famhp Federal agency for medicines and health products

Guidance for the handling of non-clinical and clinical data supporting MA or registration applications for herbal medicinal products

Version: 3 – 07/03/2013
Date of entry into force : 1/01/2013
Reference of the document: FAMHP/PRE/PHYTO/M4-M5/2012
Division: Unit Homeo/Phyto
Total number of page: 9
Annex(es): 1

This approach will be implemented for all new applications assessed after its entry into force and for applications for which the assessment is ongoing at that time.

Chapter 1. Traditional Use

Practical handling of clinical and non- clinical data submitted for herbal medicinal products registration

Different possible scenarios have been identified with different requirements for clinical and non- clinical data

CASE 1 = Herbal is on the Community list and there is a Community Monograph: (this is legally binding if the claims comply with the information contained in the list).
This case does not require an assessment of clinical and non- clinical data:

Non-clinical Overview (CTD Module 2, section 2.4) contains a reference to the Community List and Community Monograph. The Community Monograph is included in Module 4.

Clinical Overview (CTD Module 2, section 2.5) contains a reference to the Community List and Community Monograph. The Community Monograph is included in Module 5.

Federal agency for medicines and health products
Eurostation II – place Victor Horta 40/40 – 1060 Brussels
Phone +32 2 5248000 fax +32 2 5248001
E-mail welcome@fagg-afmps.be website www.afmps.be

CASE 2 = Herbal is not on the Community list, but there is a Community Monograph.

This case does not require an assessment of clinical and non- clinical data as such but does require an assessment of the applicability of the submitted data to the medicinal product under evaluation

Non-clinical Overview (CTD Module 2, section 2.4) contains a reference to the Community Monograph. The Community Monograph is included in Module 4.

Clinical Overview (CTD Module 2, section 2.5) contains a reference to the Community Monograph. The Community Monograph is included in Module 5.

The validation of the applicability of the monograph will be a joined "assessment" by analytical and clinical experts. The analytical validation will focus on the preparation and whether it falls within the preparations mentioned in the monograph.
The clinical validation will focus on the plausibility of the indication and its conformity to the monograph.
If the validation step shows that the monographs does not apply, the application is considered as equivalent to Case 3

The monograph will be considered non-applicable when it is not in line with the national policy of the famhp related to the medicinal product (category).

CASE 3 = Herbal is not on the Community list and there is no Community Monograph.

This case requires an assessment of clinical data/traditional use, after a preliminary validation as a traditional use application:

The validation of the TU-registration application will be a joined "assessment" by analytical and clinical experts. The analytical validation will focus on the preparation and whether the time of medicinal use of 30 years is sufficiently demonstrated for this preparation.
The clinical validation will focus on the plausibility and conformity of the indication to the documented traditional indication and whether the time of medicinal use of 30 years is sufficiently demonstrated for this indication.

Clinical overview (CTD Module 2, section 2.5) is based upon relevant up-to-date bibliographical data. All scientific publications (or monographs) are included in Module 5.

For THMPs, in Module 2.5, as referred to in Article 16c(1)(c) the following is required: bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Community.
In addition, the plausibility of pharmacological effects or efficacy of the medicinal product as well as information on the safety of use should be addressed in this section.

Tabulated clinical and non-clinical summaries in Module 2 shall be provided. Tables may not be necessary for well-known substances, but a proper justification for not providing them will be required.
For THMPs, in the majority of cases the agreed CTD format for the clinical reports is not applicable because clinical data are missing.
However, if there are clinical data e.g. observational studies included in order to support the plausibility of pharmacological effects or efficacy and the evidence of long standing use, these data should be presented in line with the structure of Module 5.

If safety issues are raised, this will be followed by an assessment of non-clinical data:

Non-clinical overview (CTD Module 2, section 2.4) is based upon relevant up-to-date bibliographical data. All scientific publications (or monographs) are included in Module 4.

For THMPs, in Module 2.4, as referred to in Article 16c(1)(d) the following is required:
a bibliographic review of safety data together with an expert report, and where required by the competent authority, upon additional request, data necessary for assessing the safety of the medicinal product.
It is advised that the expert report on safety data takes into consideration the agreed format for the organisation of the nonclinical overview in the CTD.
The list of relevant references for non-clinical data can be included at the end of module 2.4.
For THMPs bibliographic references regarding safety data as referred to in Article 16c(1)(d) should be presented in Module 4. Such references should be indexed following the agreed format for the organisation of Module 4.

The monograph will be considered non-applicable when it is not in line with the national policy of the famhp related to the medicinal product (category).

Different possible scenarios have been identified with different non-clinical data requirements

CASE 4: There is a Community Monograph.

