Perspectives for Herbal Medicinal Products in the EU

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1st May 2004 New EU Members
Germany & France dominate European herbals market
Total Market 2002: ~ 4 Billion € ex factory

Market share % based on value sales

Source: IMS 2003
Herbal medicinal products prescribed by medical doctors

prescription shares by country in %

<table>
<thead>
<tr>
<th>Country</th>
<th>Prescription Shares</th>
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<td>Europe</td>
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<td>UK</td>
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<td>France</td>
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Source: IMS 2002
of 06 November 2001
Article 1

Medicinal product:

Any substance ... presented for treating or preventing disease ...

Any substance ... which may be administered ... with a view to ... restoring, correcting or modifying physiological functions ... is likewise considered a medicinal product.
Medicinal Product or Food Supplement?

Problem not fully resolved by CD 2002/46/EC

CD 2002/46/EC
Art. 2
... purpose ... to supplement the normal diet ...
substances with a nutritional or physiological effect ...

CD 2001/83/EC
Art. 1
.. presented for treating or preventing disease ..
... administered ... with a view ... to restoring, correcting or modifying physiological functions ..
… the definition of “medicinal product” should be modified so as to avoid any doubt as to the applicable legislation, when a product, whilst fully falling within the definition of a medicinal product, may also fall within the definition of other regulated products. …

where a given product comes under the definition of a medicinal product, but could also fulfil the definition of other regulated products, it is necessary, in case of doubt and in order to provide legal certainty, to state explicitely which provisions have to be complied with. …
Article 1

Medicinal Product

(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings.

(b) Any substance or combination of substances which may be used in or administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions.
Review of Directive 2001/83/EC
Political Agreement

Article 2

2. In cases of doubt, where a product falls within the definition of 'medicinal product', the provisions of this Directive shall apply, even in cases where the product also falls within the scope of other Community legislation.
Claims referring to the prevention, treatment or cure of human disease are prohibited for foods.

However

a difference between “prevention” and “risk reduction” is made.

Three permitted types of claim

Nutrition content claims: e.g., “good source of fibre”, restricted to foods containing 6 grams of fibre per 100 grams (Annex).

Health claims (1): that describe the role of a nutrient in normal human physiology that are based on long established, non-controversial science (e.g., “calcium builds strong bones”); list from EFSA (Article 12)

Health claims (2): that a substance may reduce the risk of disease development, e.g., “calcium may reduce the risk of osteoporosis”; based on the review and approval of a scientific dossier in support of the relationship between the product and the disease risk reduction claim by the EFSA. (Article 13)
Marketing Authorisation Procedures in the EU

**Independent National Procedure**

- competent authority of the Member State

**Centralised Procedure**

- EMEA (CPMP) / rapporteur / co-rapporteur

**Mutual Recognition Procedure**

- reference member state (RMS) / concerned member states (CMS)
Marketing Authorisation of Medicinal Products in the EU*

Community Authorisation


Centralized Marketing Authorisation for

A  Products derived from Biotechnology

B  New active substances / therapeutic innovations

* http://pharmacos.eudra.org
Marketing Authorisation of Medicinal Products in the EU

National Authorisation


Basis for

Mutual Recognition of marketing authorizations
EDQM / European Pharmacopoeia
Group 13a and Group 13b “Phytochemistry”

Monographs

- General criteria, e.g.
  - herbal drugs (definition)
  - herbal extracts (definitions)
  - pesticides etc.
- Herbal drugs
- Extracts

Certificate of Suitability
(March 2003)
Quality assurance starts at the site of primary production

“Good Agricultural and Collection Practices”

for starting materials of herbal origin
Review of Directive 2001/83/EC
Political Agreement

Article 46

(f) to comply with the principles and guidelines of good manufacturing practice for medicinal products and, in so doing, to use only active substances employed as starting materials which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials.

Annex 1

Part III - Particular Medicinal Products

4. Herbal Medicinal Products

… To document the section on the manufacturer of the herbal preparation, the name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation shall be provided, where appropriate. …
… With respect to the description of manufacturing process and process controls for the herbal substance, information shall be provided to adequately describe the plant production and plant collection, including the geographical source of the medicinal plant and cultivation, harvesting, drying and storage conditions. …
Herbal Medicinal Products in the EU

Requirements related to Safety and Efficacy

Two / Three types of documentation

1. Full documentation with new tests and trials
   mandatory for:
   any herbal medicinal product never marketed in the EU
   therapeutic innovations
   new indication / therapeutic area for “old” products

2. Full bibliographic documentation

3. Traditional medicinal product - registration (draft)
Article 10 No. 1 a) ii

The applicant shall not be required to provide the results of ... pharmacological and toxicological tests or clinical trials if he can demonstrate:

(ii) ... *by detailed reference to published scientific literature* ... that the constituent or constituents of the proprietary medicinal product have a *well established medicinal use*, with *recognised efficacy* and an *acceptable level of safety*. 
All Types of Evidence may be used

