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**COMMITTEE ON HERBAL MEDICINAL PRODUCTS  
(HMPC)**

**GUIDELINE ON THE ASSESSMENT OF CLINICAL SAFETY AND EFFICACY IN THE  
PREPARATION OF COMMUNITY HERBAL MONOGRAPHS FOR WELL-ESTABLISHED  
AND OF COMMUNITY HERBAL MONOGRAPHS / ENTRIES TO THE COMMUNITY  
LIST FOR TRADITIONAL HERBAL MEDICINAL PRODUCTS / SUBSTANCES /  
PREPARATIONS**

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## **EXECUTIVE SUMMARY**

This guideline describes the legal background and the criteria for assessment of data that are used for preparing Community monographs on herbal medicinal products and the Community list of traditional herbal substances, preparations and combinations thereof. The areas of well-established herbal medicinal products and traditional herbal medicinal products are addressed.

### **1. INTRODUCTION (background)**

The establishment of Community herbal monographs for well-established and for traditional herbal medicinal products and the preparation of a Community list of herbal substances, preparations and combinations thereof is a major task given to the HMPC by the revised pharmaceutical legislation. Both types of documents are essential to further promote EU harmonisation in the area of herbal medicinal products, to facilitate marketing authorisation and registration and to broaden consumer choice for adequately labelled, safe products.

The assessment of herbal medicinal products presents specific challenges in different scientific areas. Herbal substances / preparations are complex mixtures and any assessment of safety and/or efficacy must rely on an adequate pharmaceutical documentation. Additional and even more difficult challenges exist in the assessment of clinical safety and efficacy. Many herbal medicinal products have been used for several decades or even hundreds of years. This long period of use has, in many cases, created a comprehensive body of experience laid down in published literature. This bibliography reflects the scientific standards of phytotherapy at the time of publication and may not be fully in line with modern methodology and reporting standards. Despite these deficiencies, long-standing experience may have a scientific value, if the quality and credibility of the bibliographic data are carefully assessed. Systematic use of published literature will be a contribution to avoid animal experiments in preclinical testing and reduce the number of new clinical trials in humans.

In other cases, the long-standing, consistent use over a long period of time may not yet be supported by sufficient pharmacological or other studies. Traditional uses may reflect different cultural preferences found in the EU. In both cases appropriate information has to be delivered to the consumer. Many traditional herbal medicinal products are evolving into a more scientific approach and this constant improvement should be encouraged.

Careful consideration is necessary to define the borderline between herbal substances / preparations with a sufficient scientific basis (well-established herbal substances / preparations) and those that are exclusively used on the basis of a long-standing use (traditional herbal medicinal products). The EU legislation provides a clear framework for both areas. This note for guidance is intended to give advice for assessing data on well-established and traditional herbal medicinal products and the corresponding herbal substances/preparations in the framework of drafting Community monographs or the Community list. It should be read in conjunction with the general requirements set out by Directive 2001/83/EC as amended, in particular its Annex I, and general methodological requirements published by the EMEA.

### **2. SCOPE**

The guideline applies to the drafting of Community monographs for well-established and traditional herbal medicinal products and of the Community list of traditional herbal substances, preparations and combinations thereof.

### 3. LEGAL BASIS

Following Article 16 h (3) of Directive 2001/83/EU, as amended, the Committee for Herbal Medicinal Products shall establish Community herbal monographs for herbal medicinal products with regard to well-established as well as traditional herbal medicinal products. When Community herbal monographs have been established, they shall be taken into account by the Member States when examining an application for marketing authorisation or for registration. Where no Community herbal monograph has yet been established, other appropriate monographs, publications or data may be referred to. When new Community monographs are established, the registration holder shall consider whether it is necessary to modify the registration dossier accordingly.

A Community herbal monograph may result from the referral to the HMPC by a Member State of an application for simplified registration of a product that has been used for less than 15 years in the Community (Article 16(c)(4)). The monograph will be taken into account by the Member State when taking its final decision.

Following Article 16 f (1) of Directive 2001/83/EU, as amended, the HMPC shall prepare a draft list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products that will be adopted through the procedure described in Article 121(2) of the same Directive. If a herbal substance, preparation or combination is included in the list, no further data on the time and extent of traditional use and on safety are required for the simplified registration (Article 16(f)(2)).

