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

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EMEA WORKING PARTY ON HERBAL MEDICINAL PRODUCTS

UPDATED DRAFT POINTS TO CONSIDER ON THE EVIDENCE OF SAFETY AND EFFICACY REQUIRED FOR WELL-ESTABLISHED HERBAL MEDICINAL PRODUCTS IN BIBLIOGRAPHIC APPLICATIONS

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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.

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Evidence of Safety and Efficacy Required for Well-established Herbal Medicinal Products in Bibliographic Applications

The EMEA Working Party on Herbal Medicinal Products prepared the following Points to Consider:

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1. Legal background

Volume 2A of the Notice to Applicants clarifies the legal background of bibliographic applications as follows:

1.1 Where the constituent or constituents of the medicinal product have a ***well established medicinal use***, with ***recognised efficacy*** and an ***acceptable level of safety***, demonstrated by detailed references to **published literature** presented in accordance with second paragraph of Article 1 of Directive 75/318/EEC, an application (so called "bibliographical") for marketing authorisation may be submitted in accordance with Directive 65/65/EEC, article 4.8 (a) ii.

1.2 An applicant wishing to use Article 4.8 (a) ii) of Directive 65/65/EEC must fully satisfy all the ***requirements*** of Article 1 of Directive 75/318/EEC as well as those of Directives 65/65/EEC and 75/319/EEC as amended, in effect, submit a "***complete" application***.

1.3 Directive 75/318/EEC Article 1 states that „where pursuant to point 8 (a) of Article 4, second paragraph, of Directive 65/65/EEC, references to published data are submitted, the provisions of this Directive (i.e. Directive 75/318/EEC) shall ***apply in like manner***." In such cases, the full article or reference should be supplied, with necessary translations. Moreover, the Expert Reports must clearly state the grounds for using published references under the conditions set out in Directive 75/318/EEC. This would include the completion of all of the tabular formats provided in „The rules governing medicinal products in the European Union, Volume 2B Notice to Applicants: Presentation and content of applications" where relevant, unless there is a justification that the study is not relevant for the medicinal product. The impurity/related substances profile and the decomposition products arising during storage must be clearly indicated in order to allow assessment of appropriate efficacy and safety.

1.4 In the event that neither detailed reference to published literature, nor appropriate justification is available to cover all the requirements, the applicant must supplement the missing data with ***appropriate additional studies***.

Scientific monographs on certain substances (e.g. those drafted by the European Scientific Co-operative on Phytotherapy (ESCOP) and the World Health Organisation (WHO) for herbal drugs) offer a valuable and updated overview on published scientific literature, which together may be used in support of the demonstration of the safety and efficacy of a medicinal product in a bibliographical application in accordance with Article 4.8 (a)ii. These monographs may help to avoid duplication of work and bring about gradual harmonisation in the evaluation of medicinal products, e.g. herbal medicinal products. Therefore the Commission and Member States recommend that both applicants and competent authorities should make use of these monographs.

1.5 Commission Directive 1999/83/EC clarifies that 'bibliographic reference 'to other sources of evidence (postmarketing studies, epidemiological studies, studies conducted with similar products, etc.) and not just tests and trials may serve as a valid proof of safety and efficacy of a product if an applicant explains and justifies the use of these sources of information satisfactorily.

1.6 It should be noted that summary assessment reports such as the EPAR for Community marketing authorisations or evaluation reports on Maximum Residue Limits which are made publicly available by competent authorities for reasons of transparency would generally not be considered to supply sufficient information to meet the requirements of Directive 75/318/EEC.

2. Points to be considered and recommendations for implementation of the legal requirements in marketing authorisations for well-established herbal medicinal products

The interpretation of open terms such as “well established medicinal use”, “recognised efficacy” (Council Directive 65/65/EEC, Art. 4.8 (a) ii) and “in like manner” have lead to conflicting interpretation within the Community. Herbal medicinal products present several particularities that are relevant for the interpretation of these open terms:

2.1 Many herbal medicinal products have been used as medicinal products for several decennies or even hundreds of years. This long-term use has created a comprehensive body of experience laid down in published literature. Systematic use of published literature will be a contribution to avoid animal experiments in preclinical testing and reduce the number of clinical trials in humans.

2.2 Herbal drug preparations are complex biological mixtures and the therapeutic effect can, in most cases, not be related to one single constituent. A statement on the safe use of a herbal drug preparation is not possible without detailed information on quality aspects including production.

2.3 Herbal medicinal products are often used in the OTC treatment of minor illness. Most of these medicinal products are available without medical prescription. In some Member States, however, herbal drug preparations are widely prescribed by medical doctors whereas in others they are practically non-existent in medical prescription.

