



***Herbal medicinal products in the EC;
Indications vs Claims;
an up-to-date scientific view***



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ΕΘΝΙΚΟΝ & ΚΑΠΟΔΙΣΤΡΙΑΚΟΝ
ΠΑΝΕΠΙΣΤΗΜΙΟΝ ΑΘΗΝΩΝ

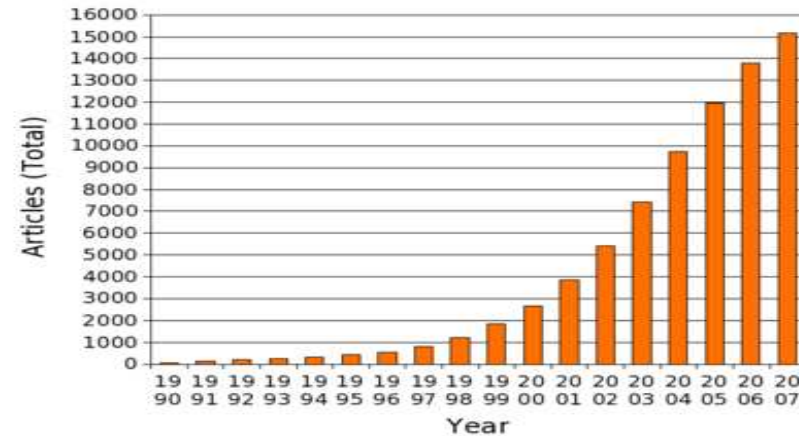
GA Congress/ Muenster 01 September 2013



Disclaimer

“I attend this conference as an individual, and do not represent the HMPC. The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the HMPC or reflecting the position of the HMPC”

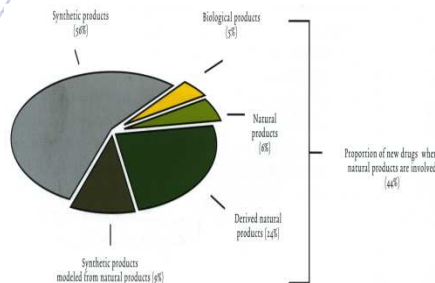
Herbal medicinal products(Hot topic)



Running total of the number of research papers listed on [PubMed](#) from 1990-2007 containing the word "phytotherapy."

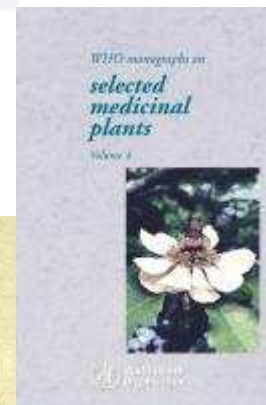
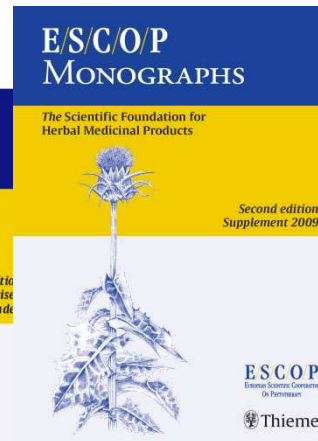
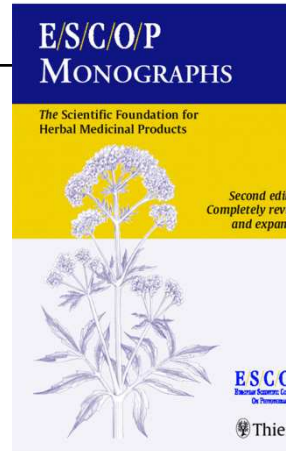
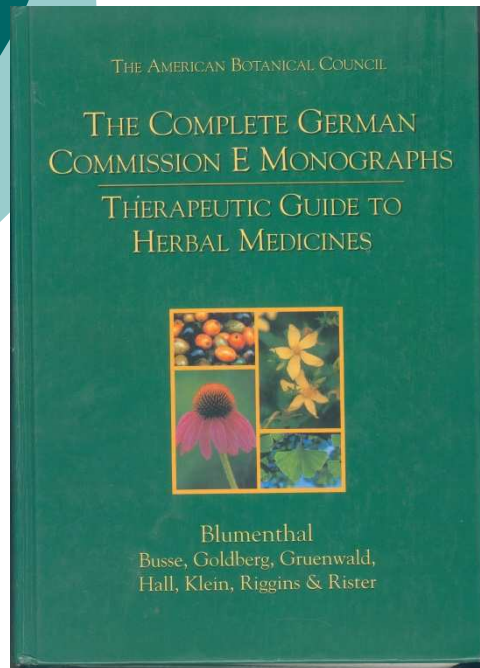
80% of 30,000 known chemical constituents are of natural origin.

