Taking the risk of the benefit
Gert Laekeman

The unbalanced situation of herbal medicines
OBJECTIVES

• Context

• Methodological approach

• Examples

• Facilitating vs hampering marketing authorisation
Find out more about what we do
The European Medicines Agency (EMA) is a decentralised body of the European Union, located in London. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.

The agency is responsible for the scientific evaluation of applications for European marketing authorisations for both human and veterinary medicines (centralised procedure). Under the centralised procedure, companies submit a single marketing-authorisation application to the Agency. Once granted by the European Commission, a centralised (or Community) marketing authorisation is valid in all European Union (EU) and EEA-FTA states (Iceland, Liechtenstein and Norway).

All medicines for human and animal use derived from biotechnology and other high-tech processes must be approved via the centralised procedure. The same applies to all advanced-therapy medicines and human medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions, and viral diseases, as well as to all designated orphan medicines intended for the treatment of rare diseases. Similarly, all veterinary medicines intended for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals have to go through the centralised procedure.

For medicines that do not fall under any of the above-mentioned categories...
The Committee on Herbal Medicinal Products (HMPC) was established in September 2004, replacing the CPMP Working Party on Herbal Medicinal Products. The Committee was established in accordance with Regulation (EC) No 726/2004 and Directive 2004/24/EC, which introduced a simplified registration procedure for traditional herbal medicinal products in EU Member States.

Composition

The HMPC is composed of scientific experts in the field of herbal medicinal products. It has one member and one alternate member nominated by each of the 27 EU Member States and by each of the EEA-EFTA states Iceland and Norway. The Chair is elected by serving HMPC members.

Up to five additional members (European experts nominated by the Member States or by the Agency) may be co-opted to contribute additional expertise to the HMPC. Currently, the Committee has co-opted members with expertise in clinical pharmacology, experimental/non-clinical pharmacology, toxicology, paediatric medicine and general and family medicine.

The HMPC also has observers from the European Directorate for the Quality of Medicines (EDQM) and - as part of the EU Enlargement Programme 'Transition Instrument for Pre-accession programme' - from Croatia, the Former Yugoslav Republic of Macedonia, Montenegro, Serbia and Turkey.

See HMPC members for the list of current members.

Meeting calendar

See full meeting planning for 2010
<table>
<thead>
<tr>
<th>Name</th>
<th>Language</th>
<th>First published</th>
<th>Last updated</th>
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<tbody>
<tr>
<td>Final community herbal monograph on Hypericum perforatum L., herba (well-established medicinal use)</td>
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<tr>
<td>Opinion of the Committee on Herbal</td>
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EFSA is responsible for verifying the scientific substantiation of the submitted claims, some of which are currently in use, some of which are proposed by applicants...
**Herbals**

**Herbal preparations**

**Food supplement**
- notification
- ‘claim’
- information to public
- HACCP

**Herbal medicine**
- registration
- therapeutic indication
- SmPC / PPI
- GMP

**EFSA**

**EMA - HMPC**
Food supplement  |  Traditional Herbal Medicine

**People**
- General population?
- In-/exclusion
- Population at risk

**Process**
- Preparation?
- Duration of use?
- Well-defined preparations
- Limited duration of use

**Product**
- Outcome: cf claim?
- Outcome: cf. indication
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HERBAL MEDICINES

- Quality
- Safety
- Effectiveness

BENEFIT \rightarrow RISK

25 questions
<table>
<thead>
<tr>
<th>No risk</th>
<th>Therapeutic benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>No therapeutic benefit</td>
<td>Risk</td>
</tr>
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</table>
... The material complies with the European Pharmacopoeia monograph ...
SAFETY

(in)voluntary intoxications

AE / SAE with normal use

toxic substances

since when used

groups at risk

interactions

genotoxicity
EFFICACY

- Essential use
- Validated indication
- Meta-analysis RCTs clinical exp.

Positioning within therapeutic group.
OBJECTIVES

• Context

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• Examples

• Facilitating vs hampering marketing authorisation
HERBALS USE

- People: patients / consumers
- Process: intervention / event
- Product: (therapeutic) outcome
GUIDELINE ON RISK ASSESSMENT OF MEDICINAL PRODUCTS ON HUMAN REPRODUCTION AND LACTATION: FROM DATA TO LABELLING

EMA - 2009
... can be used during pregnancy.

No effects during pregnancy are anticipated, since systemic exposure to {Active substance} is negligible

e.g. Avenae sativae fructus
... can be used during pregnancy if clinically needed...

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity

- Systematic pharmacovigilance of occasional exposure: only possible in pharmaceutical/medical environment
- Specific for herbal medicinal product!
Figure 1  Responses from consumers of complementary medicine who had experienced an adverse reaction to the question ‘Who did you tell about the adverse reaction?’ ADR, adverse drug reaction; CAM, complementary and alternative medicine; CM, complementary medicine.

... The use of ... may be considered <during pregnancy> <during {... trimester} of pregnancy>, if necessary ...

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity. Animal studies do not indicate reproductive toxicity.

Within reach for TU herbal products
... As a precautionary measure, it is preferable to avoid the use of ...

