EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 8 August 2012
2 EMA/HMPC/71049/2007 Rev. 1
3 Committee on Herbal Medicinal Products (HMPC)

4 Guideline on the use of the CTD format in the preparation 5 of a registration application for traditional herbal 6 medicinal products[1]

7 Draft

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
Draft revision 1 agreed by Quality Drafting Group	April 2012
Draft revision 1 adopted by HMPC for release for consultation	22 May 2012
Start of public consultation	8 August 2012
End of consultation (deadline for comments)	15 October 2012

Comments should be provided using this template to hmpc.secretariat@ema.europa.eu

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Keywords	Herbal medicinal products (HMPs); traditional herbal medicinal products (THMPs); 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.

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Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products

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Executive summary

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

Revision 1 pertains to the presentation and content of the Module 3 on Quality (chemical, pharmaceutical and biological information) for THMPs to help applicants with their submission. A best practice guide providing further clarification on the exact location of relevant parts of the documentation and the corresponding guidelines in the CTD Module 3 is included as Appendix 1. As announced in the concept paper (EMA/HMPC/111298/2011) it is foreseen that in the future a Module 3 mock-up will also be added as Appendix 2. In addition minor editorial corrections and updates have been introduced in the guideline itself.

1. Introduction

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 the CTD format should be used in applications for traditional use registration.

2. Scope

This guideline is applicable to applications for traditional use registration of THMPs for human use.

The compilation of dossiers for marketing authorisation applications for herbal medicinal products (HMPs) is not covered by this guideline. However, the guidance provided on modules 2.3 and 3 including Appendix 1 is also applicable to HMPs 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

[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).

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 Member State where the application for traditional-use registration has been submitted, the Committee for Herbal Medicinal Products (HMPC) 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[4] of Directive 2001/83/EC 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[4]:

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[5], including the reference to its international non-proprietary 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.[6]

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,

[4] The Annex currently in force is laid down in Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (Official Journal L 159, 27/6/2003 p. 46 - 94).

[5] '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 as revised)

[6] Not required for HMP according to 'Guideline on the environmental risk assessment of medicinal products for human use' (EMEA/CHMP/SWP/4447/00). However, there might be exceptional cases where further justification to the absence of an environmental risk assessment might be necessary according to EMA/HMPC/121934/2010.

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 accordance 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[7] to Directive 2001/83/EC as amended, as well as Notice to Applicants, Volume 2B - Common Technical Document (CTD).

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	

[7] The Annex currently in force is laid down in Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (Official Journal L 159, 27/6/2003 p. 46 - 94).

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). However, there might be exceptional cases where further justification to the absence of an environmental risk assessment might be necessary according to EMA/HMPC/121934/2010.
1.7. Information relating to Orphan Market Exclusivity	Not applicable
1.8. Information regarding Pharmacovigilance	Not applicable
1.9. Information relating to Clinical Trials	Not applicable

113 **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[8] 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-organisms, pesticides, toxic metals, radioactive contamination, fumigants, etc.
2.4. Non-clinical overview	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

[8] The guidance provided on modules 2.3 and 3 including Appendices is also applicable to HMPs applications for marketing authorisation.

	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.
2.5. Clinical overview	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.
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[9]

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 as revised, EMEA/CVMP/814/00 as revised).
- '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 as revised, EMEA/CVMP/815/00 as revised).

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.

[9] The guidance provided on modules 2.3 and 3 including Appendices is also applicable to HMPs applications for marketing authorisation.

	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)	<u>For herbal substances</u> 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. <u>For herbal preparations</u> 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)	<u>For herbal substances</u> 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: • 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)	For herbal substances Information on the botanical, macroscopical, microscopical, phytochemical characterisation, and biological activity if necessary, should be provided. For herbal preparations Information on the phyto- and physicochemical characterisation, and biological activity if necessary, should be provided.
3.2.S.3.2. Impurities (name, manufacturer)	For herbal substances • 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)	For herbal medicinal products 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

For more details refer to Appendix I “Best Practice Guide for the Module 3 Quality: Chemical, Pharmaceutical and Biological Information for Herbal Active Substances and Traditional Herbal Medicinal Products” and Appendix II “Module 3 mock-up for a Traditional Herbal Medicinal Product” (in preparation).

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 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.

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 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.

References

The main relevant guidelines pertaining to herbal medicinal products are listed below. The Applicant should take account of all current relevant guidelines at the time of preparation of the application.

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 as revised, EMEA/CVMP/814/00 as revised).

'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 as revised, EMEA/CVMP/815/00 as revised).

'Quality of combination herbal medicinal products/traditional herbal medicinal products' (EMEA/HMPC/CHMP/CVMP/214869/06).

'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/32116/2005).

'Guideline on the assessment of genotoxicity of herbal substances/preparations' (EMEA/HMPC/107079/2007).

'Guideline on selection of test materials for genotoxicity testing for traditional herbal medicinal products/ herbal medicinal products' (EMEA/HMPC/67644/2009).'Guideline on the clinical assessment of fixed combinations of herbal substances/herbal preparations' (EMEA/HMPC/166326/2005

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Best Practice Guide for the Module 3 Quality: Chemical, Pharmaceutical and Biological Information for Herbal Substances, Herbal Preparations and Traditional Herbal Medicinal Products[1]

Concerning chemical pharmaceutical and biological documentation for herbal substance(s), herbal preparations and traditional herbal medicinal products

The principle of GMP and the detailed guidelines are applicable to all operations which require the authorisation referred to in Article 40 of Directive 2001/83/EC as modified.

