How to Implement the New EU Legislation on Herbal Medicinal Products ?

The First Years' Experiences

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European Medicines Agency, London

Regulatory Guidance on solid Grounds

Regulation (EC) No 726/2004
of 31 March 2004

Title IV in force since
20 May 2004

Directive 2001/83/EC,
as amended by

Directive 2004/24/EC
And
Directive 2004/27/EC
of 31 March 2004

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

Herbal Medicinal Products in the EU

Access to the market

New option for access to the market:

Registration

4. "Simplified dossier" for traditional herbal medicinal products

The new simplified registration procedure

Implementation (Directives)

Member States and EMEA

Directive 2004/24/EC

Article 2

1. Member States shall comply by (18 months after entry into force; i.e. 1st November 2005)
2. Member States: Traditional herbal medicinal products already on the market prior to April 2004: 7 years after entry into force; i.e. April 2011

Regulatory Guidance on solid Grounds

Regulation 726/2004 EC of 31 March 2004

TITLE IV

THE EUROPEAN MEDICINES AGENCY - RESPONSIBILITIES AND ADMINISTRATIVE STRUCTURE

Article 56

1. The Agency shall comprise:
(a) the Committee for Medicinal Products for Human Use (CHMP),
…
(d) the Committee on Herbal Medicinal Products (HMPC);

EMEA Committee on Herbal Medicinal Products

Inaugural Meeting 23-24 September 2004

Chairperson: Dr. Konstantin Keller
Vice-Chairperson: Dr. Heribert Pittner

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

Co-opted Members (max. 5)
EEA Members: Norway, Iceland Observer: EDQM/Europ. Pharm.

Mobilizing European Expertise

Regulation 726/2004 EC of 31 March 2004

TITLE IV

THE EUROPEAN MEDICINES AGENCY - RESPONSIBILITIES AND ADMINISTRATIVE STRUCTURE

Article 61

2. The Committees may co-opt a maximum of five additional members chosen on the basis of their specific competence. …

Mobilizing European Expertise

Decision by the HMPC

Co-opted members to complete specific expertise:

- clinical pharmacology
  June 2005: Dr. Wissinger-Gräfenhahn, Berlin, DE
- toxicology
  June 2005: Prof. Pelkonen, University of Oulu; FI

Nominations for 3 additional Co-opted Members expected in September 2005:

- pediatric medicines
- Traditional Medicine, especially TCM, Ayurveda, Anthroposophic Medicine
- Non-clinical/experimental Pharmacology

Coordination with other EU bodies

EMEA

Regulation 726/2004 EC of 31 March 2004

TITLE IV, Article 59

The Agency shall take care to ensure early identification of potential sources of conflict between its scientific opinions and those of other bodies established under Community law carrying out a similar task in relation to common concern. In case of any fundamental scientific conflict with any other EU agency or scientific committee a joint document has to be prepared and submitted to the Commission

Coordination within the EMEA

EMEA

Regulation 726/2004 EC of 31 March 2004

TITLE IV, Article 64 (2)

The Executive Director … shall be responsible:

…

d) for ensuring appropriate coordination between the committees referred to in Article 56 (1)

Examples for Coordination

Scientific Committees of the EMEA

CHMP and CHMP Working Parties
(Area of Quality, Safety, Efficacy of well-established products)

COMP (Consultation on Orphan drugs of herbal origin)

Expert Groups located at the EMEA

MRFG / Coordination Group (referrals in MR procedures)

Inspectors' Working Party (GMP Annexes)

Other EU bodies

EC DG Enterprises (NTA Working Party)

EC DG SANCO (EU-SCF, EU-SC Cosm. and non-Food prod.)

