EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 April 2016
EMA/HMPC/71049/2007 Rev. 2
Committee on Herbal Medicinal Products (HMPC)

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

Final - revision 2

Draft agreed by Organisational Matters Drafting Group (ORGAM DG)	April 2007
Adoption by HMPC for release for consultation	8 May 2007
End of consultation	15 August 2007
Agreed by ORGAM DG	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 (Q DG)	April 2012
Draft revision 1 adopted by HMPC for release for consultation	22 May 2012
End of consultation	15 October 2012
Revision 1 agreed by Q DG	December 2012
Revision 1 agreed by ORGAM DG	February 2013
Adoption revision 1 by HMPC	12 March 2013
Draft revision 2 agreed by ORGAM DG	September 2014
Draft revision 2 agreed by Monograph and List Working Party (MLWP)	November 2014
Draft revision 2 adopted by HMPC for release for consultation	January 2015
Appendix 2 to Draft revision 2 agreed by Q DG	February 2015
Appendix 2 to Draft revision 2 adopted by HMPC for release for consultation	10 March 2015

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

End of consultation	15 July 2015
Revision 2 agreed by Q DG	February 2016
Revision 2 agreed by ORGAM DG	February 2016
Adoption revision 2 by HMPC	5 April 2016

Keywords	Herbal medicinal products (HMPs) ; traditional herbal medicinal products (THMPs); CTD; traditional use simplified registration; HMPC

Table of contents

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 the Applicant in their submissions.

Revision 1 pertained to the presentation and content of Module 3 on Quality (chemical, pharmaceutical and biological information) of dossiers for THMPs to help the Applicant with their submissions. 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. In addition minor editorial corrections and updates have been introduced in the guideline itself.

Revision 2 pertains to the presentation and content of Modules 2, 4 and 5 of dossiers for THMPs, to help the Applicant in their submissions. More detailed clarifications have therefore been introduced mainly in sections 1.5, 2.4, 2.5, 5.3 and 5.4. In addition, minor editorial corrections and amendments have been introduced in other sections.

For further guidance on the content of Module 3 on Quality within dossiers for THMPs, a mock-up has been included as Appendix 2 to help the Applicant with their submissions. It serves as an example for the Applicant of the format providing clarification on the exact location of relevant parts of the documentation.

1. Introduction

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

At the time of implementation of the provisions of Directive 2004/24/EC, there were a number of enquiries from industry in some European Member States regarding the structure of the dossier of applications for traditional use registration. There were especially some issues as to where certain information contained in the dossier should be positioned. In general the CTD format should be used in applications for traditional use registration.

As experience was gained registering THMPs in Europe, it was thought necessary to update the guideline to provide further clarification on quality (revision 1), clinical and non-clinical (revision 2) requirements for THMP applications taking into account the increasing number of available European Union monographs.

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 Appendices 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 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 European Union 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]

[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).
[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)

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 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 CTD).

For the purpose of this guideline, the term 'Applicable' means that the guidance provided in Notice to Applicants, Volume 2B - 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

[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.
[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).

1.3.2. Mock-up	Applicable (where available)
1.3.3. Specimens	Applicable (where available)
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, especially addressing the evidence of long standing use of the product. Where a European Union herbal monograph or list entry exists that is relevant to the proposed herbal substance/herbal preparation (HS/HP), the Applicant should outline this fact in this section of the dossier and expand on it in Module 2.5. European Union herbal monograph for THMPs comprise the scientific opinion of the HMPC on safety and efficacy data for HSs/HPs and have the objective of facilitating registration and harmonisation in this field. A final European Union herbal monograph can be used in application reference material by the Applicant and these monographs are taken into account by Member States when examining applications. Member States are not obliged to follow the monographs but any decision not to accept the content of a monograph should be duly justified, taking into account their important role in bringing harmonisation to this field. In contrast to a European Union herbal monograph, a European Union list entry is legally binding to the Applicant and competent authorities in Member States. Therefore, an applicant will not be required to provide evidence of the safe and traditional use of a medicinal product for which he seeks a traditional use registration if he demonstrates that the proposed product and related claims in the application comply with the information contained in the European Union list entry for that HS/HP. In the absence of a relevant traditional use monograph or European Union list entry for the proposed HS/HP, reference may also be made to a

	corresponding product as per Directive 2001/83/EC.
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. The requirement to operate a pharmacovigilance system and to maintain and make available on request a pharmacovigilance system master file also applies to traditional herbal medicinal products. However, the requirement to submit a summary of the pharmacovigilance system does not apply to the traditional use registration
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[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 HSs/HPs, a description of the desired product and product-related substances and a summary of general properties, characteristics features and characterisation 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, fumigants, etc. In some specific circumstances, the risk of radioactive contamination is to be considered.
2.4. Non-clinical overview	Module 2.4 should include the expert report reflecting the bibliographic review of non-clinical safety data and where required by the competent authority, upon additional request, data necessary for assessing the safety of the medicinal product (Art. 16c(1)(d) of Directive 2001/83/EC as amended). It is advised that the expert report on non-clinical data takes into

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

	consideration the 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). In addition, the Guideline on the assessment of genotoxicity of herbal substances/preparations (EMEA/HMPC/107079/2007) and the Guideline on selection of test materials for genotoxicity testing for traditional herbal medicinal products/herbal medicinal products (EMEA/HMPC/67644/2009) apply. Where a European Union herbal monograph or European Union list entry has been established that is relevant to the proposed HS/HP, the Applicant should discuss this fact in this section of the dossier. Furthermore the Applicant should refer to aspects related to the finished traditional herbal medicinal product, such as excipients influencing the safety. When missing data on genotoxicity in section 5.3 of the monograph are mentioned, they should be appropriately complemented in accordance with the Guideline on the assessment of genotoxicity of herbal substances/preparations (EMEA/HMPC/107079/2007). The Applicant is requested to demonstrate that the proposed product contains a HS/HP which corresponds to a HS/HP listed in the monograph. The non-clinical part of the assessment report of the HMPC should be used as background for the non-clinical expert report. Own literature research should be provided to fill the gap between the compilation of the assessment report and the application, providing information about the research strategy. The relevance of the newer data and/or unpublished, specific data has to be discussed in relation of the known properties of the HS/HP and the possible impact of such data on the existing assessment. Where the characteristics of a HS/HP differ from those given in the monograph (e.g. regarding DER, extraction solvent, extract type (dry/liquid)), a comprehensive justification is needed substantiating that reference to the monograph is possible. Cross reference should be made to documentation submitted in module 3 (3.2.S.1.2, 3.2.S.2.6, 3.2.P.1 and 3.2.P.2.2.1) to demonstrate comparability. The same applies, if non-published data, which should be used (e.g. tests on mutagenicity) is referring to different extract solvent and/or concentration. For combination products the assessment should not only focus on the single HSs/HPs, in fact also an assessment of the combination is necessary. If risks have been identified, the report must explain why a positive benefit/risk-balance for a traditional use is justified. 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. Copies of the references not already included in HMPC assessment report should be included in module 4.

2.5. Clinical overview	Module 2.5 should include the expert report on clinical data. It is advised that the expert report on clinical data takes into consideration the Guideline on the assessment of clinical safety and efficacy in the preparation of Community Herbal monographs for well-established and of Community herbal monographs/entries to the Community list for traditional herbal medicinal products/substances/preparations (EMEA/HMPC/104613/2005). 2.5.4 Overview of Efficacy The overview should include 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 EU (Art. 16c(1)(c) of Directive 2001/83/EC as amended). Where a European Union herbal monograph or European Union list entry has been established that is relevant to the proposed HS/HP, the Applicant should discuss this fact in this section of the dossier. European Union herbal monographs for THMPs comprise the scientific opinion of the HMPC on safety and efficacy data for HSs/HPs and have the objective of facilitating registration and harmonisation in this field. A final European Union herbal monograph can be used in application reference material by the Applicant and these monographs are taken into account by Member States when examining applications. Member States are not obliged to follow the monographs but any decision not to accept the content of a monograph should be duly justified, taking into account their important role in bringing harmonisation to this field. In contrast to a European Union herbal monograph, a European Union list entry is legally binding to the Applicant and competent authorities in Member States. Therefore, an applicant will not be required to provide evidence of the safe and traditional use of a medicinal product for which he seeks a traditional use registration if he demonstrates that the proposed product and related claims in the application comply with the information contained in the European Union list entry for that HS/HP. However, the applicant must demonstrate in this section of the dossier that the proposed HS/HP complies fully with the European Union list entry. For medicinal products, for which excipients might be of special relevance (e.g. ointments), the Applicant is asked to provide data on the safe use of the whole products applied for, if requested by the competent authority. Where no European Union list entry exists but a relevant European Union herbal monograph does exist, the Applicant should be aware of the following points. Specific HSs/HPs have been included in the monographs because they have been shown to fulfil the criteria for simplified registration as per Directive 2004/24/EC and have documented traditional use. The Applicant will need to demonstrate that the proposed product

	contains a HS/HP which corresponds to a HS/HP listed in the monograph. Where the characteristics of a HS/HP differ from those given in the monograph (e.g. regarding DER, extraction solvent, extract type (dry/liquid)), a comprehensive justification is needed substantiating that reference to the monograph is possible. Cross reference should be made to documentation submitted in module 3 (3.2.S.1.2, 3.2.S.2.6, 3.2.P.1 and 3.2.P.2.2.1) to demonstrate comparability. In the absence of a relevant traditional use monograph or European Union list entry for the proposed HS/HP, reference may also be made to a corresponding THMP on the EU market; and justification for the corresponding product should be included in the relevant sections of 2.5. 2.5.5 Overview of Safety For THMPs, in Module 2.5, as referred to in Article 16c(1)(d) the following is also 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 clinical data takes into consideration the agreed format for the organisation of the clinical overview in the CTD. The list of relevant references for clinical data can be included at the end of module 2.5. Copies of the references not already included in HMPC assessment report should be included in module 5.
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	Where a European Union monograph has been established that is relevant to the proposed HS/HP, tabulated non-clinical summaries are generally not required, unless requested by the competent authority. Where a European Union list entry has been established that is relevant to the proposed HS/HP, tabulated summaries are not required." When the Applicant is requested to supplement the data supporting the monograph with additional safety data (e.g. tests on genotoxicity, reproductive toxicity and carcinogenicity) these data should be presented in the tabulated non-clinical summaries in this section. When there is no monograph or a list entry, tabulated non-clinical summaries in Module 2 shall be provided.
2.7. Clinical Summaries 2.7.1. Summary of	Where a European Union monograph has been established that is relevant to the proposed HS/HP, tabulated clinical summaries are generally not required, unless requested by the competent authority. Where a European

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	Union list entry has been established that is relevant to the proposed HS/HP, tabulated summaries are not required. When supplementing data from (clinical) studies are addressed in section 2.5, the 2.7 clinical summary should be presented in tabulated format.

4.3. Module 3[9]: Quality

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

- 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products' (EMA/CPMP/QWP/2819/00 as revised, EMA/CVMP/814/00 as revised, EMA/HMPC/201116/2005 as revised).
- 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products' (EMA/CPMP/QWP/2820/00 as revised, EMA/CVMP/815/00 as revised, EMA/HMPC/162241/2005 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

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

	• 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 HSs/HPs 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	**For herbal substances** Information should be provided to adequately describe the plant production

and Process Controls (name, manufacturer)	and plant collection, including: • Geographical source of medicinal plant • Cultivation, pre- and post-harvest treatment, drying and storage conditions • Lot size **For herbal preparations** 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/Quantification • 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 HSs/HPs where applicable should be provided, taking into consideration the proposed route of administration and usage. The comparability of the phytochemical composition of the HS/HP used in supporting bibliographic data and the HS/HP described in 3.2.S.1.2 should be discussed as 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, macroscopic, microscopic, 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 substance production and post-harvesting treatments such as pesticides and fumigants residues, toxic metals, aflatoxins, (and ochratoxin A for herbal drugs subject to contamination), microbial contamination as well as potential adulterants should be discussed. The risk of radioactive contamination is to be considered. Degradation products should be studied if relevant, e.g. potential degradants formed on storage or those that might arise as a result of decontamination treatments. **For herbal preparations** • Potential contaminants originating from the herbal substance production and post-harvesting treatments such as pesticides and fumigants residues, toxic metals aflatoxins, (and ochratoxin A for herbal drugs subject to contamination), microbial contamination as well as potential adulterants should be discussed. The risk of radioactive contamination is to be considered. Possible impurities originating from the process or from degradation should be listed and discussed with an indication of their origin (e.g. potential degradants formed on storage or those that might arise as a result of decontamination treatments). • Residual solvents
3.2.S.4. Control of Drug Substance (name, manufacturer)	Data for HSs/HPs 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. The comparability of 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.
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	Applicable

(name, dosage form)	
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".

4.4. Module 4: Non-clinical study reports

In accordance 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. Where a European Union monograph has been established that is relevant to the proposed HS/HP (and therefore a relevant assessment report exists) bibliographic references mentioned in the assessment report are generally not required, unless requested by the competent authority. Where a European Union list entry has been established that is relevant to the

4.1. Module 4 Table of Contents	Applicable
	proposed HS/HP, bibliographic references are not required.

4.5. Module 5: Clinical study reports

In accordance 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. Copies of references supporting the traditional use data and clinical safety data should be presented in Module 5.4.
5.4. Literature References	Such references should be indexed following the agreed format for the organisation of Module 5. Where a European Union monograph has been established that is relevant to the proposed HS/HP (and therefore a relevant assessment report exists) bibliographic references mentioned in the assessment report are generally not required, unless requested by the competent authority. Where a European Union list entry has been established that is relevant to the proposed HS/HP, bibliographic references are not required.

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' (EMA/CPMP/QWP/2819/00 as revised, EMA/CVMP/814/00 as revised, EMA/HMPC/201116/2005 as revised).

'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products' (EMA/CPMP/QWP/2820/00 as revised, EMEA/CVMP/815/00 as revised, EMA/HMPC/162241/2005 as revised).).

'Quality of combination herbal medicinal products/traditional herbal medicinal products' (EMEA/HMPC/CHMP/CVMP/214869/2006).

'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).

'Guideline in the assessment of clinical safety and efficacy in the preparation of European Union herbal monographs for well-established and of European Union herbal monographs/entries to the European Union list for traditional herbal medicinal products/substances/preparations' (EMEA/HMPC/104613/2005).