All analytical test procedures described in the various sections of the chemical, pharmaceutical and biological documentation must be described in sufficient detail to enable the procedures to be repeated if necessary (e.g. by an official laboratory). All procedures need to be validated and the results of the validation studies must be provided.

Scope of the Appendix 1

This Appendix 1 of the 'Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products' (EMEA/HMPC/71049/2007) is a best practice guide, describing the exact location of relevant parts of the documentation and the corresponding guidelines in the CTD Module 3 sections.

The text following the section titles is intended to be explanatory and illustrative only. The content of these sections should include relevant information described in existing CPMP-ICH or CPMP/CHMP or HMPC guidelines and the Directive 2003/63/EC amending Directive 2001/83/EC relating to Medicinal Products for Human: Annex I: Analytical, Pharmacotoxicological and Clinical Standards and Protocols in respect of the Testing of Medicinal Products. Part III - Particular Medicinal Products: 4 - Herbal Medicinal Products.

The "Body of Data" in this Appendix 1 merely indicates where the information should be located. Neither the type nor extent of specific supporting data has been addressed in this Appendix 1.

References[2] to guidelines are inserted to assist applicants. However, it remains the applicants' responsibility to ensure that all relevant legislation and guidelines, as revised or maintained, are taken into account in the preparation of each part of their dossier. The guidelines referenced in each section provide useful information on the content expected in that section. These listings should not be regarded as comprehensive.

Wherever relevant, the requirements of the European Pharmacopoeia apply: specific monographs, general monographs and general chapters.

[1] Guidance on module 3 as described in this Appendix 1 is also applicable to herbal medicinal products (HMPs) applications for marketing authorisation.
[2] References within Module 3 sections are listed with the title only. At the end of this Appendix these quality-relevant references are compiled and listed with the corresponding document number.

3.1 Table of Contents of Module 3

A Table of Contents for Module 3 should be provided.

3.2: Body of data

Reference: Notice to Applicants, Volume 2B - Presentation and Format of the Dossier - Common technical document (CTD) - Module 3.

3.2.S Drug substance[2] (name, manufacturer)

Reference guidance:

- Summary of Requirements for Active Substances in the Quality Part of the Dossier.

- Active Substance Master File Procedure.

- Certification of Suitability of Monographs of the European Pharmacopoeia: "Content of the Dossier for Herbal Drugs and Herbal Drug Preparations Quality Evaluation".

3.2.S.1 General information (name, manufacturer)

3.2.S.1.1 Nomenclature (name, manufacturer)

Information on the nomenclature of the ***herbal substance*** and the ***herbal preparation***[3] should be provided.

Reference guidelines:

- The Use of the CTD Format in the Preparation of a Registration Application for Traditional Herbal Medicinal Products.

- Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.

3.2.S.1.2 Structure (name, manufacturer)

Description of the constituents with known therapeutic activity or markers should be provided for the ***herbal substance*** and the ***herbal preparation***. Mention should be made of other constituents. If relevant, information on toxic constituents should be provided.

Reference guideline: The Use of the CTD Format in the Preparation of a Registration Application for Traditional Herbal Medicinal Products.

3.2.S.1.3 General properties *(name, manufacturer)*

- ***Herbal substance***

Not applicable.

- ***Herbal preparation***

[2] For a traditional herbal medicinal product containing more than one herbal substance, the information requested for part "S" should be provided in its entirety for each herbal substance.
[3] The terms "herbal substance" and "herbal preparation" should be considered as equivalent to the terms "herbal drug" and "herbal drug preparation" as defined in the European Pharmacopoeia.

A list should be provided of organoleptic and physico-chemical characters (e.g. if relevant: solubility density particle size, flowability…) and other relevant properties of the herbal preparation.

3.2.S.2 Manufacture (name, manufacturer)

3.2.S.2.1 Manufacturer(s) (name, manufacturer)

Reference guideline: The Use of the CTD Format in the Preparation of a Registration Application for Traditional Herbal Medicinal Products.

- ***Herbal substance***

The name, address and responsibility of each producer or supplier, including contractors, and each proposed site or facility involved in production/collection and testing of the herbal substance should be provided, where appropriate.

The supplier should provide undertaking letters on following the herbal substance technical data sheet and the GACP.

- ***Herbal preparation***

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.

The manufacturer, and the supplier if relevant, should provide undertaking letters on following the manufacturing process described in 3.2.S.2.2.

3.2.S.2.2 Description of manufacturing process and process controls (name, manufacturer)

- ***Herbal substance***[4]

Information should be provided to adequately describe the plant production and plant collection.

Reference guidance:

- The Use of the CTD Format in the Preparation of a Registration Application for Traditional Herbal Medicinal Products.

- Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Good Agricultural and Collection Practice for Starting Materials of Herbal Origin (GACP)

- Questions & Answers on Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- ***Herbal preparation***

The description of the herbal preparation manufacturing process represents the applicant's commitment for the manufacture of the herbal preparation. Information should be provided to adequately describe the manufacturing process and in process controls. Steps in the process should have the appropriate process parameters identified, such as time, temperature or pH. Associated

[4] For a herbal substance having several manufacturers, the required information for parts "3.2.S.2.2 and 3.2.S.3.2" should be provided in its entirety for each manufacturer.

numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 3.2.S.2.4.