More than 7,000 herbal medicinal products can be found commercially coming from 100 plant sources (Phillipson, 2006),



before Information

Commission E



REVIEW ARTICLE

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Interactions Between Herbal Medicines and Prescribed Drugs An Updated Systematic Review

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Herbal medicinal products in EU

- **Definitions**
- **Legal and regulatory framework**
- **Scientific Committee**
- **Procedures and guidance documents**
- **Guidelines on quality, safety and efficacy**
- **Community herbal monographs and list entries**

Definitions

[Directive 2001/83/EC as amended]

❖ **Medicinal Product**

Any substance or combination of substances **presented as having properties for treating or preventing disease** in human beings; or

Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by **exerting a pharmacological, immunological or metabolic action**, or to making a medicinal diagnosis.

❖ **Herbal Medicinal Product (HMP)**

“Any medicinal product, **exclusively** containing as active ingredients one or more **herbal substances** or one or more **herbal preparations**, or one or more such herbal substances in **combination** with one or more such herbal preparations”

HMP is a regulatory concept!

❖ ...

Bordeline with:

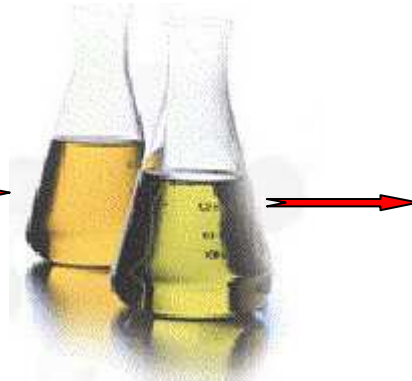
Foods
Food supplements
Cosmetics
Medical device ...

Definitions [Directive 2001/83/EC as amended]

- ❖ **Herbal substances** : All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. ~~Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances.~~ Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author)
- ❖ **Herbal preparations** : preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates



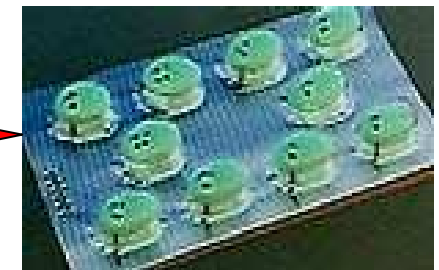
Herbal substance)



Herbal preparation
(Liquid extract)



Herbal preparation
(dry extract)



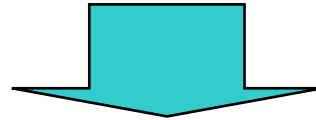
Herbal medicinal
product

Legal and regulatory framework

A number of traditional HMPs not eligible for a well-established use MA are marketed in EU Member States.

Main reason: scientific data on efficacy are not sufficient

Specific tools for Herbals:



Specific Directive (2004/24/EC)

amending, as regards traditional herbal medicinal products, Directive 2001/83/EC

- **A national specific procedure** for the registration of the traditional use of herbal medicinal products: **simplified registration procedure**
- **A European Committee** with tools to enhance harmonisation of European market + facilitate registration: **Community monographs and list entries**
- **Benefits: free trade; protection of public health; preservation of medical traditions within Member States**