This case does not require an assessment of clinical and non- clinical data as such but does require an assessment of the applicability of the submitted data to the medicinal product under evaluation

The validation of the applicability of the monograph will be a joined "assessment" by analytical and clinical experts. The analytical validation will focus on the preparation and whether it falls within the preparations mentioned in the monograph.
The clinical validation will focus on the indication and its conformity to the monograph.
If the validation step shows that the monographs does not apply, the application is considered as equivalent to Case 5

Non-clinical overview (CTD Module 2, section 2.4 and 2.6) is based upon the Community Monograph and relevant recent scientific data (that were not included in the Community Monograph) should be included. The Community Monograph and included scientific publications (or monographs) are included in Module 4.

Clinical overview (CTD Module 2, section 2.5 and 2.7) is based upon the Community Monograph and relevant recent scientific data (that were not included in the Community Monograph) should be included. The Community Monograph and included scientific publications (or monographs) are included in Module 5.

The monograph will be considered non-applicable when it is not in line with the national policy of the famhp related to the medicinal product (category).

CASE 5: There is no Community Monograph

This case requires an assessment of clinical data/non-clinical data

Non-clinical overview (CTD Module 2, section 2.4 and 2.6) is based upon relevant up-to-date bibliographical data. All scientific publications (or monographs) are included in Module 4.

Clinical overview (CTD Module 2, section 2.5 and 2.7) is based upon relevant up-to-date bibliographical data. All scientific publications (or monographs) are included in Module 5.

References and related documents

Requirements for Non-Clinical Data regarding MAA or Registrations for Herbal Medicinal Products version 1.2 (internal famhp document)

Guideline on the use of the CTD format in the preparation 4 of a registration application for traditional herbal 5 medicinal products1 - EMA/HMPC/71049/2007 Rev. 1

"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" (London, 7 September 2006, Doc. Ref. EMEA/HMPC/104613/2005)

Regulatory Q&A on herbal medicinal products (22 November 2011 EMA/HMPC/345132/2010 Rev.1)

History

Version	Date	Reason for change
1	23/11/2012	Initial version - approved by the Commission for herbal medicinal products on 6/12/2012
2	07/03/2013	Approved for publication by the Commission for herbal medicinal products via written procedure
3	07/03/2013	Editorial and lay-out changes prior to publication

Annex 1. Regulatory background

DIRECTIVE 2004/24/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use

Some relevant excerpts:

"Pre-clinical tests do not seem necessary, where the medicinal product on the basis of the information on its traditional use proves not to be harmful in specified conditions of use. However, even a long tradition does not exclude the possibility that there may be concerns with regard to the product's safety, and therefore the competent authorities should be entitled to ask for all data necessary for assessing the safety."

"In order to promote harmonization, Member States should recognize registrations of traditional herbal medicinal products granted by another Member State based on Community herbal monographs or consisting of substances, preparations or combinations thereof contained in a list to be established. For other products, Member States should take due account of such registrations."

"When Community herbal monographs within the meaning of this paragraph have been established, they shall be taken into account by the Member States when examining an application. Where no such Community herbal monograph has yet been established, other appropriate monographs, publications or data may be referred to."

"If an application for traditional-use registration relates to a herbal substance, preparation or a combination thereof contained in the list referred to in paragraph 1, the data specified in Article 16c(1)(b)(c) and (d) do not need to be provided.

DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use

Article 16c – traditional use

1. The application shall be accompanied by:
(a) the particulars and documents:
(i) referred to in Article 8(3)(a) to (h), (j) and (k);
(ii) the results of the pharmaceutical tests referred to in the second indent of Article 8(3)(i) (pre-clinical (toxicological and pharmacological) tests);
(iii) the summary of product characteristics, without the data specified in Article 11(4);
(iv) in case of combinations, as referred to in Article 1(30) or Article 16a(2), the information referred to in Article 16a(1)(e) relating to the combination as such; if the individual active ingredients are not sufficiently known, the data shall also relate to the individual active ingredients;
(b) any authorization or registration obtained by the applicant in another Member State, or in a third country, to place the medicinal product on the market, and details of any decision to refuse to grant an authorization or registration, whether in the Community or a third country, and the reasons for any such decision;
(c) bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Community. At the request of the Member State where the application for traditional-use registration has been submitted, the Committee for Herbal Medicinal Products shall draw up an opinion on the adequacy of the evidence of the long-standing use of the product,

or of the corresponding product. The Member State shall submit relevant documentation supporting the referral;
(d) a bibliographic review of safety data together with an expert report, and where required by the competent authority, upon additional request, data necessary for assessing the safety of the medicinal product.
Annex I shall apply by analogy to the particulars and documents specified in point (a).

