European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 10 January 2008
Doc. Ref. EMEA/HMPC/71049/2007

COMMITTEE ON HERBAL MEDICINAL PRODUCTS

(HMPC)

FINAL

GUIDELINE ON THE USE OF THE CTD FORMAT IN THE PREPARATION OF A REGISTRATION APPLICATION FOR TRADITIONAL HERBAL MEDICINAL PRODUCTS[1]

DRAFT AGREED BY ORGANISATIONAL MATTERS DRAFTING GROUP	April 2007
ADOPTION BY HMPC FOR RELEASE FOR CONSULTATION	8 May 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	15 August 2007
AGREED BY ORGANISATIONAL MATTERS DRAFTING GROUP	3 October 2007
ADOPTION BY HMPC	10 January 2008
DATE FOR COMING INTO EFFECT	10 January 2008

KEYWORDS	Herbal medicinal products; traditional herbal medicinal products; CTD; traditional use simplified registration; HMPC

[1] Guidance on modules 2.3 and 3 as described in this guideline are also applicable to Herbal Medicinal Product Applications for Marketing Authorisation.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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EXECUTIVE SUMMARY

1. INTRODUCTION (background)

This document aims to provide guidance on how to present the application for registration of traditional herbal medicinal products in the Common Technical Document (CTD) format, providing information to help future applicants in their submissions.

The implementation of the provisions in Directive 2001/83/EC as amended by Directive 2004/24/EC have introduced a simplified registration procedure for traditional herbal medicinal products. Therefore there is a need to develop a common understanding as to how the dossier for such simplified registration applications should be compiled.

In addition, in several European Member States there were a number of enquiries from industry regarding the structure of the dossier of applications for traditional use registration. There were especially some issues as to where certain information contained in dossier should be positioned. In general CTD format should be used in applications for traditional use registration.

2. SCOPE

This guideline is applicable to applications for traditional use registration of traditional herbal medicinal products for human use.

The compilation of dossiers for marketing authorisation applications for herbal medicinal products is not covered by this guideline. However, the guidance provided on modules 2.3 and 3 is also applicable to herbal medicinal product applications for marketing authorisation.

3. LEGAL BASIS

According to Article 16c(1) of Directive 2001/83/EC as amended, the application for traditional use registration of herbal medicinal products 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 first[2] indent of Article 8(3)(i);

  (iii) the summary of product characteristics, without the data specified in Article 11(5)[3][pharmacological properties];

  (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 authorisation 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 authorisation 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

[2] This reads "second" in Directive 2001/83/EC as amended (amendment through a corrigendum procedure by the European Commission).

[3] This reads "Article 11(4)" in Directive 2001/83/EC as amended (amendment through a corrigendum procedure by the European Commission).

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 longstanding 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).

According to Article 8(3), evoked in Article 16c(1)(a)(i) 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[4], 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.[5]

(d) Description of the manufacturing method.

(e) Therapeutic indications, contraindications 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.

(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 acordance with Article 59.

(k) A document showing that the manufacturer is authorised in his own country to produce medicinal products.

This guideline has to be read in conjunction with the introduction and general principles (4) and part I and III of the Annex I to Directive 2001/83/EC as amended, as well as Notice to Applicants, Volume 2B - Common Technical Document (CTD).

[4] 'Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products in the SPC' (EMEA/HMPC/CHMP/CVMP/287539/2005)

[5] Not required according to 'Guideline on the environmental risk assessment of medicinal products for human use' (EMEA/CHMP/SWP/4447/00)

4. MAIN GUIDELINE TEXT

Dossier for traditional use registration of traditional herbal medicinal products

The table below describes the CTD structure and provides additional guidance to that included in the Volume 2B of the Notice to Applicants (Presentation and format of the dossier Common Technical Document (CTD)).

For the purpose of this guideline, the term 'Applicable' means that the guidance provided in Notice to Applicants, Volume 2B - Common Technical Document (CTD) should apply.

If no specific heading exists, the information should be provided under the relevant module as described below.

