Herbal and Traditional Herbal Medicinal Products – Experiences in Germany

Prof. Dr. Werner Knöss
Disclaimer

• With reference to the publication policy of the European Medicines Agency (EMA) I do not speak on behalf of the Committee on Herbal Medicinal Products (HMPC) or the EMA.

• The views expressed here may not be understood or quoted as being made on behalf of the HMPC/EMA or reflecting the position of the HMPC/EMA.
DIRECTIVE 2004/24/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 31 March 2004


Having regard to the proposal from the Commission (1),

Having regard to the opinion of the European Economic and Social Committee (2),

Acting in accordance with the procedure provided for in Article 251 of the Treaty

(4) Having regard to the fact that a simplified procedure for the marketing of medicinal products having a specific benefit-risk balance is desirable to promote the development of medicinal products within the Community and to avoid duplication and distortion of competition between producers of these products. They may also have potential for the treatment of diseases not always properly covered by current medicines.

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION

DECIDE AS FOLLOWS:

Article 1

The provisions of this Directive shall apply in the Member States to herbal medicinal products intended for human use.

Article 2

1. The provisions of this Directive shall apply to herbal medicinal products intended for human use in the conditions laid down in Article 20.

2. The provisions of this Directive shall not apply:

(a) to the marketing of homeopathic medicinal products as provided for in the legislation of the Member States;
(b) to the marketing and placing on the market of traditional herbal medicinal products as provided for in the legislation of the Member States.
THE EUROPEAN COMMUNITY

Having regard to the Treaty establishing the European Community and having regard to the Decision of the Council of 20 December 1994 establishing a scheme for the marketing of traditional herbal medicinal products containing medicinal substances of plant origin designated in Annex I to Directive 2004/24/EC

Acting in accordance with the powers conferred upon it under Article 35 of Directive 2004/24/EC, the Commission has examined applications for traditional medicinal products not eligible for registration under Directive 2004/24/EC. It has established differences that are not laid down in Annex I to Directive 2004/24/EC and that may also have an effect on health since the characteristics of these products cannot be assessed in the same way as in traditional use. These differences may also be of significance for the competition between medicinal products, and efficacy and safety of these medicinal products cannot be assessed within the current framework of registration and licensing.

However, this simplified procedure should be used for these products that are not eligible for registration under Directive 2004/24/EC because the characteristics of these products cannot be assessed as for traditional use.
Overview

I. Introduction

II. Regulation of Phytomedicines in Germany

III. Regulatory Concepts and Products

IV. Germany and the European Network
Complementary and Alternative Medicines in Germany

- Science
- Research and Education
- Tradition
- Options and Limits

Phytotherapy
Homeopathy
Anthroposophy
<table>
<thead>
<tr>
<th>Medicinal Products</th>
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<tr>
<td>Chemically defined</td>
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<tr>
<td>Herbal</td>
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<tr>
<td>Traditional herbal</td>
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<tr>
<td>Homoeopathic</td>
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<tr>
<td>Anthroposophic</td>
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<td>TCM</td>
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<td>Ayurvedic</td>
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Products in a Pharmacy
Pharmaceutical Universities

About 20% of total education in Pharmaceutical Biology
Textbooks Pharmacy and Phytotherapy
Deutscher Bundestag (German Parliament)
Ausschussbericht vom 28.04.1976 BT-DS 7/5091

„... von der Tatsache ausgegangen, dass auf dem Gebiet der Arzneimitteltherapie mehrere Therapierichtungen nebeneinander bestehen, die von unterschiedlichen theoretischen Denkansätzen und wissenschaftlichen Methoden ausgehen ...“

„...politische Zielsetzung, ... dass sich im Zulassungsbereich der in der Arzneimitteltherapie vorhandene Wissenschaftspluralismus deutlich widerspiegeln muss.“

... pluralism in therapy ...
German Medicines Act (AMG)

• AMG Article 4 (26, 29, 33) Definitions
  • Expert-Commissions Article 25 (6) AMG
  • Commission C Anthroposophy
  • Commission D Homeopathy
  • Commission E Phytotherapy
  • Commission Article 109a (3) AMG

• AMG Article 25 (7)
  • “... Medicinal products of a particular therapeutic system (Phytotherapy, Homeopathy, Anthroposophy), ...“

