EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 July 2016
EMA/HMPC/104613/2005 Rev. 1
Committee on herbal medicinal products (HMPC)

Guideline on the assessment of clinical safety and efficacy in the preparation of European Union herbal monographs for well-established and traditional herbal medicinal products[1]

Draft revision 1

Draft agreed by Monograph and List Working Party (MLWP)	May 2006
Draft adopted by Committee on Herbal Medicinal Products (HMPC)	May 2006
End of consultation (deadline for comments)	15 August 2006
Final agreed by MLWP	September 2006
Final adopted by HMPC	7 September 2006
Date for coming into effect	1 March 2007
Draft Revision 1 agreed by MLWP	June 2016
Draft Revision 1 adopted by HMPC for release for consultation	12 July 2016
Start of public consultation	1 September 2016
End of consultation (deadline for comments)	30 November 2016

Comments should be provided using this template. The completed comments form should be sent to hmpc.secretariat@ema.europa.eu

Keywords	Herbal medicinal products, clinical safety, efficacy, traditional use registration, marketing authorisation, European Union herbal monographs, European Union list of traditional herbal substances, preparations or combinations thereof

[1] For traditional herbal medicinal products this guideline is also applicable in the preparation of list entries according to Art. 16f(1) and Art. 16h of Directive 2001/83/EC as amended.

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Guideline on the assessment of clinical safety and efficacy in the preparation of European Union herbal monographs for well-established and traditional herbal medicinal products

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Executive summary

This guideline describes the legal background and recommendations for the assessment of data that are used to prepare European Union herbal monographs (formerly called Community herbal monographs) on herbal medicinal products and the European Union list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products. The areas of herbal medicinal products with well-established medicinal use and traditional herbal medicinal products are addressed.

Revision 1 pertains to an update of the document to current standards taking into account advances over the last 10 years and established practice and legal interpretations. Developments and details in the assessment methodology have so far been mainly reflected in template revisions (such as Assessment report template), but also other documents such as the public statement EMA/HMPC/473587/2011. In addition to the alignment with other documents the revision aimed for improved clarity and transparency by shortening some sections or providing more detail on some particular aspects of the assessment process, e.g. as regards specific population groups.

1. Introduction (background)

The establishment of EU herbal monographs for well-established and for traditional herbal medicinal products is a major task given to the HMPC by the pharmaceutical legislation. HMPC is also responsible for the preparation of draft entries to the EU list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products. Both types of documents are essential to promote EU harmonisation in the area of herbal medicinal products, to facilitate marketing authorisation and registration, and to provide information to health care providers and consumers.

The assessment of herbal medicinal products presents specific challenges in different scientific areas. Herbal substances/preparations are complex mixtures of constituents 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.

Careful consideration is also necessary to define the borderline between herbal substances/ preparations with a well-established medicinal use and those with a traditional use. The EU legislation defines a framework covering both areas. This guideline 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 EU monographs or the EU list. It should be read in conjunction with the general requirements set out by Directive 2001/83/EC, in particular its Annex I, and general methodological requirements published by the EMA. A template with instructions and informative notes for the development of uniform assessment reports has been issued by the HMPC.

2. Scope

The guideline deals with the assessment of clinical safety and efficacy and applies to the drafting of EU monographs for well-established and traditional herbal medicinal products and of the EU list of traditional herbal substances, preparations and combinations thereof.

3. Legal basis

Following Article 16 h (3) of Directive 2001/83/EC the Committee for Herbal Medicinal Products shall establish EU herbal monographs for herbal medicinal products with regard to well-established medicinal use as well as traditional herbal medicinal products. When EU 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 EU herbal monograph has yet been established, other appropriate publications or data may be referred to. When new EU monographs are established, the authorisation/registration holder shall consider whether it is necessary to modify the authorisation/registration dossier accordingly.

A EU 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 EU (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/EC, the HMPC prepares 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)). For cutaneous products additional data on local tolerance might be necessary.

The criteria for the preparation of both types of documents and the information 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/information to support the drafting of EU herbal monographs and the EU list.

Article 10a and Annex 1 of Directive 2001/83/EC 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 non-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 EU 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 a 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 EU.

By analogy to the content of Modules 4 and 5 of Annex 1 of the Directive 2001/83/EC, a detailed scientific bibliography shall address non-clinical and clinical characteristics. The documentation 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 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 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. According to the Directive, the non-clinical and/or clinical overviews of an application 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, for which application for a marketing authorisation has been made in spite of the existing differences. By analogy in the preparation of a monograph, the rapporteur should assess if the products reported on the EU market by the NCAs in the market overview can be considered as similar to the product studied in pivotal non-clinical and clinical studies found in the literature.

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 EU herbal monographs prepared by the HMPC, may be the basis for assessment. The procedure for 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 authorisation 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 EU 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 will be available. Experience resulting from pharmacovigilance will be crucial for the assessment of clinical safety. The legislation allows that a broad spectrum of evidence may be used in the assessment of efficacy. 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.