European Food Safety Authority (SC, AFC-Panel)

Coordination with external Partners

EMEA
Regulation 726/2004 EC of 31 March 2004

TITLE IV
Article 78 (2)

The committees and any working party shall in general matters establish contacts, on advisory basis, with parties concerned ... in particular with patient organizations and health care professional organizations …

Co-ordination with internal and external partners

Ongoing activities:

- Preparation of a list of parties with an interest at European level in (traditional) herbal medicinal products, with whom to establish contacts;
- Invitation to EU organizations to express their willingness to be regarded as an interested party to the HMPC;
- co-operation with patients' and consumers' organizations

Decisions with direct regulatory impact

Directive 2004/24/EC of 31 March 2004

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

Decisions with direct regulatory impact

Directive 2004/24/EC of 31 March 2004

Article 16h

The Committee for Herbal Medicinal Products shall

- be responsible for arbitration/referral procedures originating from different views among Member States on registered herbal medicinal products
- give an opinion on other medicinal products containing herbal substances for human use referred to the EMEA

Decisions with direct regulatory impact

Directive 2004/24/EC of 31 March 2004

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

Great Expectations

Wishes from Industry, Member States, EC

Technical Guidelines, Community Herbal Monographs, the List of Traditional Herbal Substances should be made available immediately, at latest October 2005.

They should be of a high scientific level, prepared in a fully transparent way, with participation of interested parties and following clear rules of procedure and consistent criteria.

Facing Reality

In view of the very limited resources made available by the EMEA and by the MS, clear priorities are necessary. However:

Different situation of Member States results in divergent priorities from Member States;
Divergent priorities are presented by Interested Parties.

A scientific approach must be based on clear, pre-defined scientific criteria and working methodology.

The HMPC will take responsibility for the safety and the indication of HMP marketed in the EU on the basis of a HMPC monograph / list

=> **Transparency and clear criteria are indispensable,**
=> **Activities focused on general guidance, but work on monographs/list should be started in parallel.**

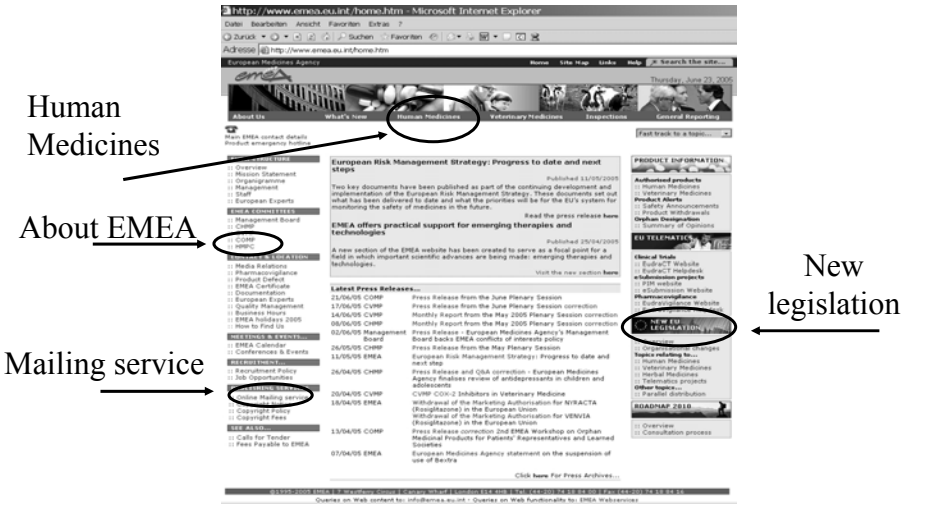
The most urgent tasks:

1. preparatory work for the establishment of the list of traditional herbal substances …;
2. preparation of draft Community herbal monographs for herbal medicinal products with a well-established use;
3. preparing procedures to be established in relation to the adoption of opinions at the request of a Member States or of the CHMP;

The most urgent Tasks:

4. clarification on the content of a dossier for a registration application, e.g.:
    - the format and content of the bibliographic review of safety data and expert report,
    - the bibliography or expert evidence on the medicinal use throughout a period of at least 30 years (format and type of evidence),
    - demonstration that the pharmacological effects or the efficacy are made plausible on the basis of long-standing use and experience,
    - ancillary action of vitamins and minerals,
    - assessment of traditional combination products.