For example:

- Description of processing (including flow diagram):
    - Detailed description of each stage of manufacturing process of the herbal preparation (extraction, distillation, expression, purification, concentration, fractionation or fermentation), including information on preliminary treatment (inactivation of enzymes, grinding, or defatting) and microbial decontamination treatment.
    - Where alternative extraction processes are proposed, each should be clearly defined and described and not subject to addition of options.
- Solvents, reagents.
- Purification stages: on intermediates and on herbal preparation.
- Description of controls applied to ensure the quality of any other starting materials (solvents, reagents…) and excipients added during the manufacture of the herbal preparation (see 3.2.S.2.3. Control of materials).
- Standardisation: if preparations from herbal substances with constituents of known therapeutic activity are standardised (i.e. adjusted to a defined content of constituents with known therapeutic activity), it must be stated how such standardisation is achieved. If another substance is used for these purposes, it is necessary to specify as a range the quantity that can be added.
- Batch size: A maximum batch size should be stipulated, corresponding to batches already manufactured.

Filling, storage and transportation (shipping)

A description of the filling procedure for the herbal preparation, process controls (including in-process tests and operational parameters) and acceptance criteria should be provided. (Details in 3.2.S.2.4.) The container closure system(s) used for storage of the herbal preparation (details in 3.2.S.6.) and storage and shipping conditions for the herbal preparation should be described.

Reference guidance:

- The Use of the CTD Format in the Preparation of a Registration Application for Traditional Herbal Medicinal Products.

- Questions & Answers on Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Certification of Suitability of Monographs of the European Pharmacopoeia: "Content of the Dossier for Herbal Drugs and Herbal Drug Preparations Quality Evaluation".

3.2.S.2.3 Control of materials *(name, manufacturer)*

- ***Herbal substance***

Not applicable.

- ***Herbal preparation***

Materials used in the manufacture of the herbal preparation (e.g. starting material, solvents, excipients) should be listed, identifying where each material is used in the process. Information on the

quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided, as appropriate.

3.2.S.2.3.1 Herbal substance starting material (name, manufacturer)

See Part 3.2.S.4 “Control of drug substance”.

3.2.S.2.3.2 Solvents (name, manufacturer)

The control should be performed according to European Pharmacopoeia monographs or, by default, internal monographs.

Where extraction solvents are recovered from the production process details of the controls applied should be documented.

Reference guideline: *Quality of Water for Pharmaceutical Use.*

3.2.S.2.3.3 Excipients (name, manufacturer)

The control of excipients used for standardisation and other excipients (= technological excipients as carrier substances that may be part of the herbal preparation) should be performed according to European Pharmacopoeia monographs or, by default, internal monographs.

Reference guidelines:

- Chemistry of new active substances.

- Chemistry of actives substances.

- Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product.

3.2.S.2.4 Controls of critical steps and intermediates *(name, manufacturer)*

- ***Herbal substance***

Not applicable.

- ***Herbal preparation***
  - Critical Steps: Tests and acceptance criteria (with justification including experimental data), performed at the critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled, should be provided.
  - Intermediates: Information on the quality and control of intermediates during the process should be provided.

3.2.S.2.5 Process validation and/or evaluation (name, manufacturer)

- ***Herbal substance***

Not applicable.

- ***Herbal preparation***

Process validation and/or evaluation studies (based on historical data) should be provided, especially if it is a non-standard process (e.g. spray dried products…).

The decontamination process validation should be included if necessary.

Reference guidelines:

- Process Validation.

- The Use of Ionizing Radiation in the Manufacture of Medicinal Products.

3.2.S.2.6 Manufacturing process development (name, manufacturer)

A brief summary describing the development of the ***herbal substance*** and ***herbal preparation*** where applicable should be provided, taking into consideration the proposed route of administration and usage.

Results comparing the phytochemical composition of the herbal substance and herbal preparation where applicable used in supporting bibliographic data and the herbal substance and herbal preparation where applicable, described in 3.2.S.1.2 should be discussed, where appropriate.

Reference guideline: The Use of the CTD Format in the Preparation of a Registration Application for Traditional Herbal Medicinal Products.

3.2.S.3 Characterisation (name, manufacturer)

3.2.S.3.1 Elucidation of structure and other characteristics (name, manufacturer)

Reference guideline: The Use of the CTD Format in the Preparation of a Registration Application for Traditional Herbal Medicinal Products.

- ***Herbal substance***

Information on the botanical, macroscopical, microscopical, phytochemical characterisation, and biological activity, if necessary, should be provided.

For a non-compendial herbal substance, iconography of the plant and the part of the plant, and of the microscopical characters should be provided.

Chromatographic profiles (TLC, HPLC, GC) should be provided.

- ***Herbal preparation***

Information on the phyto- and physicochemical characterisation and biological activity, if necessary, should be provided.

The definition of the herbal preparation by a typical chemical profile (chromatographic profiles: TLC, HPLC, GC) should be provided.

3.2.S.3.2 Impurities (name, manufacturer)

Reference guidance:

- The Use of the CTD Format in the Preparation of a Registration Application for Traditional Herbal Medicinal Products.

- Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Questions & Answers on Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Certification of Suitability of Monographs of the European Pharmacopoeia: "Content of the Dossier for Herbal Drugs and Herbal Drug Preparations Quality Evaluation".

- Reflection Paper on the use of Fumigants.

In addition for some herbal preparations:

- Impurities: Residual Solvents.

- Annexes to Specifications for Class 1 and Class 2 Residual Solvents in Active Substances.

- ***Herbal substance***

Potential contaminants originating from the herbal substance production and post-harvesting treatments such as pesticides and fumigants residues, toxic metals, mycotoxins (aflatoxins, ochratoxin A), microbial contamination and radioactive contamination as well as potential adulterants should be discussed. Degradation products should be studied if relevant, e.g. the study of the possible modifications occurring with decontamination treatments such as ionizing radiation.

