Perspectives for Herbal Medicinal Products in the EU

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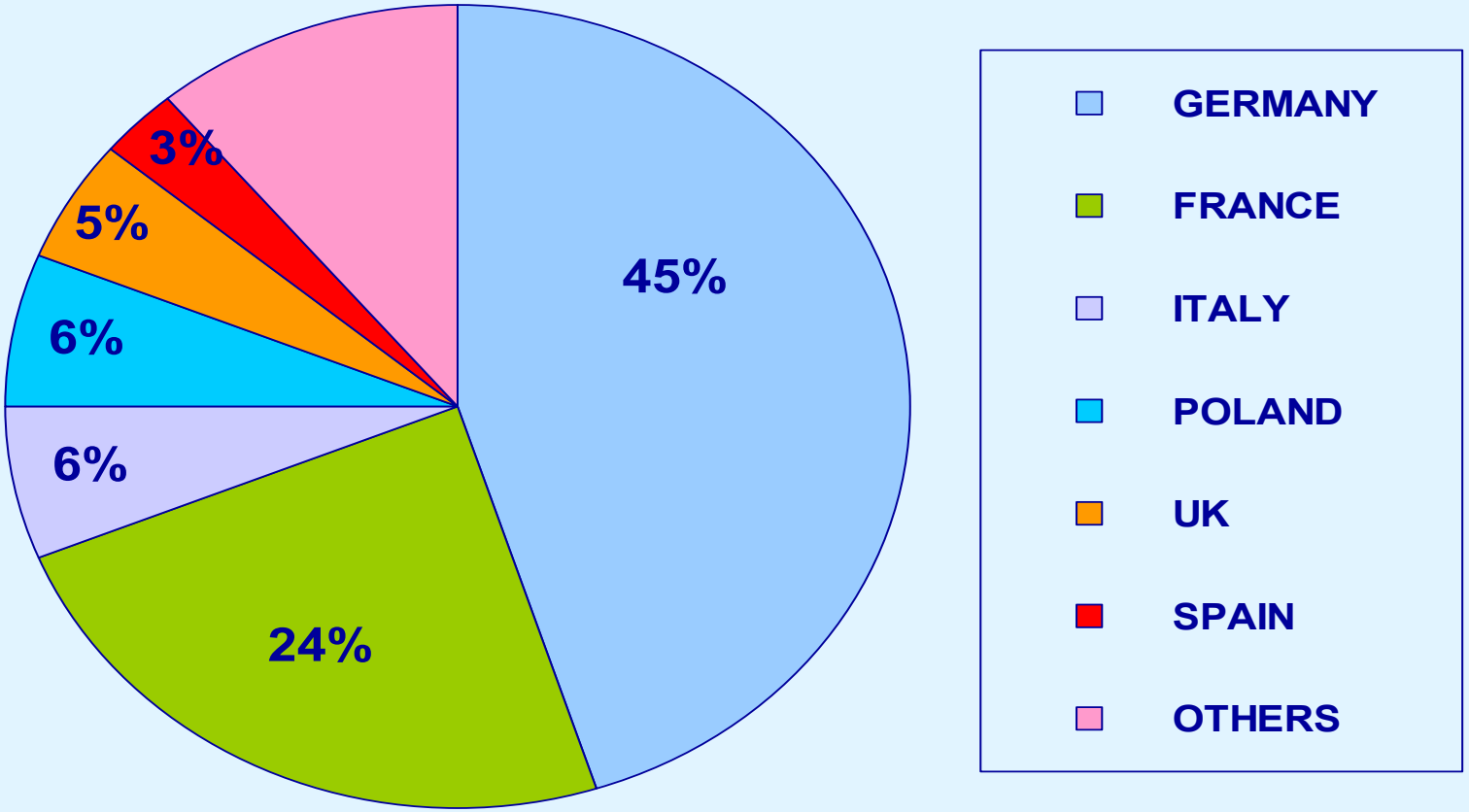
EMEA/CPMP Working Party
Herbal Medicinal Products

1st May 2004 New EU Members

Austria
Belgium
Cyprus
Czech Republic
Denmark
Estonia
Finland
France
Germany
Greece
Hungary
Ireland
Italy
Latvia
Lithuania
Luxembourg
Malta
Netherlands
Poland
Portugal
Slovak Republic
Slovenia
Spain
Sweden
United Kingdom

