

# EXPANDING THE BOUNDARIES OF SELF-MEDICATION IN A GLOBAL CONTEXT

## The internationalisation of herbal medicinal products

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### Internationalisation of Herbal Medicinal Products

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**WHO 9th International Conference of Drug Regulatory Agencies ICDRA**  
Berlin 25-29 April 1999



#### Workshop on Herbal Medicines

*chaired by*

Germany, Ghana

*agencies presenting*

Australia, China, Indonesia, USA,  
United Arab Emirates and WHO

**WHO 9th International Conference of Drug Regulatory Agencies ICDRA**  
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#### Recommendations:

... Member States should formulate national policies on traditional medicines  
... Emphasis ... to the *development or updating of the national legislation for registration and licensing of industrially prepared herbal medicines*, ... as an integral component of the national health systems ...

#### Definition of Terms WHO / EU

##### *Herbal medicinal products*

medicinal products containing as active substances exclusively herbal drugs or herbal drug preparations

##### *Herbal drugs*

plants or part of plants in an unprocessed state

##### *Herbal drug preparations*

comminuted or powdered herbal drugs, extracts (incl. purified extracts), tinctures, fatty or essential oils, resins or gums, etc..

*Chemically defined isolated constituents* or their mixtures *are not herbal drug preparations*. ...

## European Court of Justice

Several decisions classify herbal preparations as medicinal products (Article 1 of CD 65/65 EEC):

- presented with prophylactic and / or therapeutic claims
- administered to humans with a view to modify physiological functions
- pharmacological action, e.g. on immune system
- packaging, presentation and marketing as a medicinal product

## Classification of Medicines and Dietary Supplements / Foods Herbal Ingredients

### Peppermint tea

- Claim: refreshing beverage ⇒ **food**
- Claim: treatment/prevention of stomach upset ⇒ **medicine**  
(claim, presentation, consumers' expectation)

### Senna tea

- Claim: healthy supper-time tea to help digestion ⇒ **medicine**  
(objective pharmacological action, consumers' expectation)

## German "Arzneiverordnungsreport 1998" (Drug Prescription Report 1998)

Rank (of 2000)	Product <sup>o</sup>	Prescriptions (x 1000)	Sales (x DM 1000)
12	Sinupret	3,431	46,375
38	Prospan	1,952	24,810
85	Tebonin	1,427	96,665
97	Jarsin	1,296	51,247
93	Lasix	1,311	46,164
127	Iberogast	1,088	19,946
141	Gingium	1,025	49,788
173	Ginkgobil	894	45,143
175	Crataegutt	880	34,823
221	Rökan	736	52,423
229	Kytta Sedativum	720	18,946
644	Zantic	314	43,415

# Medicine and Culture

Lynn Payer

**France:**  
Cartesian Thinking and the *Terrain*

**Germany:**  
The Lingering Influences of Romanticism

**Great Britain:**  
Economy, Empiricism, and Keeping the Upper Lip Stiff

**United States:**  
The Virus in the Machine



## Trends in Alternative Medicine Use in the US 1990-1997

Eisenberg et. al. JAMA 280:1569-1575 (1998)

Use increased from 33.8 to 42.1%

	1990	1997
1. Relaxation techniques	13.1%	16.3%
<b>2. Herbal medicine</b>	<b>2.5%</b>	<b>12.1%</b>
6. Megavitamins	2.4%	5.5%
13. Homoeopathy	0.7%	3.4%
16. Acupuncture	0.4%	1.0%

## Trends in Alternative Medicine Use in the US 1990-1997

Eisenberg et. al. JAMA 280:1569-1575 (1998)

### Estimated expenditures in 1997

**US \$ 21.2 billion**

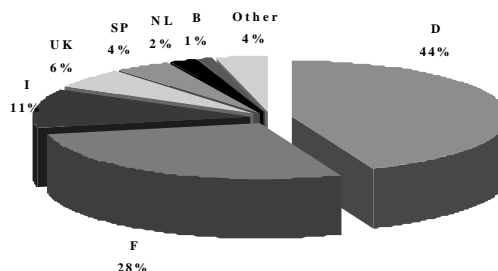
for alternative medicine professional service

**US \$ 27.0 billion**

for alternative therapies  
(including US \$ 5.1 billion for herbal medicines)

## IMS 1998 EU-Market Estimates Herbal Medicinal Products 1995

Total Market 5,5 Billion US \$ ex factory



## Trends in Alternative Medicine Use in the US 1990-1997

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### Conditions for using alternative therapies

back problems	lung problems
allergies	skin problems
fatigue	digestive problems
arthritis	anxiety
hypertension	depression
insomnia	headaches

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## Herbal medicinal products may present risks

- 8 / 11 "natural TCM herbal creams" contained 64 to 1500 µg/g dexamethasone, severe eczema herpaticum
- ~ 100 cases of "Chinese herbs nephropathy"
- aggravation of seizures in a child by an Ayurvedic "cerebral tonic"
- > 3000 herbal medicinal products subject to pharmacovigilance actions since 1981 in Germany
- relevant interaction with co-medication (Phenprocoumon, Ciclosporine, Alprazolam, Lithium)

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## European Council Directive 65/65

of 26 January 1965

### Article 3

No medicinal product may be placed on the market of a Member State unless an **authorisation** has been issued by the competent authority of that Member State

### Article 4

In order to obtain an authorisation ... the person responsible for placing that product on the market shall make **application to the competent authority**