'Guideline on declaration of herbal substances and herbal preparations[1]in herbal medicinal products[2]/traditional herbal medicinal products' (EMA/HMPC/CHMP/CVMP/287539/2005 Rev. 1)

'Requirements for pharmacovigilance system, PSMF, RMS and RMP for herbals and homeopathic medicinal products' (EMA/190210/2012).

'Regulatory Q&A on herbal medicinal products' (EMA/HMPC/345132/2010 Rev. 2[1] *Corr*).

Appendix 1 to guideline EMA/HMPC/71049/2007

Best Practice Guide for the Module 3 Quality: Chemical, Pharmaceutical and Biological Information for Herbal Substances, Herbal Preparations and Traditional Herbal Medicinal Products[10]

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 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[11] to guidelines are inserted to assist the Applicant. 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.

3.1 Table of Contents of Module 3

A Table of Contents for Module 3 should be provided.

[10] Guidance on module 3 as described in this Appendix 1 is also applicable to herbal medicinal product (HMPs) applications for marketing authorisation.
[11] 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.

3.2 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[12] (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***[13] 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***

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.

[12] 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.
[13] 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.

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.

- ***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***[14]

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

[14] 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.

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 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.

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.

The comparability of the phytochemical composition of the HS/HP used in supporting bibliographic data and the HS/HP described in 3.2.S.1.2 should be discussed as 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 phytochemical characterisation consisting of chromatographic profiles (TLC, HPLC, GC) is important to define the herbal drug and herbal preparation, especially for the toxicological studies and clinical studies. This characterisation is sometimes made with additional chromatographic profiles (e.g. HPLC profiles in addition to TLC profile retained for routine testing).

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, aflatoxins, (and ochratoxin A for herbal drugs subject to contamination), microbial contamination as well as potential adulterants should be discussed. The risk of radioactive contamination is to be considered. Degradation products should be studied if relevant, e.g. potential degradants formed on storage or those that might arise as a result of decontamination treatments.

- ***Herbal preparation***

Potential contaminants originating from the herbal substance production and post-harvesting treatments such as pesticides and fumigants residues, toxic metals, aflatoxins (and ochratoxin A for herbal drugs subject to contamination), microbial contamination as well as potential adulterants should be discussed. The risk of radioactive contamination is to be considered. Possible impurities originating from the process or from degradation should be listed and discussed with an indication of their origin (e.g. potential degradants formed on storage or those that might arise as a result of decontamination treatments).

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. pyrrolizidine alkaloids, essential oils containing safrole), maximum limits should be defined.

- ***Herbal preparation***

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

For potentially toxic constituents and impurities of some herbal preparations (e.g. pyrrolizidine 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,*** the following should be provided as appropriate:

- *Where the European Pharmacopoeia applies, reference to the relevant monograph*
- *Where monographs other than those in the European Pharmacopoeia are referred to, a copy of the monograph*
- *In all cases, details of any additional tests*
- *Where an in-house specification is referred to, a detailed description of all 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). For aflatoxins determination (and ochratoxin A determination for herbal drugs subject to contamination), 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***, the results of analysis of at least one batch 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”.

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. In addition, at least certificates of food compatibility should be provided.

- ***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***

In cases where the herbal substance is the active pharmaceutical ingredient, 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, 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 summarised. 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 will have been demonstrated by the evidence of traditional use.

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. The comparability of 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.

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 disintegration and/or 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, 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 summarised. 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.P.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.*

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*, the Applicant 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 the Applicant 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. The Applicantare 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.	

Active substance guidelines

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

Medicinal product guidelines

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

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/214869/2006
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

Appendix 2 to guideline EMA/HMPC/71049/2007

Mock-up for the Module 3 Quality: Chemical, Pharmaceutical and Biological Information for Herbal Substances, Herbal Preparations and Traditional Herbal Medicinal Products

Scope of Appendix 2

This Appendix 2 to 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 mock-up of a Quality dossier (Module 3) for a Traditional Herbal Medicinal Product (THMP).

The purpose of the mock-up is to serve as an example for the Applicant of the format and is to be read in conjunction with the main text and Appendix 1 (best practice guide) of this Guideline EMA/HMPC/71049/2007 taking also into account all other relevant guidelines.

Disclaimer

The mock-up (S-part and P-part) has been created to serve as an example only. The product specific characteristics must be considered, so depending on the product appropriate information is necessary.

The example chosen concerns a typical THMP product, Valerian Film-coated Tablets, containing Valerian root dry aqueous extract. The product is in accordance with the traditional use section of the European Union herbal monograph on Valerian root (EMEA/HMPC/340719/2005).

The Valerian root dry aqueous extract is the subject of a Ph. Eur. monograph and is an "other extract'' as defined by Ph. Eur.

The mock-up does not exhaustively illustrate the complete details of module 3 for an individual application. Where additional data are included in the individual application but not presented in detail here it is indicated in a boxed text:

e.g.

Calculation formula for the quantities of excipients is provided here.

Valerian film-coated tablets
Valerian root dry aqueous extract

S-Part

3.2.S Drug substance

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

Herbal Substance

Scientific name of the plant: *Valeriana officinalis* L. *s.l.*

Ph. Eur. name: Valerian root (Ph. Eur. N° 0453)

Definition of herbal substance: Valerian root consists of the dried whole or fragmented underground parts of *Valeriana officinalis* L. *s.l.*, including the rhizome surrounded by the roots and stolons.

Synonyms: Baldrian, St. George´s herb, Valerian root, Racine de valériane, Radice di valeriana, Baldrianwurzel

Laboratory Code: 45678

Herbal Preparation

The herbal preparation is obtained from valerian root by extraction with water and consists of 80% valerian native extract and 20% of excipients. It corresponds to the Ph. Eur. monograph on **Valerian dry aqueous extract (07/2010: 2400)**

Extraction solvent: water

Ratio of herbal substance to native extract: 5 - 9 : 1 (DER native)

The herbal preparation contains 80% (m/m) of native extract.

Excipients: spray dried liquid glucose (15% m/m) and colloidal anhydrous silica (5% m/m).

The DER native is determined at the stage of the soft extract. The formulae applied for calculation is included in “3.2.S.2.2 - Herbal preparation”.

Laboratory code: 141414.

3.2.S.1.2 Structure

Herbal substance

The herbal substance Valerian root is reported to have the following constituents:

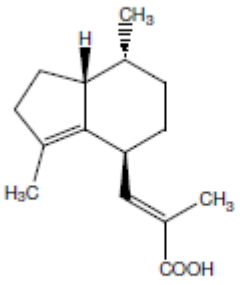
- Essential oil 0.5 - 1% (formic, acetic, butyric, isovalerianic acids, borneol bornyl acetate, bornyl isovalerianate, α-pinene, camphene, myrtenol, α-terpineol, β-ionone, caryophyllene)
- Sesquiterpenes (valerenic, acetoxyvalerenic, hydroxyvalerenic acids and valerenal)
- Iridoids including valepotriates (valtrate, acevaltrate, isovaltrate)
- Alkaloids approximately 0.1% (valerine, chatinine, α-methyl pyrrylketone identified as acetyl-1-pyrrol)
- Tannins
- Resins
- Mucilages
- Starch
- β-sitosterol
- Phenolic acids (e.g. chlorogenic and caffeic acids)
- Choline

Literature references are presented in module 3.3

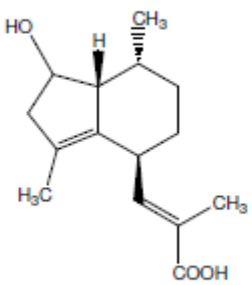
The characteristic constituents used as analytical markers in control tests are the sesquiterpenic acids: acetoxyvalerenic acid, hydroxyvalerenic acid and valerenic acid.

The herbal substance Valerian root (Ph. Eur.) contains not less than 0.17% of sesquiterpenic acids expressed as valerenic acid ($C_{15}H_{22}O_2$; M_r 234.3) (dried drug) and not less than 4 ml/kg of essential oil (dried drug).

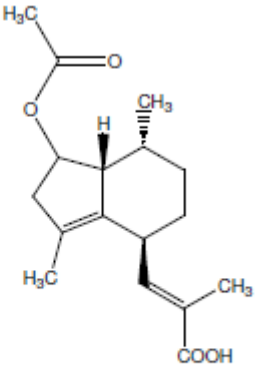
The chemical structures of the valerenic acids are given below:



Valerenic acid



Hydroxyvalerenic acid



Acetoxy-valerenic acid

Herbal preparation

Dry aqueous extract produced from Valerian root contains not less than 0.02% of sesquiterpenic acids expressed as valerenic acid ($C_{15}H_{22}O_2$; M_r 234.3) (dried extract), (Ph. Eur.).

Constituents with known therapeutic activity are not known; analytical markers are as described for the herbal substance.

3.2.S.1.3 General Properties

Herbal substance

Not applicable

Herbal preparation

Description: light brown powder.
Granulometry: granule size is min. 95% < 0.315 mm.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

3.2.S.2.1.1 Herbal substance

Supplier of the herbal substance:	Name of supplier Address
Laboratory for testing of the herbal substance:	Name of testing laboratory Address
Manufacturer/site where batch testing takes place:	Name of the manufacturer Address

3.2.S.2.1.2 Herbal preparation

Manufacturer of the herbal preparation:	**Name of supplier** Address
Laboratory for testing of the herbal preparation:	Name of testing laboratory Address
Manufacturer/site where batch testing takes place:	Name of the manufacturer Address

3.2.S.2.2 Description of Manufacturing Process and Process Controls

3.2.S.2.2.1 Herbal substance

The batch size of the herbal substance Valerian root is between 2,000 and 20,000 kg.

Origin:	The herbal substance Valerian root originates from Germany, Poland, The Netherlands, Bulgaria.
Cultivation/Collection:	Cultivation. Valerian is planted on sandy ground in spring time. Weed

Origin:	The herbal substance Valerian root originates from Germany, Poland, The Netherlands, Bulgaria. control is carried out by hoeing; if necessary herbicides are used.
Harvest:	In late autumn
Drying conditions and post-harvesting treatment:	Roots are washed with potable water and fragmented while moist, and dried at not more than 45 °C.

The dried herbal substance is stored protected from light, heat and humidity.

Packaging: Dry and clean air-permeable bags (for detailed information see 3.2.S.6).

The supplier observes the GACP rules, see the respective confirmation:

GACP CONFIRMATION

PRODUCT	ARTICLE NO.
Valerianae radix	151018

We hereby confirm that the above mentioned product is sourced according to the principles of the "Guideline on goods agricultural and collection practice (GACP) for starting materials of herbal origin" (EMEA, London, February 2006).

These guidelines are a defined part of our supplier contracts.

The following GACP-Documentation is provided from the herbal substance supplier (GACP-like questionnaire):

<table>
<tr><td colspan="2">Name of the herbal substance: Valerian root</td></tr>
<tr><td colspan="2">Code: 052014</td></tr>
<tr><td colspan="2">Name of Supplier/Exporter</td></tr>
<tr><td colspan="2">Country/Address</td></tr>
<tr><td colspan="2">Name of the herbal substance

- Commercial name: Valerian root
- Latin name: Valeriana officinalis L.</td></tr>
<tr><td colspan="2">Origin of herbal substance

- Country : Germany, Poland, The Netherlands, Bulgaria
- Area/Region: “...”-
- Cultivated: Yes~~/No~~
- Collected in wild habitats: ~~Yes/~~No</td></tr>
<tr><td>Cultivation

- Annual: +/Perennial: +
- Kind of soil: sandy
- Surroundings: agriculture
- Fertilisers: Yes/~~No~~: Mineral: +/Organic:+
- Plant gene manipulated: ~~Yes/~~No
- Others: ---</td><td>Collection from wild habitats

- Wild harvesting on private land:
- From one area (organised):
- From different areas and brought to a collecting point:
- Type of soil:
- Surroundings:
- Others:</td></tr>
</table>

Information on the harvesting

- Harvesting time/period: Spring: /Summer: /Autumn: + /Winter:
- Conditions: Manually: +/Mechanically:+
- Vegetative stage:
  . Before flowering: Yes/No
  . Flowering: Yes/No
  . After flowering: Yes/No
  . Grade of maturity of berries and seeds: ---
  . Complete ripe fruits: Yes/No
  . Others: ---

Treatment before and during harvesting

Herbicides: Yes/No/ Fungicides: Yes/No/ Insecticides: Yes/No

Note: Pesticides should be declared. The acceptance limits are in accordance with Ph. Eur. in its current edition (2.8.13.). Where pesticides are used that are not listed in the Ph. Eur., suitable control tests and limits should be applied. Limits should comply with the Directive 91/414/EEC.

Treatment of the herbal substance between harvesting and storage

- Washing with potable water after harvesting: Yes/None/Machine: +/By hand
- Cutting before drying: Yes/No
- Fumigation: Yes/No
- Freezing: Yes/No
- Drying: None/Natural: +/Artificial: +

Natural open air drying	Artificial drying
- On the field: Yes/No - On grids: Yes/No - Under the roof: Yes/No - In the shade: Yes/No - In the sun: Yes/No - Others: --- - Drying conditions: ---	- Drying conditions: - Source of energy: . Gas: ~~Yes~~/No . Electrical: Yes/~~No~~ . With oil: ~~Yes~~/No . Others: --- - Drying temperature: at < 45 °C

Storage

- In bulk: Yes/~~No~~
- With packaging: Yes/~~No~~
- Kind of packaging: plastic bags
- Under the roof: ~~Yes~~/No
- Dry warehouse: Yes: cool, dry, protected from insects, in the dark/~~No~~

State of the material after drying or during storage

- Visible moulds: ~~Yes~~/No
- Other foreign matters: ~~Yes~~/No
- Sand and stones: ~~Yes~~/No
- Foreign plant parts: ~~Yes~~/No
- Non product-specific plant parts: ~~Yes~~/No
- Insects: ~~Yes~~/No

Transport/loading

Kind of transport: Truck: +/Railway: /Boat: /Air:

Treatment before or during the transportation and storage? Fumigation: ~~Yes~~/No/ Irradiation: Y~~es~~/No/ CO_2 pressure treatment (Maba-PEX): ~~Yes~~/No
The supplier assures deliveries with the same quality? Yes/No
Others:

The herbal substance supplier confirms that the drug has not been fumigated or irradiated. Supplier's confirmation given here.

3.2.S.2.2.2 Herbal preparation

Batch size of the herbal preparation: 350 kg (300 – 400 kg).

