European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 31 May 2006
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RESPONSE TO: Commission Public Consultation: As Assessment of the Community System of Pharmacovigilance

Name[1]:
EMEA Committee for Herbal Medicinal Products

Type of stakeholder (e.g. patient/ healthcare professional/ regulator/ industry):
Regulator

Organisation (e.g. European patient group or National industry association - if relevant):
EMEA

Your comments:
General Comment
The report does not address the revised legal framework for herbal medicinal products at all, although the drafting of the report had been started after the finalisation of the pharmaceutical review. The report falls far behind what could be expected and it is not a useful tool for analysing the present situation and to come to proposals for improvement in the area of well-established and traditional herbal medicinal products. As a result of these deficiencies, a specific report should be carried out on behalf of the Commission.

- **on the specific areas highlighted in the Commission sponsored study which can be summarised as follows:**

  1. Data sources and safety issue detection
  The report does not reflect the fact that the current system, in general, is not sensitive with regard to signal generation. According to reports in literature, (Bégaud B, Martin K, Haramburu F, Moore N JAMA 288: 1588 (October 2, 2002)) no more than 5% of serious adverse events are reported. Following a series of studies published within the last few years, the rate of underreporting can be even much higher in the area of herbal medicinal products (Barnes J et. al. Br. J. Clin Pharmacology 1998, Vol. 45: 496-500, Cuzzolin L et. al. Eur. J. Clin Pharmacology 2006, Vol. 62: 37-42, Ernst E Eur. J. Clin Pharmacology 2006, Vol 62: 1-2) because their use is disclosed to physicians (Eisenberg et. al. JAMA 280:1569-1575 (1998), Haefeli WE et al. (2004) Brit J Clin Pharmacol 58:437-441) and the medical doctors are not even informed on serious ADR. In many cases, ADR originating from the concomitant use of herbal medicinal products and other medication, even in serious conditions, (Werneke U et al. (2004) Brit Journal of Cancer 90:408-413) may not be detected as the use is undisclosed to the physician. There are doubts if the current system is really able to deliver the "prove of concept in safety" for new active

[1] requests for attendance at the workshops should be sent separately to peter.arlett@cec.eu.int and should include the organisation you represent and your contact details. The deadline for these requests is 31 March 2006.

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substances (Strom BL (2006) JAMA May 3, Vol. 295 No. 17). It seems to be even more questionable if the system is appropriate for "old" well-established substances, since it will be difficult to create incentives to collect substance-specific data in a systematic way. However, the system is deficient for HMPC, especially for traditional HMP that have been used in a purely OTC environment, even in market chains where there is no contact at all with any health professional.

2. The legal framework and new legal tools

It is appropriate to fully apply the legal framework to all types of medicinal products, including traditional herbal medicinal products. At present, the European Commission holds the view that for registered THMP, no person responsible for pharmacovigilance needs to be nominated by the pharmaceutical company. This is not appropriate, because responsibilities need to be clearly assigned.

Further development of legislation should create incentives and impose obligations for systematic post-marketing studies on the clinical, safety of old/well-established substances, including traditional herbal medicinal products. It should be taken into account that there are no incentives for marketing authorisation/registration holders to perform product-specific studies and that prospective studies focussing on different products with the same active ingredients would probably have to be co-ordinated between MA holders that would also including cost-sharing. The scientific basis for appropriate epidemiological studies including non-interventional/observational studies needs to be strengthened.

3. Decision making in pharmacovigilance

As regards registered medicinal products, criteria need to be developed on how to balance a risk to the expected efficacy in absence of an indication (Article 14 of CD 2001/83) or in absence of a full evaluation of a claim (THMP).

4. Impact of communications and actions

As regards HMPC, it needs to be addressed that pharmacovigilance actions in the pharmaceutical area have triggered the move of products into other areas of consumer goods such as cosmetics, so-called "cosmeceuticals", food supplements or so called "nutraceuticals", where the legal tools for controlling and implementing quality and labelling are much more restricted than in the pharmaceutical area.

Even if this is not the case, some herbal substances or medicinal herbs will continue to be available, as these substances are not "industrially produced finished products".

As the consumers do not seem to have confidence in "official" or professional advice related to herbal medicinal products (see references above), specific ways of communication and stakeholders' participation have to be developed.

5.Facilitation and monitoring of compliance with pharmacovigilance requirements

One major obstacle to the full implementation of the current system is the fact that the current pharmacovigilance databases do not contain a harmonised thesaurus/catalogue for herbal substances/preparation. Case reports included in databases cannot be found, because active substances are assigned to different terms. For instance, reports connected to garlic can be found under either of the following search terms: “garlic”, “allium sativum”, “allicin” or “Knoblauch”. The database does not differentiate between different plant parts, so that indications can not be precisely attributed to a certain plant part. Taking Urtica urens for example, the indication for Urticae herba et folium is rheumatic complaints, the indication for Urticae radix is benign prostatic hyperplasia. The

implementation of a consistent catalogue would be an important first step to improve the current situation.

A thesaurus should be established based on
- the scientific plant name, author in Latin
- plant part in Latin.

This thesaurus should include, as far as possible, entries covering
- the declaration of extracts following the draft guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products in the SPC of the HMPC.
- synonyms and common names
- constituents which are used for a standardisation because their therapeutic activity is known

The ATC-Code concerning herbal substances/preparations/medicinal products should be adequately substantiated by scientific data. The herbal topics of the ATC-Code 2006 are often scientifically wrong and/or misleading.

Deficiencies in coding and existing catalogues have a negative impact on signal generation, too. For example, the German pharmacovigilance database contains 286 ADR connected to Ginkgo biloba and 256 ADR connected to St. John´s wort, which cannot be found in the Eudravigilance database.

6. The need for quality management and continuous quality improvement.
In view of the major deficiencies in the design and content of the Fraunhofer-Report and in the current implementation of the provisions, specific recommendations cannot be given at this moment.

- **on your experiences of the Community system overall**
  see comments above.

- **on any part of the Community system (section 1 of this consultation paper describes the system and those involved directly)**
  incorporated in section 1

- **on how you could better contribute to the Community pharmacovigilance system**

- **on suggestions to strengthen the Community pharmacovigilance system.**

- **any other comments**

  It is strongly advised to complement the Fraunhofer study by a specific study addressing the situation of well-established and traditional herbal medicinal products. Without such a study detailed mid- to long-term recommendations are not possible. Such a study should address the specific situation of HMP and should comprise interviews with agencies' pharmacovigilance units and with all stakeholders, including health practitioners, pharmacists and consumers.

Short-term actions should include the development of a precise catalogue/thesaurus for herbal substances/preparations in the Eudravigilance database. Initiatives have already been started at the EMEA.
The legislation needs to be modified insofar as clear responsibilities for pharmacovigilance need to be assigned to registration holders of traditional herbal medicinal products.

For improving signs detection it would be considered that “yellow cards” could be prepared in two copies. One could be sent to person responsible for pharmacovigilance in MAH and second directly to national pharmacovigilance centre. This would allow to pharmacovigilance centres to compare both numbers.

Attention should be paid to the alternative circuit for plant products. So one of the recommendation may be to enlarge the investigation to the 'gray' sector in order to get a grip on possible side-effects occurring with herbal products not yet fully covered by the current legal system.

In order to have a clear estimation of the risks, data about the volume of product distributed should be available and collected.