2.4 Whereas a considerable part of the citizens of the European Union has a preference for using herbal medicinal products because they are of natural origin and are believed to have fewer undesirable effects there is a more sceptical attitude towards them in modern medicine and clinical pharmacology. These differences in perspective have to be balanced in a scientific assessment.

2.5 In some Member States herbal preparations had a legal status different from medicinal products. Most of the herbal drugs have access to the market in the form of crude botanical drugs without being subject to Council Directive 65/65/EEC. These uses appear to have generated information on the safety and efficacy of herbal medicinal products that should be used in assessment.

The EMEA Working Party on Herbal Medicinal Products has prepared guidance and proposals for modifications of existing legislation. Reference is made to these texts for interpretation of the Annex to Council Directive 75/318/EEC.

In the interpretation of the open terms in Council Directive 65/65/EEC and Article 1 of Council Directive 75/318/EEC and in the preparation of new legislation on well-established herbal medicinal products the following aspects should be considered:

3. Well-established use

3.1 According to WHO, a "*long history of medical use*" may be defined, depending on the history of a given country [or community], as not less than several decades. The particular context of the medical, historical, spiritual, ethnological/cultural backgrounds of the given community have to be respected in this classification.

Well-established use implies that a sufficient number of patients were treated by the concerned product or by a product essentially similar to the concerned product.

3.2 Herbal drug preparations that have a long history of medical use are expected to have useful bibliographic data and information published in official pharmacopoeias and scientific reference textbooks. The inclusion of a herbal drug in official

pharmacopoeias of different Member States or the inclusion in scientific reference textbooks may contribute to substantiate a well-established medicinal use.

3.3. The provisions of Commission Directive 1999/83/EC are in line with WHO recommendations and allow an appropriate consideration of particularities of herbal medicinal products: Factors which have to be taken into account in order to establish a "well established medicinal use "of constituents of medicinal products are the time over which a substance has been used, quantitative aspects of the use of the substance, the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments. Therefore different periods of time may be necessary for establishing a "well established use "of different substances. In any case, however, the period of time required for establishing a "well established medicinal use "of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the EU.

3.4. In bibliographic applications it has to be decided in each case, if published literature on one herbal medicinal product can be used in the assessment of another herbal medicinal products. CD 1999/83/EC clarifies that the Expert report must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product which will be granted a marketing authorisation in spite of the existing differences. Because complex biological mixtures, e.g. herbal extracts produced by different manufacturers, are never identical the following aspects must be considered: Herbal drug preparations used as active substance can be considered as sufficiently identical if the specification is the same and no relevant differences in the manufacturing process exists. The identity of specification and manufacturing process is particularly important in those cases where bibliographic data on highly purified extracts are presented or where a new method of preparation of an extract is used. In the case of "classical" herbal drug preparations such as tinctures and extracts described in pharmacopoeias and used for long time, a "comprehensive" specification will not be available from published literature in most cases. For these preparations the starting material, the extraction solvent must be identical. Reference is made to the Note for guidance on quality of herbal medicinal products (EMEA/HMPWG/9/99), Chapter A 1 and A 2. If there are reasons to expect a different pharmacological or toxicological profile, additional data and an update of the specification and/or appropriate data on bioavailability may be necessary.

3.5. It should be taken into account that herbal medicinal products had a different legal status in some Member States. Herbal drugs may have a widespread medicinal use over a long time without being finished medicinal products. In those cases, the information from such parallel should be included in an assessment.

4. Recognised efficacy

The "entry-point" to bibliographic applications, i.e. the possibility to use Art. 4.8 (a) ii of Council Directive 65/65/EEC, and the assessment of the data presented in the application must be differentiated.

It is important that in the case of well-established herbal medicinal products the requirements for proof of efficacy and the documentation required to support the indicated claims should depend on the nature and the level of the indication(s). For treatment of minor disorders a lower level of evidence may be adequate, especially when the extent of long-term use, the experience with that particular herbal medicinal product and supportive pharmacological data are taken into account. The level of evidence and the grading of recommendations must

correspond to the nature of the disease that is to be treated. The therapeutic alternatives available, the risks of a delayed or insufficient treatment and the risks of the herbal drug preparation have to be taken into account.

In the assessment of well-established herbal medicinal products all bibliographic documents should be taken into consideration. Old reports should be judged for their credibility. The following type of documents could be used: controlled clinical trials, other clinical trials, cohort or longitudinal studies, observational (non-interventional) studies, case-control-studies, other collections of single cases allowing a scientific evaluation, scientifically documented medical experience, for example scientific literature and expertise from scientific medical associations. These bibliographic data must be assessed in order to establish if they can demonstrate a sufficient level of safety and efficacy. When studying clinical safety and efficacy by using bibliographic references, the following aspects should be evaluated: the number of patients, specific diagnosis, preparation used (see point 1.3), dosage, duration of administration, criteria for evaluation (e.g. improvement of symptoms), and applicable statistical analysis. The following factors will increase the relevance and credibility of published data[1]:

a) if there are multiple studies conducted by different investigators and/or independent literature reports where the findings across studies / reports are consistent;

b) if there is a high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients;

c) if there are clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgement (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as relief of symptoms.

d) if there are robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or “evaluable” subset).

e) if there is a conduct of studies by groups with properly documented operatingprocedures and a history of implementing such procedures effectively.