For a production-scale batch of 350 kg Valerian root dry extract (280 kg native extract), 2110 kg Valerian root and 13500 l of water are used.

2110 kg of starting material Valerian root is milled (not less than 85% of the drug particles are ≤ 6 mm). The milled material is submitted to exhaustive percolation with approx. 13500 l of water at a temperature of 65 – 75 °C for at least 16 hours.

After removal of the solid parts of the plant material by pressing out, the miscella is concentrated under vacuum (temperature ≤ 75 ^{0}C, under reduced pressure of 100 – 120 mbar) to obtain a soft extract corresponding to 65 – 85% of dry residue. The soft extract is mixed homogeneously with the calculated quantities of the excipients and dried at a temperature of max. 45 – 60 °C in a spray dryer, spray belt dryer or vacuum belt dryer until the loss on drying is below 6% (m/m).

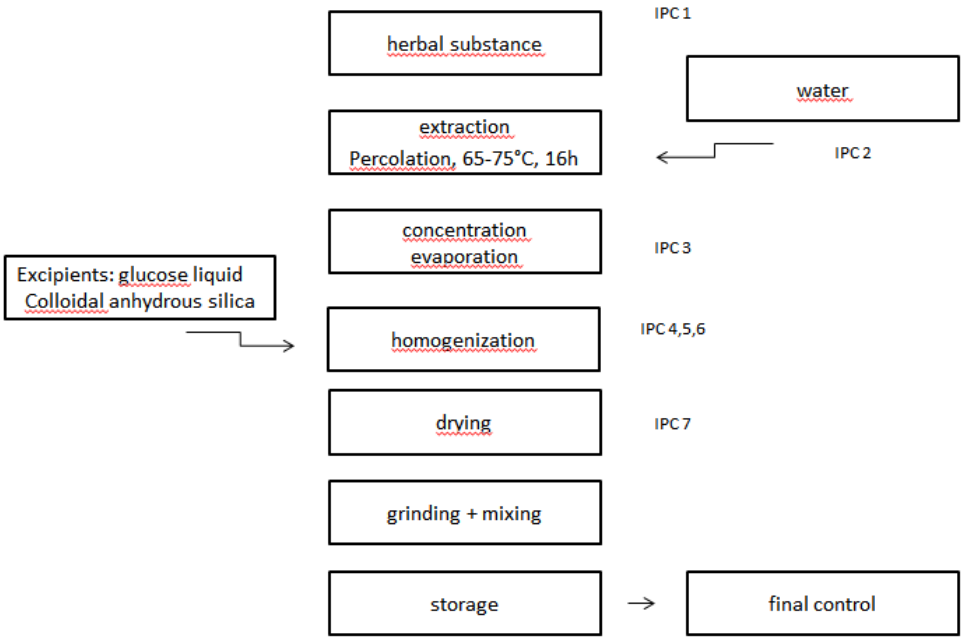
To enhance the galenic characteristics of the dry extract, the excipients liquid glucose and colloidal anhydrous silica are added during the drying process. The quantities are calculated on the basis of the dry residue of the soft extract in order to achieve a content of 80% (m/m) of valerian root dry extract, 15% (m/m) of liquid glucose and 5% (m/m) of colloidal anhydrous silica in the herbal preparation.

Calculation formula for the quantities of excipients is provided here.

In process controls and acceptance criteria

Manufacturing stage	Test parameter (method)	Acceptance criteria
Grinding of herbal substance (IPC 1)	Size of the comminuted herbal substance (sieve analysis)	≥ 85% ≤ 6 mm
Extraction (IPC 2)	Temperature, time	≥ 65 °C, 16 h
Concentration (IPC 3)	Absence of herbal substance (visual examination)	Absent
Homogenisation (IPC 4)	Homogeneity (visual examination)	Homogeneous
Homogenisation (IPC 5)	Dry residue of the soft extract (Ph. Eur. 2.8.16)	65 – 85%
Homogenisation (IPC 6)	Yield of dry substance (arithmetically)	Determine value
Drying (IPC 7)	Loss on drying (Ph. Eur. 2.8.17)	≤ 6% (m/m)

Flow chart of the manufacturing process of the herbal preparation



The finished dry extract preparation is stored in a well-closed container, protected from light, heat and moisture (see 3.2.S.6).

3.2.S.2.3 Control of Materials

Materials used in the manufacturing of the herbal preparation Valerian root dry extract:

Herbal substance:	Ph. Eur., see 3.2.S.4.1
Water	Internal specification according to Ph. Eur. "Water for preparation of extracts" (2249)
Liquid glucose, spray dried	Ph. Eur. (1525)
Colloidal anhydrous silica	Ph. Eur. (0434)

Specification of "Water for extraction"

The water used for extraction is drinking water and corresponds to the Ph. Eur. monograph "Water for preparation of extracts - Aqua ad extractas praeparandas", as well as to "Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption". The specification and results for one batch are presented below:

Conformity to the Ph.Eur Monograph "Water for preparation of extracts" is provided.

3.2.S.2.4 Controls of Critical Steps and Intermediates

The manufacturing process of the herbal preparation Valerian root dry extract is a standard process. The critical parameter in this manufacturing process is the temperature during the extraction and concentration steps.

3.2.S.2.5 Process Validation and/or Evaluation

The manufacturing process of the herbal preparation is a standard process.

3.2.S.2.6 Manufacturing Process Development

Overview

Preparations of Valerian root have a long tradition of use in herbal medicines. The European Pharmacopoeia includes a monograph for Valerian root and for Valerian root dry aqueous extract.

Herbal substance characteristics

Valerian root (*Valeriana officinalis* L.) is characterised by the sesquiterpenic constituents, in particular valerenic and acetoxyvalerenic acids. The specification for the herbal substance is based on the Ph. Eur. monograph "Valerian root" (0453). To ensure acceptable quality of the herbal substance, the sesquiterpenic acids content should be ≥ 0.17% expressed as valerenic acid and ≥ 4 ml/kg of essential oil (dried drug).

Justification for the range of temperature is given here.

Herbal preparation

The extraction methodology was developed in accordance with the Ph. Eur. monograph "Extracts" (0765).

Cut herbal material was extracted using water, which is covered by the Ph. Eur. monograph “Valerian dry aqueous extract” (2400). Temperature and duration for extraction process at 65 – 75 °C over at least 16 hours lead to satisfactory contents of valerenic acids. Temperature to evaporate the extraction solvent should not exceed 75 °C; a pressure of 100 – 120 mbar was found to be appropriate.

Different quantities of liquid glucose (spray dried) and colloidal anhydrous silica, commonly used carriers, were added and the extract properties were investigated. A content of 15% of spray-dried liquid glucose and 5% of colloidal anhydrous silica in the spraying solution significantly improved the texture of the spraying solution and the powdered extract properties.

3.2.S.3 Characterisation

3.2.S.3.1 Elucidation of Structure and other Characteristics

Herbal substance

The herbal substance used as a starting material for the manufacturing of the herbal preparation Valerian root dry extract complies with the Ph. Eur. monograph “Valerian root” (0453).

The botanical source of the herbal substance Valerian root is *Valeriana officinalis* L. It belongs to the family of the *Valerianaceae*.

The plants are 50 to 100 cm high and have a short, cylindrical rhizome with finger length, bushy round roots. The stem is erect, unbranched. The leaves are odd pinnate with 11 to 23 lanceolate, indented dentate leaflets. The lower ones are petiolate and the upper ones sessile and clasping with a white sheath. The androgynous bright, pink to white flowers, are in panicled cymes.

Characteristics: The flowers are fragrant and the rhizome smells very strongly when dried. *Valeriana officinalis* L. is indigenous to Europe and the temperate regions of Asia. The plant is cultivated mainly in Europe, Japan and the USA.

The rhizome is yellowish-grey or pale brownish-grey, obconical to cylindrical, up to about 50 mm long and 30 mm in diameter; the base is elongated or compressed, usually entirely covered by numerous roots. The apex usually exhibits a cup-shaped scar from the aerial parts; stem bases are rarely present. When cut longitudinally, the pith exhibits a central cavity transverse by septa. The roots are numerous, almost cylindrical, of the same colour as the rhizome, 1-3 mm in diameter and sometimes more than 100 mm long. A few filiform fragile secondary roots are present. The fracture is short. The stolons show prominent nodes separated by longitudinally striated internodes, each 20-50 mm long, with a fibrous fracture.

For the chromatographic profiles (TLC and HPLC) of the sesquiterpenic acids: see 3.2.S.4.4.1.

Herbal preparation

The herbal preparation is a light brown, slightly flowable powder and has a characteristic odour; its granule size is min. 95% < 0.315 mm. It contains 80% (m/m) of valerian root dry (native) extract, 15% of spray-dried liquid glucose and 5% of colloidal anhydrous silica. The dry extract partly dissolves in water, ethanol 90% and in ethanol 70%.

The characteristic constituents are sesquiterpenic acids, mainly valerenic, acetoxyvalerenic and hydroxyvalerenic acids.

For the chromatographic profiles (TLC and HPLC) of the sesquiterpenic acids: see 3.2.S.4.2.2 and 3.2.S.4.4.2.

3.2.S.3.2 Impurities

Purity tests on the herbal substance are described in 3.2.S.4.2.1. The scope of purity tests complies with the standards set in Ph. Eur. monograph “Valerian root“ (foreign matter, total ash, ash insoluble in hydrochloric acid). In addition the following tests are applied: pesticide residues, heavy metals, microbiological quality and aflatoxins in accordance with the general monograph “Herbal drugs”.

Purity tests on the herbal preparation are described in 3.2.S.4.2.2. The scope of purity tests complies with the standards set in Ph. Eur. monograph “Valerian dry aqueous extract”.

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification

3.2.S.4.1.1 Herbal substance

The herbal substance Valerian root is tested in accordance with the Ph. Eur. monographs “Valerian root” (0453) and “Herbal drugs”(1433).

Specification

Valerian root specification	**Valid from: 11.11.2014**	**Version number xxx**
Parameters	**Acceptance criteria**	**Test procedures**
Macroscopic, microscopic examinations	Ph. Eur. monograph "Valerian root"	Visual 3.2.S.4.2.1
Identity	According to current Ph. Eur. monograph	Ph. Eur. 2.2.27

	"Valerian root"	
Foreign matter	According to current Ph. Eur. monograph "Valerian root"	Ph. Eur. 2.8.2 3.2.S.4.2.2
Loss on drying	According to current Ph. Eur. monograph "Valerian root"	Ph. Eur. 2.2.32
Total ash	According to current Ph. Eur. monograph "Valerian root"	Ph. Eur. 2.4.16
Ash insoluble in hydrochloric acid	According to current Ph. Eur. monograph "Valerian root"	Ph. Eur. 2.8.1
Assay (essential oil)	According to current Ph. Eur. monograph "Valerian root"	Ph. Eur. 2.8.12
Assay (sesquiterpenic acids, expressed as valerenic acid)	According to current Ph. Eur. monograph "Valerian root"	Ph. Eur. 2.2.29
Test for pesticide residues *	Ph. Eur. 2.8.13	EN 12393/12396-3 3.2.S.4.2.1
Test for heavy metals *	lead: ≤ 5.0 ppm cadmium: ≤ 1.0 ppm mercury: ≤ 0.1 ppm	Ph. Eur. 2.4.27 3.2.S.4.2.1
Microbiological quality	maximum acceptable count in accordance with Ph. Eur. 5.1.8 A TAMC: ≤ 5 x 10^7 TYMC: ≤ 5 x 10^5 *E. coli*: ≤ 10^3 *Salmonella*: absence (in 25 g)	Ph. Eur. 2.6.31/ Ph. Eur. 2.6.12
Test for aflatoxins	Aflatoxin B1: ≤ 2 µg/kg Aflatoxins B1, B2, G1, G2:≤ 4 µg/kg	Ph. Eur. 2.8.18 3.2.S.4.2.1

*tested once a year, refer to 3.2.S.4.5.1

3.2.S.4.1.2 Herbal preparation

The herbal preparation Valerian root dry extract is tested in accordance with the Ph. Eur. monograph "Valerian dry aqueous extract" (2400) and the Ph. Eur. monograph "Extracts, dry extracts" (0765). In addition microbiological quality is tested.

Specification

Valerian root-dry-extract specification	**Valid from: 12.12.2010**	**Version number aaa**
Parameters	**Acceptance criteria**	**Test procedures**
Organoleptic test	brown, hygroscopic powder, with characteristic valerian smell	Visual, sensory
Particle size	min. 95% ≤ 0.315 mm	3.2.S.4.2.2
Loss on drying	≤ 6%	Ph. Eur. 2.8.17
Identity test	TLC complies with the description according to Ph. Eur. monograph "Valerian dry aqueous extract"	Ph. Eur. 2.2.27
Assay (sesquiterpenic acids, expressed as valerenic acid)	≥ 0.02%* of sesquiterpenic acids (dried extract) HPLC	Ph. Eur. 2.2.29
Microbiological quality	maximum acceptable count in accordance	Ph. Eur. 2.6.31/

Valerian root-dry-extract specification	Valid from: 12.12.2010	Version number aaa
	with Ph. Eur. 5.1.8 B TAMC ≤ 5 x 10^4 TYMC ≤5 x 10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella:* absence (in 25 g) *E. coli:* absence (in 1 g)	Ph. Eur. 2.6.12

*specification is in the validated range

Specification for stability testing (to define the retest-period)

Valerian root-dry-extract retest-specification	Valid from: 12.12.2010	Version number aaa
Parameters	**Acceptance criteria**	**Test procedures**
Organoleptic test	brown, hygroscopic powder , with characteristic valerian smell	sensory
Loss on drying	≤ 6%	Ph. Eur. 2.8.17
Fingerprint test	TLC is comparable to the initial fingerprint	Ph. Eur. 2.2.27
Assay (sesquiterpenic acids, expressed as valerenic acid)	90 – 110%* of the initial value (dried extract) HPLC	Ph. Eur. 2.2.29
Microbiological quality **	maximum acceptable count in accordance with Ph. Eur. 5.1.8 B TAMC ≤ 5 x 10^4 TYMC ≤5 x 10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella:* absence (in 25 g) *E. coli:* absence (in 1 g)	Ph. Eur. 2.6.31/ Ph. Eur. 2.6.31

*refer to 3.2.S.4.5.2 **not tested within every testing point

3.2.S.4.2 Analytical Procedures

3.2.S.4.2.1 Herbal substance

The analytical methods used for the identity and purity testing of the herbal substance Valerian root are in accordance with the Ph. Eur. monographs “Valerian root” (0453) and “Herbal drugs” (1433).