Germany & France dominate European herbals market

Total Market 2002: ~ 4 Billion € ex factory

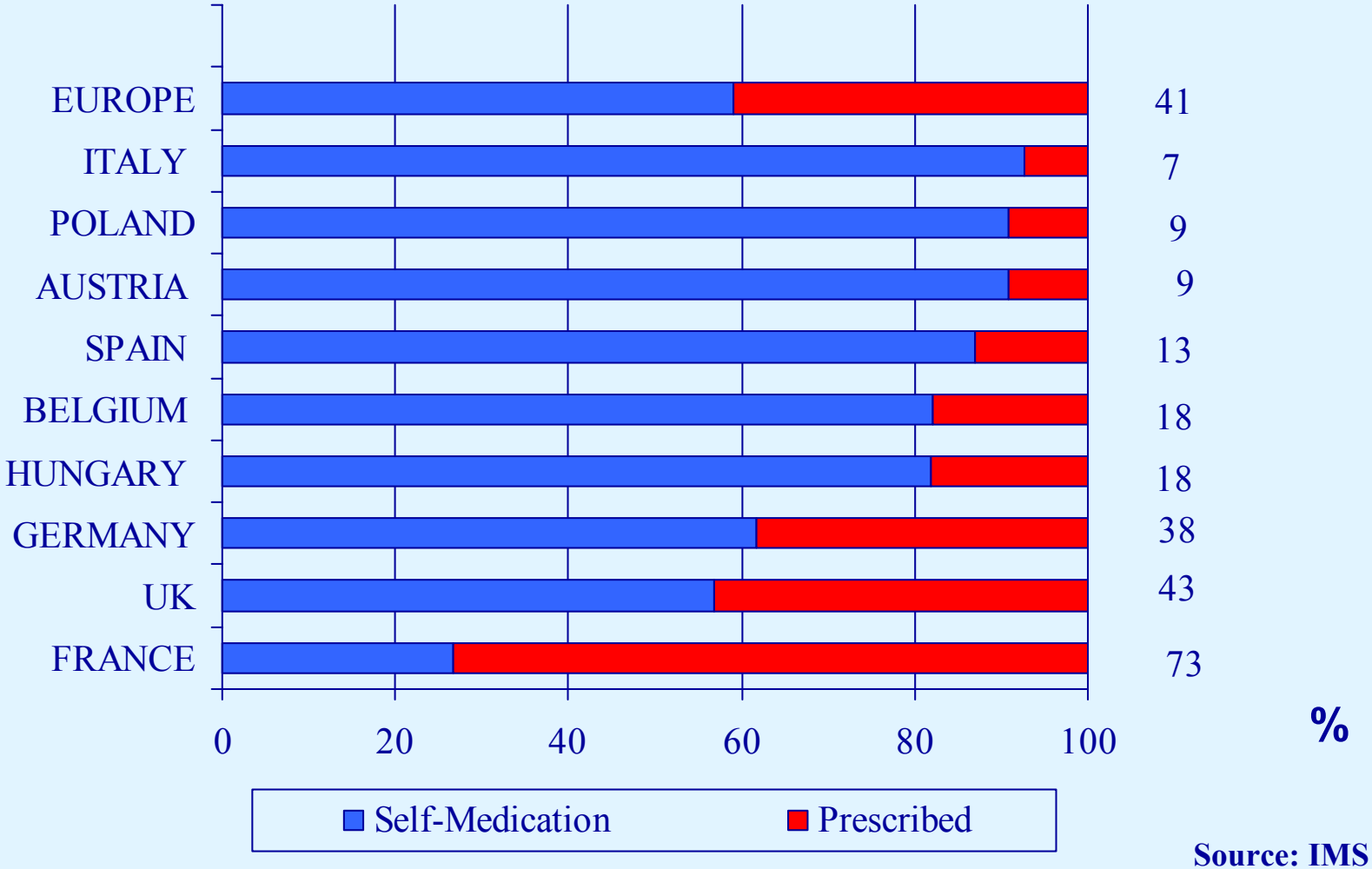


Market share % based on value sales

Source: IMS 2003

Herbal medicinal products prescribed by medical doctors

prescription shares by country in %



Source: IMS 2002

European Council Directive 2001/83/EC

of 06 November 2001

Article 1

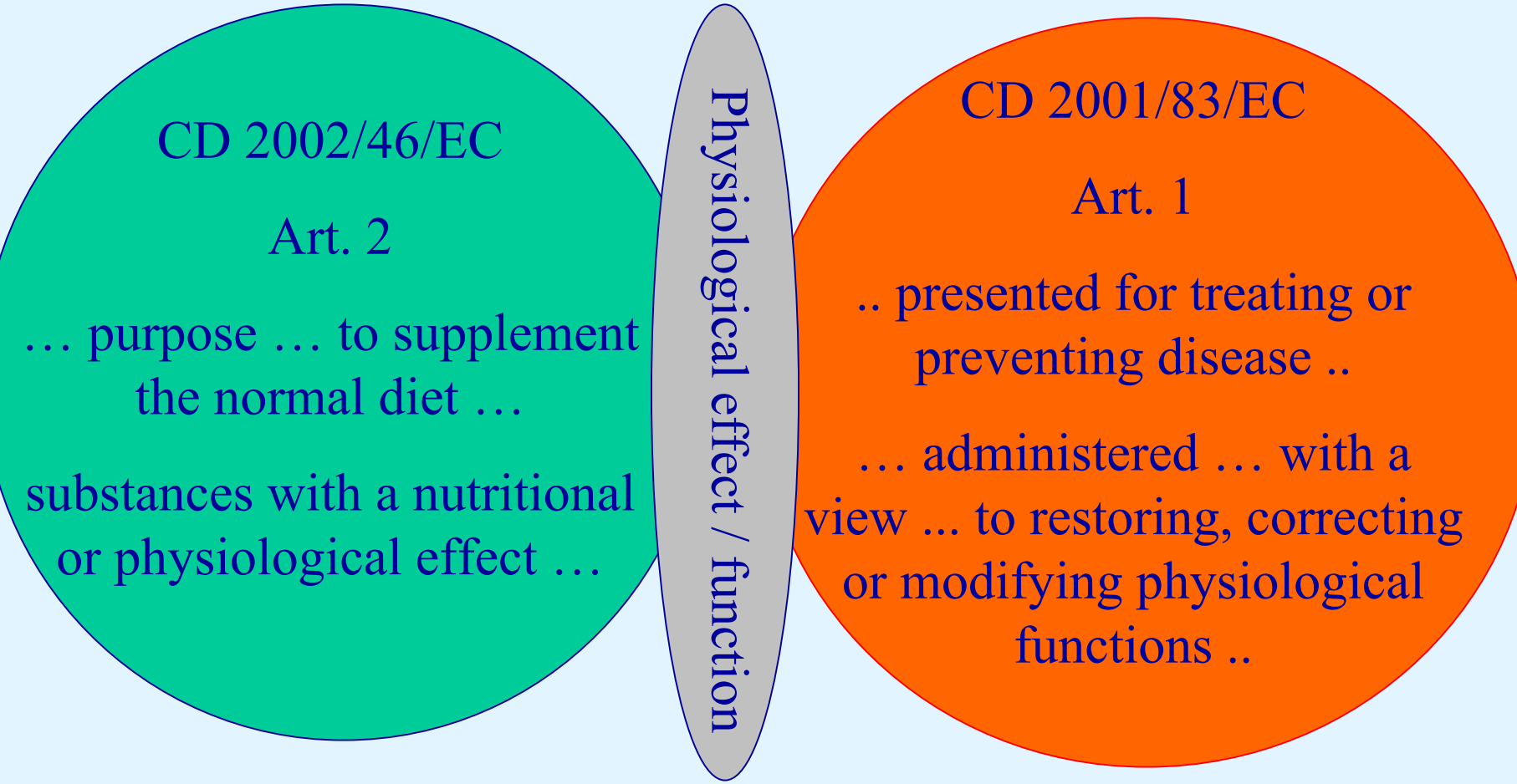
Medicinal product:

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



Review of Directive 2001/83/EC

Amended Proposal 12. June 2003
Political Agreement

… 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. …

Review of Directive 2001/83/EC

Amended Proposal 12. June 2003
Political Agreement

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

Amended Proposal 12. June 2003

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.

EC Proposal for a Regulation of the European Parliament and of the Council on Nutrition and Health Claims made for Foods

July 16, 2003

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.