During pregnancy or during each trimester of pregnancy ...

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Most of the herbal medicinal products...
... is not recommended during pregnancy and in women of childbearing potential not using contraception ...

There are no or limited amount of data from the use of {Active substance} in pregnant women.

A. Studies in animals have shown reproductive toxicity

or

B. Animal studies are insufficient with respect to reproductive toxicity

e.g. essential oils or reports on isolated compounds
... is not recommended during pregnancy and in women of childbearing potential not using contraception ...

There are no or limited amount of data from the use of \{Active substance\} in pregnant women:

A. Studies in animals have shown reproductive toxicity

or

B. Animal studies are insufficient with respect to reproductive toxicity

e.g. essential oils or reports on isolated compounds
HERBAL USE

- People: patients / consumers
- Process: intervention / event
- Product: (therapeutic) outcome
2001-83-EC
Specific provisions applicable to traditional herbal medicinal products... Bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Community... Marketed herbal medicine? Formulary?
Camellia sinensis

... Fulminant hepatitis during self-medication with hydroalcoholic extract of green tea ...

Exolise = 80% ethanolic extract of Camellia sinensis
- On the market in B, E, F & UK > 1999
- 25% catechins

WARNINGS & RESTRICTIONS

Belgium: RC 1997 & 2005

Population based
- Ginkgo biloba: anticoagulants!
- Hypericum perforatum (St. Johnswort); other medicines!
- Glycyrrhiza glabra (licorice): limit of 6 weeks!
- Rheum (rubarb) & Senna: ≥ 12y / medical advice / pregnancy
- Urtica (common nettle): advice doctor / pharmacist

Posology based
Daily dose restricted to ≤ 80% of minimal therapeutic dose
HERBAL USE

• People: patients / consumers
• Process: intervention / event
• Product: (therapeutic) outcome
Toxicity of *Passiflora incarnata* L.

Alex A. Fisher; Patrick Purcell; David G. Le Couteur

*The Canberra Hospital, Garran, Australia (AAF); Therapeutic Goods Administration, Symonston, Australia (PP); The Canberra Clinical School of the University of Sydney, Garran, Australia (AAF; DGLC)*

**ABSTRACT**

**Background:** Herbal medicines may have significant adverse effects which are not suspected or recognized. **Case Report:** A 34-year-old female developed severe nausea, vomiting, drowsiness, prolonged QTc, and episodes of nonsustained ventricular tachycardia following self-administration of a herbal remedy, *Passiflora incarnata* L., at therapeutic doses. The possible association of symptoms with passiflora was not recognized for several days. She required hospital admission for cardiac monitoring and intravenous fluid therapy. **Conclusions:** *Passiflora incarnata* was associated with significant adverse effects in this patient. It is important to ask specifically about the use of herbal medicines in patients with undiagnosed illnesses.
CAUSAL RELATIONSHIP

Austin Bradford-Hill criteria
(Environment & disease)

• Strength
• Consistency
• Temporality
• Biological gradient
• Specificity
• Coherence
• Experimental evidence
• Analogy

CAUSAL RELATIONSHIP

Strength of associations

e.g. smoking – lung cancer (10-30)
= strong association

Fisher et al. 2000

Causality based on strength = absent
Consistency of findings

- Different populations
- Different circumstances

Fisher et al. 2000

One case in 34-year old Caucasian female
- Other females in other countries?
- Male patients
- Different age?
CAUSAL RELATIONSHIP

Specificity of associations

= linked to preparation
• what is known about the preparation?

Fisher et al. 2000

... Sedacalm contains 500 mg of the active ingredients...
Characterisation: digitalis glycosides excluded by analysis, but methodology not specified
CAUSAL RELATIONSHIP

Temporality

• first cause
• than effect!

*Fisher et al. 2000*

QTc occurred after taking the herbal but also after taking metoclopramide, prochlorperazine, droperidol & ondansetron
CAUSAL RELATIONSHIP

Biological gradient

- dose dependency of ADR
- duration of therapy

Fisher et al. 2000

No dose-relationship dressed
Short duration of therapy
CAUSAL RELATIONSHIP

Coherence

= ... the cause-and-effect interpretation whose data should not seriously conflict with generally known facts of the natural history and biology of a disease ... 

Fisher et al. 2000

No coherence: publication about a cardioprotective action in pigs

CAUSAL RELATIONSHIP

Experimental evidence

= observations to be completed by experimental evidence in biological models

Fisher et al. 2000

No such evidence from *in vitro* or *in vivo* models reported in literature
CAUSAL RELATIONSHIP

Analogy

= mostly based on 'class' effects

*Fisher et al. 2000*

Passiflora does not belong to a defined class Properties of secondary metabolites known and not including the described risk
58y male Caucasian

- Exclusion of co-medication
- Liver enzymes quantified
- Virus markers detected: only CMV IgG positive but no antigen in blood sample
- Follow-up of patient with check after 1 year
- Fatty acids in capsules quantified (chromatogram included) and heavy metals excluded
- References on other case reports included
When making an approach
- System for evaluation
- Pro-active pharmacovigilance
- Protection of licences
- Critical causality analysis