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

17 September 1998
EMEA/HMPWP/11/99

AD HOC WORKING GROUP ON HERBAL MEDICINAL PRODUCTS

PROPOSAL FOR A NOTE FOR GUIDANCE ON NON-CLINICAL TESTING OF HERBAL DRUG PREPARATIONS WITH LONG-TERM MARKETING EXPERIENCE - GUIDANCE TO FACILITATE MUTUAL RECOGNITION AND USE OF BIBLIOGRAPHIC DATA

RELEASE FOR CONSULTATION BY THE EMEA	January 1998
DEADLINE FOR COMMENTS	April 1998
RELEASE OF FINAL PROPOSALS	September 1998

Note:

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

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Proposal for a Note for Guidance on Non-clinical Testing of Herbal Drug Preparations with Long-term Marketing Experience - Guidance to Facilitate Mutual Recognition and Use of Bibliographic Data

The working group finalised the following proposal for a Note for guidance on non-clinical testing of herbal drug preparations with long term marketing experience. The group acknowledged the need to update this document taking into account comments expected from the CPMP Safety Working Party, and in view of the anticipated finalisation of the CPMP Note for guidance on non-clinical testing of substances with long-term marketing experience - old substances- (CPMP/SWP/799/95).

INTRODUCTION

Article 4 point 8 a) ii) of Council Directive 65/65/EEC makes it clear that the applicant shall not be required to provide the results of pharmacological and toxicological tests if he can demonstrate by detailed reference to published scientific literature presented in accordance with the second paragraph of Article 1 of Council Directive 75/318/EEC that the constituent(s) of the medicinal product have a well-established medicinal use, with recognised efficacy and an acceptable level of safety. This regulation in no way relaxes the requirements of proof of safety set out by the Annex to Council Directive 75/318/EEC. All aspects must be covered by appropriate bibliographic data and the expert report.
Published non-clinical tests for well-established herbal drug preparations are often incomplete or not in accordance with today's state of the art. Well-presented clinical experience (with regard to the time and extent of use in humans) as well as post-marketing experience gained by wide spread use in humans contribute to the avoidance of unnecessary tests in animals. Protection of animals should be taken into consideration when requesting non-clinical testing of well-established herbal drug preparations (86/609/EEC). Studies that do not agree with the current state of the art (e.g. GLP-conformity), should be judged for credibility; subsequent demands that could lead to a "blind" repetition of animal experiments should be avoided. In particular, it should be assessed whether the observed effects in animals studies would modify the benefit/risk assessment and would lead to a negative decision for the granting of a Marketing Authorisation.

In cases of reasonable suspicion, additional appropriate non-clinical tests can be requested.

NON-CLINICAL TESTING

Where there is sufficient experience available in humans, single dose and repeated dose toxicity, immunotoxicity as well as local tolerance testing of well-established herbal drug preparations is not necessary. Likewise, pharmacological tests including safety pharmacology and pharmacokinetics are not necessary. The expert report must address these aspects and give the grounds why the documented medical experience justifies a safe use of the herbal drug preparation.

Non-clinical testing of well-established herbal drug preparations should be directed towards the study of effects that are difficult, even impossible to detect clinically. These effects would include toxicity to reproduction, genotoxicity and carcinogenicity.

Reproductive toxicological investigations regarding fertility are generally not necessary, insofar as there are no grounds for suspicion that would necessitate testing.

The reproductive toxicological potential with regard to embryo-foetal and peri-post-natal development is to be clarified. Reproductive toxicity data are available for many old substances, however, these data are often not reliable. A repetition of the tests is only justified in cases in which the significance of the results is not clear and there are grounds for suspicion. Reproductive toxicological tests in animals are not necessary if one of the following criteria is fulfilled:

- Results from epidemiological data of adequate power or post-marketing safety studies are available.

- Results from investigations in pregnant women and neonates are present.

- The medicinal product is not intended to be used in women of child-bearing age or during pregnancy and lactation.

The clinical Expert Report should justify the distinction made between women of child-bearing age and pregnancy.

The genotoxic potential of herbal drug preparations should be clarified.

A repetition of the studies is only required in cases in which the significance of the results is unclear or they yield grounds for suspicion. Positive findings for one herbal drug preparation or for substances from one chemical class can frequently be extrapolated to another herbal drug preparation without necessitating further testing.

It is recommended to first perform *in vitro* tests for substances in which the genotoxicity tests are insufficient. Substances with negative results *in vitro* also exhibit negative results *in vivo* in the majority of cases. In cases in which positive results in vitro are present, these are to be clarified by way of appropriate investigations, mainly *in vivo.* (CPMP Note for guidance on genotoxicity: a standard battery for genotoxicity testing of pharmaceuticals (CPMP/ICH/174/95), CPMP Note for guidance on genotoxicity: guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals (CPMP/ICH/141/95) and OECD 1995).

It is appropriate to assess genotoxicity initially in a bacterial reverse mutation test using a test battery of different bacterial strains and metabolic activation (s. CPMP/ICH and OECD Guidelines). This test has been shown to detect relevant genetic changes and the majority of genotoxic rodent carcinogens. If positive results can not be clearly attributed to specific constituents with a well-established safety-profile (e.g. Quercetin) additional *in vitro* and, if necessary, *in vivo* studies should be performed. A co-operative approach is encouraged to investigate herbal drug preparations with the same specification.

Carcinogenicity studies are not needed in cases where there is no suspicion for a carcinogenic potential (Council Directive 75/318/EEC of 20 May 1975, Part 3, IIE. Carcinogenic Potential; CPMP Note for guidance on the need for carcinogenicity studies of pharmaceuticals (CPMP/ICH/140/95), CPMP Note for guidance on carcinogenicity: testing for carcinogenicity of pharmaceuticals (CPMP/ICH/299/95), Addendum to Note for guidance on dose selection for carcinogenicity studies of pharmaceuticals: addition of a limit dose and related notes (CPMP/ICH/366/96)).

Even a positive suspicion of a carcinogenic effect of an well-established herbal drug preparation does not necessarily require a study to be performed. The following considerations should be included in the assessment:

- Is the suspicion based on positive results of genotoxicity studies and can it be clarified in further genotoxicity studies, mainly *in vivo?*

- Is there sufficient epidemiological experience in humans that could refute the suspicion?

EXPERT REPORT

The expert is obliged to point out the necessity or not of non-clinical testing for the herbal drug preparation. Plausible presentation of the facts contributes to the acceptance of the application for marketing authorisation and facilitates the evaluation performed by the authorities.
The expert should discuss available published toxicological data on closely related herbal drug preparations, different parts of the plant, data on related species of the same genus or plant family. If there are toxicological data on well-defined constituents of a herbal drugs preparation, the expert should discuss the relevance of these data for the safety-assessment of the herbal drug preparation.