How to find information? www.emea.eu.int



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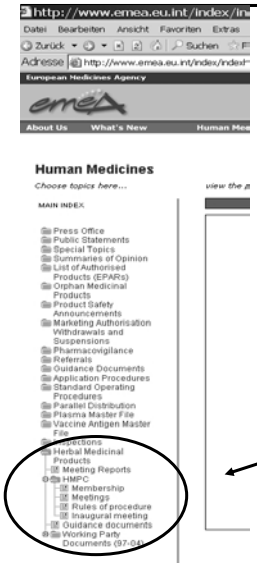


Human medicines

HMPC

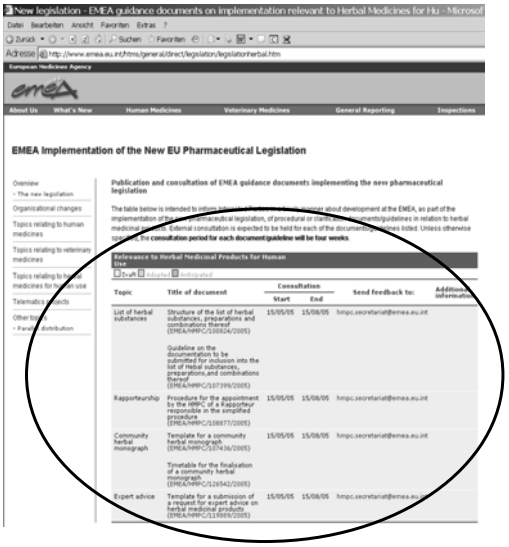
draft / final technical guidelines

meeting reports

rules of procedure

HMPWP documents

How to find information? www.emea.eu.int



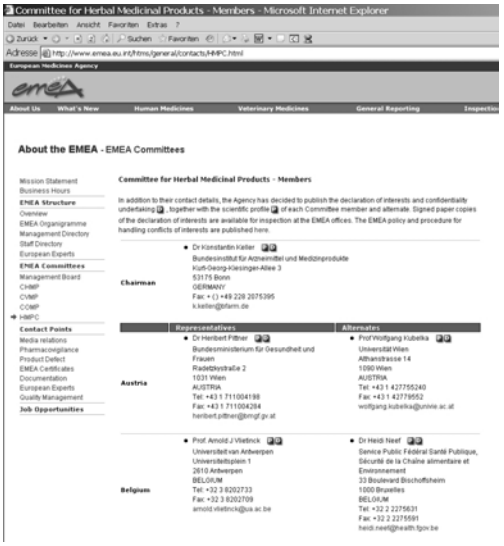
New legislation

HMPC

draft / final ORGAM

guidelines

How to find information?
www.emea.eu.int



About EMEA

HMPC

Members

co-opted Members

Alternates

Observers

Establishment of Drafting Groups

Temporary Drafting Groups with the mandate to review and update available guidance and to identify missing parts of guidance related to

1. ORGAM (Chair E. v. Galen. NL)
2. Quality and NTA (Chair D. Dempsey, IRL)
3. Safety and Efficacy (Chair H. Pittner, AU)

Decision on joint CHMP/HMPC WP on Quality, Safety at a later stage.

Co-operation with CHMP Pharmacovigilance WP needs to be explored further.

Drafting Group on ORGAM

Tasks arising from Articles 16f of CD 2001/83/EC

List of Traditional herbal substances …

- Structure of the list of herbal substances, preparations and combinations thereof (Draft March 2005)
- Guideline on the documentation to be submitted for inclusion into the list of Herbal substances, preparations,and combinations thereof (Draft March 2005)

- Procedure for the submission of a proposal for inclusion in the list by a MS. (ongoing)
- Procedure and timeline for the inclusion of an herbal substance, preparation and combination into the list. (ongoing)