The criteria for the preparation of both types of documents and the documentation needed to support their content are the same as for any individual application for marketing authorisation / simplified registration submitted by an applicant to national authorities. Thus, the following legal provisions apply by analogy to the preparation and to the assessment of data/documentations to support the drafting of Community herbal monographs and the Community list.

Article 10a and Annex 1 of Directive 2001/83, as amended, clarify the legal basis of applications for marketing authorisation of well-established and for registration of traditional herbal medicinal products as follows:

By way of derogation of Article 8(3)(i) the results of pre-clinical tests or clinical trials are not required if it can be demonstrated that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I. In that event, the test and trial results shall be replaced by appropriate scientific literature. The detailed scientific bibliography shall address non-clinical and clinical characteristics.

Factors which have to be taken into account in order to establish a well-established medicinal use of active substances 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 well-established use of different substances. In any case, however, the period of time required for establishing a well established medicinal use of herbal substance / herbal preparation must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community.

By analogy to the content of Modules 4 and 5 of Annex 1 of the Directive 2001/83/EU, a detailed scientific bibliography shall address non-clinical and clinical characteristics. The documentation should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing 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, must be assessed.

With respect to the provisions on ‘well-established medicinal use’ it is in particular necessary to clarify that ‘bibliographic reference’ to other sources of evidence such as post marketing studies, epidemiological studies, appropriate monographs etc. and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a herbal medicinal product if the use of these sources of information is satisfactorily explained and justified.

Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking.

Post-marketing experience with other products containing the same active substance(s) is of particular importance and the assessor should put a special emphasis on this issue.

## **4. RECOMMENDATIONS FOR IMPLEMENTATION**

### **4.1 Guidance on monographs for well-established herbal medicinal products**

According to Article 10 (a) of Directive 2001/83/EC as amended, a dossier in which the results of own non-clinical and clinical tests have been replaced by detailed references to published scientific literature, including Community herbal monographs prepared by the HMPC, may be the basis for assessment. The procedure of drafting monographs and the criteria for assessment are, in many aspects, similar to the preparation and assessment of a non-clinical and clinical part of a bibliographic application for marketing authorization or of a dossier for registration of a traditional herbal medicinal product. For “well-established” herbal medicinal products *all conditions* set out in Annex I, Part II (1) have to be fulfilled. The concept relies on the thinking that the wide-spread medicinal use of a product within the Community for at least 10 years may have generated a sufficient body of conclusive scientific literature that will allow an assessment of safety and efficacy. In most cases, the product has been granted a marketing authorisation and data on pharmacovigilance and PSURs will be available. Experience resulting from pharmacovigilance will be crucial for the assessment of clinical safety. The legislation allows a broad spectrum of evidence that may be used in the assessment of efficacy. In addition to published controlled clinical trials, the assessment of safety and of efficacy may be based on non-controlled clinical studies, epidemiological studies such as cohort or observational studies etc. The original literature may be replaced by an adequate review of the literature or by an appropriate monograph. All aspects of safety and/or efficacy included in module 4 and 5 have to be addressed and the assessment must include or refer to a review of the relevant literature. If information related to a specific aspect is lacking, it is necessary to assess if the safe use of the active substance described in the monograph can be justified. If such a justification cannot be provided, a monograph should address those areas where information is missing.

The explicit requirements are given in the directive texts and the following guidance on the scientific interpretation of the clinical requirements and documentation is given:

The documentation must include a systematic review of literature, including recent searches in medical and toxicological databases. The search profile and the literature consulted must be documented.

The review of the literature should identify the current level of evidence related to the safety and efficacy of the herbal medicinal product. This should be reflected in the assessment report. Levels of evidence

(from Ia to IV) and the grading of recommendations (Grade A, B or C) used in Evidence Based Medicine should be used and may be taken from WHO General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine, WHO/EDM/TRM/2000.1, WHO Geneva, 2000:

### Levels of evidence

Level	Type of evidence
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 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
A (Evidence levels quality Ia, Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good 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.