For testing of pesticides, aflatoxins and heavy metals the following methods are used:

Test for pesticide residues	Ph. Eur. 2.8.13; method DIN EN 12393-1 - 12393-3: Multiresidue methods for the gas chromatographic determination of pesticide residues
Test for dithiocarbamates	Ph. Eur. 2.8.13, method DIN EN 12396-3: Determination of dithiocarbamate and thiuram disulfide residues
Test for heavy metals	Internal procedure: AAS according to Ph. Eur. 2.4.27 Atomic absorption spectrometer model F451 with electrothermal graphite tube furnace for measuring Cadmium and Lead and another atomic

absorption spectrometer model F9/11 with cold-vapour atomiser for measuring Mercury. Specific hollow cathode lamps are used as light source in connection with a monochromatic detector. Operating is strictly performed according manufactures manual.

Description of the procedure (described in detail by the Applicant).

Test for aflatoxins

Internal HPLC procedure according to Ph. Eur. 2.8.18.
High pressure liquid chromatograph HPLC model JB007 with fluorescence detection and post-column iodine derivatisation with a KOBRA®-cell.

Column: RP-18, 250 mm length, 4 mm internal diameter, particle size: 5 nm, 40°C

Mobile phase: acetonitrile, methanol, water (2:3:6 V/V/V) + 120 mg KBr/l + 350 µl HNO3/l

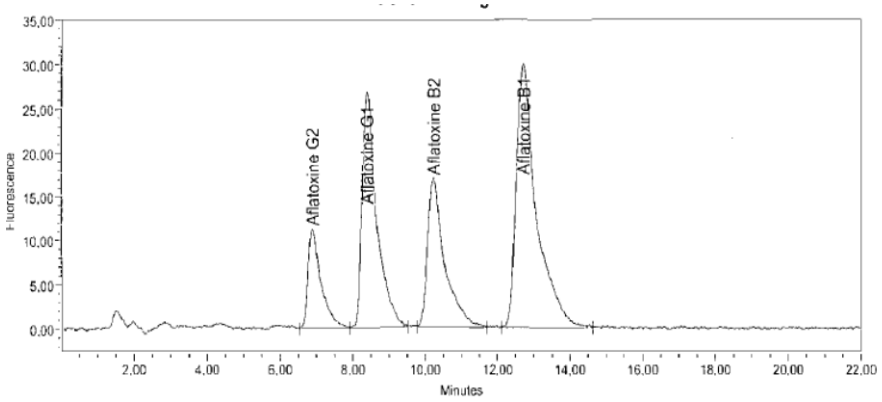
Injection: 250 µl

Flow rate: 1.0 ml/min

Detection: Excitation: 363 nm, Emission: 465 nm

Description of the procedure (described in detail by the Applicant).

Typical chromatogram for aflatoxins



Microbiological quality

Ph. Eur. 5.1.8, method Ph. Eur. 2.6.31/Ph. Eur. 2.6.12

3.2.S.4.2.2 Herbal preparation

The analytical methods used for the identity and purity tests on the herbal preparation Valerian root dry extract are in accordance with the Ph. Eur. monograph “Valerian dry aqueous extract” (2400) and “Extracts, Dry extracts” (0765)

Organoleptic tests	brown, hygroscopic powder;
Particle size	particle size is at least 95% ⩽ 0.315 mm 10 g extract is weighed exactly on the sieve with 0.315 mm mesh and sieved by hand; the result is the quantity of the extract that remains on the sieve in per cent
Identity test (TLC)	carried out in accordance to the Ph. Eur. monograph “Valerian dry aqueous extract”
Assay (HPLC)	carried out in accordance to method described for the assay in the Ph. Eur. monograph “Valerian dry aqueous extract”
Loss on drying	carried out according to Ph. Eur. 2.8.17: max. 6.0%

3.2.S.4.3 Validation of Analytical Procedures

3.2.S.4.3.1 Herbal substance

Validation of TLC identity test and assay

The TLC identity test and the assay are carried out following the TLC method (identity) and the HPLC (assay) of the Ph. Eur. Monograph "Valerian root", respectively.

Further validation of the TLC and HPLC method are therefore not necessary.

Validation of microbiological quality

Tests are carried out with Ph. Eur. methods 2.6.31 and 2.6.12. Therefore no additional data are required.

Validation of pesticide residues determination

The test is carried out according to DIN EN 12393-1 to 12393-3: Non-fatty foods -"Multiresidue methods for the gas chromatographic determination of pesticide residues", (DIN EN 12393-1 General considerations; DIN EN 12393-2 Methods for extraction and clean-up; EN 12393-3 Determination and confirmatory tests).

The analytical methods used are official methods of the collection of the German Food-Legislation (§ 64 LFGB method L 00.00-34). They were validated on different herbal matrices (to be specified by the Applicant) according to the indication given in Ph. Eur. 2.8.13.

Therefore no additional data are required.

Validation of dithiocarbamate determination

The test is carried out according to DIN EN 12396-3: Non-fatty foods - "Determination of dithiocarbamate and thiuram disulfide residues".

The analytical method used is an official method (§ 64 LFGB method L 00.00 49/3). It was validated on different herbal matrices (specified by the Applicant) according to the indication given in Ph. Eur. 2.8.13.
Therefore no additional data are required.

Validation of heavy metals determination (internal method)

Cadmium

Atomic absorption spectroscopy (cold-vapour atomiser)

Limit of detection	0.001 ppm
Limit of quantification	0.003 ppm
Linearity (correlation coefficient)	0.9996
Accuracy by recovery (n = 9)	115%
Intermediate precision (stand. deviation)	0.006 mg/kg
(rel. stand. dev.)	5.0%
Specificity	Depending on specific hollow cathodes (253.7 nm)
Robustness (solutions)	Analytical solutions are stable for at least 1 year

Lead

Atomic absorption spectroscopy (cold-vapour atomiser)

Limit of detection	0.03 ppm
Limit of quantification	0.10 ppm
Linearity (correlation coefficient)	0.9964
Accuracy by recovery (n = 9)	107%
Intermediate precision (stand. deviation)	0.06 mg/kg
(rel. stand. dev.)	1.7%
Specificity	Depending on specific hollow cathodes (253.7 nm)
Robustness (solutions)	Analytical solutions are stable for at least 1 year

Mercury

Atomic absorption spectroscopy (cold-vapour atomiser)

Limit of detection	0.01 ppm
Limit of quantification	0.04 ppm
Linearity (correlations coefficient)	0.997
Accuracy by recovery (n = 9)	119%
Intermediate precision (standard deviation)	0.0055 mg/kg
(rel. stand. dev.)	4.7%
Specificity	Depending on specific hollow cathodes (253.7 nm)
Robustness (solutions)	Analytical solutions are stable for at least 1 year

Validation of aflatoxins determination (internal method)

Aflatoxin B1

HPLC/Kobra-cell/Fluorescence detection

Limit of detection	0.0356 ppb
Limit of quantifiaction	0.1186 ppb
Linearity (correlation coefficient)	0.998
Accuracy by recovery (n = 9)	100.3 %
Intermediate precision (rel. stand. deviation)	2.15 %
Selectivity	Spiking with standard solution
Robustness (solutions)	Analytical solutions are stable for 24 hours
(method)	Slight variations in temperature, flow rate and wavelengths show no significant influence

Aflatoxin B2

HPLC/Kobra-cell/Fluorescence detection

Limit of detection	0.0171 ppb
Limit of quantification	0.0569 ppb
Linearity (correlation coefficient)	1.000
Accuracy by recovery (n = 9)	93.96%
Intermediate Precision (rel. stand. deviation)	1.20%
Selectivity	Spiking with standard solution
Robustness (solutions)	Analytical solutions are stable for 24 hours
(method)	Slight variations in temperature, flow rate and wavelengths show no significant influence

Aflatoxin G1

HPLC/Kobra-cell/Fluorescencedetection

Limit of detection	0.0381 ppb
Limit of quantification	0.1270 ppb
Linearity (correlation coefficient)	1.000
Accuracy by recovery (n = 9)	100.06%
Intermediate Precision (rel. stand. deviation)	0.96%
Selectivity	Spiking with standard solution
Robustness (solutions)	Analytical solutions are stable for 24 hours
(method)	Slight variations in temperature, flow rate and wavelengths show no significant influence

Aflatoxin G2

HPLC/Kobra-cell/Fluorescencedetection

Limit of detection	0.0042 ppb
Limit of quantification	0.0839 ppb
Linearity (correlation coefficient)	0.998
Accuracy by recovery (n = 9)	82.33%
Intermediate Precision (rel. stand. deviation)	2.25%
Selectivity	Spiking with standard solution
Robustness (solutions)	Analytical solutions are stable for 24 hours
(method)	Slight variations in temperature, flow rate and wavelengths show no significant influence

Validation data are provided including information on and justification of the herbal matrix used for validation of the method.

3.2.S.4.3.2 Herbal preparation

The TLC identity test and the assay are carried out following the TLC method (identity) resp. the HPLC (assay) of the Ph. Eur. Monograph "Valerian dry aqueous extract". Further validation of the TLC and HPLC method is therefore not necessary.

3.2.S.4.4 Batch Analyses

Batch analyses of two batches of the herbal substance and two batches of the herbal preparation are provided. TLC and HPLC chromatograms are included. All results conform to the respective release specification.

3.2.S.4.4.1 Herbal substance

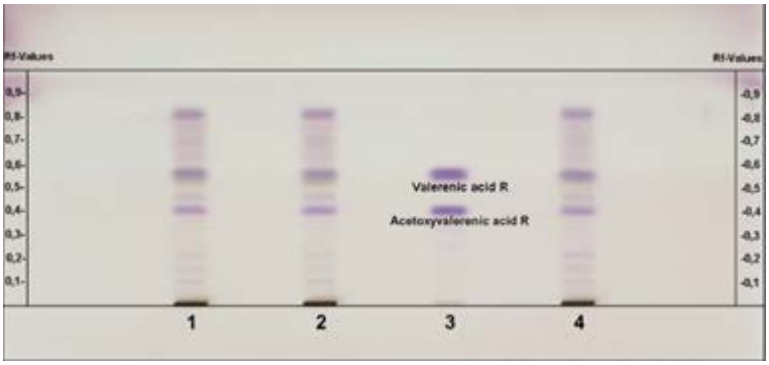
Batch No: 11223344, Batch size: 18192 kg

Parameters	Acceptance criteria	Results
Macroscopic, microscopic examinations	Ph. Eur. monograph "Valerian root"	complies
Identity TLC	Ph. Eur. monograph" Valerian root"	complies (see addendum)
Foreign matter	maximum 5% of stem bases and maximum 2% of other foreign matter	2.5 ≤ 2
Loss on drying	≤ 12.0%	7.9
Total ash	≤ 12.0%	10.1

Batch No: 11223344, Batch size: 18192 kg

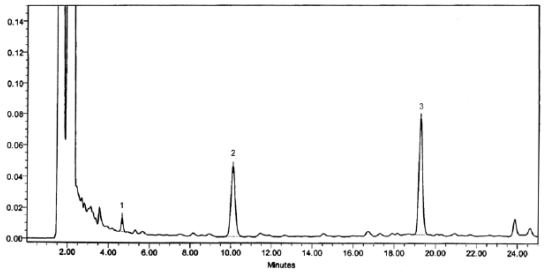
Ash insoluble in hydrochloric acid	≤ 5.0%	4.9
Assay (essential oil)	Ph. Eur. monograph "Valerian root" ≥ 4 ml/kg (dried drug)	4.6
Assay (sesquiterpenic acids, expressed as valerenic acid)	Ph. Eur. Monograph "Valerian root" ≥ 0.17% (dried drug)	0.19
Test for pesticide residues	Ph. Eur. 2.8.13	complies (see addendum)
Test for heavy metals	lead: ≤ 5 ppm cadmium: ≤ 1.0 ppm mercury: ≤ 0.1 ppm	1.5 0.3 0.01
Microbiological quality	complies with Ph. Eur. 5.1.8 A TAMC: ≤ 10^7 TYMC: ≤ 10^5 *E. coli*: ≤ 10^3 *Salmonella*: absence (25 g)	 900000 40000 < 10 absent
Test for aflatoxins	Aflatoxin B1: ≤ 2 µg/kg Aflatoxin B1, B2, G1, G2: ≤ 4 µg/kg	< 0.5 < 1.0

TLC chromatogram for the parameter identity



1 = Batch No: 11223344
3 = Acetoxyvalerenic and valerenic acids
4 = Valerian root

HPLC chromatogram for the parameter assay



1. hydroxyvalerenic acid 2. acetoxyvalerenic acid 3. valerenic acid

TLC/HPLC chromatograms including peak areas and retention times should be presented.