• AMG Article 25 (7a) Children and Adolescents
  • see Commissions
Commission E Monographs – Regulatory and Educational Standards

Elaboration of monographs until 1994
History of Regulation of Herbal Medicines

- 1976 German Parliament emphasises therapeutic pluralism in health care
- 1976 German medicines act (Arzneimittelgesetz AMG) notification of 148,000 existing medicinal products
  marketing authorisation of new medicinal products
- 1994 5th amendment of AMG transition according articles 105 and 109a applicants had to proof also safety and efficacy
- 2005 Registration of Traditional herbal medicinal products, implementation by 14. AMG-novellation
Herbal Medicinal Products

In Europe, ~ 4 Bill. €

Germany (CAM and TM)

- longstanding tradition
- department at BfArM with 57 staff members
- about 700 pharmaceutical companies
- about 10,000 medicinal products marketed
- about 2000 (traditional) herbal medicinal products

Source: IMS 2005
BfArM – Structure and Tasks

Head
Prof. Dr. Broich
Deputy
N. N.

Media and Public Relations
Mr. Pommer

Ombuds-Woman
Dr. Rieh

EU, International Affairs
Dr. Lehmann

Strategy and Planning
Dr. Scheffler

Research Council
N. N.

Licensing 1
Dr. Horn

Licensing 2
Dr. Enzmann

Licensing 3
Dr. Weiergräber

Licensing 4
Prof. Dr. Knöss

Research
Prof. Dr. Stingl

Scientific Services
Dr. Sudhop

Federal Narcotic Drug Centre
Dr. Cremer-Scheffer

Pharmacovigilance
Dr. Paeschke

Pharmacovigilance

Marketing Authorisation and Clinical Trial Approval

59,000 medicinal products
Licensing 4, BfArM

Prof. Dr. W. Knöss

Complementary and Alternative Medicines and Traditional Medicines (57 staff members)

Unit 41
Procedural Management

Unit 42
Herbal and Traditional Medicinal Products

Unit 43
Homoeopathic and Anthroposophic Medicinal Products

Research Medicinal Plants

- 22% pharmacists
- 37% biologists
- 30% chemists
- 5% physicians
- 3% food chemists
- 3% pharmacologists

Federal Institute for Drugs and Medical Devices | The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health (Germany)
Basic Figures – CAM and Traditional Medicines in Germany

Regulation since 1976 – Medicinal Products Act

- 2000 herbal medicinal products (23% combinations)
  1750 licensed herbal medicinal products (15%)
  250 registered trad. herbal medicinal products (40%)

- 1350 licensed homeopathic medicinal products (86%)
- 1050 licensed anthroposophic medicinal products (62%)
- 3900 registered homeopathic and anthroposophic (48%)
  medicinal products
Hinweise zum Verfahren der Registrierung traditioneller pflanzlicher Arzneimittel gemäß § 39a ff. AMG

Vom 30.08.2005

Mit der in Kürze in Kraft tretenden 14. Gesetz zur Änderung des Arzneimittelgesetzes (AMG) wird für traditionelle pflanzliche Arzneimittel unter den Voraussetzungen der § 39a-d AMG die Möglichkeit einer Registrierung als "traditionelles Arzneimittel" eröffnet.

In der Zulassungsabteilung 5 „Besondere Therapiegruppen und Traditionelle Arzneimittel“ des BfArM werden die erforderlichen Rahmenbedingungen und Verfahren etabliert, mit dem im Internet-Titelten Anträge auf Registrierung nach § 39a-d AMG bearbeitet und bearbeitet zu können. Im Sinne einer partnerschaftlichen Zusammenarbeit zwischen BfArM und den Antragstellern sollen die hier zuständigen Verfahrensablauf und weitere Fragen zur Antragstellung klar. Zukunftig werden diese Hinweise regelmäßig aktualisiert.

Zur strukturierten und effizienten Bearbeitung des Verfahrens bettet das BfArM die pharmazeutischen Unternehmen um Beachtung der folgenden Hinweise zur Einreichung des Antrages und der erforderlichen Unterlagen:

- Als Antragsformulare sind bis zum Verfahren der zur Zeit in Übersetzung befindlichen Formulare - die bisherigen Formulare – für Zulassungsanträge entsprechend den Verfahrensabläufen auf der Homepage des BfArM zu verwenden. Dabei ist zu beachten, dass die Anträge unter Punkt 1.4 dem als Anlage beigefügten Einleitungsantrag angegeben sein müssen.
- Zuletzt ist in dem Formular unter Punkt 1.1.3 ein entsprechender handschriftlicher Zusatz, dass es sich um eine Registrierung eines traditionellen Arzneimittels gemäß § 39a-d AMG handelt, zu ergänzen.