It should be noted that all types of evidence have to be checked for their scientific quality and consistency. No type of evidence is a priori scientifically valid or not.

In the assessment of well-established herbal medicinal products/substances all bibliographic documents, including bibliography that is specific to phytotherapy, should be taken into consideration. Old reports should be judged for their scientific credibility. The following type of documents might 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 appropriate monographs. The quality and the consistency of 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 6), 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:

- 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), inclusion criteria 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, sub setting, 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 operating procedures and a history of implementing such procedures effectively.

#### **Elements of the clinical documentation supporting a monograph:**

The clinical documentation should include / address the following elements:

A systematic review of all relevant clinical data available for the herbal medicinal product/substance must be performed and reflected in the assessment report and list of references.

A scientific assessment of the clinical data must be performed and reflected in the assessment report. Results of all clinical data included in the systematic review shall be taken into account. Coherent and conclusive clinical recommendations cannot be obtained if major methodological deficiencies are identified in the pivotal clinical data.

Demonstration that the clinical data are covering a sufficient number of patients and that they are conclusive and coherent with respect to the indication, safety and efficacy.

In general, at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study) of good quality is required to substantiate efficacy. In the absence of a controlled clinical trial a case-by-case assessment taking into account possible benefits, risks and types of disease may be acceptable, if clinical experience with the herbal medicinal product is well documented and supportive, conclusive (human) pharmacological data of good quality are available. Evidence of grade C/level IV supported only by pre-clinical data are not sufficient to make the clinical efficacy of a product recognised.

The use of opinions from scientific expert committees, such as consensus conferences, monographs etc. requires additional information: The composition of the committee and the procedure how the results were obtained, including the scientific basis of decision, must be made transparent. Any potential bias has to be discussed.

Data relating only to in-vitro pharmacology or general pharmacology in animals will not deliver sufficient supportive evidence to allow a marketing authorisation. Such data may, however, contribute to the plausibility of a "traditional use". Description of traditional use without any supportive clinical or

experimental data is not sufficient to establish a level of evidence of efficacy that would be acceptable for marketing authorisation. Such information might be accepted for traditional use registration.

Information on the time over which the substance has been used, quantitative aspects of the use of the substance, and the degree of scientific interest (number, quality and consistency of published scientific information) in the use of the substance must be submitted. In most cases, the herbal medicinal product or a similar one (see point 6) will have been authorised in the Community for more than 10 years. If, in exceptional cases, no marketing authorisation has been granted in the EU, it must be clarified, under which conditions a substantial, wide use as a medicinal product throughout a period of time of 10 years within the Community has taken place.

Documentation used in preparation of monographs may be in form of: proof of authorisation/registration by national competent authorities, information from handbooks (medicine, pharmacy, pharmacology, pharmacognosy, phytotherapy, herbal medicine etc.), scientific monographs, and specific product related information, such as approved SPCs, sales statistics, estimated number of users, etc. Unless the documentation indicates otherwise, the publication year of the documentation will be accepted as proof of medicinal use in that year.

### **Therapeutic indications**

There are no restrictions on the indications for herbal medicinal products with ‘well-established medicinal use’. However, the clinical evidence and the documentation required to support the indicated claims should be appropriate to the nature of the indication(s) and to the risks of the substance. 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. Products can be for use under medical supervision or for self-medication. The therapeutic indication for an herbal medicinal product with well-established medicinal use should normally be introduced in the following way: “Herbal medicinal product for ....”.

## **4. 2 Guidance on monographs and on the list of traditional herbal substances / preparations**

In essence, Directive 2004/24/EC introduced the legal basis to register a so-called “traditional” herbal medicinal product for human use. 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. Article 16c (c) of CD 2001/83 requires a documented medicinal use throughout a period of at least 30 years preceding the date of application, including at least 15 years within the EU. There is no requirement that this evidence should relate to the 30 years immediately preceding the date of application. However, if the documentation does not contain evidence of recent usage of the product but instead refers to a period many years earlier, it is likely that such evidence would be of considerably less value in helping to demonstrate plausibility of indications and safety of the product. The requirement to demonstrate 30/15 years of medicinal use does not relate to a marketing authorisation. Other herbal products that have been in medicinal use, as defined by Article 1 (2) or Article 2 (2) of CD 2001/83/EC, as amended, may be registered as a traditional herbal medicinal product.