EC Proposal for a Regulation of the European Parliament and of the Council on Nutrition and Health Claims made for Foods

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

Council Regulation (EEC) No 2309/93, of 22 July 1993, laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products.

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

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

Basis for

Mutual Recognition of marketing authorizations

EDQM / European Pharmacopoeia

Group 13a and Group 13 b "Phytochemistry"

***E**uropean **D**irectorate for the **Q**uality of **M**edicines*

www.edqm.org

Monographs

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

Certificate of Suitability

(March 2003)

www.emea.eu.int

EMEA Herbal Medicinal Products Working Party

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

Amended Proposal 12. June 2003
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.*

European Council Directive 2001/83/EC

of 06 November 2001 amended by CD 2003/63 of 25 June 2003

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. …

European Council Directive 2001/83/EC

of 06 November 2001 amended by CD 2003/63 of 25 June 2003

Annex 1

Part III - Particular Medicinal Products

4. Herbal Medicinal Products

… 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)

European Council Directive 2001/83/EC

of 28 November 2001

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. …

"well-established use"

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

(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.

EMEA Herbal Medicinal Products Working Party

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*

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

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

EC Proposal for a Regulation of the European Parliament and of the Council on Nutrition and Health Claims made for Foods

July 16, 2003

The following health claims shall *not* be allowed (Article 11):

oo 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, ncrease 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)

European Commission Proposal for a Directive on Traditional Herbal Medicinal Products

17 January 2002, amended 09 April 2003

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***

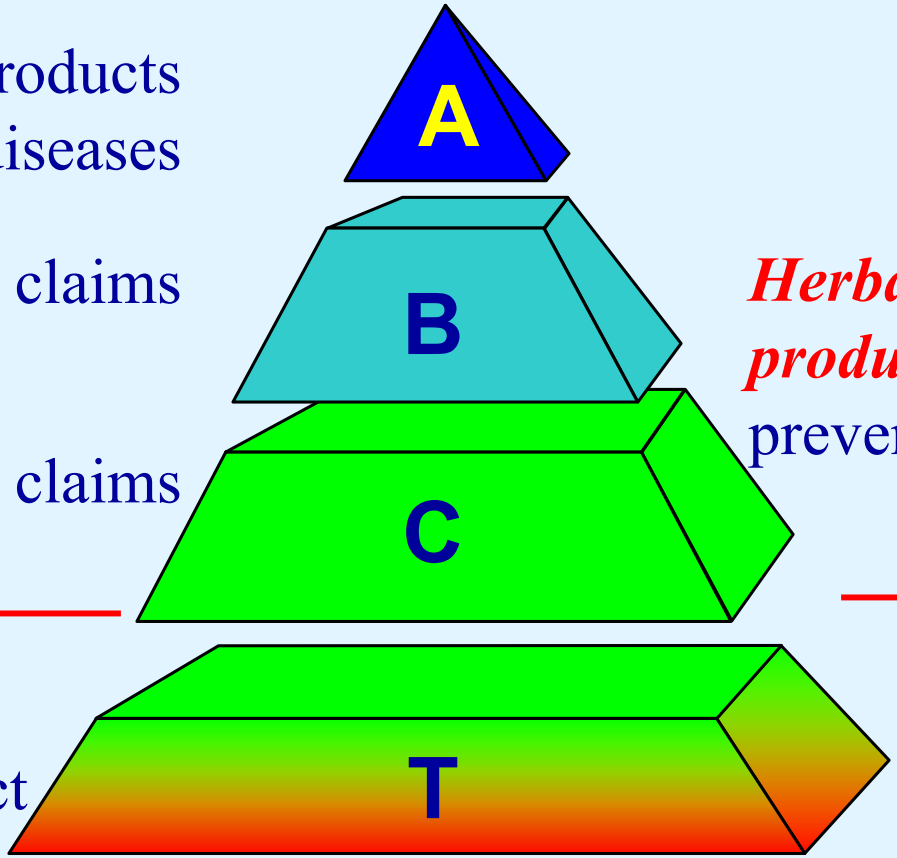
Grading of Evidence / Recommendations

well-established

New products
serious diseases

major claims

minor claims



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

raditional
edicinal product

Traditionally used without supportive scientific evidence

Fraudulent or misleading claims

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

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