4.1. Module 1: Administrative information

1.0. Cover letter	Applicable
1.1. Comprehensive Table of contents	Applicable
1.2. Application form	Applicable
1.3. Product Information	Applicable
1.3.1. SPC, Labelling and package leaflet	Applicable
1.3.2. Mock-up	Applicable
1.3.3. Specimens	Applicable
1.3.4. Consultation with Target Patients Groups	Applicable
1.3.5. Product Information already approved in the Member States	Applicable
1.3.6. Braille	Applicable
1.4. Information about the experts	
1.4.1 Quality	Applicable (To be signed by the expert responsible for the information included in Module 2.3)
1.4.2 Non-Clinical	Applicable (To be signed by the expert responsible for the information included in Module 2.4)
1.4.3 Clinical	Applicable (To be signed by the expert responsible for the information included in Module 2.5)
1.5. Specific requirements for different types of applications	In this point it is necessary to submit a brief statement as to why the product meets the requirements for traditional use registration, specially addressing the evidence of long standing use of the product.
1.6. Environmental risk assessment	Not required according to 'Guideline on the environmental risk assessment of medicinal products for human use' (EMEA/CHMP/SWP/4447/00).
1.7. Information relating to Orphan Market	Not Applicable

Exclusivity	
1.8. Information regarding Pharmacovigilance	Not Applicable
1.9. Information relating to Clinical Trials	Not Applicable

4.2. Module 2: Common Technical Document Summaries

2.1. CTD table of contents (Module 2-5)	Applicable
2.2. Introduction	Applicable
2.3. Quality overall summary 2.3.S. Quality Overall Summary Drug Substance 2.3.P. Quality Overall Summary Drug Product 2.3.A. Quality Overall Summary Appendixes 2.3.R. Quality Overall Summary Regional Information	For herbal substances and herbal preparations, a description of the desired product and product-related substances and a summary of general properties, characteristics features and characterization data, as described in S.3.1, should be included. The QOS should summarise the data on potential contamination by micro-organisms, products of micro-oorganisms, pesticides, toxic metals, radioactive contamination, fumigants, etc
2.4. Non-clinical overview	For traditional herbal medicinal products, 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 Common Technical Document. The list of relevant references for non-clinical data can be included at the end of module 2.4.
2.5. Clinical overview	For traditional herbal medicinal products, 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.

2.6. Non-clinical written and tabulated summaries 2.6.1 Introduction 2.6.2 Pharmacology Written Summary 2.6.3 Pharmacology Tabulated Summary 2.6.4 Pharmacokinetics Written Summary 2.6.5 Pharmacokinetics Tabulated Summary 2.6.6 Toxicology Written Summary 2.6.7 Toxicology Tabulated Summary	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.
2.7. Clinical Summaries 2.7.1. Summary of Biopharmaceutics and associated analytical methods 2.7.2. Summary of Clinical Pharmacology Studies 2.7.3. Summary of Clinical Efficacy 2.7.4. Summary of Safety 2.7.5. References 2.7.6. Synopsis of individual studies	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.

4.3. Module 3

The explanatory notes have been prepared in line with the following revised guidelines:

- 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products' (EMEA/CPMP/2819/00 Rev.1, EMEA/CVMP/814/00 Rev.1).

- 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products' (EMEA/CPMP/2820/00 Rev.1, EMEA/CVMP/815/00 Rev.1).

3.1 Table of contents of Module 3	Applicable
3.2 Body of data	Applicable
3.2.S. DRUG SUBSTANCE (NAME, MANUFACTURER)	Applicable
3.2.S.1 General Information (name, manufacturer)	Applicable
3.2.S.1.1 Nomenclature (name, manufacturer)	Information on the nomenclature of the herbal substance should be provided: - Binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable) - Parts of the plants - Definition of the herbal substance - Other names (synonyms mentioned in other Pharmacopoeias) - Laboratory code Information on the nomenclature of the herbal

	preparation should be provided: - Binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable) - Parts of the plants - Definition of the herbal preparation - Ratio of the herbal substance to the herbal preparation - Extraction solvent(s) - Other names (synonyms mentioned in other Pharmacopoeias) - Laboratory code - Possible addition of excipients (e.g. preservatives, carrier)
3.2.S.1.2 Structure (name, manufacturer)	The following information for herbal substance(s) and herbal preparation(s) where applicable, should be provided: - Physical form - Description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass). - Other constituent(s)
3.2.S.1.3 General Properties (name, manufacturer)	Applicable
3.2.S.2 Manufacture (name, manufacturer)	Applicable
3.2.S.2.1 Manufacturer(s) (name, manufacturer)	For herbal substances The name, address, and responsibility of each supplier, including contractors, and each proposed site or facility involved in production/collection and testing of the herbal substance should be provided, where appropriate. For herbal preparations The name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation should be provided, where appropriate.
3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)	For herbal substances Information should be provided to adequately describe the plant production and plant collection, including: - Geographical source of medicinal plant - Cultivation, harvesting, drying and storage