The basic requirements encompass that the product is not harmful under normal conditions of use, fulfils the requirements on pharmaceutical quality and has an efficacy that is plausible on the basis of long-standing use. The indication must be such that no medical supervision is needed for diagnosis, prescription or monitoring of the treatment. The requirement to demonstrate “plausibility” and to exclude direct and indirect risks introduces a request for careful assessment of the indication proposed.

A well-documented, consistent and long-standing use over at least 30/15 years will, in most cases, provide the basis for acceptance of an indication. In addition to the period of use, the plausibility of the pharmacological effects or the efficacy must be assessed. Plausibility of a traditional indication may include, but is not limited to clinical data, pharmacological studies or case reports. An indication



“exclusively based upon long-standing use” may be plausible, even if no supporting scientific data are available. However, in such a situation evidence on the consistent use that includes a well-defined posology, administration form and indication will be required. If a traditional herbal medicinal product had long fallen into disuse, this might of itself raise questions as to whether this was due to the possibility that it had been found in practice that the efficacy of the traditional herbal medicinal product was not plausible.

The following types of bibliographical or/and expert evidence may be used:

- Excerpts from archives of national competent authorities showing that a product intended for registration or a corresponding product has been approved (authorised or registered) for medicinal purposes. The product may have been approved nationally under different types of legislation (not necessarily as medicinal products) and have different designations such as herbal medicinal product, herbal remedy, natural remedy, healing product, traditional herbal drug on a national list etc. The product may have been formerly regulated under national legislation applicable to food or to cosmetics. The excerpt from the archive may contain all necessary information, but particular attention should be given to information on which years the product has been approved for human use. Unless the documentation indicates otherwise, the publication year of the documentation will be accepted as proof of medicinal use in that year. In the case of official pharmacopoeias or formularies of Member States a continuous use is expected for the period of validity of the corresponding pharmacopoeia monograph. The use of the medicinal product in a medicinal context in the Community throughout a period of at least 30/15 years must be demonstrated.
- A comprehensive literature search, especially in electronic medical and toxicological databases, with the main focus on safety aspects.
- Information from handbooks of medicine, pharmacy, pharmacology, pharmacognosy, phytotherapy, herbal medicine etc. Information on therapeutic indication, type of preparation/strength, posology, and specific information on safe use will typically be found in handbooks.
- Official expert committee reports or monographs from learned societies, such as WHO, Commission E, ESCOP and national formularies/compendia etc. Information on therapeutic indication, type of preparation/strength, posology, and specific information on safe use are usually found in such reports/monographs.
- A monograph in Ph. Eur. or an official national pharmacopoeia will be accepted as a general proof of medicinal use during the years the monograph has been valid. It may also provide relevant information on strength/type of extract. Usually no information on therapeutic indications, posology, or safety will be found in pharmacopoeia monographs, so this information must be obtained from other sources of that time.
- Product related documentation, such as post marketing studies, product information leaflets, sales catalogues, sales statistics, etc.

The assessor should make a compilation of the available information above and based on that a therapeutic indication, posology and specific product information for the product in question should be proposed. Only oral, external and/or inhalation preparations are within the scope of the simplified registration scheme. It is recognised that the requested information from the different sources given above may be dated many years back in time and may be incomplete and partly contradictory. It is nevertheless important that the requested information is presented in a transparent way and that the assessor as far as possible explains and justifies the proposed therapeutic indication, strength, posology and specific information on safe use.

In summary, 5 pivotal pieces of information must be compiled: (a) time in medicinal use, b) therapeutic indication, c) strength/type of preparation, d) posology, and e) specific information on safe

use and evidence of safety. The documentation must give a clear indication that the medicinal use of the product has been a continuum for the required time period of 30/15 years and that the use has been reasonably consistent during that time. It may again be emphasised that the basis for accepting a product as a traditional herbal medicinal product lies within the fact that it has been used in humans for a certain medicinal purpose during a long period of time and that there are no indications that it could be harmful under normal conditions of use as reflected in the Community herbal monograph/Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products.