Drafting Group on ORGAM

Tasks arising from Articles 16f of CD 2001/83/EC

Rapporteurship

- Procedure for the appointment by the HMPC of a rapporteur responsible for the simplified procedure. (Draft March 2005)

Drafting Group on ORGAM

Tasks arising from Articles 16f of CD 2001/83/EC

List of Traditional herbal substances …

Procedure for the adoption and transmission to the European Commission of an opinion of the Committee to include or to suspend or to withdraw from the list an herbal substance, preparation or combination. (ongoing)

Drafting Group on ORGAM

Tasks arising from Articles 16 h (3) of CD 2001/83/EC

Community Herbal Monographs

- Timetable for the finalization of the Community monographs by the HMPC. (Draft March 2005)
- SOP on Preparation of Community monographs for traditional herbal medicinal products (Draft June 2005)
- SOP on Preparation of Community monographs for well-established herbal medicinal products (Draft June 2005)
- Proposed template for HMPC Assessment report for List and Community herbal monograph (ongoing)
- Template for a community herbal monograph (Draft March 2005)

Drafting Group on ORGAM

Tasks arising from Articles 16 h (3) of CD 2001/83/EC

Community Herbal Monographs

- Template for a community herbal monograph (Draft March 2005)

3. PHARMACEUTICAL FORM

Well-established use	Traditional use

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Well-established use	Traditional use
	<The product is a traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use.>

4.2. Posology and method of administration

Well-established use	Traditional use

4.3. Contraindications

Well-established use	Traditional use

Drafting Group on ORGAM

Tasks arising from Art. 16 c (1) & (4) of CD 2001/83/EC

Committee Opinions / Traditional use criteria:

- Procedure and template for the adoption of an opinion on the adequacy of the evidence of the long-standing use of a product, or of a corresponding product, at the request of a Member State. (ongoing)

- Procedure and necessary forms and templates for the adoption of an opinion/Community herbal monograph on a product, which has been used in the Community for less than 15 years but is otherwise eligible for simplified registration, and referred to the Committee by a Member State. (ongoing)

The new simplified registration procedure

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

Article 16c 1 (c)

> 30 years of medicinal use within the EU or

> 15 years in and > 15 years outside the EU

Deviations may be decided by the Herbal Committee if requested by a Member State

Drafting Group on ORGAM

Implementation of Title IV of Regulation (EC) 726/2004
Scientific services

Article 57 (1) j
Providing general scientific support and advice to Member States
Template for submission of request for scientific support by MS to HMPC and structure for the information required for such request. (ongoing)

Article 57 (1) n
Providing (pre-submission) scientific support and advice to Applicants/Marketing authorisation holders:

Template for a submission of a request for expert advice on herbal medicinal products (Draft March 2005)

Drafting Group on Quality

Priorities and First results

- No legal basis for a "second class" quality, identical criteria apply to well-established and to traditional herbal medicinal products
- Agreement to build on the guidance documents developed by the HMPWP and the CPMP;
- No fundamental changes are expected to be required in the published guidelines, but update of CPMP guidance necessary, mainly to comply with CTD terminology.
- Additional guidance to applicants for traditional use registration on the interpretation of the quality requirements, especially when considering complex traditional combination products.

Drafting Group on Quality

Priorities and First results

- Proposal for an update of the CPMP/CVMP note for guidance on Quality of Herbal Medicinal Products submitted to CHMP/CVMP in June 2005, DE/ES
- Proposal for an update of the CPMP/CVMP note for guidance on specifications draft published in June 2005; DE/ES
- Revised draft Annex 7 of the EU Guide on Good Manufacturing Practice; comments submitted to EMEA Inspectors WP, expected in September 2005, IT
- Q/A-document on the EMEA homepage

Drafting Group on Quality

Priorities and First results

- Q/A-document on the EMEA homepage published March 2005
- Concept Paper on the Declaration of Herbal Substances/Preparations in Finished Herbal Medicinal Products published in June 2005

Drafting Group on Safety / Efficacy

Priorities and First results

- Existing guidance from the HMPWP on safety and efficacy of herbal medicinal products will be revised.
- The borderline between herbal medicinal products with a well-established use and traditional herbal medicinal products must be clarified.
- Existing guidance from the HMPWP on fixed combinations must be updated to include traditional herbal medicinal products.
- Existing HMPWP core-data on herbal drugs will be re-assessed and transformed / extended into Community Herbal Monographs / entries to the list, where applicable.