Annex 1 to CD 2001/83 EC
amended by CD 2003/63 of 25 June 2003

… The documentation … should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. … With respect to the provisions on “well-established medicinal use” it is in particular necessary to clarify that “bibliographic reference” to other sources of evidence (postmarketing studies, epidemiological studies, etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily. …
(a) Factors which have to be taken into account

- the *time* over which a substance has been used
- *quantitative aspects* of the use of the substance
- the *degree of scientific interest* in the use of the substance (reflected in the published scientific literature)
- the *coherence of scientific assessments*

Different periods of time may be necessary for establishing ”well established use” of different substances *minimum of one decade* from the first systematic and documented use of that substance as a medicinal product in the EU.
Guidance on the assessment of safety and efficacy

“Points to consider on the evidence of safety and efficacy required for well-established herbal medicinal products”

“Draft concept paper on the implementation of different levels of scientific evidence in core-data for herbal drugs”

May 2003
Grading of Evidence / Recommendations

Grade A: Evidence Ia, Ib

Requires at least one randomised controlled trial as part of the body of literature of overall good and consistency addressing the specific recommendation.

Grade B: Evidence IIa, IIb, III

Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation.

Grade C: Evidence IV

Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.
C) General evidence (Level IV, Grade C)

The following claims may be acceptable:

Relief or management of symptoms or description of a pharmacological action related to management of symptoms of a minor, self-limiting disease / disorder that does not require medical intervention for diagnosis or monitoring.

If general evidence is submitted, additional supporting scientific evidence, e.g. pharmacological data, may be necessary for acceptance.
European Commission Proposal for a Directive on Traditional Herbal Medicinal Products

17 January 2002, amended 09 April 2003

Criteria for eligibility:

- Indications (without intervention of medical practitioner)
- Labeling “traditionally used ...”
- Specified strength / posology
- Oral, external, inhalation
- Period of traditional use 30 years (15 + 15)
- Not harmful, efficacy plausible on the basis of long-term use and experience
The following health claims shall not be allowed (Article 11):

- too general, non specific claims such as “helps to support the immune system”, improvement of general well-being, overall good health;

- reference to psychological and behavioral functions;

- weight loss claims which may result from a reduction of hunger, increase of satiety or reduction of available energy from the diet;

- claims targeting endorsements by health professionals.

_Beverages containing > 1.2 % V/V ethanol_ shall not present any health claims (Article 4).
European Commission Proposal for a Directive on Traditional Herbal Medicinal Products

17 January 2002, amended 09 April 2003

Documentation requested

- Quality dossier (full dossier identical to bibliographic applications)
- Bibliographic review of safety data together with an expert report (not necessary if listed or monograph)
- Bibliographical or expert evidence that the product or a corresponding medicinal product has been in medicinal use for at least 30 years (not necessary if listed or monograph)
Article 16h

Committee for Herbal Medicinal Products at the EMEA

• Community **herbal monographs** for traditional and well-established herbal medicinal products. Monographs shall be used as the basis for any application.

• **List** of traditional herbal substances

• Responsible committee for the scientific assessment of all EU procedures originating from national decisions, **arbitration**
Grading of Evidence / Recommendations

New products
- Serious diseases

major claims

minor claims

Traditional medicinal product

Traditionally used
- Without supportive scientific evidence

Fraudulent or misleading claims

Herbal medicinal product for...
- (treatment, prevention ...)

well-established
Perspectives for Herbal Medicinal Products

Two Concepts

1. The Food Concept (USA/herbal)
   - lack of clear guidance relating to quality, GMP, safety, efficacy; claims become the most important issue;
   - duplication / mirroring of “pharmaceutical activities”, e.g. GMP, Safety, DS-Vigilance; easy access to market.

2. The Medicines / Subset of Medicines Concept
   - the existing regulatory / pharmaceutical framework can be used; specific expertise must be implemented; clear criteria for GMP, Quality, Safety, Efficacy; implementation of requirements, e.g. labelling, high standard of consumer protection; access depends on effectiveness of licensing procedure.
Perspectives for Herbal Medicinal Products

Parallel developments in other countries
e.g. in Asia, America (except USA for herbal products), Australia, Europe

Active role of WHO
General guidelines and strategy papers

Monographs

Main discussion topic at the 10th International Conference of Drug Regulatory Agencies, ICDRA, Hong Kong, June 2002
WHO Essential Drugs and Medicines Policy
Traditional Medicine Program

Regional Workshops for Training for Regulatory Agencies

• Regional Office for the Western Pacific 2002
• Pan American Health Organisation 2002
• Regional Office for the Eastern Mediterranean Region 2002
• Regional Office for the European Region 2003
Perspectives for Herbal Medicinal Products

European Union

Consolidation of the legal framework

• adaptation of requirements and procedures to the situation of herbal medicinal products

• three types of documentation (new tests and trials, bibliographic, traditional use) and two procedures (marketing authorization, trad. registration)

• legal definition of food supplements

• legal definition of health claims for foods