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## Particularities of herbal medicinal products

### General aspects

- ⇒ different legal status in the past, history of parallel uses
- ⇒ preference in the lay-public, sceptical attitude in professionals

### Pharmaceutical aspects

- ⇒ complex biological mixtures, active constituents not identified
- ⇒ influence of production parameters / Process validation
- ⇒ acceptance criteria for specification indispensable for any decision making on safety and efficacy

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## Particularities of herbal medicinal products

### Preclinical and clinical aspects

- ⇒ long-term use and experience laid down in published literature
- ⇒ used for OTC treatment in minor conditions
- ⇒ few studies in clinical pharmacology
- ⇒ few new clinical studies

### Other aspects

- ⇒ no protection of new data /intellectual property
- ⇒ availability as crude botanical partly independent from marketing authorisation

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## WHO 8<sup>th</sup> ICDRA Bahrain, 10-13 November 1996

### Recommendations

.... WHO, in collaboration with governments, NGOs, institutions, and collaborating-centres, should continue to develop and review technical documents dealing with herbal medicines, and should **encourage MS to establish groups of experts on herbal medicines in their own countries or regions.....**



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## Australia

Implementation of specific advice and consultation

### • Complementary Healthcare Consultative Forum

Industry, government, consumers  
chaired by parliamentary secretary

### • Office of Complementary Medicines

separateness within TGA

Senior principle research scientists with mixed skills

### • Complementary Medicines Evaluation Committee

advisory body, experts of different expertise

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## Canada

March 1999

### • Office of Natural Health Products

all regulatory functions, pre-marketing assessment, licensing, post-approval monitoring

### • Expert Advisory Committee with Working Parties

advisory body, experts of different expertise

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## USA

### Commission on Dietary Supplement Labels

November 1997

“many botanical products sold as dietary supplements are *used for prevention or treatment* purposes. .... *The consumer would be better served by clear information* regarding preventive and therapeutic uses than by the limited statements of nutritional support..”

“The Commission strongly recommends that FDA promptly *establish a review panel* for OTC claims for botanical products that are proposed by manufacturers for drug uses. The panel should have *appropriate representation of experts* on such products.”

## USA

### FDA / CDER

#### Guidance for Industry Botanical Drug Products

Draft expected in 1999

### European Harmonisation for Herbal Medicinal Products

- European Parliament
- European Council
- European Commission
- European Pharmacopoeia
- European Agency for Medicinal Products, EMEA
- National Authorities of EU Member States
- Industry e.g. AESGP Working Group
- Scientific Organisations, e.g. ESCOP  
Intern. Soc. for Medicinal Plant Research, GA  
European Society of Ethnopharmacology

### Report from the EMEA ad hoc Working Group on Herbal Medicinal Products 1997/1998

[Presented to the Management Board on 10 February 1999]

<http://www.eudra.org/gendocs/general/hmpwg.htm>



The European Agency for the  
Evaluation of Medicinal Products  
Human Medicines Evaluation Unit

### European Council Directive 65/65 EEC

of 26 January 1965

#### Article 4 No. 8 a) ii

The applicant shall not be required to provide the results of ... 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*.

### Levels of Evidence

WHO / EU 1999

US Agency for Health Care Policy and Research  
1992

Level	Type of Evidence
Ia	Meta-analysis of randomized controlled trials
Ib	at least one randomised controlled trial
IIa	at least one well-designed controlled study without randomisation
IIb	at least one other type of well-designed quasi-experimental study
III	well-designed non experimental descriptive studies, such as comparative studies, correlation studies, case-control studies
IV	expert committee reports or opinions and/or clinical experiences of respected authorities.

### core-SPC for VALERIANAE RADIX

(September 1998)

2. *QUALITATIVE AND QUANTITATIVE COMPOSITION*  
Valerian root  
Extract prepared with water, ethanol/water (max 70%)  
Tinctures (1:5, ethanol 70% V/V)
- 4.1. *THERAPEUTIC INDICATIONS*  
*Herbal medicinal product* for the relief of temporary nervous tension and temporary difficulty in falling asleep.

### Summary

**Herbal medicinal products have to be classified as drugs :**

- ⇒ used for treatment and/or prophylaxis of disease
- ⇒ are presented with therapeutic / prophylactic claims
- ⇒ have defined pharmacological actions
- ⇒ may have risks that have to be monitored, assessed, labelled
- ⇒ need strict quality control and GMP

**However**

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### Summary

#### **The long-term experience and the particularities of herbal drug preparations have to be taken into due account**

- ⇒ open minded approach by experts that have the specific expertise and experience (WHO ICDRA recommendation, examples in Australia, Canada, EU/EMA)
- ⇒ adequate interpretation of existing requirements, e.g. appropriate level of evidence of efficacy in minor indications (example EMA Report)
- ⇒ transparent assessments of efficacy (e.g. core Summary of Product Characteristics facilitating mutual recognition within EU )

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### Summary

#### **Future activities / proposals**

- ⇒ implementation of requirements / legislation
- ⇒ implementation of specific expertise and responsibility within national agencies
- ⇒ simplified procedure for simple products such as traditional herbal teas on the basis of clear quality-requirements and core-SPCs
- ⇒ conditions for marketing of traditional products specific to one Member State or of traditional products used by ethnic minorities
- ⇒ option for a centralised marketing authorisation for Europe
- ⇒ international harmonisation of requirements for herbal medicinal products (International Conference on Herbs?)

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