- ***Herbal preparation***

Potential contaminants originating from the herbal substance production and post-harvesting treatments such as pesticides and fumigants residues, toxic metals, mycotoxins (aflatoxins, ochratoxin A), microbial contamination and radioactive contamination as well as potential adulterants should be discussed. Possible impurities originating from the process or from degradation should be listed and discussed with an indication of their origin (e.g. the study of the possible modifications occurring with decontamination treatments as ionizing radiation).

The presence of potential residual solvents should be discussed.

3.2.S.4 Control of drug substance (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer)

Reference guidance:

- Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Markers used for Quantitative and Qualitative Analysis of Herbal Medicinal Products and Traditional Herbal Medicinal Products.

- Certification of Suitability of Monographs of the European Pharmacopoeia: "Content of the Dossier for Herbal Drugs and Herbal Drug Preparations Quality Evaluation".

- ***Herbal substance***

The analysis and their acceptance criteria retained for routine testing should be presented in a table.

A comprehensive specification must be developed for each herbal substance even if the starting material for the manufacture of the herbal medicinal product is a herbal preparation.

In the case of fatty or essential oils used as active substances of herbal medicinal products, a specification for the herbal substance is required unless justified.

In addition, for potentially toxic constituents and impurities of some herbal substances (e.g. pyrrolizidinic alkaloids, essential oils containing safrole), maximum limits should be defined.

- ***Herbal preparation***

The analysis and their acceptance criteria retained for routine testing should be presented in a table.

A comprehensive specification must be developed for each herbal preparation in line with the guideline on specifications.

In addition, for potentially toxic constituents and impurities of some herbal preparations (e.g. pyrrolizidinic alkaloids, essential oils containing safrole), maximum limits should be defined.

3.2.S.4.2 Analytical procedures (name, manufacturer)

For the ***herbal substance*** and the ***herbal preparation,*** according to the case, should be provided:

- A photocopy of the pharmacopoeial monograph, with, if necessary, the description of the additional tests,

- Or for an in-house monograph, a detailed description of the retained analytical procedures.

3.2.S.4.3 Validation of analytical procedures (name, manufacturer)

Analytical validation information, including experimental data for non-pharmacopoeial procedure used for testing the ***herbal substance*** and the ***herbal preparation*** should be provided.

For impurities, quantitative analysis of pesticides residues must be validated on a suitable herbal matrix (according to the indication given in European Pharmacopoeia in 2.8.13)5. For aflatoxins and ochratoxin A determinations, the suitability of the European Pharmacopoeia methods (2.8.18 and 2.8.22, respectively) to the herbal matrix tested must be performed. For microbiological examination, the suitability of the method must be performed (according to the indication given in 2.6.31).

Reference guideline: Validation of Analytical Procedures: Text and Methodology.

3.2.S.4.4 Batch analyses (name, manufacturer)

For the ***herbal substance*** and the ***herbal preparation****,* results of testing of at least two representative batches with their description (batch size, date of production, date of analysis) should be provided.

When they are several sites of production for the ***herbal substance***, at least one certificate of analysis per site should be given.

When alternatives / different sites are described in the dossier for the ***herbal preparation***, the results of the analysis of the batches shall be provided for each.

The results of the analysis are given as actual figures whenever possible instead of statements such as “conforms”, “complies” etc. In cases of use of TLC, a coloured photographic picture should illustrate the results.

Reference guidance: Certification of Suitability of Monographs of the European Pharmacopoeia: “Content of the Dossier for Herbal Drugs and Herbal Drug Preparations Quality Evaluation”.

[5] Guédon D. *et al.* Impurities in herbal substances, herbal preparations and herbal medicinal products, III. Pesticides residues. STP Pharma Pratiques 18 (2) 2008

3.2.S.4.5 Justification of specification (name, manufacturer)

A justification for the specification of the ***herbal substance*** and of the ***herbal preparation*** should be provided unless it is based on a European Pharmacopoeia monograph or one in the Pharmacopoeia of a Member State.

The manufacturer should provide the rationale and justification for including and/or excluding testing for specific quality attributes. If available, historical experimental data should be taken into account to set the acceptance criteria.

Reference guidance:

- Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Markers used for Quantitative and Qualitative Analysis of Herbal Medicinal Products and Traditional Herbal Medicinal Products.

3.2.S.5 Reference standards or materials (name, manufacturer)

Information on the reference standards or reference materials used for testing the ***herbal substance*** and of the ***herbal preparation*** should be provided.

The composition of non-pharmacopoeial reference standards intended for use in assays should be adequately controlled and the purity should be measured by validated quantitative procedures.

For these non-pharmacopoeial standards, the supplier's name and the standard reference number should be provided and storage conditions should be stated.

Reference guideline: Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.

3.2.S.6 Container closer system (name, manufacturer)

- ***Herbal substance***

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications.

- ***Herbal preparation***

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

In the absence of European Pharmacopoeia guidance, a certificate of food compatibility should be provided.

For non-functional secondary packaging components (e.g. those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the herbal preparation.

Reference guideline: *Plastic Primary Packaging Materials.*

3.2.S.7 Stability (name, manufacturer)

- ***Herbal substance***

Herbal substances, which are used as starting material in the manufacturing process of a herbal preparation, shall comply with specification before use (e.g. before extraction).

Storage conditions of the herbal substance by the producer and the supplier and by the active substance manufacturer should be stated.

