia senna L., Cassia angustifoliaVAHL, fructus (W)
Cassia senna L., Cassia angustifoliaVAHL, folium (W)
Linum usitatissimum L., semen (W) (T)
Plantago ovata FORSSK., seminis tegumentum (W)
Plantago ovata FORSSK., semen (W)
Plantago afra L. / Plantago indica L., semen (W)
Rhamnus frangula L., cortex (W)

Valeriana officinalis L., radix (W) (T) (W) well-established

(T) traditional
Plantago ovata, sem. tegumentum
final monograph 26 October 2006

Well-established use
a) treatment of habitual constipation;
b) conditions in which easy defaecation with soft stool is desirable, e.g. in cases of painful defaecation after rectal or anal surgery, anal fissures and haemorrhoids;
c) in patients to whom an increased daily fibre intake may be advisable e.g. as an adjuvant in constipation predominant irritable bowel syndrome, as an adjuvant to diet in hypercholesterolemia

Traditional use
none
### Menthae piperitae aetheroleum

**Well-established use**

**Oral use**

1. symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain, especially in patients with irritable bowel syndrome.

**Cutaneous use**

2. symptomatic relief of mild tension type headache.

**Traditional use**

**Cutaneous and transdermal use**

1. relief of symptoms in coughs and colds
2. symptomatic relief of localised muscle pain
3. symptomatic relief of localised pruritic conditions in intact skin

**Inhalation**

4. relief of symptoms in coughs and colds

**Oromucosal use**

5. relief of symptoms in coughs and colds

---

### Foeniculi fructus

**Well-established use**

none

**Traditional use**

a) symptomatic treatment of mild, spasmodic gastro-intestinal complaints including bloating and flatulence.

b) symptomatic treatment of minor spasm associated with menstruation period.

c) as an expectorant in cough and cold.
8 Drafts under discussion

Avena sativa
Calendulae flos
Eleutherooccci radix
Harpagophyti radix
Lupuli flos
Menthae piperitae folium
Rhei radix
Urticae herba
List entries published

5 Drafts published for comments:

• Echinaceae purp. herba (topical use)
• Foeniculi amari fructus
• Foeniculi dulcis fructus
• Lini semen *
• Valerianae radix *

* procedure suspended

The impact of EU herbal monographs

Article 16 h (3)
Community herbal monographs

3.
....
When Community herbal monographs within the meaning of this paragraph have been established, they shall be taken into account by the Member States when examining an application. ....

When new Community herbal monographs are established, the registration holder shall consider whether it is necessary to modify the registration dossier accordingly. The registration holder shall notify any such modification to the competent authority of the Member State concerned.
The impact of the EU 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:
- information on previous authorisations/registrations
- evidence on traditional use
- bibliographic / expert evidence on safety

Competent authority cannot refuse the application:
- because the product could be harmful
- because of lack of plausibility / sufficient traditional use

The impact of the EU list and / or EU Herbal Monographs

Directive 2001/83, Article 16d

1. Without prejudice to Article 16h(1), Chapter 4 of Title III shall apply by analogy to registrations granted in accordance with Article 16a, provided that:

(a) a Community herbal monograph has been established in accordance with Article 16h(3), or
(b) the herbal medicinal product consists of herbal substances, preparations or combinations thereof contained in the list referred to in Article 16f.

Mutual recognition and decentralized procedures open to registered THMP
The simplified registration procedure

*Future development*

draft Report from the European Commission
30 May 2007

- extension to other products than herbal substances (alone or in combination with herbal ingredients) could be considered;
- the limitation to products with 15 years use in the Community, to certain routes of administration and to products which do not need the supervision of a medical practitioner, should be maintained;
- concerns that obstacles to the use of the simplified registration by the economic operators may lead to the placing on the market of some products under another qualification which would not necessarily offer the same guarantees of quality, safety and efficacy.
Perspectives

- Essential guidance on quality, safety, efficacy and procedural guidance finalised
- Important monographs adopted, new drafts published
- Legislation has been implemented in most of EU Member States; EC enforces implement. through ECJ
- EMEA offers scientific services to applicants
- Extension to other active substances is proposed by EC

**Essential tools are ready, the opportunities are there!**

We are ready to go!

Applications are welcome!