Future and global perspectives of regulation of herbal and traditional medicinal products.
## Communication – Scientific Advice

### Scientific advice - applications

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<td>2014</td>
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### Advice and cooperation

- **Indications**
- **Proof of tradition**
- Divergent opinions in different Member States
- **Combinations**
- **Quality**
- **Economic considerations**
- **CTD**
Evaluation of (Traditional) Herbal Medicinal Products

Medicinal plant

Herbal substance

GACP

GMP

Defined by manufacturing process and specifications

Herbal preparation

Finished product
Pharmacovigilance

Marketing Authorisation

Consumer information; labeling; advertising

Efficacy
- new trials
- bibliographic
- traditional use

Safety
- new tests
- bibliographic
- expert report
- bibliographic
- new tests

Quality Control

Good Manufacturing Practices

Good Agricultural and Collection Practices

Registration

applies to registered and to authorised HMP

may be replaced by a monograph or the list from the HMPC in registrations

identical for marketing authorisations and registrations

new

well-established

traditional
Example of a Traditional Herbal Medicinal Product – First Registration in EU in 2005

Traditional registration
Access to the market
Combination
Quality guideline conform
Plausibility
Additional data
Example of a Traditional Herbal Medicinal Product – Herbal Tea

Herbal tea
Transition from existing regulation
Fast track procedure because of complete documentation
Decision within six weeks after application
Example of a Traditional Herbal Medicinal Product

Problem from re-licensing (Nachzulassung)
Court case
Acceptance of tradition
Suitable quality documentation supported by Scientific advice
European Regulation – United in Diversity

Political union of 28 Member States

about 500 Mio inhabitants

24 official languages
The European Network

European Commission
European Parliament
Regulatory framework, law
Directives, Regulations

NCA and HMA
Assessment
Marketing authorisation
DCP, MRP, national

EDQM
Quality standards
General
Herbal drugs/preparations

EMA
Coordination
Guidance
Centralised procedure
European Medicines Agency - EMA

• Central European Authority with specified tasks
• Committees and Working Parties
• Herbal Medicinal Products Committee – HMPC
• Monographs and List Working Party - MLWP
• Coordination of National Competent Authorities
From Commission E to Community Monographs

Harmonised assessment (but „United in diversity“)
Current Sets of Monographs

- **HMPC-Monographs**
  Legally enforced, official monographs for Member States of the European Union

- **Commission E monographs**
  German-based standard since the 1990ies, out of age

- **ESCOP**
  European societies on phytotherapy, scientific compilation of bibliographic data, not official

- **WHO**
  Bibliography to suggest models to members of WHO, not official
European Medicines Agency

CHMP
Committee on Medicinal Products for Human Use

COMP
Committee on Orphan Medicinal Products

PDCO
Paediatric Committee

HMPC
Committee on Herbal Medicinal Products

CAT
Committee on Advanced Therapies

CVMP
Committee on Medicinal Products for Veterinary Use

PRAC
Pharmacovigilance Risk Assessment Committee

COMPOSITION:
1 member per Member State
1 member each from Norway and Iceland (EEA-EFTA states)
optional co-opted Members

Each member nominated by a Member State also has an alternate

HMPC Chairperson Werner Knöss
MLWP Chairperson Ioanna Chinou
Input in Development of Monographs
Rapporteurships

AT BE FR DE EL HU IT NL PL SI ES SE NO
Regulatory Development

Past

Ancient usage of medicinal plants

Written and oral conservation „No regulatory affairs“

Current situation

European regulation

Future

National regulations

Global approach
Conclusions

- Long history, scientific and regulatory expertise
- Access to the market of (Traditional) Herbal Medicinal Products is linked to assessment of quality, efficacy and safety
- Post-marketing surveillance
- National and European Procedures
- Harmonisation based on European standards provided by the HMPC (EMA)
- Transparency for users
Thank you for your attention!