Reference guideline: *Stability Testing of Existing Active Substances and Related Finished Products.*

- ***Herbal preparation***

The purpose of the stability study is to establish, based on testing a minimum of two or three batches of the active substance and evaluating the stability information, a re-test date or a shelf-life, applicable to all future batches of the active substance manufactured under similar circumstances.

3.2.S.7.1 Stability summary and conclusions (name, manufacturer)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include conclusions with respect to storage conditions and re-test date or shelf-life, as appropriate. Stress tests are usually considered unnecessary for herbal preparations.

Reference guidance:

- Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Reflection paper on Stability Testing of Herbal Medicinal Products and Traditional of Herbal Medicinal Products.

- Stability Testing of New Drug Substances and Products.

- Stability Testing of Existing Active Substances and Related Finished Products.

- Stability Testing for Application for Variations to a Marketing Authorisation.

- Annex: Declaration of Storage Conditions for Medicinal Products Particulars and Active Substances.

- Evaluation of Stability Data.

- Questions & Answers on Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

3.2.S.7.2 Post-approval Stability Protocol and Stability (name, manufacturer)

The post-approval stability protocol and stability commitment should be provided.

Reference guidelines:

- Stability Testing of New Drug Substances and Products.

- Stability Testing of Existing Active Substances and Related Finished Products.

- Stability Testing for Application for Variations to a Marketing Authorisation.

3.2.S.7.3 Stability Data (name, manufacturer)

Results of the stability studies should be presented in an appropriate format such as tabular, graphical, or narrative. The description of batches (batch size, date of production, date of analysis) should be provided. Information on the analytical procedures used to generate the data and validation of these procedures should be included. Chromatographic profiles should be provided.

Reference guidance:

- Stability Testing of New Drug Substances and Products.

- Stability Testing of Existing Active Substances and Related Finished Products.

- Stability Testing for Application for Variations to a Marketing Authorisation.

- Questions & Answers on Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Validation of Analytical Procedures: Text and Methodology.

3.2.P Drug Product (name, dosage form)

3.2.P.1 Description and composition of the drug product (name, dosage form)

A description of the herbal medicinal product and its composition should be provided. The information provided should include, for example:

- **Description of the dosage form,**
- **Composition**, i.e.: list of all components of the dosage form and their amount on a per-unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g. compendial monographs or manufacturer's specifications),
- **Description of accompanying reconstitution diluent(s),**
- **Type of container and closure** used for the dosage form and accompanying reconstitution diluent, if applicable.

Reference guideline: Declaration of Herbal Substances and Herbal Preparations in Herbal Medicinal Products/Traditional Herbal Medicinal Products.

3.2.P.2 Pharmaceutical development (name, dosage form)

The Pharmaceutical development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container/closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications.

Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and herbal medicinal product quality.

Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical development section.

Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

The classification of an extract according to the European Pharmacopoeia monograph “Extracts” and the choice of the markers should be justified.

Reference guidance:

- Development Pharmaceutics.

- Pharmaceutical Development.

- Markers used for Quantitative and Qualitative Analysis of Herbal Medicinal Products and Traditional Herbal Medicinal Products.

- Questions & Answers on Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

3.2.P.2.1 Components of the drug product (name, dosage form)

3.2.P.2.1.1 Drug substance (name, dosage form)

The compatibility of the drug substance with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g. water content, solubility, particle size distribution) of the drug substance that can influence the performance of the herbal medicinal product should be discussed.

For combination products, the compatibility of drug substances with each other should be discussed.

3.2.P.2.1.2 Excipients (name, dosage form)

The choice of excipients listed in 3.2.P.1, their concentration, their characteristics that can influence the herbal medicinal product performance should be discussed relative to their respective functions.

Reference guidance:

- Regulatory Questions & Answers on Herbal Medicinal Products. Question R1.

- Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product.

3.2.P.2.2 Drug product (name, dosage form)

3.2.P.2.2.1 Formulation development (name, dosage form)

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 3.2.P.1 should be discussed, where appropriate, especially for a well-established use herbal medicinal product.

Reference guideline: The use of the CTD format in the preparation of a registration application for traditional herbal medicinal products.

3.2.P.2.2.2 Overages (name, dosage form)

Any overages in the formulation(s) described in 3.2.P.1 should be justified.

3.2.P.2.2.3 Physicochemical and biological properties (name, dosage form)

Parameters relevant to the performance of the herbal medicinal product, such as dissolution, particle size distribution, rheological properties, biological activity should be addressed.

3.2.P.2.3 Manufacturing process development (name, dosage form)

The selection and optimisation of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained.

3.2.P.2.4 Container Closer system (name, dosage form)

The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the herbal medicinal product should be discussed. This discussion should consider, e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching), safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the herbal medicinal product).

Reference guidance: *Quality of Medicines Questions & Answers Part 2: Specific types of products: Graduation of Measuring Devices for Liquid Dosage Forms.*

3.2.P.2.5 Microbiological attributes (name, dosage form)

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale by validation studies for not performing microbial limits testing for non-sterile products (e.g. oral dosage form) and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

Reference guidance:

- Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products - Chemical Substances - Decision tree 8.

- Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products.

- Questions & Answers on Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

3.2.P.2.6 Compatibility (name, dosage form)

The compatibility of the herbal medicinal product with reconstitution diluent(s) or dosage devices (e.g. precipitation of drug substance in solution, stability) should be addressed to provide appropriate and supportive information for the labelling.

3.2.P.3 Manufacture (name, dosage form)

3.2.P.3.1 Manufacturer(s) (name, dosage form)

The name, address and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

Reference guideline: *Manufacture of the Finished Dosage Form.*

3.2.P.3.2 Batch formula (name, dosage form)

A batch formula for the intended batch size (an application for variable and/or alternative batch size should be justified) should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overage, and a reference to their quality standards.