Procedures

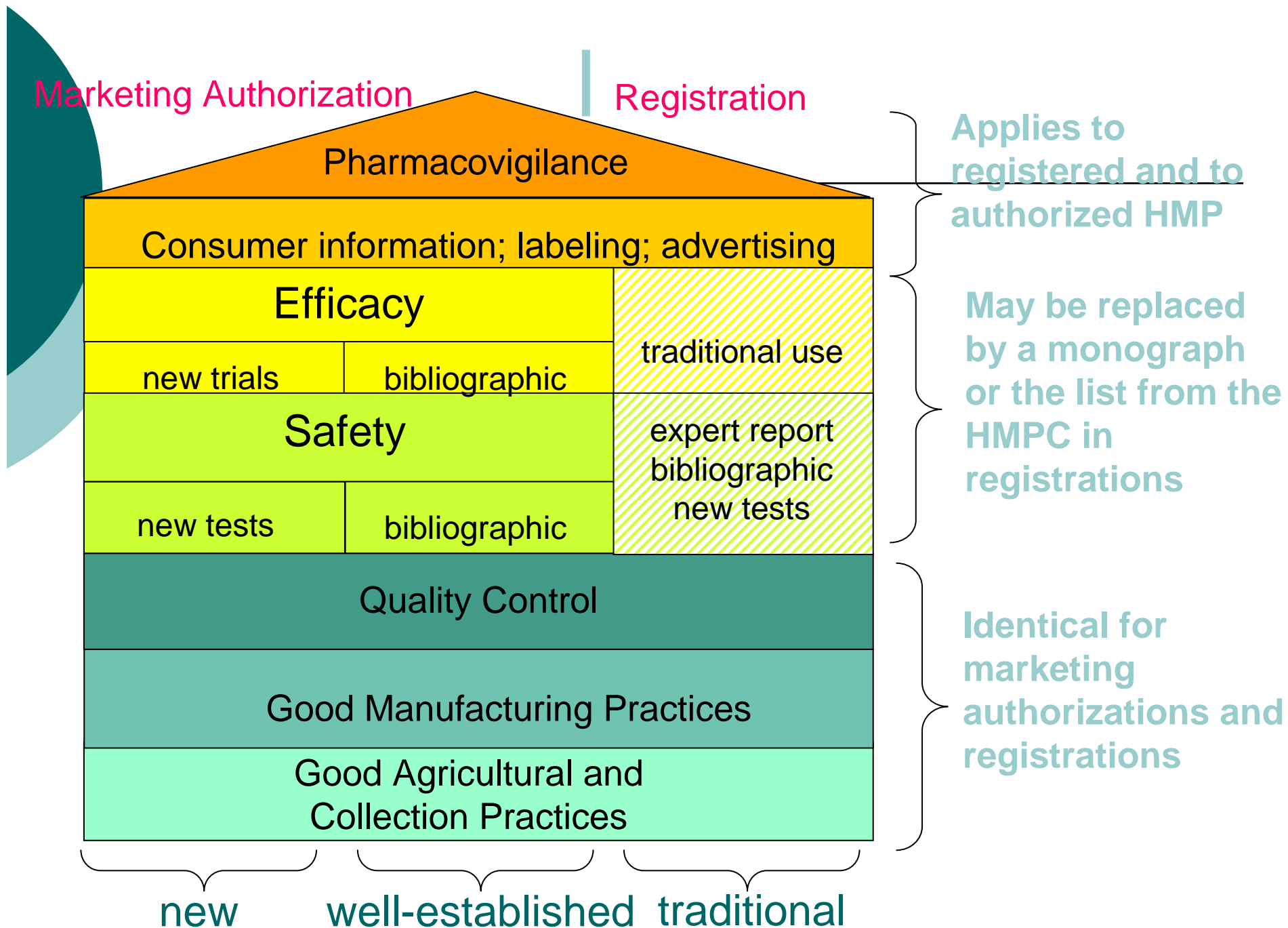
Traditional use registration (simplified registration)

Traditional herbal medicinal product (art. 1(29)):

a herbal medicinal product that fulfils the conditions laid down in Article 16a(1) (eligibility criteria for the Traditional Use registration)

Period of traditional use

- **> 30 years of medicinal use on the territory of the EU or**
- **> 15 years in and > 15 years outside the EU or**
- **deviation decided by the Herbal Committee (HMPC)**
- **Vitamins and minerals may be added if their action is ancillary to the herbal constituent(s)**
- **Indication(s) exclusively appropriate to traditional herbal MP**
- **For use without supervision of a medical practitioner for diagnosis, prescription or monitoring of treatment**
- **Specified strength and posology**
- **Only oral use, external use and inhalation**
- **data on the traditional use of the medicinal product sufficient**
 - to **prove safety** in the specified conditions of use
 - to make **plausible** the **pharmacological effects** or **efficacy** on the basis of long-standing use and experience.