Pesticide residues of batch 11223344

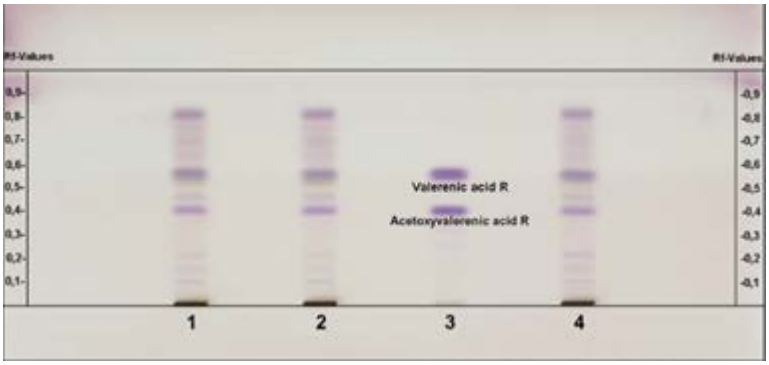
Substance	Limit (mg/kg)	Value
Acephate	0.1	n.d.
Alachlor	0.05	n.d.
Aldrin and Dieldrin (sum of)	0.05	n.d.
Azinphos-ethyl	0.1	n.d.
Azinphos-methyl	1	n.d.
Bromophos-ethyl	0.05	n.d.
Bromophos-methyl	0.05	n.d.
Brompropylate	3	n.d.
Chlordane, sum	0.05	n.d.
Chlorfenvinphos	0.5	n.d.
Chlorpyrifos (ethyl)	0.2	n.d.
Chlorpyrifos-methyl	0.1	n.d.
Chlorthal-dimethyl	0.01	n.d.
Cyfluthrin, sum	0.1	n.d.
Cyhalothrin, lambda	1	n.d.
Cypermethrin and isomers	1	n.d.
DDT, sum	1	n.d.
Deltamethrin	0.5	n.d.
Diazinon	0.5	n.d.
Dichlofluanid	0.1	n.d.
Dichlorvos	1	n.d.
Dicofol	0.5	n.d.
Dimethoate and Omethoate (sum of)	0.1	n.d.
Dithiocarbamates (expressed as CS2)	2	n.d.
Endosulfan, sum	3	n.d.
Endrin	0.05	n.d.
Ethion	2	n.d.
Etrimfos	0.05	n.d.
Fenchlorphos, sum	0.1	n.d.
Fenitrothion	0.5	n.d.
Fenpropathrin	0.03	n.d.
Fensulfothion, sum	0.05	n.d.
Fenthion, sum	0.05	n.d.
Fenvalerate	1.5	n.d.
Flucytrinate	0.05	n.d.
Fluvalinate-tau	0.05	n.d.
Fonofos	0.05	n.d.
Heptachlor, sum	0.05	n.d.
Hexachlorbenzene	0.1	n.d.
HCH-isomers (others than gamma)	0.3	0.1
Lindan (gamma-Hexachlorhexane)	0.6	n.d.
Malathion and Malaoxon (sum of)	1	n.d.
Mecarbam	0.05	n.d.
Methacrifos	0.05	n.d.
Methamidophos	0.05	n.d.
Methidathion	0.2	n.d.

Substance	Limit (mg/kg)	Value
Methoxychlor	0.05	n.d.
Mirex	0.01	n.d.
Monocrotophos	0.1	n.d.
Parathion-ethyl and Paraoxonethyl (sum of)	0.5	n.d.
Parathion-methyl and Paraoxon-methyl (sum of)	0.2	n.d.
Pendimethalin	0.1	n.d.
Pentachloranisol	0.01	n.d.
Permethrin (and isomers)	1	n.d.
Phosalone	0.1	n.d.
Phosmet	0.05	n.d.
Piperony butoxide	3	n.d.
Pirimiphos-ethyl	0.05	n.d.
Pirimiphos-methyl	4	n.d.
Procymidone	0.1	n.d.
Profenofos	0.1	n.d.
Prothiofos	0.05	n.d.
Pyrethrum, sum	3	n.d.
Quinalphos	0.05	n.d.
Quintozene, sum	1	n.d.
S-421	0.02	n.d.
Tecnazene	0.05	n.d.
Tetradifon	0.3	n.d.
Vinclozolin	0.4	n.d.

Batch No: 55667788, Batch size: 11500 kg

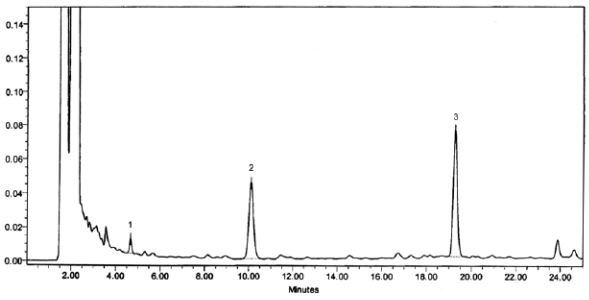
Parameters	**Acceptance criteria**	**Results**
Macroscopic, microscopic examinations	Ph. Eur. monograph "Valerian root"	complies
Identity TLC	Ph. Eur. monograph "Valerian root"	complies (see addendum)
Foreign matter	maximum 5% of stem bases and maximum 2% of other foreign matter	2.1 ≤ 2
Loss on drying	≤ 12.0%	6.7
Total ash	≤ 12.0%	9.1
Ash insoluble in hydrochloric acid	≤ 5.0%	4.7
Assay (essential oil)	Ph. Eur. monograph "Valerian root" ≥ 4 ml/kg (dried drug)	7.2
Assay (sesquiterpenic acids, expressed as valerenic acid)	Ph. Eur. monograph "Valerian root" ≥ 0.17% (dried drug)	0.34
Test for pesticide residues	Ph. Eur. 2.8.13	complies (see addendum)
Test for heavy metals	lead: ≤ 5 ppm cadmium: ≤ 1.0 ppm mercury: ≤ 0.1 ppm	1.7 0.16 0.01
Microbiological quality	complies with Ph. Eur. 5.1.8 A TAMC: ≤ 10^7 TYMC: ≤ 10^5 *E. coli*: ≤ 10^2 *Salmonella*: absence (25 g)	 100000 30000 < 100 absent
Test for aflatoxins	Aflatoxin B1: ≤ 2 µg kg Aflatoxin B1, B2, G1, G2: ≤ 4 µg/kg	< 0.5 < 1.0

TLC chromatogram for the parameter identity



2 = Batch No: 55667788
3 = Acetoxyvalerenic- and valerenic acids
4 = Valerian root

HPLC chromatogram for the parameter assay



1. hydroxyvalerenic acid 2. acetoxyvalerenic acid 3. valerenic acid

TLC/HPLC chromatograms including peak areas and retention times should be presented.

Pesticide residues of batch 55667788

Substance	**Limit (mg/kg)**	**Value**
Acephate	0.1	n.d.
Alachlor	0.05	n.d.
Aldrin and Dieldrin (sum of)	0.05	n.d.
Azinphos-ethyl	0.1	n.d.
Azinphos-methyl	1	n.d.
Bromophos-ethyl	0.05	n.d.
Bromophos-methyl	0.05	n.d.
Brompropylate	3	n.d.
Chlordane, sum	0.05	n.d.
Chlorfenvinphos	0.5	n.d.
Chlorpyrifos (ethyl)	0.2	n.d.
Chlorpyrifos-methyl	0.1	n.d.
Chlorthal-dimethyl	0.01	n.d.
Cyfluthrin, sum	0.1	n.d.
Cyhalothrin, lambda	1	n.d.
Cypermethrin and isomers	1	n.d.
DDT, sum	1	n.d.
Deltamethrin	0.5	n.d.
Diazinon	0.5	n.d.
Dichlofluanid	0.1	n.d.
Dichlorvos	1	0.2
Dicofol	0.5	n.d.
Dimethoate and Omethoate (sum of)	0.1	n.d.
Dithiocarbamates (expressed as CS2	2	n.d.
Endosulfan, sum	3	n.d.
Endrin	0.05	n.d.
Ethion	2	n.d.
Etrimfos	0.05	n.d.
Fenchlorphos, sum	0.1	n.d.

Substance	Limit (mg/kg)	Value
Fenitrothion	0.5	n.d.
Fenpropathrin	0.03	n.d.
Fensulfothion, sum	0.05	n.d.
Fenthion, sum	0.05	n.d.
Fenvalerate	1.5	n.d.
Flucytrinate	0.05	n.d.
Fluvalinate-tau	0.05	n.d.
Fonofos	0.05	n.d.
Heptachlor, sum	0.05	n.d.
Hexachlorbenzene	0.1	n.d.
HCH-isomers (others than gamma)	0.3	n.d.
Lindan (gamma-Hexachlorhexane)	0.6	n.d.
Malathion and Malaoxon (sum of)	1	n.d.
Mecarbam	0.05	n.d.
Methacrifos	0.05	n.d.
Methamidophos	0.05	n.d.
Methidathion	0.2	n.d.
Methoxychlor	0.05	n.d.
Mirex	0.01	n.d.
Monocrotophos	0.1	n.d.
Parathion-ethyl and Paraoxonethyl (sum of)	0.5	n.d.
Parathion-methyl and Paraoxon-methyl (sum of)	0.2	n.d.
Pendimethalin	0.1	n.d.
Pentachloranisol	0.01	n.d.
Permethrin (and isomers)	1	n.d.
Phosalone	0.1	n.d.
Phosmet	0.05	n.d.
Piperony butoxide	3	n.d.
Pirimiphos-ethyl	0.05	n.d.
Pirimiphos-methyl	4	1.3
Procymidone	0.1	n.d.
Profenofos	0.1	n.d.
Prothiofos	0.05	n.d.
Pyrethrum, sum	3	n.d.
Quinalphos	0.05	n.d.
Quintozene, sum	1	n.d.
S-421	0.02	n.d.
Tecnazene	0.05	n.d.
Tetradifon	0.3	n.d.
Vinclozolin	0.4	n.d.

3.2.S.4.4.2 Herbal preparation

Batch-No: 211, Manufacture date 22.05.11, Release date 24.06.2011, Batch size 320 kg

Parameters	Acceptance criteria	Results
Organoleptic test	light-brown granulated powder	complies
Particle size	min. 95% < 0.315 mm	97.5%
Loss on drying	≤ 6.0%	3.9
Identity test (TLC)	TLC on valerenic acids according to Ph. Eur. monograph "Valerian dry aqueous extract"	complies (see addendum)
Assay (sesquiterpenic acids, expressed as valerenic acid)	≥ 0.02% (dried extract)	0.05
Microblological quality	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *E. coli*: absence (1 g) *Salmonella*: absence (25 g)	 < 10 < 10 < 1 absent absent

TLC chromatogram for the parameter identity

HPLC chromatogram for the parameter assay

TLC/HPLC chromatograms including peak areas and retention times should be presented

Batch-No: 212, Manufacture date 28.05.11, Release date 30.06.11, Batch size 297 kg

Parameters	Acceptance criteria	Results
Organoleptic test	light-brown granulated powder	complies
Particle size	min. 95% < 0.315 mm	99.9%
Loss on drying	≤ 6.0%	4.1
Identity test (TLC)	TLC on valerenic acids according to Ph. Eur. monograph "Valerian dry aqueous extract"	complies (see addendum)
Assay (sesquiterpenic acids, expressed as valerenic acid	≥ 0.02% (dried extract)	0.06
Microbiological quality	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *E. coli*: absence (1 g) *Salmonella*: absence (25 g))	 < 10 < 10 < 1 absent absent

TLC chromatogram for the parameter identity

HPLC chromatogram for the parameter assay

TLC/HPLC chromatograms including peak areas and retention times should be presented

3.2.S.4.5 Justification of Specification

3.2.S.4.5.1 Herbal substance

The identity tests, purity tests and the assay of Valerian root comply with Ph. Eur. monograph "Valerian root" (0453).

Tests for pesticide residues, heavy metals, aflatoxins and microbiological quality are carried out in accordance with Ph. Eur. monograph "Herbal drugs".

Pesticides are tested according DIN EN 12393 and dithiocarbamates according DIN EN 12396-3. Heavy metals and aflatoxins are tested using validated internal methods.

Microbiological quality is tested using Ph. Eur. methods; the specification from Ph. Eur. 5.1.8 A was applied analogously.

The tests for pesticide residues and heavy metals are carried out once a year.

The provided results on three batches plus an additional nine batches support the once a year test frequency for pesticide residues and heavy metals.

On the basis of literature data a test for ochratoxin A is not relevant for Valerian root.

Assurance is provided that the herbal substance is not fumigated, therefore tests on residues from fumigation agents such as phosphine are not specified.

Radioactivity is not tested, because the herbal substance originates from areas where this parameter is not relevant.

Data on further nine consecutive batches of herbal substance are provided here to justify the skip-testing for pesticides and heavy metals.

3.2.S.4.5.2 Herbal preparation

The identity tests, purity tests and the assay of Valerian root dry extract comply with Ph. Eur. monograph "Valerian dry aqueous extract". Acceptance limits for the assay are based on the experiences of the extract manufacturer in accordance with the validated range.

In addition, tests for microbiological quality are carried out in accordance with Ph. Eur. monograph "Extracts".

Historical experimental data are provided here to set the acceptance criteria.

The analytical methods are described sufficiently. Further validation is not necessary because only Ph.Eur. methods are used. According to Ph. Eur. the suitability of the method under the actual conditions of use has been demonstrated.

A consistent quality of the herbal preparation is ensured based on the manufacturing process and the the release specification that is set in accordance with the Ph. Eur. and the EU Guidelines CPMP/QWP/2819/00 Rev. 2 and CPMP/QWP/2820/00 Rev. 2.

In the retest specification, the acceptance criterion for assay is set to +/-10% from the initial value. The dry extract is a complex mixture of constituents which contains two excipients. Taking into account these facts and the low concentration of the analytical markers, the variability of the test results is increased. Therefore, it is not possible to set the specification to +/- 5% from the initial value. The stability data support the acceptance criterion.

3.2.S.5 Reference Standards or Materials

TLC markers

Acetoxyvalerenic acid and valerenic acid are used as reference standards for the identification test of the herbal substance and the herbal preparation in the release and stability testing.

In line with the Ph. Eur. monograph “Valerian root” and “Valerian dry aqueous extract” the Ph. Eur. substances Acetoxyvalerenic acid R and Valerenic acid R are used.

Valerian root dry extract HRS (EDQM)

The Valerian root dry extract HRS serves as reference standard within the assay of the extract within the release and the stability testing. The validity is ensured by the statement of the EDQM.

Valerian dry extract HRS Ph. Eur is used as reference standard for the assay of sesquiterpenic acids.

A reference sheet is added here by the Applicant.

3.2.S.6 Container Closure System

Herbal substance

The herbal substance is stored in flat bags of polyethylene low density (LDPE). The bag is suitable to come in contact with foodstuffs.

Herbal preparation

The herbal preparation is stored in polyethylene low density (LDPE) transparent flat bags with antistatic additives for use in food packing. The container is suitable to come in contact with foodstuffs and complies with Commission regulation (EU) No 1183/2012. It also complies with Ph. Eur (3.2.2). The bags are packed in polypropylene (PP) drums.

Detailed specifications are provided here of the packaging manufacturers and the in house specification of the extract manufacturer used for the testing on receipt

The manufacturer of the bags confirms their suitability. A corresponding certificate is provided.

Satisfactory certificates are provided here.

3.2.S.7 Stability

Herbal substance

The herbal substance complies with the specification immediately before use in the manufacturing of the herbal preparation. Therefore no stability studies are performed.

Herbal preparation

A stability study is performed based on three batches of the herbal preparation to evaluate stability and to define a retest period and storage conditions.

Microbiological quality is not tested at every test point; the parameter is tested at least at the initial and the last test point.