A review of the literature should identify the current level of evidence of the safe and effective use of a herbal medicinal product. The definitions of the types of evidence and the grading of recommendations set out in the following tables originate from the US Agency for Health Care Policy and Research (AHCPR) and WHO. They may be considered as guidance:

Levels of evidence

Level	***Type of evidence[2]***
Ia	*Evidence obtained from meta-analysis of randomised controlled trials*
Ib	*Evidence obtained from at least one randomised controlled trial*
IIa	*Evidence obtained from at least one well-designed controlled study*

[1] based on FDA May 1998: Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products

[2] based on WHO and AHCPR 1994

	without randomisation
IIb	*Evidence obtained from at least one other type of well- designed quasi-experimental study*
III	*Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies*
IV	*Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities*

Grading of recommendations

Grade	***Recommendation*3**
A *(Evidence levels quality Ia, Ib)*	*Requires at least one randomised controlled trial as part of the body of literature of overall good and consistency addressing the specific recommendation.*
B *(Evidence levels IIa, IIb, III)*	*Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation.*
C *(Evidence level IV)*	*Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.*

An indication may be accepted, if the documented long-term safe use in a well-defined indication is made plausible by supportive experimental data. Such an approach is, however, limited to minor indications (e.g. symptomatic treatment of self-limiting conditions). Description of traditional use without any supportive clinical or experimental data is not sufficient to establish a sufficient level of evidence of efficacy.

The use of type C / level IV evidence in the assessment of safety and/or efficacy will be facilitated if the reports or recommendations were prepared in a systematic and transparent way with involvement of sufficiently broad range of experts. [4]

5. Acceptable level of safety

The level of safety must correspond to the indication claimed for the product. Reference is made to the Note for guidance on non-clinical testing of well-established herbal medicinal products (EMEA/HMPWP/11/99).

[3] based on WHO and AHCPR 1994

[4] Guidance can be found in AHCPR Interim Manual for Clinical Practice Guideline Development of May 1991, AHCPR Pub. No. 91-0018

6. Requirements to be satisfied

An applicant wishing to use Article 4.8 (a) ii) of Directive 65/65/EEC must fully satisfy all the requirements of Article 1 of Directive 75/318/EEC as well as those of Directives 65/65/EEC and 75/319/EEC as amended, in effect, submit a „complete“ application. Directive 75/318/EEC Article 1 states that „where pursuant to point 8(a) of Article 4, second paragraph, of Directive 65/65/EEC, references to published data are submitted, the provisions of this Directive (i.e. Directive 75/318/EEC) shall apply in like manner.“ It should be kept in mind that the main goal of the European pharmaceutical legislation is protection of public health. The information necessary for the acceptance of safe use is mainly laid down in the Annex to Directive 75/318/EEC. For new drugs this information can only be extracted from new preclinical tests and clinical studies. For well-established herbal medicinal products the information may be extracted from bibliographic data and other evidence available. In order to avoid unnecessary experiments in animals and unnecessary involvement of patients in clinical trials the existing body of evidence has to be checked. CD 1999/83/EC makes it clear that the documentation submitted by the applicant should cover all aspects of the safety and efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre-and postmarketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, should be communicated. Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety and efficacy can be supported although some studies are lacking. Post-marketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue.’

7. Appropriate additional study

In the case that information addressed in the requirements of the annex to Directive 75/318/EEC is lacking, appropriate additional studies may be necessary to establish sufficient evidence of safe and effective use. Reference is made to the comments of the ad hoc Working Group on Herbal Medicinal Products on Part 3 (EMEA/HMPWG/10/99, EMEA/HMPWG/11/99) and 4 of Annex to Council Directive 75/318/EEC (EMEA/HMPWG/13/99).

8. Sufficient information, complete application

A documentation will be considered as sufficient basis for an application for marketing authorisation if all relevant questions derived from the headings of the Annex to Directive 75/318/EEC are addressed by the experts in a competent way and if the relevant bibliographic information is submitted. If a European harmonisation in form of core-SPCs was achieved by the working group on the basis of ESCOP or WHO monographs, reference to the bibliographic data mentioned in these monographs may be accepted. Because these bibliographies may not be present in all Member States, the applicant should clarify in each case if copies of the bibliographic data have to be submitted to the reference and/or concerned Member States.