Reference guideline: *Manufacture of the Finished Dosage Form.*

3.2.P.3.3 Description of manufacturing process and process controls (name, dosage form)

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g. tumble blender, in-line homogeniser) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature or pH, hardness and friability of tablet cores, which will be coated. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 3.2.P.3.4.

Reference guideline: *Manufacture of the Finished Dosage Form.*

3.2.P.3.4 Controls of critical steps and intermediates (name, dosage form)

- Critical Steps: Tests and acceptance criteria should be provided (with justification including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled.
- Intermediates: Details of all control tests, with details of test procedures and limits applied at any intermediate stages of the manufacturing processes, are required especially if these tests cannot be performed on the herbal medicinal product and supported by documentation.

Where an intermediate is not used immediately, the conditions of storage (packaging, temperature, holding time…) should be described and supportive documentation provided.

Reference guidelines:

- Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Validation of Analytical Procedures: Text and Methodology.

3.2.P.3.5 Process validation and/or evaluation (name, dosage form)

Description, documentation and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process.

Reference guidance:

- Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Process Validation.

- Annex II: Process Validation - Non-Standard Processes.

- Real Time Release Testing (formerly Guideline on Parametric Release).

- Quality of Medicines Questions & Answers Part 1 and Part 2.

3.2.P.4 Control of excipients (name, dosage form)

Reference guidelines:

- Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product.

- Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products.

3.2.P.4.1 Specifications (name, dosage form)

The specifications for excipients should be provided (European Pharmacopoeia monographs or, by default, internal monographs).

Their functionality-related characteristics should be considered.

Reference guidance:

- Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances.

- Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.

- Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Markers used for Quantitative and Qualitative Analysis of Herbal Medicinal Products and Traditional Herbal Medicinal Products.

- Impurities: Residual Solvents

3.2.P.4.2 Analytical procedures (name, dosage form)

The analytical procedures used for testing the excipients should be provided, where appropriate.

3.2.P.4.3 Validation of analytical procedures (name, dosage form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Reference guideline: Validation of Analytical Procedures: Text and Methodology.

3.2.P.4.4 Justification of specifications (name, dosage form)

Justification for the proposed excipient specifications should be provided, where appropriate.

For herbal excipients (e.g. in herbal teas combinations) full details of manufacture, characterisation, and control should be provided in order to justify the specification (details in 3.2.A.3).

Reference guidance:

- Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances.

- Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.

- Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Markers used for Quantitative and Qualitative Analysis of Herbal Medicinal Products and Traditional Herbal Medicinal Products.

- Impurities: Residual Solvents

3.2.P.4.5 Excipients of human or animal origin (name, dosage form)

For excipients of human or animal origin (e.g. magnesium stearate, lactose, gelatin…) information should be provided regarding adventitious agents (e.g. sources, specifications; description of the testing performed; viral safety data) (Details in 3.2.A.2).

Reference guidelines:

- Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.

- Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

3.2.P.4.6 Novel excipients (name, dosage form)

For excipient(s) used for the first time in a herbal medicinal product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (non clinical and/or clinical) should be provided according to the drug substance format (Details in 3.2.A.3).

Reference guideline: Development Pharmaceutics.

3.2.P.5 Control of drug product (name, dosage form)

Reference guideline: Specifications and Control Tests on the Finished Product.

3.2.P.5.1 Specification(s) (name, dosage form)

Release and shelf-life specifications for the herbal medicinal product should be provided in a table.

Reference guidance:

- Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Quality of Combination Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Markers used for Quantitative and Qualitative Analysis of Herbal Medicinal Products and Traditional Herbal Medicinal Products.

- Impurities: Residual Solvents

3.2.P.5.2 Analytical procedures (name, dosage form)

The analytical procedures used for testing the herbal medicinal product should be provided.

3.2.P.5.3 Validation of analytical procedures (name, dosage form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the herbal medicinal product should be provided.

Reference guideline: Validation of Analytical Procedures: Text and Methodology.

3.2.P.5.4 Batch analyses (name, dosage form)

A description of batches (batch size, date of production, date of analysis) and results of at least three batches analyses should be provided. When different alternatives / different sites are described in the dossier, the results of the analysis of the batches shall be provided for each.

The results of the analysis are given as actual figures whenever possible instead of statements such as “conforms”, “complies” etc.

If TLC is used a coloured photographic picture should be included to illustrate the results.

3.2.P.5.5 Characterisation of impurities (name, dosage form)

See "Section 3.2.P.5.1 Specification(s)".

Information on the characterisation of impurities should be provided, if not previously provided in "3.2.S.3.2 Impurities".

Reference guidelines:

- Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Impurities: Residual Solvents

3.2.P.5.6 Justification of specification(s) (name, dosage form)

Justification for the proposed herbal medicinal product specification(s) should be provided.

Reference guidance:

- Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Quality of Combination Herbal Medicinal Products / Traditional Herbal Medicinal Products.

- Markers used for Quantitative and Qualitative Analysis of Herbal Medicinal Products and Traditional Herbal Medicinal Products.

- *Impurities: Residual Solvents*

3.2.P.6 Reference standards or materials (name, dosage form)

Information on the reference standards or reference materials used for testing of the herbal medicinal product should be provided, if not previously provided in "3.2.S.5 Reference Standards or Materials".

3.2.P.7 Container Closer system (name, dosage form)

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification.

The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate.

In the absence of European Pharmacopoeia guidance, a certificate of food compatibility should be provided.