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. 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.

Elements of the clinical data supporting a monograph

The clinical data 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. Old reports should be judged for their scientific credibility. Coherent and conclusive clinical recommendations cannot be obtained if major methodological deficiencies are identified in the pivotal clinical data.

It must be demonstrated that the clinical data report a clear description of the herbal substance/preparation, cover a sufficient number of patients (for each age group if it is the case) and that they are conclusive and coherent with respect to the indication, safety and efficacy.

The clinical relevance of the documented efficacy of the product/substance must be assessed.

In general, at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study) of good quality is required to substantiate efficacy.

Table 1 gives the data structure in the assessment report template which is used for the evaluation of the quality of a clinical study.

Table 1

References	Author, year, country
Study design	
Type of control	
Aim and Objectives	
Herbal preparation	Pharmaceutical form
	Dosage regimen
	Route of administration
Duration of treatment	
Subjects (n°)	Inclusion criteria
	Range and Medium Age
	Age group
	Sex
	Drop out

References	Author, year, country
Outcomes and endpoints	Primary
	Secondary
Statistical analysis data	ITT(y/n), C.I, quality score
Comments on results	

For some products/substances, several controlled clinical studies of good or acceptable quality may be available, and sometimes the results may be contradictory. The fourth bullet point of the Directive's text as regards relevant factors, 'coherence of scientific assessments' (see Section 3 above), then becomes applicable. The studies with positive outcomes must be balanced against the ones with negative outcomes. Meta-analyses of the results of the different trials may be useful for this purpose if the studies taken into account regard the same herbal preparation. Often published meta-analyses include trials performed on widely different herbal preparations (although of the same plant material), or not completely described preparations, and in such a case the meta-analysis may be considered of less importance for the monograph in question. It should be noted that the guideline's requirement of 'one controlled clinical study of good quality' to substantiate efficacy does not mean that one such study *per se* is sufficient to settle that a substance has a 'well-established medicinal use'. Such a clinical study is expected to be part of the information, but the concept of 'well-established medicinal use' relies on the broader thinking that a wide-spread medicinal use of a product within the EU for at least 10 years may have generated a sufficient body of conclusive scientific literature to allow an assessment of its efficacy. If the total body of evidence that emerges upon assessment leads to the conclusion that the substance has a 'recognised efficacy', the substance may be concluded to have a 'well-established medicinal use' from an efficacy point of view. Data relating solely to *in vitro* pharmacology or general pharmacology in animals will not provide evidence of efficacy to allow the development of a 'well-established use-monograph'. Such data may, however, contribute to the credibility of the clinical efficacy data of the product/substance.

Information on the time over which the substance has been used and quantitative aspects of the use of the substance must be assessed. In most cases, the herbal medicinal product or a similar one (see Section 6 below) will have been authorised in the EU 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 EU has taken place.

Data on the time and use aspects may be in form of: information on 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 SmPCs, sales statistics, estimated number of users, etc. Unless available data indicate otherwise, the publication year of the information will be accepted as proof of medicinal use from that year on.

Therapeutic indications

There are no restrictions on the indications for herbal medicinal products with 'well-established medicinal use'. However, the clinical evidence and the data should be appropriate to the nature of the indication(s) and to the risks of the herbal substance/preparation. The risks of delayed or insufficient treatment should be taken into account. Products can be for use under medical supervision or for self-medication. The therapeutic indication for a 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 so-called 'traditional' herbal medicinal products for human use. Article 16c (c) of Directive 2001/83/EC 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 Directive 2001/83/EC, 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 provide the basis for acceptance of an indication. An indication 'exclusively based upon long-standing use' may be plausible, even if no supporting scientific data are available. Evidence on the consistent use should include a well-defined posology (for specific age groups if available), administration form and indication. If a traditional herbal medicinal product has long fallen into disuse, this might indicate that in practice the efficacy of the traditional herbal medicinal product is 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 containing a defined herbal substance/preparation has been approved (authorised or registered) for medicinal purposes (for specific age groups if available). 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 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 was approved for human use. Unless available data indicate otherwise, the publication year of the information will be accepted as proof of medicinal use from that year on. In the case of official pharmacopoeias or formularies of EU 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 EU throughout a period of at least 15 years must be demonstrated.
- A comprehensive literature search, especially in 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 safety 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) period of medicinal use,

b) therapeutic indication,

c) strength/type of preparation,

d) posology,

e) specific information on safe use and evidence of safety.

The above information should be specified for different age groups, if such information is available.

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 is harmful under normal conditions of use.