3.2.S.7.1 Stability Summary and Conclusion

The following three commercial-scale batches of the herbal preparation Valerian root dry extract were used for stability testing:

Batch no.	Batch size	Date of manufacturing	Date of T0	Manufacturer
211	320 kg	22/05/2011	21/08/2011	Extrakt
212	297 kg	28/05/2011	30/08/2011	Extrakt
213	360 kg	28/10/2012	30/12/2012	Extrakt

Storage conditions: 25 °C/60% RH, 40 °C/75% RH; protection from light (in electronically monitored storage cabinets)

Points of testing: Start - 3 – 6 – 9 – 12 – 18 – 24 months under long term storage conditions
Start - 3 – 6 months under accelareted storage conditions

Packaging: LDPE bags

The specification for stability testing (to define the retest-period) is presented in 3.2.S.4.1.2.
The specification comprises all stability indicating parameters.
The test procedures correspond with the procedures used for batch release.
Concerning the validation of the test procedures please refer to 3.2.S.4.2.2.

Stability studies of the herbal preparation have been carried out over a period of 12 months at 25 °C/60% RH and 6 months at 40 °C/75% RH with three batches (211, 212 and 213).

Results

Long term conditions

Loss on drying is increasing slightly but remains within the acceptance criterion.

The assay of the sesquiterpenic acids shows no specific trend within the acceptance criterion of +/- 10% of the initial value.

The TLC fingerprint chromatograms of the dry extract (batches 211, 212 and 213) comply with the initial chromatogram in terms of position, shape, colour and number of substance zones after storage for 12 months at 25 °C/60% RH.

The results of the long term testing are in accordance with the specification for stability testing (to define the retest-period).

Accelerated conditions

Accelerated testing gave outlying fingerprints and out of specification results for loss of drying at 3 months. Hence, the testing under accelerated storage conditions was discontinued.

According to Guideline CPMP/QWP/122/02 Rev. 1 corr a justification is provided not to perform intermediate studies.

A re-test period of 12 months is supported by the real-time testing when stored below 25°C.

3.2.S.7.2 Postapproval Stability Protocol and Stability commitment

No stability commitment is given as the stability studies are considered as completed

3.2.S.7.3 Stability Data

Batch 211 long term testing

Parameters	**Acceptance criteria**	**t_0**	**t_3**	**t_6**	**t_9**	**t_{12}**
Organoleptic test	brown, hygroscopic powder with valerian smell	complies	complies	complies	complies	complies
Loss on drying	≤ 6.0%	3.9	3.9	4.2	4.0	4.2
Fingerprint (TLC)	complies with the chromatogram at the start	complies	complies	complies	complies	complies
Assay calculated via sesquiterpenic acids (HPLC)	90 – 110% of the initial value	100.0%	98.6	101.1	95.7	93.9
Microbiological quality (CFU)	TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella*: absence (25g) *E. coli*: absence (1 g)	< 10 < 10 < 10 absent absent	n.t.	n.t.	n.t.	< 10 < 10 < 10 absent absent

n.t. = not tested

TLC/HPLC chromatograms including peak areas and retention times should be presented			
Product: Valerian root dry extract Batch: 211 Storage conditions: long-term 25 °C ± 2 °C, 60% RH ± 5% TLC – fingerprint	**0 months**	**3 months**	**6 months**

Product: Valerian root dry extract Batch: 211 Storage conditions: long-term 25 °C ± 2 °C, 60% RH ± 5% TLC – fingerprint	**9 months**	**12 months**

Product: Valerian root dry extract Batch: 211 Storage conditions: long-term 25 °C ± 2 °C, 60% RH ± 5% HPLC – fingerprint	**0 months**	**3 months**	**6 months**

Product: Valerian root dry extract Batch: 211 Storage conditions: long-term 25 °C ± 2 °C, 60% RH ± 5% HPLC – fingerprint	**9 months**	**12 months**

Batch 212 long term testing

Parameters	**Acceptance criteria**	t_0	t_3	t_6	t_9	t_{12}
Organoleptic test	brown, hygroscopic powder with valerian smell	complies	complies	complies	complies	complies
Loss on drying	≤ 6.0%	4.1	4.5	5.2	5.5	5.7
Fingerprint (TLC)	complies with the chromatogram at the start	complies	complies	complies	complies	complies
Assay calculated via sesquiterpenic acids	90 – 110 % of the initial value	100.0%	101.0	96.3	93.5	92.9
Microbiological quality (CFU)	TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella*: absence (25g) *E. coli*: absence (1 g)	< 10 < 10 <100 absent absent	n.t.	n.t.	n.t.	< 10 < 10 <100 absent absent

n.t. = not tested

TLC/HPLC chromatograms including peak areas and retention times should be presented			
Product: Valerian root dry extract Batch: 212 Storage conditions: long-term 25 °C ± 2 °C, 60% RH ± 5% TLC – fingerprint	**0 months**	**3 months**	**6 months**

Product: Valerian root dry extract Batch: 212 Storage conditions: long-term 25 °C ± 2 °C, 60% RH ± 5% TLC – fingerprint	**9 months**	**12 months**

Product: Valerian root dry extract Batch: 212 Storage conditions: long-term 25 °C ± 2 °C, 60% RH ± 5% HPLC – fingerprint	**0 months**	**3 months**	**6 months**

Product: Valerian root dry extract Batch: 212 Storage conditions: long-term 25 °C ± 2 °C, 60% RH ± 5% HPLC – fingerprint	**9 months**	**12 months**

Batch 213 long term testing

Parameters	**Acceptance criteria**	**t_0**	**t_3**	**t_6**	**t_9**	**t_{12}**
Organoleptic test	brown, hygroscopic powder with valerian smell	complies	complies	complies	complies	complies
Loss on drying	≤ 6.0%	5.1	5.1	4.9	5.0	5.2
Fingerprint (TLC)	complies with the chromatogram at the start	complies	complies	complies	complies	complies
Assay calculated via sesquiterpenic acids (HPLC)	90 – 110% of the initial value	100.0%	98.6	104.1	99.7	97.9
Microbiological quality (CFU)	TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella*: absence (25g) *E. coli*: absence (1 g)	< 10 < 10 < 10 absent absent	n.t.	n.t.	n.t.	< 10 < 10 < 10 absent absent

n.t. = not tested

TLC/HPLC chromatograms including peak areas and retention times should be presented			
Product: Valerian root dry extract Batch: 213 Storage conditions: long-term 25 °C ± 2 °C, 60% RH ± 5% TLC – fingerprint	**0 months**	**3 months**	**6 months**

Product: Valerian root dry extract Batch: 213 Storage conditions: long-term 25 °C ± 2 °C, 60% RH ± 5% TLC – fingerprint	**9 months**	**12 months**

Product: Valerian root dry extract Batch: 213 Storage conditions: long-term 25 °C ± 2 °C, 60% RH ± 5% HPLC – fingerprint	**0 months**	**3 months**	**6 months**

Product: Valerian root dry extract Batch: 213 Storage conditions: long-term 25 °C ± 2 °C, 60% RH ± 5% HPLC – fingerprint	**9 months**	**12 months**

Batch 211 accelerated testing

Parameters	**Acceptance criteria**	**t_0**	**t_3**
Organoleptic test	brown, hygroscopic powder with valerian smell	complies	complies
Loss on drying	≤ 6.0%	3.9	6.1
Fingerprint (TLC)	complies with the chromatogram at the start	complies	oos
Assay calculated via sesquiterpenic acids (HPLC)	90 – 110% of the initial value	100.0%	98.6
Microbiological quality (CFU)	TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria ≤ 10^2 *Salmonella*: absence (25 g) *E. coli*: absence (1 g)	< 10 < 10 < 10 absent absent	n.t.

n.t. = not tested

TLC/HPLC chromatograms including peak areas and retention times should be presented		
Product: Valerian root dry extract Batch: 211 Storage conditions: long-term 40 °C ± 2 °C, 75% RH ± 5% TLC – fingerprint	**0 months**	**3 months**

Product: Valerian root dry extract Batch: 211 Storage conditions: long-term 40 °C ± 2 °C, 75% RH ± 5% HPLC – fingerprint	**0 months**	**3 months**

Batch 212 accelerated testing

Parameters	**Acceptance criteria**	t_0	t_3
Organoleptic test	brown, hygroscopic powder with valerian smell	complies	complies
Loss on drying	≤ 6.0%	4.1	6.1
Fingerprint (TLC)	complies with the chromatogram at the start	complies	oos
Assay calculated via sesquiterpenic acids	90 – 110% of the initial value	100.0%	101.0
Microbiological quality (CFU)	TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria ≤ 10^2 *Salmonella*: absence (25 g) *E. coli*: absence (1 g)	< 10 < 10 <100 absent absent	n.t.

n.t. = not tested

TLC/HPLC chromatograms including peak areas and retention times should be presented

Product: Valerian root dry extract Batch: 212 Storage conditions: long-term 40 °C ± 2 °C, 75% RH ± 5% TLC – fingerprint	**0 months**	**3 months**

Product: Valerian root dry extract Batch: 212 Storage conditions: long-term 40 °C ± 2 °C, 75% RH ± 5% HPLC – fingerprint	**0 months**	**3 months**

Batch 213 accelerated testing

Parameters	**Acceptance criteria**	**t_0**	**t_3**
Organoleptic test	brown, hygroscopic powder with valerian smell	complies	complies
Loss on drying	≤ 6.0%	5.1	6.1
Fingerprint (TLC)	complies with the chromatogram at the start	complies	oos
Assay calculated via sesquiterpenic acids (HPLC)	90 – 110% of the initial value	100.0%	98.6
Microbiological quality (CFU)	TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria ≤ 10^2 *Salmonella*: absence (25 g) *E. coli*: absence (1 g)	< 10 < 10 < 10 absent absent	n.t.

n.t. = not tested

TLC/HPLC chromatograms including peak areas and retention times should be presented		
Product: Valerian root dry extract Batch: 213 Storage conditions: long-term 40 °C ± 2 °C, 75% RH ± 5% TLC – fingerprint	**0 months**	**3 months**

Product: Valerian root dry extract Batch: 213 Storage conditions: long-term 40 °C ± 2 °C, 75% RH ± 5% HPLC – fingerprint	**0 months**	**3 months**

Valerian film-coated tablets

Valerian root dry aqueous extract

P-Part

Drug product

3.2.P.1 Description and composition of the drug product

Dosage form

The dosage form is a film-coated tablet containing 500 mg dry extract preparation (corresponding to 400 mg native dry extract) of valerian root. The shape is oblong and the colour yellow.

Composition

One film-coated tablet contains

No.	Substance	Function	Amount mg/tablet	Specification
Extract preparation consisting of:				**Ph. Eur.**
1	Native dry extract of valerian root (5-9:1) Extraction agent: water	Active substance	400.00	
2	Glucose, liquid, spray-dried	Technical excipients in the extract preparation	75.00	Ph. Eur.
3	Silica, colloidal anhydrous		25.00	Ph. Eur.
Tablet core				
4	Lactose monohydrate*	Filler, binder	121.50	Ph. Eur.
5	Powdered cellulose*	Filler, binder	40.50	Ph. Eur.
6	Soya-bean oil, hydrogenated	masks the bitter API	40.00	Ph. Eur.
7	Croscarmellose sodium	Disintegrant	30.00	Ph. Eur.
8	Silica, colloidal anhydrous	Flow regulator	12.00	Ph. Eur.
9	Magnesium stearate	Lubricant	6.00	Ph. Eur.
			total: 750.00	
Film coating				
10	Opadry II white 85 F 18422 consisting of: Polyvinyl alcohol 40.0% Macrogol 3350 20.2% Titanium dioxide 25% Talc 14.8%	Coating agent	32.80	Ph. Eur. Ph. Eur. Ph. Eur. Ph. Eur.
11	Iron oxide E 172 (yellow)	Colouring agent	1.50	2008/128/EG
12	Vanillin	Flavour	0.60	Ph. Eur.
13	Saccharin sodium	Sweetener	0.10	Ph. Eur.
14	Antifoam emulsion dry substance consisting of: Simethicone 92.02% Methyl cellulose 7.67% Sorbic acid 0.31%	Antifoam agent	0.10	Ph. Eur. Ph. Eur. Ph. Eur.
			total: 785.10	
15	Purified water**	approx.	690.95	Ph. Eur.

* Combined as Cellactose 80

**not contained in the finished product

Container

The container is a blister strip, consisting of a PVC/PVdC foil and an aluminium foil. For further information, please refer to Section 3.2.P.7.

3.2.P.2 Pharmaceutical development

3.2.P.2.1 Components of the drug product

3.2.P.2.1.1 Drug Substance

Valerian root dry extract is obtained from valerian roots by extraction with water. Since the native dry extract is very hygroscopic, it is blended at the stage of the soft extract with a mixture of spray dried liquid glucose and colloidal anhydrous silica to achieve a dry extract with improved pharmaceutical properties. After final drying, the herbal preparation is a light-brown free-flowing coarsely ground powder which does not agglomerate. It consists of 80% native valerian dry extract, 15% spray dried liquid glucose and 5% colloidal anhydrous silica. Its size is min. 95% < 0.315 mm. The extract preparation fully complies with the Ph. Eur. Monograph “Valerian dry aqueous extract”.

Stability of the herbal preparation is confirmed by stability testing in Chapter 3.2.S.7 (Valerian root dry extract).

3.2.P.2.1.2 Excipients

The excipients were chosen on the basis of their capacity to give a finished product with adequate characteristics; the excipients selected during the development are of conventional use in the production of oral dosage forms. Compatibility of the chosen excipients and the herbal preparation is confirmed by stability testing of the drug product (see Chapter 3.2.P.8.1).

Function of the excipients

Core	
Cellactose	Filler and binder
Soya-bean oil, hydrogenated	masks the bitter taste of the API
Croscarmellose sodium	Disintegrant
Silica, colloidal anhydrous	Flow regulator
Magnesium stearate (vegetable)	Lubricant
Coating	
Opadry II white 85 F 18422	Coating agent
Iron oxide E 172 (yellow)	Colouring agent
Vanillin	Flavouring agent
Saccharin sodium	Sweetening agent
Antifoam emulsion dry substance	Antifoam agent
Purified water	Solvent used during manufacturing

3.2.P.2.2 Drug product

3.2.P.2.2.1 Formulation Development

A film-coated tablet was found to be the most appropriate solid oral dosage form because of the following advantages:

Doses are very accurate and administration is easy.