Drafting Group on Safety / Efficacy

First results:

Discussion on draft guidelines on:

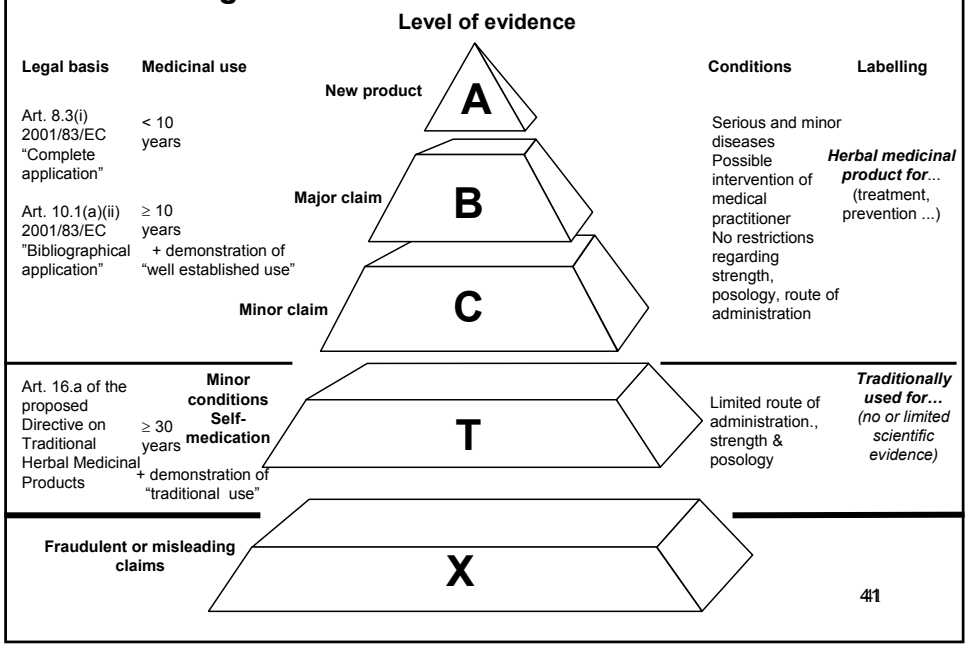
- Non-clinical safety, draft ready in March 2005 coordination with CHMP-SWP, DE
- Clinical safety and efficacy, discussion ongoing, legal clarification from EC expected in July 2005, DE/SE

What 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. …

Overview
Legal Framework for Herbal MPs in the EU



41

New Obligations – New Responsibilities

Examples where clarification is necessary

Documents (Article 16c)

bibliographic review of safety data and expert report (format, content)

bibliographic or expert evidence on the medicinal use throughout a period of at least 30 years (format; type of evidence)

Pharmacological effects / efficacy plausible on the basis of long-standing use and experience

New Obligations – New Responsibilities

Main Challenges

Making the best use of legal provisions to address the particularities of herbal medicinal product

Providing pragmatic decisions based on sound scientific standards

Finding the appropriate balance between benefits and risks for traditional herbal medicinal products

Assessment of traditional herbal medicinal products not originating from European traditions

Defining the limit between well-established and traditional herbal medicinal products

Drafting Group on Safety / Efficacy

First results:

discussion on draft Community herbal monographs

- Linseed (specified preparations/indications), DE
- Valerian root (specified preparations/indications), DE
- Isphagula husk, DE
- Isphagula seed, DE
- Psyllium seed, DE
- Senna leaf, DE
- Senna fruit, DE