European Medicines Agency - EMA

Central European Authority with specified tasks

Committees and Working Parties

Guidance Documents

(www.ema.europa.eu)

Monitoring of safety of human + veterinary medicines through a pharmacovigilance network and establishment of safe limits for residues in food

○ **Data Bases**

- **community register of GMP certificates**
- **pharmacovigilance (EUDRAVIGILANCE)**
- **register of authorised medicinal products (EudraPharm)**

○ **Coordination of National Competent Authorities**

- **Coordination of the scientific network/resources from Member States, including more than 5000 European experts supported by high quality scientific resources (NCAs)**
- **Robust quality assurance system (peer review system)**
- **Coordination of the scientific evaluation of ongoing applications**
- **Scientific advice to companies**
- **Arbitration in the MRP/DCP**
- **European Medicines Agency - EMA**



Among EMA's Committees



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



A screenshot of the European Medicines Agency website, specifically the page for the Committee on Herbal Medicinal Products (HMPC). The browser window title is "European Medicines Agency - HMPC - Committee on Herbal Medicinal Products (HMPC) - Windows Internet Explorer". The URL is "http://www.ema.europa.eu/ema/index.jsp?cof=pages/about_us/general_content_000264.jsp&menu=about_us/about_us.jsp&id=WC001ac0580029c7c03ena". The page content includes a navigation menu on the left with "Committees" selected, and a main content area with a blue circle highlighting the "Committee on Herbal Medicinal Products (HMPC)" link. The main content area also features a small image of herbs and text describing the committee's establishment in September 2004, its composition, and its meeting calendar for 2010.

HMPC Composition

EEA- EFTA states: NO, IS

28 Member states

28 Members + 28 Alternates

5 Coopted members

- Clinical pharmacology
- Experimental/non-clinical pharmacology
- Toxicology
- General and family medicine
- Pediatrics

○ Norway, Iceland (EEA-EFTA States)

○ Observers:

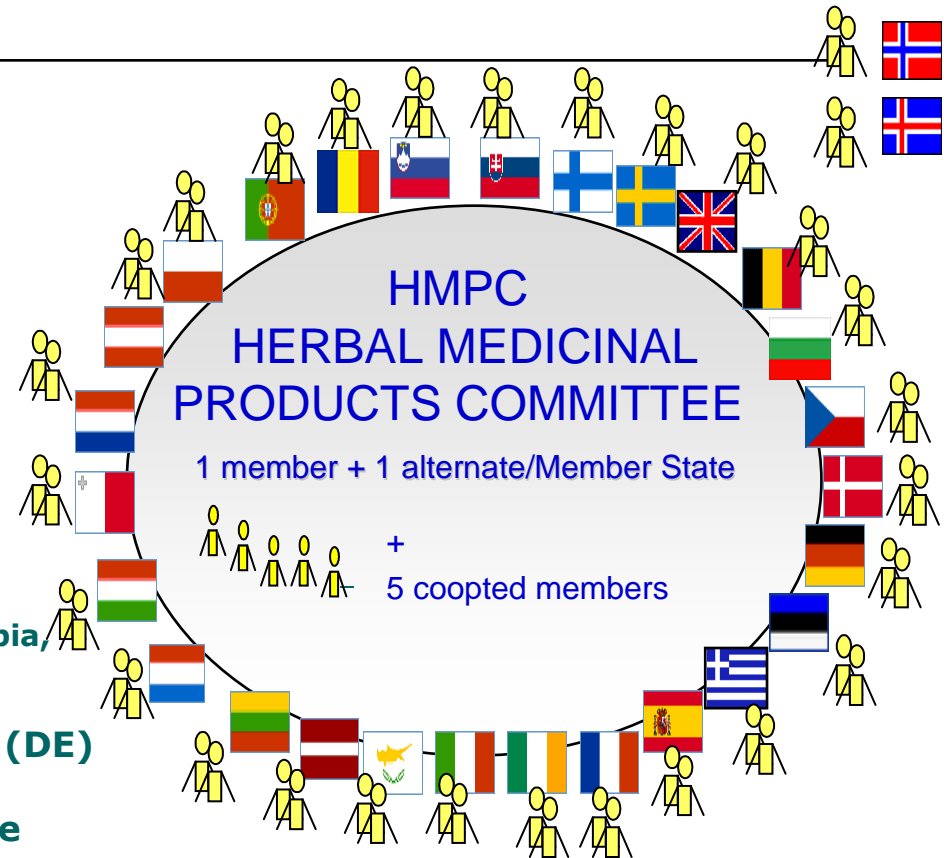
- European Commission
- EDQM
- EU candidates (Albania, Bosnia Herzegovina, Croatia, Kosovo, Macedonia, Montenegro, Serbia, Turkey)

○ **Chair:**
since 2010
Vice-Chair:
2007

Dr Werner Knöss (DE)