	conditions - Batch size <u>For herbal preparations</u> Information should be provided to adequately describe the manufacturing process of the herbal preparation as follows, including data on the herbal substance as described above[6]: - Description of processing (including flow diagram) - Solvents, reagents - Purification stages - Standardisation - Batch size
3.2.S.2.3 Control of Materials (name, manufacturer)	Applicable
3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)	Applicable
3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)	Applicable
3.2.S.2.6 Manufacturing Process Development (name, manufacturer)	A brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phytochemical composition of the herbal substance(s) and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substance(s) and herbal preparation(s) where applicable described in S1 should be discussed, where appropriate.
3.2.S.3 Characterisation (name, manufacturer)	Applicable
3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)	<u>For herbal substances</u> Information on the botanical, macroscopical, microscopical, phytochemical characterisation, and biological activity if necessary, should be provided. <u>For herbal preparations</u> Information on the phyto- and physicochemical characterisation, and biological activity if necessary, should be provided.

[6] In addition, consideration should be given to include information on the addition of excipients (e.g. preservatives, carrier)

3.2.S.3.2 Impurities (name, manufacturer)	<u>For herbal substances</u> - Potential contaminants originating from the herbal drug production and post-harvesting treatment such as pesticides and fumigants residues, toxic metals, mycotoxins, radioactive contamination and microbial contamination as well as potential adulterants should be discussed <u>For herbal preparations</u> - Potential contaminants originating from the herbal drug production and post-harvesting treatment such as pesticides and fumigants residues, toxic metals, mycotoxins, radioactive contamination and microbial contamination as well as potential adulterants should be discussed - Residual solvents
3.2.S.4 Control of Drug Substance (name, manufacturer)	Data for herbal substance(s) and herbal preparations should be provided.
3.2.S.4.1 Specification (name, manufacturer)	Applicable
3.2.S.4.2 Analytical Procedures (name, manufacturer)	Applicable
3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)	Applicable
3.2.S.4.4 Batch Analyses (name, manufacturer)	Applicable
3.2.S.4.5 Justification of Specification (name, manufacturer)	Applicable
3.2.S.5 Reference Standards or Materials (name, manufacturer)	Applicable
3.2.S.6 Container Closure System (name, manufacturer)	Applicable
3.2.S.7 Stability (name, manufacturer)	Applicable
3.2.S.7.1 Stability Summary and Conclusions (name, manufacturer)	Applicable
3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)	Applicable
3.2.S.7.3 Stability Data (name, manufacturer)	Applicable

3.2.P. DRUG PRODUCT (NAME, DOSAGE FORM)	Applicable
3.2.P.1 Description and Composition of the Drug Product (name, dosage form)	Applicable
3.2.P.2 Pharmaceutical Development (name, dosage form)	Applicable
3.2.P.2.1 Components of the Drug product (name, dosage form)	Applicable
3.2.P.2.1.1 Drug Substance (name, dosage form)	Applicable
3.2.P.2.1.2 Excipients (name, dosage form)	Applicable
3.2.P.2.2 Drug Product (name, dosage form)	Applicable
3.2.P.2.2.1 Formulation Development (name, dosage form)	<u>For herbal medicinal products:</u> A brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phytochemical composition of the products used in supporting bibliographic data and the product described in P1 should be discussed, where appropriate.
3.2.P.2.2.2 Overages (name, dosage form)	Applicable
3.2.P.2.2.3 Physicochemical and Biological Properties (name, dosage form)	Applicable
3.2.P.2.3 Manufacturing Process Development (name, dosage form)	Applicable
3.2.P.2.4 Container Closure System (name, dosage form)	Applicable
3.2.P.2.5 Microbiological Attributes (name, dosage form)	Applicable
3.2.P.2.6 Compatibility (name, dosage form)	Applicable
3.2.P.3 Manufacture (name, dosage form)	Applicable
3.2.P.3.1 Manufacturer(s) (name, dosage form)	Applicable
3.2.P.3.2 Batch Formula (name, dosage form)	Applicable
3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)	Applicable
3.2.P.3.4 Controls of Critical Steps and Intermediates (name, dosage form)	Applicable
3.2.P.3.5 Process Validation and/or Evaluation (name, dosage form)	Applicable