Drafting Group on Safety / Efficacy

First results:

Discussion on possible List entries for

- Linseed (specified preparations/indications), DE
- Valerian root (specified preparations/indications), DE

Drafting Group on Safety / Efficacy

First results:

Guideline on the clinical assessment of fixed combinations of herbal substances / herbal preparations
Draft published in July 2005

Update of the HMPWP Note for Guidance on fixed combinations to include well-established and traditional HMP, including vitamins / minerals with ancillary action

Guideline on the Clinical Assessment of fixed Combinations of Herbal Substances / Preparations

Draft July 2005

The rationale of the combination must be given:

- Well-established fixed combination products will only be considered acceptable if the proposed combination is based on valid therapeutic principles.
- Traditional fixed combination products must be plausible within the relevant system of traditional medicine. The requirements relating to efficacy will be reduced to the level of plausibility, whereas considerations related to safety will become more critical in an overall benefit/risk-assessment, because scientific evidence on efficacy is not available for traditional herbal medicinal products.

47

Guideline on the Clinical Assessment of fixed Combinations of Herbal Substances / Preparations

Draft July 2005

The rationale of the combination must be given:

- The function of each constituent of the herbal medicinal product must be clarified, taking into account the indication of the combination, the profile of the active substance and its dosage / concentration.
- It must be clarified if a constituent of the fixed combination has to be considered as an active substance or as an excipient, e.g. to improve the taste or to influence physical properties of the product.

48

The new simplified registration procedure

Vitamins and minerals
may be present in traditional herbal medicinal products, 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).*

Guideline on the Clinical Assessment of fixed Combinations of Herbal Substances / Preparations

Draft July 2005

Ancillary Vitamins and Minerals:

For the definition of the terms “vitamin” and “mineral” reference is made to Annex I and II of the Directive 2002/46/EC. The posology must be such that their action is “ancillary” as compared to the action of herbal active substance(s).

Guideline on the Clinical Assessment of fixed Combinations of Herbal Substances / Preparations

Draft July 2005

***Ancillary* Vitamins and Minerals:**

Taking into account the pharmacodynamic profile of typical traditional herbal substances / preparations, dosages of vitamins/minerals that correspond to currently accepted Recommended Daily Allowance (RDA)-values will be considered to be appropriate, unless justified. Dosages of vitamins/minerals that exceed the upper safe limits established by other scientific committees of the Community as applicable will not be acceptable for traditional herbal medicinal products.

Guideline on the Clinical Assessment of fixed Combinations of Herbal Substances / Preparations

Draft July 2005

***Ancillary* Vitamins and Minerals:**

The action has to be ancillary to the herbal active ingredient(s) regarding the specific indication(s). In general, the presence of vitamins/minerals will not modify the indication of the fixed combination. An ancillary action must be made plausible, e.g. by providing bibliographic or expert evidence of the traditional use of these substances in the respective traditional indication.

Proposal for a Regulation of the European Parliament and of the Council on nutrition an health claims made for foods

Political Compromise 07 June 2005

Article 5
General conditions

1. The use of nutrition and health claims shall only be permitted if the following conditions are fulfilled:

(a) the presence, absence or reduced content in a food or food category of a nutrient or other substance in respect of which the claim is made has been shown to have a beneficial nutritional or physiological effect, as established by generally accepted scientific data;

Proposal for a Regulation of the European Parliament and of the Council on nutrition an health claims made for foods

Political Compromise 07 June 2005

Article 5
General conditions

1. The use of *nutrition and health claims shall only be permitted* if the following conditions are fulfilled:

(c) where applicable, the nutrient or other substance for which the claim is made is in a form that is available to be used by the body;

(d) the quantity of the product that can reasonably be expected to be consumed provides a significant quantity of the nutrient or other substance to which the claim relates, as defined in Community legislation or, where such rules do not exist, a significant quantity that will produce the nutritional or physiological effect claimed as established by generally accepted scientific data