Dr Ioanna Chinou (EL) since

3 years Mandate renewable



Observers:
EDQM
European Commission

Albania, Bosnia Herzegovina, Kosovo, Macedonia, Montenegro, Serbia, Turkey





HMPC Working structure

HMPC inaugural Meeting: 23-24 September 2004

Replaced the former CHMP HMPWP

- HMPC Plenary meetings
 - **6 meetings / year**
- Working Party on Community Monographs and List Entries (MLWP)
 - **24 members-experts,**
 - **Chair Dr I. Chinou (EL) since 2008,**
 - **Vice Chair Dr M. Delbo (Italy) since 2010**
- Quality Drafting Group (QDG)
 - **10 members, Chair Dr Burt Kroes, NL**
- Organisational Matters Drafting Group (ORGAM DG)
 - **10 members, Chair Dr Emiel van Galen, NL**
- HMPC-Secretariat at the EMA



HMPC meeting room (3A)

Tasks of HMPC

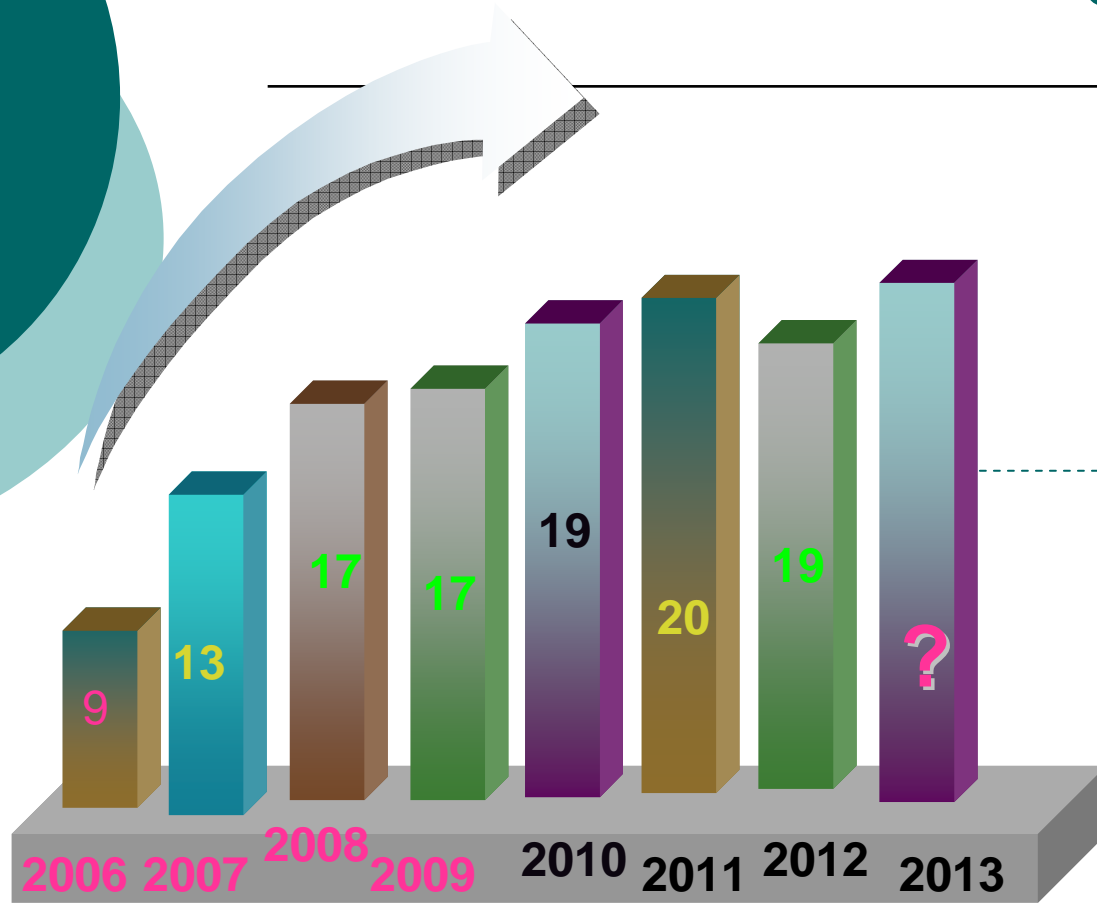
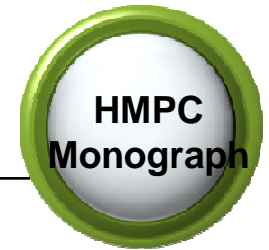
Community herbal monographs for WEU and TU