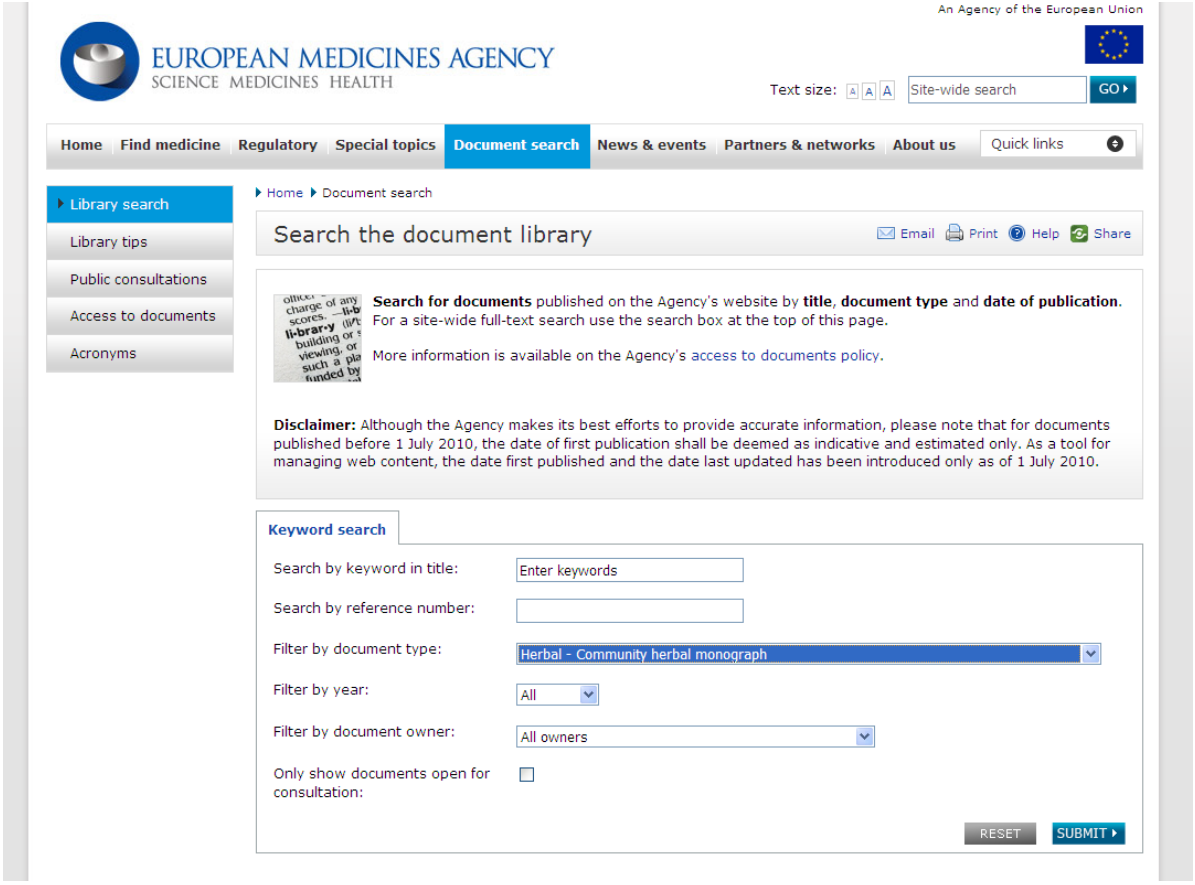
Article 16e – traditional use
1. Traditional-use registration shall be refused if the application does not comply with Articles 16a, 16b or 16c or if at least one of the following conditions is fulfilled:
(a) the qualitative and/or quantitative composition is not as declared;
(b) the indications do not comply with the conditions laid down in Article 16a;
(c) the product could be harmful under normal conditions of use;
(d) the data on traditional use are insufficient, especially if pharmacological effects or efficacy are not plausible on the basis of long-standing use and experience;
(e) the pharmaceutical quality is not satisfactorily demonstrated.

Article 8- well established use
3. The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:
(a) Name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.
(b) Name of the medicinal product.
(c) Qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international nonproprietary name (INN) recommended by the WHO, where an INN for the medicinal product exists, or a reference to the relevant chemical name.
(ca) Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.
(d) Description of the manufacturing method.
(e) Therapeutic indications, contra-indications and adverse reactions.
(f) Posology, pharmaceutical form, method and route of administration and expected shelf life.
(g) Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.
(h) Description of the control methods employed by the manufacturer.
(i) Results of:
— pharmaceutical (physico-chemical, biological or microbiological) tests,
— pre-clinical (toxicological and pharmacological) tests,
— clinical trials.
(j) A summary, in accordance with Article 11, of the product characteristics, a mock-up of the outer packaging, containing the details provided for in Article 54, and of the immediate packaging of the medicinal product, containing the details provided for in Article 55, together with a package leaflet in accordance with Article 59.
(k) A document showing that the manufacturer is authorized in his own country to produce medicinal products.