In those cases, where a monograph results from a referral by a Member State, the referring Member State will submit all relevant scientific documentation to support the referral. The assessor should consider if the draft assessment report prepared by the Member State and the submitted data fully support the safe use in the proposed traditional indication, despite the fact that only limited data on human exposure in the Community may be available.

### **Therapeutic indications for traditional herbal medicinal products**

In principle all indications that can be considered safe for the user without the supervision of a medical practitioner for diagnostic purposes or prescription or monitoring of treatment and that are adequate for a "traditional" medicinal product are possible. This would include minor disorders or symptoms that are of benign or self-limiting character. It is important to assess if the symptoms can be easily recognised/ diagnosed by the layman and if delayed contact with a medical practitioner due to attempted self-medication may lead to risk to the patient. Therapeutic indications that involve diseases, disorders or conditions such as cancer, psychiatric diseases /disorders, benign prostatic hyperplasia (BPH), infectious diseases such as hepatitis or influenza, cardio-vascular diseases such as heart failure, metabolic diseases such as diabetes etc. are not acceptable. Claims such as "radical scavenger" and/or "antioxidant" are not considered to be appropriate. Claims relating to clinical parameters such as the cholesterol-level, blood pressure, immune status etc. require robust scientific data and are not considered to be appropriate for that reason. The therapeutic indication for a traditional herbal medicinal product should be introduced in the following way: "Herbal medicinal product traditionally used ...."

Indications that are too general and that might be considered as misleading are not acceptable, e.g. "promotion of good health", "to give general strength" etc.

Indications relating to specific concepts of traditional medicines may be acceptable if they fulfil the criteria given for safe self-medication. The nature and the type of the tradition should be clearly expressed with the indication. A "translation" of complex traditional terms in terms of modern medicine should be avoided, unless it is guaranteed that both meanings are fully identical. Terms deriving from pharmacological actions should be avoided if the claim is based on a specific traditional concept that does not derive from a pharmacological model.

## 5. CLINICAL SAFETY

For well-established herbal medicinal products all items addressed in Annex 1 of CD 2001/83 related to clinical safety have to be addressed. Serious risks, e.g. case reports of serious ADR, have to be balanced by sufficient evidence of an appropriate benefit.

For traditional herbal medicinal products the clinical safety must be fully documented. If the product has been subject to pharmacovigilance and PSURs, similar criteria as established for well-established herbal medicinal products are applicable. Evidence of widespread, long-standing use without significant safety problems emerging is likely to be an element of a typical safety report. The assessment report has to address all aspects included in module 4 of the Annex I to CD 2001/83 EC. If no bibliographic data are available, available unpublished data may be used. Deficiencies in the documentation have to be clearly identified. For products that were not subject to post-marketing control in the same way as medicinal products, additional new preclinical tests are more likely to be necessary. If risks have been identified, the assessment report must explain why a positive benefit/risk-balance for a traditional use is justified, although scientific evidence of efficacy is missing. If a traditional herbal medicinal product had long fallen into disuse, this might of itself raise questions as to whether this was due to safety concerns.

The assessment must address the situation of special patient populations especially of children and pregnant/lactating women.

## 6. Reference to other products

### 6.1 Active substances

**The assessment report and the monograph/list must clearly address and reflect the different herbal preparations studied or described in literature.**

#### **Well-established herbal medicinal products:**

Because complex biological mixtures, e.g. herbal extracts produced by different manufacturers, are never identical the following aspects must be considered: Assessment of comparability must include details of composition, available data on the specification of the preparation and information on the manufacturing process. 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 and the drug/extract ratio must be comparable. Reference is made to CPMP/QWP/2820/00 *Rev 1* (EMEA/CVMP/815/00) Guideline on specifications: Test procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products and to CPMP/QWP/2819/00 (EMEA/CVMP/814/00) *Rev. 1* Guideline on Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products. In general, a judgement of similarity would be easier for standardised or quantified extracts rather than for other extracts. If there are reasons to expect a different pharmacological or toxicological profile, additional data may be necessary to come to conclusions.