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 EU 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 are possible. This would

include minor disorders or symptoms that are of benign or self-limiting character. Preferably, the therapeutic indication should clearly define the target disease or condition. 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 risks for the patient. Therapeutic indications that involve serious diseases, disorders or conditions such as cancer, psychiatric diseases /disorders, infectious diseases such as hepatitis or influenza, cardio-vascular diseases such as heart failure, metabolic diseases such as diabetes etc. are not acceptable. However, a disease or condition that *per se* is not considered serious, but displays symptoms that are common to a serious disease, may be acceptable for a traditional herbal medicinal product provided that the patient is requested to consult a physician before use of the product to exclude that serious disease is causing the symptoms. An example of such an indication is 'Traditional herbal medicinal product for the relief of lower urinary tract symptoms related to benign prostatic hyperplasia after serious conditions have been excluded by a medical doctor.' Other therapeutic indications that may be acceptable 'after exclusion of serious conditions by a medical doctor' include e.g. prophylaxis of migraine headache, reduction of heavy menstrual bleeding in women with regular menstrual cycles, symptomatic relief of itching and burning associated with haemorrhoids and relief of lower urinary tract symptoms related to an overactive bladder. Each indication needs a careful medical evaluation and decisions should be taken on a case-by-case basis.

Claims such as 'radical scavenger' and/or 'antioxidant' are not considered appropriate. Claims relating to clinical parameters such as the cholesterol-level, blood pressure, immune status etc. require robust scientific data and are not considered appropriate for that reason. The therapeutic indication for a traditional herbal medicinal product should be given in the following way:

'Traditional herbal medicinal product used for...

The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.'

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

Therapeutic indications solely based on pharmacological actions/effects traditionally attributed to the herbal substance/preparation (e.g. diuretic, analgesic or spasmolytic) should not be used.

Indications relating to specific concepts of traditional medicines may be acceptable if they fulfil the criteria given for safe self-medication.

5. Clinical safety

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

For **traditional herbal medicinal products**, evidence of widespread, long-standing use without significant safety problems, is the core element of the safety assessment. Deficiencies in available information must be clearly identified. 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.

For both **well-established and traditional herbal medicinal products**, the assessment must address the situation of special patient populations especially of children and pregnant/lactating women. As far as children are concerned, any kind of clinical study, referred to specific age groups, can be taken into account, as a complement to clinical safety information (e.g. from pharmacovigilance

and scientific literature) generated during longstanding use of the herbal medicinal product in the specific age group.

Concerning risk assessment of use of a herbal medicinal product in relation to reproduction and lactation, and the wording of section 4.6 Fertility, pregnancy and lactation of the monograph, the CHMP guideline 203927/2005 should be taken into account.

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 herbal substances/preparations are complex mixtures of constituents, 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 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 should be comparable. Reference is made to the 'Guideline on specifications: Test procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products' and to the 'Guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products'. If there are reasons to expect different pharmacological or toxicological profiles for otherwise comparable preparations, specific limits for substances of pharmacological or toxicological concern may be given in the monograph.

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 at least include the plant/part of the plant, the type of herbal preparation and, for extracts, the primary solvent.

6.2. Medicinal products

Well-established herbal medicinal products

The relevance of any data 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 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 is acceptable.

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 for evidence of traditional use is also satisfied, if the number or the quantity of ingredients has been reduced during the time of traditional use. However, elimination of active ingredients or a significant reduction in posology may make it difficult to accept the 'plausibility' of the pharmacological effects or efficacy of the remaining product and a justification of the acceptability should be given. Such a justification may consist of additional data confirming long-standing use and experience of the remaining ingredient(s).

Data on combination products can be taken into account for safety assessment of a single herbal substance/preparation, if justified in the assessment report.

6.3. Additional considerations for well-established and traditional herbal medicinal products

Additional information on the biopharmaceutical characterisation may be necessary.

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 entry will not be possible if additional information is necessary to establish the safe use.

Definitions

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

References

Directive 2001/83/EC as amended

Procedure for the Preparation of EU monograph for traditional herbal medicinal products (EMEA/HMPC/182320/2005 Rev. 2)

Procedure for the Preparation of EU monograph for herbal medicinal products with well-established medicinal use (EMEA/HMPC/182352/2005 Rev. 2)

Structure of the list of herbal substances, preparations and combinations thereof (EMEA/HMPC/100824/2005 Rev. 1)

Guideline on the documentation to be submitted for inclusion into the list of Herbal substances, preparations, and combinations thereof (EMEA/HMPC/107399/2005 Rev. 1)

Template for a EU herbal monograph (EMA/HMPC/107436/2005 Rev. 7)

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)

Guideline on the Clinical Assessment of fixed Combinations of Herbal Substances/Herbal Preparations EMEA/HMPC/166326/05

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. 2 (EMEA/CVMP/815/00 Rev. 2; EMA/HMPC/162241/2005 Rev. 2)

Guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products CPMP/QWP/2819/00 Rev. 2 (EMEA/CVMP/814/00 Rev. 2, EMA/HMPC/201116/2005 Rev. 2).

Public statement on the interpretation of therapeutic indications appropriate to traditional herbal medicinal products in Community herbal monographs (EMA/HMPC/473587/2011)

Template for Assessment report for the development of European Union herbal monographs and European Union list entries (EMA/HMPC/418902/2005 Rev. 5)

Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005)