---

How to find information on Guidelines?

www.emea.eu.int

- Guidance Human Medicines
- About EMEA / HMPC
- Mailing service

hmpc.secretariat@emea.eu.int

Implementation of new legislation
IMPLEMENTING THE NEW LEGISLATION: PERSPECTIVES FORM A REGULATOR

Heribert PITZNER
AGES PharmMed, Austria
14 June 2006

Directive 2004/24

- Issued on 31 March 2004
- Member States should comply with this directive by 30 October 2005
- As of 31 March 2007, five Member States had not yet implemented Directive 2004/24 into national law
Why so few THMPs until now?

Although HMPC has created several guidelines on THMPs during the last years, there is still a lot of uncertainty both in industry and among regulators.
Question 1:

- A full marketing authorisation was granted earlier for a herbal medicinal product, now a request for registration as THMP is submitted for the same product in the same MS.

**Answer:**
The submission should be refused in the validation phase.

Question 2:

- A full authorisation was granted for a HMP in one MS, while in another MS a request for registration as THMP is submitted.

**Answer:**
MS which has to decide on THMP could initiate a referral procedure. In practice, the request for registration as THMP should be refused, or the applicant submits a dossier which is different from the authorised one.
Question 3:

• The number of ingredients of a medicinal product has been reduced from 9 to 3: Is this acceptable?

Answer:
Case-by-case decision. The character of the product (e.g. indication) should not change.

Question 4:

• The traditional use for 30 years has been demonstrated for two single herbal preparations, but not for the combination.

Answer:
Directive 2004/24 explains that in case of combinations the information on traditional use should relate to the combination as such.
Question 5:

• Will the HMPC accept only such preparations which contain not more than the RDA values of vitamins?

Answer:
Directive 2004/24 is stating an “ancillary“ action of the vitamins and minerals in THMPs and does not give a particular level of RDA.

Question 6:

• Can natural camphor, menthol, soy lecithin and propolis be classified as THMPs?

Answer:
The HMPC is of the view that these substances do not meet the legal definition of a herbal substance.
Future extension of traditional use registration to other categories of medicinal products?
Question 7 (Query):

• It is both too difficult and too expensive to submit the results of the pharmaceutical tests in full length.

Answer:
With respect to quality, the EU legislation does not foresee any exemptions for THMPs in comparison to other authorisation / registration procedures.

Question 8:

• There are no mutagenicity data for a certain herbal preparation. Can this preparation be registered as a THMP?

Answer:
At present HMPC is discussing with CHMP SWP the requirements on mutagenicity testing. For national applications the decision has to be taken on a case-by-case basis.
Question 9:

- What kind of safety data will HMPC ask for herbal medicinal products with a tradition outside Europe (e.g. TCM, Ayurvedic Medicine?)

**Answer:**

These products have to fulfil the same requirements as all other THMPs with respect to quality and safety.

---

Question 10:

- Are indications such as “prostatic hypertrophy” or “diabetes mellitus” possible for registrations as THMPs?

**Answer:**

Directive 2004/24 states that THMPs have indications which are intended for use without the supervision of a medical practitioner.
Theoretical risks for registrations of THMPs:

Until now:
- No request to HMPC on the adequacy of long-standing use
- Not one MRP for any THMP
- Not one referral to EMEA in relation to a THMP
- Not one referral to EMEA in relation to other products containing herbal substances

Conclusions:

1. It is essential that more regulatory experience is gained with THMPs.
2. Applicants should not only consider the risks, but also the chances given by Directive 2004/24.
3. Regulators in the NCAs should handle applications for registration as THMP in a more pragmatic and more flexible way.
Implementing the new legislation:
Perspectives from industry

Bombardelli V., Indena S.p.A.
June 14th, 2007

WHY A NEED FOR A COMMON LEGAL FRAMEWORK?

LACK OF HARMONISATION

DIVERGING RULES IN MEMBER STATES FOR THE SAME HERBAL PRODUCT

EUROPE

FRANCE
GERMANY
SPAIN

GINKGO BILOBA

ITALY

SCANDINAVIAN
UNITED KINGDOM

LACK OF HARMONISATION

FOOD
DRUG
HEALTH

FOOD
TRADITIONAL HERBAL MEDICINAL PRODUCTS

What is the present situation?