3.2.P.4 Control of Excipients (name, dosage form)	Applicable
3.2.P.4.1 Specifications (name, dosage form)	Applicable
3.2.P.4.2 Analytical Procedures (name, dosage form)	Applicable
3.2.P.4.3 Validation of Analytical Procedures (name, dosage form)	Applicable
3.2.P.4.4 Justification of Specifications (name, dosage form)	Applicable
3.2.P.4.5 Excipients of Human or Animal Origin (name, dosage form)	Applicable
3.2.P.4.6 Novel Excipients (name, dosage form)	Applicable
3.2.P.5 Control of Drug Product (name, dosage form)	Applicable
3.2.P.5.1 Specification(s) (name, dosage form)	Applicable
3.2.P.5.2 Analytical Procedures (name, dosage form)	Applicable
3.2.P.5.3 Validation of Analytical Procedures (name, dosage form)	Applicable
3.2.P.5.4 Batch Analyses (name, dosage form)	Applicable
3.2.P.5.5 Characterisation of Impurities (name, dosage form)	Applicable
3.2.P.5.6 Justification of Specification(s) (name, dosage form)	Applicable
3.2.P.6 Reference Standards or Materials (name, dosage form)	Applicable
3.2.P.7 Container Closure System (name, dosage form)	Applicable
3.2.P.8 Stability (name, dosage form)	Applicable
3.2.P.8.1 Stability Summary and Conclusion (name, dosage form)	Applicable
3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (name, dosage form)	Applicable
3.2.P.8.3 Stability Data (name, dosage form)	Applicable
3.2.R Regional information	Applicable
3.3 Literature References	Applicable

ANNEX TO MODULE 3

(Updated June 2003)

A. List of references to quality guidelines

- General Guidelines
- Active Substance Guidelines
- Medicinal Product Guidelines

B. List of references to biotechnology guidelines

C. List of references to herbal guidelines

Document Title	**Number / version**
Guideline on quality of herbal medicinal products/traditional herbal medicinal products	CPMP/QWP/2819/00 Rev.1 EMEA/CVMP/814/00 Rev.1
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 Rev.1

4.4. Module 4: Non-clinical study reports

According with Article 16f(2), if an application for traditional use registration relates to a herbal substance, preparation or combination, the data specified in Article 16c(1)(b)(c)and (d) do not need to be provided.

4.1 Module 4 Table of Contents	Applicable
4.2. Study Reports	If Applicable. If data are available or have been requested they should be provided and summarised in Module 2.6 for which the corresponding expert report would be included in Module 2.4.
4.3 Literature References	For traditional herbal medicinal products, 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.

4.5. Module 5: Clinical study reports

According with Article 16f(2), if an application for traditional use registration relates to a herbal substance, preparation or combination, the data specified in Article 16c(1)(b)(c)and (d) do not need to be provided.

5.1 Module 5 Table of Contents	Applicable
5.2 Tabular Listing of All Clinical Studies	If Applicable
5.3. Clinical Study Reports	If Applicable. If data are available or have been requested they should be provided and summarised in Module 2.7 for which the corresponding expert report would be included in Module 2.5.
5.4 Literature References	Such references should be indexed following the agreed format for the organisation of Module 5. For traditional herbal medicinal products, 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.

REFERENCES (SCIENTIFIC AND / OR LEGAL)

Rules governing medicinal products in the European Union, Volume 2B Notice to Applicants, 'Presentation and content of the dossier'– incorporating the Common Technical Document (CTD)

'Guideline on quality of herbal medicinal products/traditional herbal medicinal products' (CPMP/QWP/2819/00 Rev.1, EMEA/CVMP/814/00 Rev.1)

'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 Rev.1)

'Concept paper on CTD for traditional herbal medicinal products' (EMEA/HMPC/261344/2005)