- draft Community List entries of herbal substances, preparation and combination thereof for use in traditional herbal medicinal products
- Scientific opinions
- Scientific advice
- Scientific guidelines
- Coordination
- Questions



HMPC meeting room (3A)

Evolution on Monographs



117 Final monographs

12 PUBLIC STATEMENTS,

3 M. for peer review

11 Monographs under active pub consult

18 Monographs Under discussion

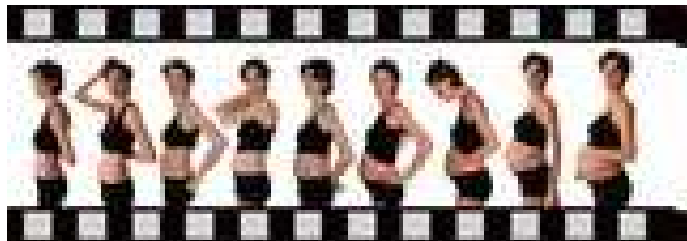
30 Rapporteurs assigned

10 List entries

All needed information, and resources, fully covered by EMA
Full support by HMPC Secretariat

General Restrictions

- Pregnancy
- Lactation
- Children below 12 years
- Serious illnesses
- Historic of allergies
(Asteraceae-Compositae////
Umbeliferae-Apiaceae)



Key safety risk questions:

How many products are on the EU market

What is their active herbal ingredient

What is the quality of these products

How many patients are using these products and How long have they been using them

How many annual Daily Doses have been consumed in EU

What about any adverse effects??

We don't know!

SO

- No good product quality
- No independent safety assessment
- No appropriate consumer information
- No GMP
- No distribution standards
- No PhV



Examples of non-licensed herbal medicines



Cinamom tabs

**40
tabs**



- No brand name
- No requirements concerning dosage, safety
- No duration of use
- No adverse effects
- No contraindications
- No storage conditions

No indication

**No SPC, Patient
Information Leaflet**

Herbal medicinal products **vs** Food supplements



E.U



Indications vs Claims

- **Indication** (medicine) From Wikipedia,
In medicine, an indication is a valid reason to use a certain test, medication, procedure, or surgery. The opposite of indication is contraindication.
- In the United States, indications for medications are strictly regulated by the FDA, which includes them in the package insert under the phrase "Indications and Usage". The EMA holds this responsibility for the whole of the EU./Merriam-Webster". 14/12/2010.

Indication: 1. In medicine, a condition which makes a particular treatment or procedure advisable.

- 2. A sign or a circumstance which points to or shows the cause, pathology, treatment, or outcome of an attack of disease.

- **Claim** (Noun);
- **1.an assertion of the truth of something, typically one that is disputed or in doubt.**
synonyms: assertion, declaration, profession, affirmation, avowal, protestation; More
- 2.a demand or request for something considered one's due.

From Wikipedia,

- **Claim** may refer to:
- **Proposition, a statement which is either true or false**
- A right Sequent, in mathematics
- A main contention, see conclusion of law

Herbals

Herbal preparations

Food supplements

- notification
- 'claim'
- information to public
- HACCP

EFSA

Herbal medicines

- registration
- therapeutic indication
- SmPC / PPI
- GMP

EMA - HMPC



Food supplement

For General population

Preparation

No Duration of use

Outcome: Claim

**Traditional Herbal
Medicine**

**Inclusion and/or
exclusion of Population
at risk**

Well-defined preps

Limited duration of use

Outcome: Indication



moreover

EFFL 3|2013

Project BELFRIT | 187

Project BELFRIT

Harmonizing the Use of Plants in Food Supplements in the European Union: Belgium, France and Italy – A first Step

Guillaume Cousyn,* Stefania Dalfrà, Bruno Scarpa,** Joris Geelen,***
Robert Anton,* Mauro Serafini[©] and Luc Delmulle[©]

European legislation for food supplements with botanicals is not harmonized and not adapted to meet the particular challenges of these heterogeneous ingredients. Faced with this situation, the Belgian, French and Italian authorities, each assisted by a renowned scientific expert, have decided to develop a common approach for the evaluation of botanicals in the 'BELFRIT' project. A first step in this initiative is the compilation of a list of plants whose use in food supplements could be possible, provided that the necessary measures to ensure consumer safety are respected. It provides a precise identification of the plants, indicates some key points in the production to be controlled, while also taking traditional knowledge into account. This harmonized list can be a pragmatic tool for risk managers and operators and an important piece of the puzzle for harmonization of this field. Nevertheless, it is not a legally binding instrument and cannot be opposed to legal provisions, including those of the Member States involved in the project.