### **Traditional herbal medicinal products:**

As the legislation refers to the “**same active substances**” the herbal substance / herbal preparation must be the same in terms of the declaration of active substances. This will include the plant/part of the plant, the type of herbal preparation and, for extracts, the primary solvent. As the drug/extract ratio may be difficult to retrieve from literature comparison with a range of similar products on the market might be acceptable.

## **6.2 Medicinal Products**

### **Well-established herbal medicinal products:**

The relevance of any data submitted which concern a product/active substance different from the product/active substance reflected in the monograph/list needs to be discussed. A judgement must be made whether the product/active substance studied can be considered as similar to the product/active substance for which an inclusion into the monograph/list is intended in spite of the existing differences.

### **Traditional herbal medicinal products:**

Reference can be made to a “corresponding product” having:

- the same active ingredients, irrespective of the excipients,
- the same or similar intended purpose,
- the equivalent strength and posology,
- the same or similar route of administration.

If no comparable product is currently marketed, reference to scientific reference handbooks, official compendia for prescriptions (e.g. *Formulae normales*) or official pharmacopoeias of Member States would be acceptable, if the combination can be found in these references.

Evidence on the traditional use of the single active substances of a fixed combination will not be sufficient to establish a traditional use of a combination product.

The requirement is also satisfied, if the number or the quantity of ingredients has been reduced during that time period. It should be considered, however, that such a reduction / elimination may have resulted in an increased dose of the remaining constituents thus making a more extensive assessment of safety necessary. The elimination of a number of active constituents or a significant reduction in posology may make it difficult to accept the “plausibility” of an indication.

For any other new or modified fixed combination the procedure as described in Article 16 c (4) of Directive 2001/83/EC may be used.

## **6.3 Additional considerations for Well-established and traditional herbal medicinal products:**

Additional information on the biopharmaceutical characterisation may be necessary. For traditional herbal medicinal products such information will only be required if there are concerns relating to safety or if a specific pharmaceutical form is not a traditional one.

The efficacy and safety of preparations for topical use strongly depends on the galenical preparation and on the excipients. Additional data on clinical safety/local tolerance (marketing authorisation and registration) and on efficacy (marketing authorisation) may be necessary.

Similar considerations may be applicable for herbal medicinal products intended for inhalation if the method of administration differs from the traditional one or the method described in literature, e.g. ultrasound nebuliser versus steam inhalation.

As no additional safety data can be required in applications for traditional use registration if a herbal substance/preparation or combination is included in the EU list, the drafting of a list will not be possible if additional information is necessary to establish the safe use. In such a situation the drafting of a Community herbal monograph may be more appropriate.

## **DEFINITIONS**

For definitions reference is made to the relevant guidelines on quality (see below).

## **REFERENCES (scientific and / or legal)**

1. Directive 2001/83/EC as amended by Directives 2003/63/EC, 2004/24/EC and CD2004/27/EC.
2. Draft Procedure for the Preparation of Community monograph for traditional herbal medicinal products (EMEA/HMPC/182320/2005)
3. Draft Procedure for the Preparation of Community monograph for herbal medicinal products with well established medicinal use (EMEA/HMPC/182352/2005)
4. Structure of the list of herbal substances, preparations and combinations thereof (EMEA/HMPC/100824/2005)
5. Guideline on the documentation to be submitted for inclusion into the list of Herbal substances, preparations, and combinations thereof (EMEA/HMPC/107399/2005)
6. Template for a community herbal monograph (EMEA/HMPC/107436/2005)
7. Draft Guideline on Non-Clinical Documentation for Herbal Medicinal Products in Applications for Marketing Authorisation (Bibliographical and Mixed Applications) and in Applications for Simplified Registration (EMEA/HMPC/32116/05)
8. Guideline on the Clinical Assessment of fixed Combinations of Herbal Substances / Herbal Preparations EMEA/HMPC/166326/05
9. Guideline on specifications: Test procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products CPMP/QWP/2820/00 Rev 1 (EMEA/CVMP/815/00)
10. Guideline on Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products CPMP/QWP/2819/00 (EMEA/CVMP/814/00) Rev. 1.