For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in 3.2.P.2.4.

Reference guideline: *Plastic Primary Packaging Materials.*

3.2.P.8 Stability (name, dosage form)

The purpose of the stability study is to establish, based on testing a minimum of two or three batches of the finished product, a shelf-life and label storage instructions applicable to all future batches of the finished product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf-life.

3.2.P.8.1 Stability summary and conclusions (name, dosage form)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.

Reference guidance:

- *Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.*

- *Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products.*

- *Reflection paper on Stability Testing of Herbal Medicinal Products and Traditional of Herbal Medicinal Products.*

- *Stability Testing of New Drug Substances and Products.*

- *Stability Testing of Existing Active Substances and Related Finished Products.*

- *Stability Testing for Application for Variations to a Marketing Authorisation.*

- *In-Use Stability Testing of Human Medicinal Products.*

- *Annex: Declaration of Storage Conditions for Medicinal Products Particulars and Active Substances.*

- *Evaluation of Stability Data.*

- *Questions & Answers on Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products.*

- *Quality of Medicines Questions & Answers Part 1 and Part 2.*

3.2.P.8.2 Post-approval stability protocol and stability commitment (name, dosage form)

The post-approval stability protocol and stability commitment should be provided.

Reference guidelines:

- *Stability Testing of New Drug Substances and Products.*

- *Stability Testing of Existing Active Substances and Related Finished Products.*

- *Stability Testing for Application for Variations to a Marketing Authorisation.*

3.2.S.8.3 Stability Data (name, dosage form)

Results of the stability studies should be presented in an appropriate format such as tabular, graphical, or narrative. The description of batches (batch size, date of production, date of analysis) should be provided.

Information on the analytical procedures used to generate the data and validation of these procedures should be included. Chromatographic profiles should be provided.

Information on characterisation of impurities is located in 3.2.P.5.5.

References guidelines:

- *Stability Testing of New Drug Substances and Products.*

- *Stability Testing of Existing Active Substances and Related Finished Products.*

- *Stability Testing for Application for Variations to a Marketing Authorisation.*

- *In-Use Stability Testing of Human Medicinal Products.*

- *Validation of Analytical Procedures: Text and Methodology.*

3.2.A Appendices

3.2.A.1 Facilities and equipment (name, manufacturer): Biotech

3.2.A.2 Adventitious agents safety evaluation (name, dosage form, manufacturer)

3.2.A.3 Excipients

Reference: Notice to Applicants, Volume 2B - Presentation and Format of the Dossier - Common technical document (CTD) - Module 3.

3.2.R Regional information

Any additional herbal substance/active substance and/or herbal medicinal product information specific to each region should be provided in section R of the application. Applicants should consult the appropriate regional guidelines and/or regulatory authorities for additional guidance.

Reference: Notice to Applicants, Volume 2B - Presentation and Format of the Dossier - Common technical document (CTD) - Module 3.

For EU:

- Process validation scheme for the herbal medicinal product

  Reference guideline: Note for Guidance on Process Validation

- Medical device
- Certificate(s) of suitability
- Medicinal products containing or using in the manufacturing process materials of animal and/or human origin

Compliance with the Annex I to Dir. 2001/83/EC, Part I, Module 2, paragraph 3.2 (9)

"Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies (materials from ruminant origin): at each step of the manufacturing process, the applicant must demonstrate the compliance of the materials used with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union. Demonstration of compliance with the said Note for Guidance can be done by submitting either, preferably a certificate of suitability to the relevant monograph of the European Pharmacopoeia that has been granted by the European Directorate for the Quality of Medicines or by the supply of scientific data to substantiate this compliance."

In the case that scientific data to substantiate this compliance is included in the Quality Part of the dossier, then this data should be reviewed in the Quality Overall Summary (Module 2.3).

For all applications, the table A on "*Materials of animal origin covered by the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products*" should be completed. TSE Certificates of Suitability (if available) are to be attached.

For materials of animal origin other than those covered by the *Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products*, applicants are requested to complete the table B on "*Other materials of animal origin*".

Reference: *Notice to Applicants, Volume 2B - Presentation and Format of the Dossier - Common technical document (CTD) - Module 3.*

3.3 Literature references

Key literature references should be provided, if applicable.

References relevant for Module 3

References to EU guidelines are provided to assist applicants when compiling the chemical, pharmaceutical and biological part of the application. However, it remains the applicants' responsibility to ensure that all relevant legislation and guidelines are taken into account in the preparation of each part of their dossier.

The guidelines referenced below are available on the EMA Website:

http://www.ema.europa.eu

or in Volume 3 of the "Rules Governing medicinal products in the EU"– Eudralex, available on the Website of the European Commission:

http://ec.europa.eu/health/documents/eudralex/index_en.htm

The following guidelines and their versions represent the current status at time of adoption. Applicants are advised to use always the latest versions and additions to the guidelines listed below.