11 EU Member States have not yet implemented THMP Directive

79 applications in 12 member States

8 products registered in 3 member States

HMPC Committee for Herbal Medicinal Products

Well established use and Traditional use Monographs

ALOE
FRANGULAE CORTEX
LINUM SEMEN
PLANTAGINIS OVATAE SEMEN
PLANTAGO OVATA SEMinis
TEGUMENTUM

PSYLLII SEMEN
SENNAE FRUCTUS
SENNAE FOLIUM
VALERIANAE RADIX
TRADITIONAL HERBAL MEDICINAL PRODUCTS

Why should we register an herbal as a THMP?

OTC medicinal indication with a warning

Pharmaceutical quality + GMPs

Easier registration track

Access to EU market via mutual recognition procedure
### TRADITIONAL HERBAL MEDICINAL PRODUCTS

**Why should not we register an herbal as a THMP?**

| OTC medicinal indication very similar to food indication |
| Costs (registration, production, documentation etc.) |
| Registration track more and more difficult |
| Time to market |

---

### WELL ESTABLISHED USE (HERBAL) MEDICINAL PRODUCTS

- **♣** THE DIRECTIVE ALLOWS TO GET PHARMACOLOGY, TOXICOLOGY AND EFFICACY DATA ON THE BASIS OF PUBLISHED SCIENTIFIC LITERATURE

- **♣** GOOD OPPORTUNITY TO REGISTER “OLD PRODUCTS”

- **♣** NOT A VALID SOLUTION FOR THE “NEW PRODUCTS” BECAUSE IT MAY BE NOT POSSIBLE TO ACCESS CLINICAL TRIALS IN THE EU AND

- **♣** TEN YEARS TIME TO GET THE WELL ESTABLISHED USE STATUS

Claim: Prescription only and OTC indications
**THE DOCUMENTATION SUBMITTED BY THE APPLICANT SHOULD COVER ALL ASPECTS OF THE SAFETY AND EFFICACY ASSESSMENT**

<table>
<thead>
<tr>
<th>SAFETY/PHARMACOLOGY</th>
<th>EFFICACY</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOXICITY</td>
<td>CLINICAL PHARMACODYNAMICS</td>
</tr>
<tr>
<td>REPRODUCTIVE FUNCTION</td>
<td>CLINICAL PHARMACOKINETICS</td>
</tr>
<tr>
<td>PERINATAL TOXICITY</td>
<td>CLINICAL Efficacy</td>
</tr>
<tr>
<td>MUTAGENIC POTENTIAL</td>
<td>(POST-MARKETING EXPERIENCE)</td>
</tr>
<tr>
<td>CARCINogenic POTENTIAL</td>
<td>INTERACTIONS</td>
</tr>
<tr>
<td>PHARMACODYNAMICS</td>
<td>(BIOAVAILABILITY/BIOEQUIVALENCE)</td>
</tr>
<tr>
<td>PHARMACOKINETICS</td>
<td></td>
</tr>
<tr>
<td>(LOCAL TOLERANCE)</td>
<td></td>
</tr>
</tbody>
</table>

**WELL ESTABLISHED USE (HERBAL) MEDICINAL PRODUCTS**

- **EUROPE**
- **HMPC** Committee for Herbal Medicinal Products
- Well established use and Traditional use Monographs

<table>
<thead>
<tr>
<th>HERBAL</th>
<th>MEDICINAL PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALOE</td>
<td>PSYLLII SEMEN</td>
</tr>
<tr>
<td>FRANGULAE CORTEX</td>
<td>SENNAE FRUCTUS</td>
</tr>
<tr>
<td>LINUM SEMEN</td>
<td>SENNAE FOLIUM</td>
</tr>
<tr>
<td>PLANTAGINIS OVATAE SEMEN</td>
<td>VALERIANAE RADIX</td>
</tr>
<tr>
<td>PLANTAGO OVATA SEMINIS TEGUMENTUM</td>
<td></td>
</tr>
</tbody>
</table>

**HMPC** Committee for Herbal Medicinal Products

Well established use and Traditional use Monographs

- ALOE
- PSYLLII SEMEN
- FRANGULAE CORTEX
- SENNAE FRUCTUS
- LINUM SEMEN
- SENNAE FOLIUM
- PLANTAGINIS OVATAE SEMEN
- VALERIANAE RADIX
- PLANTAGO OVATA SEMINIS TEGUMENTUM
CONCLUSIONS

• Herbal medicinal products are a reality in the European market: what about traditional ones?

• Public health concerns related to uncontrolled herbal products and starting materials

• Herbal food products even under THMP Directive? 2011 is approaching

• Raise the bar of quality rules for herbal supplements/flexible approach for THMPs