From BELFRIT proj



Ensuring the availability of safe products of a high-quality level involves:

- – the precise identification of the raw materials;
- – quality control based on standardization criteria of the finished product;
- – stability studies;
- – clear recommendations of use for the consumer.

The use of botanical preparations must imperatively meet the following criteria:

- – Presents no health risk for consumers,
- – Is not characterized by **a pharmacological activity, capable of restoring, correcting or modifying physiological function (although the boundary between physiological and pharmacological activities is sometimes difficult to establish),**
- – **Does not mislead consumers about the expected effects including presentation with therapeutic effect.**

This resulted in three new lists:

- – A “three countries” list consisting of 396 plants, for the plants listed in three contributing countries,
- – A “two countries” list consisting of 180 plants, and
- – A “one country” list consisting of 449 plants, according to the same rule

More specific restrictions of use in the form of maximum levels of secondary metabolites or

- warnings to populations at risk must complete this first step.
- Harmonization of data essential to controlling the quality and safety of botanical products should also be proposed.
- Finally, further research on specific plants, new preparations that deviate from the **traditional**, **(What about THMPs ??)**
- essential oils, mixtures and some little-known compounds present in the accepted plants, are all roads to explore in the longer term.

Personal Safety concerns

of the use of food suppl

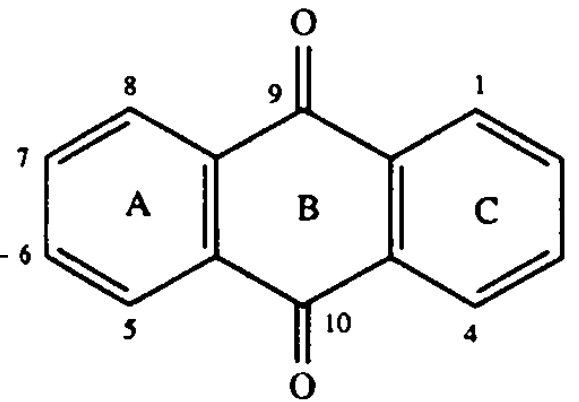
What would be the meaning of Trad. Food suppl.?

After how many years a food suppl. Would become a trad food supp?

Should we expect WEU food suppl. as well?