A - List of references on general texts or guidelines on the content of the dossier

Document title	Number / Version
Notice to Applicants, Volume 2B - Presentation and Format of the Dossier - Common technical document (CTD) - Module 3.	Edition July 2008
The Use of the CTD Format in the Preparation of a Registration Application for Traditional Herbal Medicinal Products.	EMEA/HMPC/71049/2007
Active Substance Master File Procedure.	EMEA/QWP/227/02 Rev. 3
Certification of Suitability of Monographs of the European Pharmacopoeia: "Content of the Dossier for Herbal Drugs and Herbal Drug Preparations Quality Evaluation".	Addendum to the certification procedure AP-CSP (93) 5 as amended

B - List of references to quality guidelines

General guidelines

Document title	Number / Version
Summary of Requirements for Active Substances in the Quality Part of the Dossier.	CHMP/QWP/297/97 Rev. 1 corr
Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products - Chemical Substances (ICH Q6A).	CPMP/ICH/367/96 – ICH Q6A
Validation of Analytical Procedures: Text and Methodology (ICH Q2 (R1)).	CPMP/ICH/381/95 - ICH Q2 (R1)
Development Pharmaceutics.	CPMP/QWP/155/96

Document title	Number / Version
Pharmaceutical Development (ICH Q8 (R2)). *See also:* ICH Guidelines Q8, Q9, Q10 Questions and Answers, Volume 4.	EMEA/CHMP/167068/2004-ICH Q8 (R2) EMA/CHMP/ICH/265145/2009
Suitability of the Graduation of Delivery Devices for Liquid Dosage Forms. Draft, replaced by Quality of Medicines Questions & Answers (Q&A) Part 2: Specific types of products: Graduation of Measuring Devices for Liquid Dosage Forms.	CHMP/QWP/178621/04
Quality of Water for Pharmaceutical Use.	CPMP/QWP/ 158/01 Rev. 1
The Use of Ionizing Radiation in the Manufacture of Medicinal Products.	3AQ4A
Quality of Medicines Questions & Answers (Q&A) Part 1 and Part 2.	

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Document title	Number / Version
Chemistry of New Active Substances.	CPMP/QWP/130/96 Rev. 1
Chemistry of Active Substances.	3AQ5A
Impurities in New Drug Products (ICH Q3B (R2)).	CPMP/ICH/2738/99 - ICH Q3B (R2)
Impurities: Residual Solvents (ICH Q3C (R4)	CPMP/ICH/ 283/95-ICH Q3C (R4)
ICH Topic Q3C (R5). Impurities: Guideline for Residual Solvents.	EMA/CHMP/ICH/82260/2006
Annexes to Specifications for Class 1 and Class 2 Residual Solvents in Active Substances.	CPMP/QWP/450/03

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Document title	Number / Version
Process Validation. Process Validation (Concept Paper). Annex II: Process Validation - Non-Standard Processes.	CPMP/QWP/848/96 EMA/CHMP/CVMP/QWP/809114/2009 CPMP/QWP/2054/03
Parametric Release. Real Time Release Testing (formerly Guideline on Parametric Release).	CPMP/QWP/3015/99 EMA/CHMP/QWP/811210/2009
Manufacture of the Finished Dosage Form.	CPMP/QWP/486/95
Specifications and Control Tests on the Finished Product.	3AQ11A
Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product. Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product. Under revision	EMEA/CHMP/QWP/396951/06 3AQ9A
Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products.	CPMP/CVMP/QWP /115/95
Plastic Primary Packaging Materials.	CPMP/QWP/4359/03
Stability Testing for Applications for Variations to a Marketing Authorisation. Stability Testing for Applications for Variations to a Marketing Authorisation. Draft.	CPMP/QWP/576/96 Rev. 1 EMA/CHMP/CVMP/QWP/63033/2010
Stability Testing of New Drug Substances and Products (Q1A(R2)). Stability Testing of Existing Active Substances and Related Finished Products. Annex: Declaration of Storage Conditions for Medicinal Products Particulars and Active Substances.	CPMP/ICH/2736/99 - Q1A (R2) CPMP/QWP/122/02 Rev. 1 corr CPMP/QWP/609/96 Rev. 2
Evaluation of Stability Data (ICH Q1E).	CPMP/ICH/ 420/02-ICH Q1E
In-Use Stability Testing of Human Medicinal Products.	CPMP/QWP/2934/99

869 ***C - List of references to biotechnology guidelines***

Document title	Number / Version
Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products (ICH Q6B).	CPMP/ICH/365/96 - ICH Q6B
Minimising the Risk of transmitting Animal Spongiform Encephalopathy agents via Human and Veterinary	EMA/410/01 Rev. 3

Document title	Number / Version
Medicinal Products.	

D - List of references to quality guidelines on herbal active substances and herbal medicinal products

General guidelines

Document title	Number / Version
Declaration of Herbal Substances and Herbal Preparations in Herbal Medicinal Products/Traditional Herbal Medicinal Products.	EMA/HMPC/CHMP/CVMP/287539/05 Rev. 1
Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products.	CPMP/QWP/2819/00 Rev. 2 EMEA/CVMP/814/00 Rev. 2
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
Reflection paper on Markers used for Quantitative and Qualitative Analysis of Herbal Medicinal Products and Traditional Herbal Medicinal Products.	EMEA/HMPC/253629/07
Questions & Answers (Q&A) on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products.	EMA/HMPC/41500/10 Rev. 1

Active substance guidelines

Document title	Number / Version
Reflection Paper on Level of Purification of Extracts to be considered as Herbal Preparations.	EMA/HMPC/186645/08
Good Agricultural and Collection Practice for Starting Materials of Herbal Origin.	EMEA/HMPC/246816/05
Reflection paper on The Use of Fumigants.	EMEA/HMPC/125562/06

Medicinal product guidelines

Document title	Number / Version
Quality of Combination Herbal Medicinal Products / Traditional Herbal Medicinal Products.	EMEA/HMPC/CHMP/CVMP/214869/06
Reflection paper on Stability Testing of Herbal Medicinal Products and Traditional of Herbal Medicinal Products.	EMA/HMPC/3626/09
Regulatory Questions & Answers (Q&A) on Herbal Medicinal Products.	EMA/HMPC/345132/2010 Rev. 1