Every colouring is possible.

The taste of the herbal substances could be masked.

The dosage form is much smaller than a sugar-coated tablet.

Therefore compliance will be good.

The formulation had to be suitable for direct compression. During the development, special care had to be given to good flow ability, trouble-free tableting behaviour and rapid disintegration of the tablet cores. A film-coating with low water permeability had to be applied to protect the tablets from uptake of humidity during storage.

Antioxidants, preservatives or other stabilising agents are not used or necessary.

To demonstrate the immediate release nature of the formulation an exemplary disintegration test was performed under Ph. Eur. conditions:

Data are provided here.

Tablet core

Croscarmellose sodium was added to the formulation to achieve fast tablet disintegration. A range of 2% to 6% was investigated. Tablets containing 4% croscarmellose sodium showed similar disintegration times when compared to tablets with 6% disintegrating agent. Since higher contents of croscarmellose sodium increase the risk of higher humidity uptake during film-coating and storage, the amount was set at 4% for further trials. Further studies supported the final concentration of 3.8% in the final composition.

To achieve tablets with suitable hardness and disintegration properties but without stickiness during tableting, the concentration of magnesium stearate was investigated in the range of 0.6% to 1.2%. Since tablets prepared with 0.8% magnesium stearate did not show any stickiness during tableting, the subsequent optimisation was done using this percentage. Results of further trials showed that the amount of lubricant could be further reduced to approximately 0.76% as used in the final composition.

Formulation development data are provided here.

Film-coating

In order to protect the tablets from water/humidity uptake during storage, film coating with low water permeability were selected for the formulation development. Opadry white 85F 18422, a polyvinyl-alcohol-based film-coating from Colorcon, and Sepifilm LP 761 white, a hydroxypropyl-methylcellulose based film-coating containing stearic acid were selected for that purpose. Ferric oxide yellow was the colouring agent of choice to cover the brownish surface of the tablets. The appropriate amount of film-coating applied was determined from previous development studies with tablet of similar dimensions requiring adequate humidity protection.

Both film-coatings covered the brownish surface of the tablet cores sufficiently and resulted in film-coated tablets which have a disintegration time of approximately 5 – 10 min longer than the uncoated tablet cores but were still in line with the Ph. Eur. However, since Sepifilm LP 761 was more difficult to process (larger particles in suspension resulting in material build-up on the spray-nozzles) it was not used in further development trials for this drug product, and Opadry white 85 F 18422 was selected as final film-coating material for the formulation.

Formulation development data are provided here.

In line with Guideline CPMP/QWP/2820/00 Rev. 2. a dissolution test is not required for batch release

The body of data demonstrated that the chosen formulation is suitable for an immediate release solid, oral dosage form.

3.2.P.2.2.2 Overage

Not applicable

3.2.P.2.2.3 Physicochemical and Biological Properties

Not applicable

3.2.P.2.3 Manufacturing process development

The manufacture of the drug product by tableting and coating is a standard process (see Chapter 3.2.P.3.3). The formulation is properly designed and manufactured in accordance with the principles of GMP.

3.2.P.2.4 Container closure system

The film-coated tablets are sealed into binary blisters made of PVC/PVdC and aluminium foils which is a common container for the dosage form (for specification see Chapter 3.2.P.7).

3.2.P.2.5 Microbiological attributes

Testing of microbiological quality is carried out during batch-to-batch release of the drug product (c.f. Section 3.2.P.5.4).

3.2.P.2.6 Compatibility

Interaction of the drug product and the container is not expected because the product is a solid dosage form. Compatibility of the chosen excipients and the herbal preparation is confirmed by stability testing of the drug product (see Chapter 3.2.P.8.1). For detailed information please refer to the results of the stability testing in Section 3.2.P.8.1.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Manufacturer and responsible for release:	Testing laboratory:
Name of the manufacturer	Name of testing laboratory
Address	Address

3.2.P.3.2 Batch formula

The batch size is 720,000 film-coated tablets, corresponding to 565.272 kg.

Item	Starting material core	per film-coated tablet (mg)	per batch (kg)
1	Dry extract of valerian root (preparation) consisting of: 80% native extract 15% liquid glucose dry substance 5% anhydrous colloidal silica	500.00	360.00
2	Lactose monohydrate*	121.50	87.48
3	Powdered cellulose*	40.50	29.16
4	Soya-bean oil, hydrogenated	40.00	28.80
5	Croscarmellose sodium	30.00	21.60
6	Silica, colloidal anhydrous	12.00	8.64
7	Magnesium stearate	6.00	4.32
1 - 7	***Total ready for pressing the core***	***750.00***	***540.00***

* as Cellactose 80

Item	Starting material coating agent	per film-coated tablet (mg)	per batch (kg)
8	Opadry II white 85 F 18422	39.36***	28.334***
9	Iron oxide E 172	1.80***	1.296***
10	Vanillin	0.72***	0.512***
11	Saccharin sodium	0.12***	0.086***
12	Antifoam emulsion substance USP* corresponding to dry substance	(0.368)*** 0.12***	(0.266)*** 0.086***
13	Purified water**	(690.95)***	(414.570)***
8 - 13	***Subtotal coating agent corresp. to dry substance***	***42.12******	***30.31******

* water amount not contained in the final product, ** not contained in the final product,
*** overage of 20% is included

Item		per film-coated tablet (mg)	per batch (kg)
1 - 13	**Total film-coated tablets**	**785.100**	**565.272**

3.2.P.3.3 Description of manufacturing process and process controls

Manufacture of the granulate

Item	Starting material	per film-coated tablet (mg)	per batch (kg)
1	Dry extract of valerian root (preparation)	500.00	360.00
2	Cellactose 80	85.00	61.20
3	Soya-bean oil, hydrogenated	40.00	28.80
4	Croscarmellose sodium	20.00	14.40
5	Silica, colloidal anhydrous	6.00	4.32
1 - 5	***Subtotal compact***	***651.00***	***468.72***

Items 1 - 5 are mixed and dry granulated (compacted, dry milled over sieving machine δ ≤ 1.5 mm-sieve) = dry granulate.

Manufacture of mixture ready-to-compress

Item	Starting material	per film-coated tablet (mg)	per batch (kg)
1 – 5	Dry granulate	651.00	468.72
6	Cellactose 80	77.00	55.44
7	Croscarmellose sodium	10.00	7.20
8	Silica, colloidal anhydrous	6.00	4.32
9	Magnesium stearate	6.00	4.32
1 - 9	***Total ready for pressing mixture***	***750.00***	***540.00***

Items 6, 7 and 9 are mixed (≥ 2 min). Then this pre-mixed powder is mixed with item 8 and the dry granulate (items 1 - 5) (30 min) = mixture ready-to compress.

In-process controls and specifications of mixture ready-to compress see IP 1.

Manufacture of cores

The mixture ready-to-compress is tabletted on a rotary tableting machine = tablet cores

Shape and size: oblong, 8.2 x 17.2 mm

Mass: 750 mg

During coating the following conditions are kept:

Temperature of exhaust air: 55 °C – 65 °C

Drum speed: 5 – 10 rpm

In-process controls and specifications of cores see IP 2 - 5

Manufacture of the film-coated tablets

Item	Starting material coating agent	per film-coated tablet (mg)	per batch (kg)
10	Opadry II white 85 F 18422	39.36***	28.334***
11	Iron oxide E 172	1.80***	1.296***
12	Vanillin	0.72***	0.512***
13	Saccharin sodium	0.12***	0.086***
14	Antifoam emulsion substance USP corresponding to dry substance	(0.368)*** 0.12***	(0.266)*** 0.086***
15	Purified water**	(690.95)***	(414.570)***
8 - 15	***Subtotal coating agent corresponds to dry substance***	***(733.436)*** ***42.12***	***(528.074)*** ***30.31***

** not contained in the final product, *** overages of 20% is included

To compensate for spraying losses, a production overage of up to + 20% of the film-coating suspension is used during spraying.

Item 10 – 14 are suspended and mixed in purified water (15). The pigment suspension obtained is sprayed on the cores in a drum coater using two-component jet nozzles = film-coated tablets.

During coating the following conditions are maintained: temperature of exhaust air: 55°C – 65°C.

Drum speed: 5 – 10 rpm

Item		per film-coated tablet (mg)	per batch (kg)
1 - 9	Cores	750.000	540.000
10 - 15	Coating agent	35.100	29.520
1 - 15	**Total film-coated tablets**	**785.100**	**565.272**

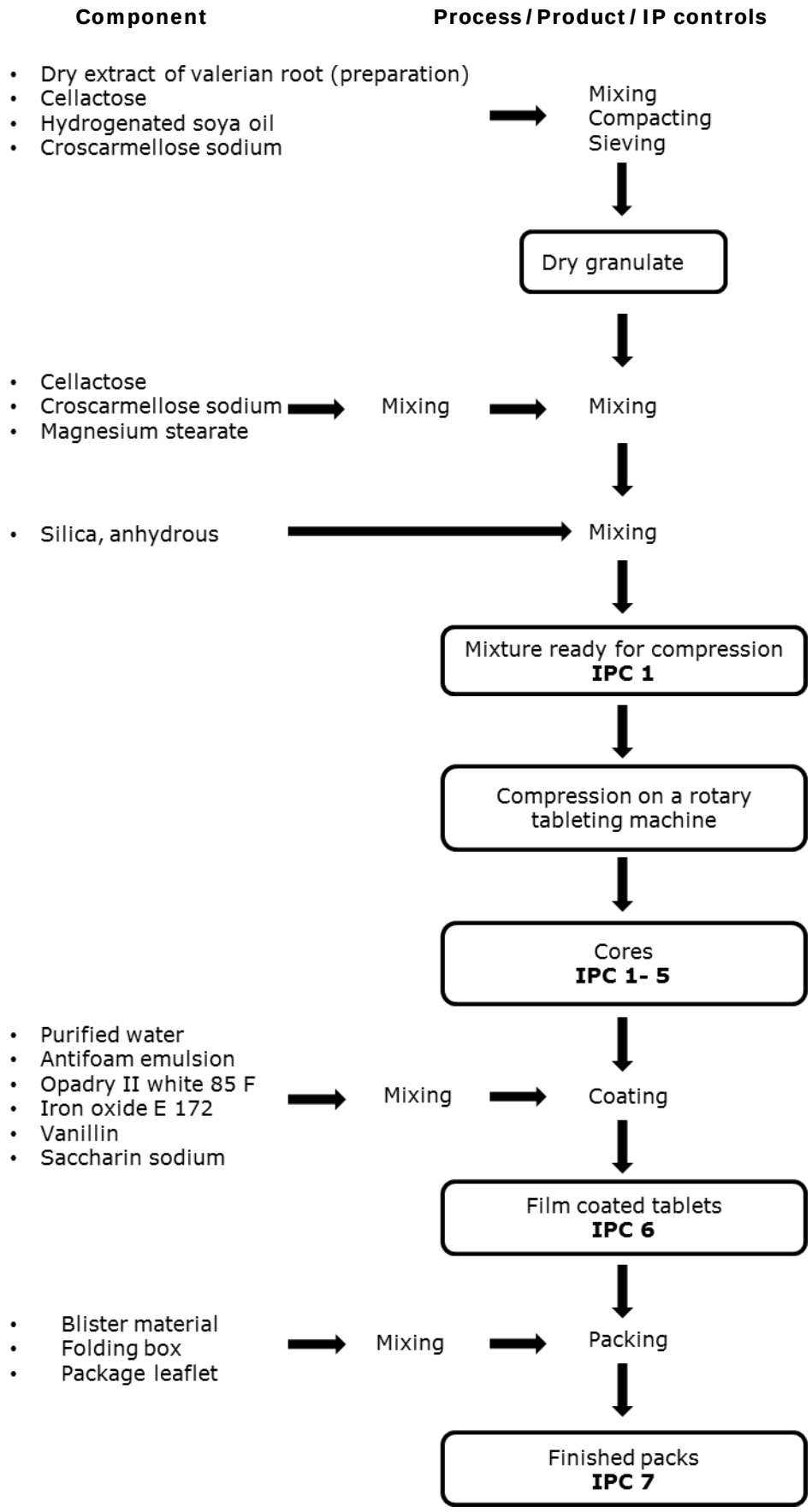
In-process controls and specification of film-coated tablets: see IP 6.

Manufacture of finished packs

The film-coated tablets are sealed into a corresponding number of blisters; the blisters are packed into folding boxes together with the package insert = finished packs.

In-process controls and specification of blister strips: see IP 7.

Manufacturing flow diagram


Component
Process / Product / IP controls
• Dry extract of valerian root (preparation)
• Cellactose
• Hydrogenated soya oil
• Croscarmellose sodium
Mixing
Compacting
Sieving
Dry granulate
• Cellactose
• Croscarmellose sodium
• Magnesium stearate
Mixing
Mixing
• Silica, anhydrous
Mixing
Mixture ready for compression
IPC 1
Compression on a rotary tableting machine
Cores
IPC 1- 5
• Purified water
• Antifoam emulsion
• Opadry II white 85 F
• Iron oxide E 172
• Vanillin
• Saccharin sodium
Mixing
Coating
Film coated tablets
IPC 6
• Blister material
• Folding box
• Package leaflet
Mixing
Packing
Finished packs
IPC 7

In-process controls

Process stage	IPC No.	IP-parameters	Test rhythm	Test methods	Acceptance criteria
Mixture ready-for-compression	IPC 1	bulk volume	1 x per hour	Ph. Eur. 2.9.15	1.0 – 2.0 ml/g
Cores	IPC 2 IPC 3 IPC 4 IPC 5	resistance to crushing disintegration uniformity of mass friability	≥ 1x per hour 1 x per batch ≥ 1x per hour 1 x per batch	Ph. Eur. 2.9.8 Ph. Eur. 2.9.1 Ph. Eur. 2.9.5 Ph. Eur. 2.9.7	70 - 190 N ≤ 30 min 750 mg + 5% ≤ 0.5%
Film-coated tablets	IPC 6	appearance	per 360.000 coated tablets ≥ 1500 tablets	visual	yellow coloured film-coated tablets, oval/homogenous coating without cracks
Finished packs	IPC 7	blister tightness	≥ 1 x per day (1 x 6 blisters)	in acc. with SOP	corresponds

3.2.P.3.4 Control of critical steps and intermediates

There are no critical steps in the manufacturing process.