The European Directives to which reference is made, were transposed into Belgian legislation. The cited articles are retaken in the Royal Decree of 14 december 2006, article 43 (traditional use) and following as well as in the Law of 25 march 1964 article 6 bis §2 (well established use)

HMPC

Community herbal monographs are not legally binding, however from existing jurisdiction it would seem that they are to be respected, unless justified. A Community herbal monograph covering the traditional use of a substance, preparation or combination shall be taken into account by competent authorities when examining a traditional use registration application, which is based on the information contained in this monograph. A national competent authority may have a different position on a certain recommendation or statement set out in the monograph. The applicant may therefore be requested by a competent authority to provide supplementary information during the national evaluation procedure, in particular on the safety and the traditional use of the product.
Current list of monographs can be found on the EMA website via the document search option:

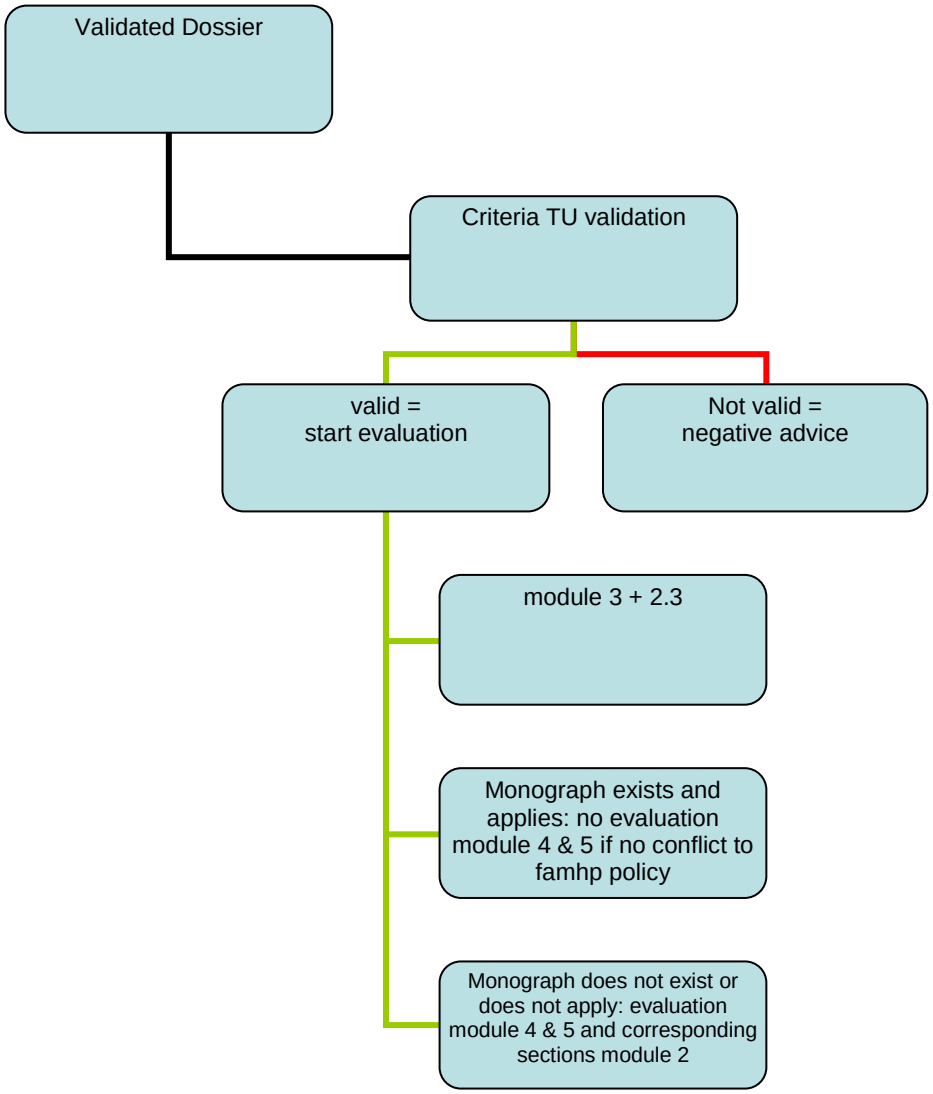


The Community list is legally binding to applicants and competent authorities in the Member States in so far as:
- an applicant will not be required to provide evidence of the safe and traditional use of a medicinal product for which he seeks a traditional use registration if he demonstrates that the proposed product and related claims in the application comply with the information contained in the list;
- competent authorities will not have the opportunity to require additional data to assess the safety and the traditional use of the product.

Current Community list entries can be found on the EMA website via the document search option (choose filter: Herbal – Community List Entry)

Annex 2. Flow Charts

FLOW CHART for the handling of Non-Clinical and Clinical Data supporting Registration Applications for Herbal Medicinal Products



FLOW CHART for the handling of Non-Clinical and Clinical Data supporting MA Applications for Herbal Medicinal Products