Drafting Group on Safety / Efficacy

Priorities and First results:

Public consultation on risk-evaluations related to

- Aristolochia
- Estragole
- Methyleugenole
- Safrole
- Asarone
- Pulegone / Menthofurane
- Chamomile (allergic potential)
- Capsicum / Capsaicine
- Products containing soya- or peanut-protein (allergic potential)

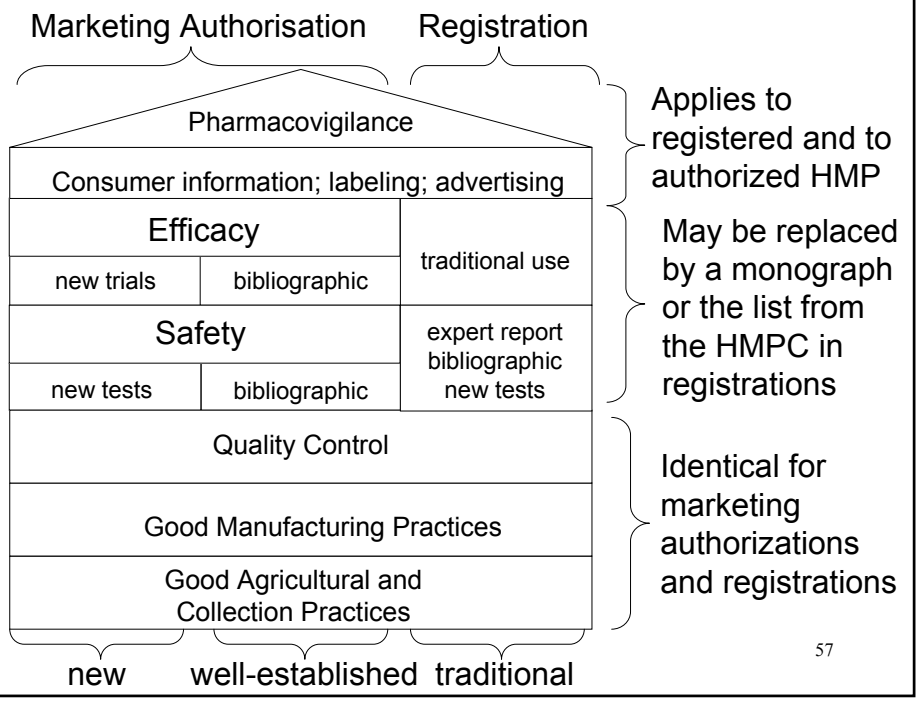
Drafting Group on Safety / Efficacy

First results:

Draft assessment of ADR case reports on Cimicifuga rhizome co-ordinated assessment with CHMP PhVWP finalised June/July 2005, DE

Assessment of central AE associated with certain essential oils (ongoing; DE)

Request from Iceland to clarify the risks of Angelica leaf/fruit (Status of the CPMP list of herbs with serious risks)



57

The next steps

- Meeting dates fixed until 2007
- Preparing for implementation of the new legislation
- Decision on 3 co-opted Members by end of 2005
- Decision on co-operation with CHMP or self-standing HMPC permanent Working Parties (QWP, EWP, SWP, PhVWP) by end of 2005
- Meeting with ESCOP / AESGP in September 2005 (support for drafting monographs/list)
- Meeting with interested parties in November 2005
- Time table and procedures for monographs/lists
- Co-operation with CHMP to be explored further, esp. EWP and PhVWP
- Co-operation with EFSA to be explored further

58

Summary

- The HMPC is fully operational since November 2004.
- First decisions on procedural aspects already published in January 2005.
- Positive attitude and commitment of all experts.
- The HMPC is committed to deliver scientifically valid results, as fast as possible and in a fully transparent way.
- Both, traditional and well-established herbal medicinal products will benefit from these activities.
- New legal and scientific areas are to be explored
- Significant workload in preparing the grounds for robust results.
- Resources from EMEA and from Member States need to be clearly allocated.