Some examples for discussion



9,10-Ανθρακινόνη



na Miller

Anthraquinone containing plants **WEU**
HMPs

Duration of use **8 - 10 days**,

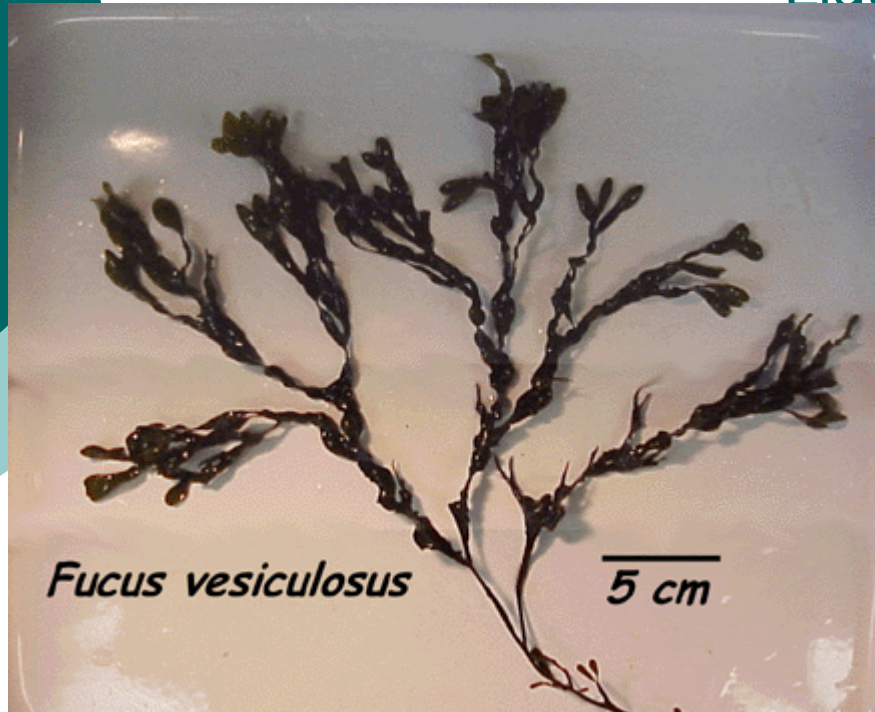
Adverse reactions

- ❖ **diarrheas**,
- ❖ **hypokaliaemia**
- ❖ **intestine melanosis.....**



Fucus vesiculosus

Liquiritiae



Echinaceae purp. herba

7 March 2008



Well-established use

- **Not to be used for children below 12 years of age**



Foeniculi fructus

September 2007

Traditional use

- Mild gastrointestinal disorders**

Not to be used for infants below 9 months



Hypericum (Saint John's Wort)

- **Indinavir (HIV therapies)**
- * **Irinotecan**
- * **Cyclosporine,**
- * **Digoxin,**
- * **Warfarin and other anticoagulant**
- * **Antidepressant drugs etc...**



Ginkgo



Cinnamomum verum – *C. zeylanicum*

http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Community_herbal_monograph/2011/08/WC500110095.pdf

Indication 1

- **Traditional herbal medicinal product for symptomatic treatment of mild, spasmodic gastro-intestinal complaints including bloating and flatulence.**

Indication 2

- **Traditional herbal medicinal product for symptomatic treatment of mild diarrhoea.**



Food supplement : Lowering blood glucose

Antiseptic, against hypertension etc...

What is the safety for people taking antidiabetic drugs???



Viscum album (Nov 2012)

Public statement (PS)

No possibility for the use under Indication for cardiovascular system

Article 1 of Directive 2001/83 EC as amended by 2004/24/EC

Inclusion Criteria (Article 16a)

Indication(s) appropriate to THMP, use without the supervision of a medical practitioner for diagnosis, prescription or monitoring of treatment, only oral use, external use and inhalation, sufficient data on traditional use of the product (...safety), pharmacological effects / efficacy plausible on the basis of long-standing use and experience

**Does it Exist as Food supplement in the Community???:
against hypertension etc...**





Chelidonii

13 September 2011

Chelidonium majus (greater celandine)


**Does it Exist as
Food supplement
in the
Community???**

It contains over 20 different alkaloids, benzyloisoquinoline type (0.01-1%) as benzophenanthridines (chelerythrine, chelidonine, sanguinarine etc), protoberberines (berberine, dihydrocoptisine, stylopine) and protopine.

In the Vigisearch database of WHO, there are 124 reported adverse drug reactions affecting the liver-biliary system after intake of products containing C. The products withdrawn to date have been those which would lead to a **daily intake of more than 2.5 mg alkaloids** from *Chelidonium majus*, according to the posology of the SPC.

The HMPC concluded that evidence of clinical efficacy was lacking for monotherapy so no WEU indication. The documented TUs for *Chelidonium majus*, because of high number of spontaneously reported liver-biliary adverse drug reactions, the benefit-risk assessment of oral use of *Chelidonium majus* is considered **negative** with respect to the establishment of a community monograph.

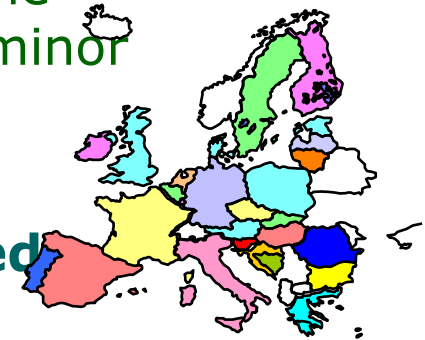
If new information on clinical safety and efficacy of *Chelidonium majus* L., were to be made available, such documentation may be re-assessed by the HMPC.



Conclusions : The implementation of Directive 2004/24/EC (THMPD) in EU has increased the availability of high quality HMPs with reliable patient information for the consumers.

Improvement of the safe use of HMPs in EU by consumers and enabled healthcare experts to advise their patients with confidence on the appropriate use of HMPs for self-limiting minor ailments.

What kind of Herbal products do we need and should we prefer in EU???????





ΕΘΝΙΚΟΝ & ΚΑΠΟΔΙΣΤΡΙΑΚΟΝ
ΠΑΝΕΠΙΣΤΗΜΙΟΝ ΑΘΗΝΩΝ

Thank you for your attention !

