The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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AD HOC WORKING GROUP ON HERBAL MEDICINAL PRODUCTS

Final Comments and Proposals for Revision of Part 4 of Annex to Council Directive 75/318/EEC of 20 May 1975 'Clinical Documentation'

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Note:

Modifications from the original texts proposed by the group are in *bold italic.*

The views presented in this document are those of the HMPWP, which has been created as a forum for exchange of experience in the field of herbal medicinal products. This document is released for the purposes of transparency and has no legal force with respect to Directive 2001/83/EC.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.eu.int http://www.emea.eu.int

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The working group offers the following comments, including some suggestions for amendment.

The group found the terminology not well adapted to bibliographic applications. The group discussed the issue of the broader definition of a clinical trial as provided in the text with comparison to the definitions laid down in the Good Clinical Practice (GCP) Directive for "clinical trials" and "non-interventional studies". The group wondered whether epidemiological studies would be covered by the proposed definition. To clarify this matter, the group agreed to suggest the introduction of a new paragraph stating:
"***Documentation on experience in the form of epidemiological studies can be taken into account in bibliographical applications for well-established medicinal products***".

Section A. General requirements
It is suggested to modify the last sentence of the first paragraph as follows: "***Consequently, an essential requirement is that all clinical data should be communicated, both favourable and unfavourable***".

Section C. Presentation of results
In section C.1., the group agreed to introduce ***a statement on the need for identity or essential similarity between the product tested in the clinical trials and the product intended for marketing***. The precise composition and specification of the product investigated must be provided. For compounds with well-known therapeutic activity, the Expert Report must explain the relevance of any data submitted which concern a product different from the product intended for marketing. It is indeed up to the Expert to judge that the differences are small enough to consider that the product studied is similar to the product which will be granted a marketing authorisation.

In section C.2., the group also felt the need for ***a paragraph in the text which clearly mentions that the Expert Report must pay particular attention to any missing information in a bibliographical application*** for a well-established product. Justification must be given why demonstration of efficacy can be supported although some studies are lacking.

The group recognised that, beside the fact that there are mandatory requirements, which are to be met in principle, it is known that some of the data required are not available from bibliographic sources. It was stated that in the case of well-established herbal medicinal products the need for new clinical studies should not only derive from formal criteria. The expected benefit of additional studies for the safeguard of public health should be considered in each particular case. The group highlighted that this issue is linked to the claimed indication(s) and that more severe criteria for the acceptability of clinical data presented/missing data would be used in the case of "modern" indication, e.g. hypercholesterolemia.

Section D.1. Pharmacodynamics

The group reviewed this section and considered that the paragraph stating that "the demonstration of pharmacodynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect" is an essential remark. This statement fully applies to herbal medicinal products. In some circumstances, where a well-established use is adequately documented, pharmacodynamic data may contribute to an acceptance of bibliographic applications for herbal medicinal products.

It was recognised that the demonstration of the mode of action of an herbal medicinal product often cannot be clarified by the applicant and that the documentation of efficacy, in those cases, should be a priority.

Section D.2. Pharmacokinetics

The issue of the request for pharmacokinetic data for herbal medicinal products, and in particular for complex mixtures with constituents of unknown therapeutic activity was discussed. *Ginkgo biloba* extract was mentioned as a relevant example of a complex active substances mixture in which case pharmacokinetic data should not be required. Requirements for pharmacokinetic data should always be realistic and relate to the Public Health and safety risks associated with the product. When there are safety concerns (example of photosensitisation in the case of Hypericum) pharmacokinetic data are useful to provide safety margins.

The group concluded its discussion on pharmacokinetic by stating that, for well-established medicinal products where the efficacy is based on bibliographical documentation, pharmacokinetic data would not be required unless there are ground for safety concerns from the presence of one or several constituents. If there is a constituent with known therapeutic activity and a narrow therapeutic range, pharmacokinetic data will be required. The Expert Report should carefully address all these issues.

Section E. Bioavailability/bioequivalence

The same principle as defined above for pharmacokinetic data shall apply for bioavailability/bioequivalence data. The group would also recommend the introduction of ***a statement on the need to provide bioavailability data for galenic preparations with modified release***, in view of the difficulty to use bibliographical data in such case.

Section F. Clinical efficacy and safety

The group reported some elements, which make it difficult for applicants to conduct proper comparative clinical trials. The blinding feature of a clinical trial cannot always be respected, for example in the case of essential oils with strong smell.

Section F.5 on vaccines and serums was considered irrelevant for herbal medicinal products. The group indicated that the principles of points 6 to 9 (safe use) apply to bibliographical applications and that these points should be underlined in the Expert Report for each individual product.

Section G. Documentation for applications in exceptional circumstances

This section was considered to be not relevant to well-established herbal medicinal products.

Section H. Post-marketing experience

This section was, on the contrary, felt to be of particular importance for herbal medicinal products. The group indicated that applicants should put a special emphasis to this issue for individual products and for all related products originating from the same herbal drug.

As a conclusion, the group recognised the validity of the framework provided by this document. The basic concepts and general rules should apply to bibliographical data, but taking into account the specific comments made by the group.