In addition, there are no isolated intermediates. Suitable in-process controls are in place during the manufacturing process.

3.2.P.3.5 Process validation and/or evaluation

The manufacturing process is a standard process for tableting, coating and blistering. The results of the in-process controls on three full-scale production batches are presented below. The results confirm the consistent quality of the drug product. In addition the suitability of the manufacturing process is confirmed by the results of release testing (see 3.2.P.5.4).

IPC for mixture ready-to-compress

IPC	Acceptance criteria	Batch P003	Batch P004	Batch P005
Bulk volume	1.0 – 2.0 ml/g	1.6 ml/g	1.4 ml/g	1.7 ml/g

Additionally, the mixing time was validated. Therefore, the marker content at different time points (15, 30 and 45 min) and at different vessel positions was determined. A mixing time of 30 min ensured a marker content within the specified 5% limit throughout the vessel.

IPC for cores

IPC	Acceptance criteria	Batch P003	Batch P004	Batch P005
Resistance to crushing	70 - 190 N	90 N	175 N	125 N
Disintegration	≤ 30 min	11 min	9 min	13 min
Uniformity of mass	750 mg + 5%	760.9 mg	748.3 mg	771.0 mg

Friability	≤ 0.5%	0.35%	0.23%	0.26

IPC for coated tablets

IPC	Acceptance criteria	Batch P003	Batch P004	Batch P005
Appearance	white coloured film-coated tablets, oval/homogenous coating without cracks	Conforms	Conforms	Conforms

IPC for finished packs

IPC	Acceptance criteria	Batch P003	Batch P004	Batch P005
Blister tightness	In accordance with SOP	Conforms	Conforms	Conforms

3.2.P.4 Control of excipients

3.2.P.4.1 Specifications

Pharmacopoeial excipients

Substance	Specification
Lactose monohydrate	Ph. Eur.*[1]
Powdered cellulose	Ph. Eur.*
Soya-bean oil, hydrogenated	Ph. Eur.*
Croscarmellose sodium	Ph. Eur.*
Silica, colloidal anhydrous	Ph. Eur.*
Magnesium stearate (vegetable origin)	Ph. Eur.*[1]
Opadry II white 85 F 18422 consisting of: Polyvinyl alcohol 40.0% Macrogol 3350 20.2% Titanium dioxide 25% Talc 14.8%	 Ph. Eur. Ph. Eur. Ph. Eur. Ph. Eur.
Vanillin	Ph. Eur.*
Saccharin sodium	Ph. Eur.*
Antifoam emulsion dry substance consisting of: Simethicone 92.02% Methyl cellulose 7.67% Sorbic acid 0.31%	 Ph. Eur. Ph. Eur. Ph. Eur.
Purified water	Ph. Eur.*

* current edition [1]safe with reference to possible TSE risk

Non-Pharmacopoeial excipients

Substance	Specification	
Iron oxide, E 172	RL 2009/35/EG in conjunction with VO (EG) Nr. 1333/2008 VO (EU) 231/2012 and Directive 2008/128/EC	
	Molecular weight	88.85: FeO(OH) 159.70: Fe_2O_3 231.55: $FeOFe_2O_3$
	Assay	Yellow not less than 60%, red and black not less than 68% total iron, expressed as iron
	Description	Powder; yellow, red, brown or black in hue
	Identification	
	Solubility	Insoluble in water and in organic solvents Soluble in concentrated mineral acids
	Purity	
	Water soluble matter	Not more than 1%
	Arsenic	Not more than 5 mg/kg
	Barium	Not more than 50 mg/kg
	Cadmium	Not more than 5 mg/kg
	Chromium	Not more than 100 mg/kg
	Copper	Not more than 50 mg/kg
	Lead	Not more than 20 mg/kg
	Mercury	Not more than 1 mg/kg
	Nickel	Not more than 200 mg/kg
	Zinc	Not more than 100 mg/kg

Opadry II white 85 F 18422		
Parameter	Acceptance criteria	Test procedures
Appearance	White powder	Optical
Identity (IR)	complies with reference spectrum	Ph. Eur. 2.2.24
Colour differences	conforms	Optical
Ash	35.8 – 43.8%	Ph. Eur. 2.4.16
Test of different coloured particles	conforms	In-house

3.2.P.4.2 Analytical procedures

Opadry II white 85 F 18422

The used components of Opadry 11 white 85 F 18422 are tested according to the corresponding valid Ph. Eur. monograph. The coating mixture is tested as follows:

Appearance

Spread the sample over a piece of white card. Note the colour, odour and homogeneity of the sample and check for presence of foreign matter.

Identity

Identity is performed by FTIR spectrometry. The spectrum has to comply with the reference standard spectrum.

FTIR spectra are provided here.

Colour difference (optical)

Accurately weigh 45 g water into an appropriate size beaker. Add 20 g of sample as quickly as the stirrer will allow without excess build-up of product on the surface. Place a labelled card on the drawn-down plate, (matte side facing up), and apply a vacuum. Using a 0.006 film applicator, apply a uniform film to the card. To obtain a uniform film, apply enough pressure to prevent the bar from floating and make a smooth and consistent motion, lasting approximately 3 seconds.

The reflectance spectrum of the sample draw-down card should be measured and compared to a previously measured standard, stored in Colorcon' s database. Multiple measurements (minimum of 2) should be made at different locations on the cards, with the values being averaged to obtain accurate and representative data. The measurements should be made on the most uniform part of the film.

Ash

The test is performed according to Ph. Eur. 2.4.16. Total ash on 1 g of sample by heating at 800°C for at least 2 hours.

Test on different coloured particles

Place approximately 100 g of material onto a clean paper towel or white piece of paper. In a single motion, use a lab spatula to cut across the top of the material, forming a smooth surface. Note any observed off-colour particle. Continue removing layers of material and noting any off-colour particles observed. If any off-colour particles are observed, material should be compared to last three previously approved lots. If the amount of off-colour particles is similar (in quantity and size) to previously approved lots, the test lot can be approved.

3.2.P.4.3 Validation of analytical procedures

Not applicable

3.2.P.4.4 Justification of specifications

All excipients are in accordance to EC-Directive or Ph. Eur. No further information is necessary.

3.2.P.4.5 Excipients of human or animal origin

The excipients marked with [1] in Chapter 3.2.P.4.1 are safe with reference to possible TSE risk. For the respective documentation see Section 3.2.R.3 - Materials of animal origin.

The magnesium stearate is of vegetable origin. Confirmation is presented.

3.2.P.4.6 Novel excipients

Not applicable

3.2.P.5 Control of drug product

3.2.P.5.1 Specifications

Release specification

Parameter	Acceptance criteria	Test procedures
Appearance	yellow film-coated tablets, oblong, approx. 8.2 x 17.2 mm	visual
Average mass	785.1 mg ± 5% (745.85 – 824.36 mg)	Ph. Eur. 2.9.5
Uniformity of mass	corresponds	Ph. Eur. 2.9.5
Disintegration	≤ 30 min	Ph. Eur. 2.9.1
Loss on drying	≤ 6%	Ph. Eur. 2.2.32
Dry extract of valerian root (TLC)	corresponds to the example-fingerprint (see P.5.2)	acc.to Ph. Eur. Valerian dry aqueous extract
Dry extract of valerian root (HPLC)	corresponds to the example-fingerprint (see P.5.2)	HPLC profile from assay
Native dry extract of valerian root (HPLC)	400 mg ± 5%/film-coated tablet batch-specific via the analytical marker "sum of Sesquiterpenic acids" calc. as valerenic acid, the content of the sum of the markers in the batch-specific extract should also be stated in the CoA "x"	HPLC see P.5.2
Microbiological quality	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤ 10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* : absence (25 g) *E. coli* : absence (1 g)	Ph. Eur. 2.6.12/2.6.31

Shelf-life specification

Parameter	Acceptance criteria	Test procedures
Appearance	yellow-coloured film-coated tablets, oblong, without cracks	visual
Average mass	Initial value +/- 7.5%	Ph. Eur. 2.9.5
Uniformity of mass	corresponds	Ph. Eur. 2.9.5
Disintegration	≤ 30 min	Ph. Eur. 2.9.1
Loss on drying	≤ 7%	Ph. Eur. 2.2.32
TLC-fingerprint (valerian root)	corresponding to initial TLC chromatographic profile	acc.to Ph. Eur. Valerian dry aqueous extract of the ID test (see 3.2.P.5.2)
HPLC-fingerprint (valerian root)	corresponding to initial HPLC-chromatographic profile	HPLC see 3.2.P.5.2

Parameter	Acceptance criteria	Test procedures
Dry extract of valerian root	Initial value +/- 5%/film-coated tablet determined via the analytical marker “sum of Sesquiterpenic acids calc. as valerenic acid”	HPLC see 3.2.P.5.2
Microbiological quality	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤ 10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* : absence (25 g) *E. coli* absence (1 g)	Ph. Eur. 2.6.12/2.6.31

3.2.P.5.2 Analytical procedures

Appearance

Appearance is controlled visually.

Identity dry extract of valerian root

The test is done using TLC and HPLC.

TLC identification

Test solution

Crush 10 film-coated tablets. Mix an aliquot of the obtained tablet mass with methanol (approx. 1.5 g/10 ml) and place it in an ultrasonic bath for 10 min. Centrifuge and filter the solution and apply for chromatography [5 µl per 1 cm strip].

Reference solution

Dissolve acetoxyvalerenic acid R and valerenic acid R in methanol R (5 mg + 5 mg/20 ml). Alternatively, use valerian standardised dry extract HRS, suspend it in methanol R (1 g/10 ml), sonicate for 10 min., centrifuge and filter.

Apply the obtained solution for chromatography (5 µl per 1 cm strip)

Chromatographic conditions

According to Ph. Eur. monograph “Valerian dry aqueous extract” (“Identification”).

HPLC identification

See Assay of native dry extract in the finished product

Average mass

The test is done according to Ph. Eur. 2.9.5.

Uniformity of mass

The test is done according to Ph. Eur. 2.9.5.

Disintegration

The test is done according to Ph. Eur. 2.9.1.

Loss on drying

The test is done according to Ph. Eur. 2.2.32.

Microbiological quality

The test is done according to Ph. Eur., 2.6.12/2.6.31

Assay of native dry extract of valerian root (HPLC)

The assay of the native dry extract of valerian root in the drug product is determined batch-specific via the content of the sum of the sesquiterpenic acids (calculated as valerenic acid) in the batch-specific extract used in the manufacture of the drug product:

$$\text{Assay} = \frac{400}{\text{content sesquiterpenic acids/400 mg extract}} \text{ x content sesquiterpenic acids /tablet}$$

Assay sesquiterpenic acids (analytical markers)

Test solution

Crush 10 film-coated tablets and place an aliquot of the obtained mass (approx. 810.5 mg, exactly weighed) into a 25 ml volumetric flask and fill up to the mark with methanol. Treat the solution in an ultrasonic bath for about 30 min and filtrate. Use the filtrate for HPLC.

Reference solution (extract, batch-specific)

Suspend the extract in methanol (approx. 1 g exactly weighed/50 ml), sonicate for 30 min and filter.

Valerenic acid is used as reference standard (approx. 100 mg exactly weighed/50 ml), sonicate for 30 min and filter.

Calibration solution

Prepare at least five reference solutions corresponding to different valerenic acid concentrations within the range from 0.5 to 1.5 mg/10 ml methanol R1.

Measurement conditions

High pressure liquid chromatograph HPLC with diode-array detector and auto sampler.

Column:	RP-18, 200 mm length, 4.6 mm internal diameter, particle size: 5 nm, Column temp.: 30 °C
Injection:	25 µl
Flow rate:	1.5 ml/min
Detection:	UV 220 nm
Mobile phase 1:	Acetonitrile, phosphoric acid 85% (5 g/l) (20 : 80 V/V)
Mobile phase 2:	Phosphoric acid 85% (5 g/l), acetonitrile (20 : 80 V/V)

Gradient:

Time (min)	Mobile phase 1 (% V/V)	Mobile phase 2 (% V/V)
0 – 5	55	45
5 – 18	55 → 20	45 → 80
18 – 22	20	80
22 – 30	20	80
22 – 30	20 → 55	80 → 45

The HPLC conditions are in accordance with the current version of the Ph. Eur. (monograph "Valerian dry aqueous extract").

Calculation formula is provided here.

3.2.P.5.3 Validation of analytical procedures

Validation on the TLC and HPLC identity test

Validation data including chromatograms and data are provided here.

Validation on the HPLC method assay

Sesquiterpenic acids

HPLC/DAD

Range:	0.1 – 4.0%
Linearity (correlation coefficient)	0.999
Accuracy by recovery (n = 12)	102.3%
Repeatability (rel. standard deviation)	1.19%
Intermediate precision:	2.53%
Specificity	Spiking with standard solution HRS
Robustness (solutions)	Analytical solutions are stable for 24 hours
(method)	Slight variations in column temperature, eluent concentration and composition flow rate and wavelengths show no significant influence.

Validation data including chromatograms and raw data are provided here.

3.2.P.5.4 Batch analyses

Valerian film-coated tablets

Batch no:P003 **Batch size: 552.2 kg**

Date of manufacturing: 27.10.2010 Date of analysis:26.11.2010

(Active substance Batch-No: 111, manufactured August 2010)

Parameter	**Acceptance criteria**	**Result**
Appearance	yellow film-coated tablets, oblong/, app. 8.2 x 17.2 mm	conforms
Average mass	785.1 mg ± 5% (745.85 – 824.36 mg) Ph. Eur. 2.9.5	800.5 mg
Uniformity of mass	Ph. Eur. 2.9.5	+ 2.35 - 3.92% conforms
Disintegration	≤ 30 min Ph. Eur. 2.9.1	22 min
Loss on drying	≤ 6%	3.1%
TLC-fingerprint (valerian root)	corresponds	corresponds*
HPLC-fingerprint (valerian root)	corresponds	corresponds*
Assay of native dry extract	400 mg (380 – 420 mg)	402.6 mg*[1]
Assay sesquiterpenic acids		0.49%
Microbiological quality	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* : absence (25 g) *E. coli*: absence (1 g)	 < 100 < 10 < 1 absent absent

*TLC and HPLC chromatograms should be provided

[1]The assay is determined via the batch specific sesquiterpenic acid in the extract batch used.

TLC chromatogram for the parameter identity

HPLC chromatogram for the parameter assay

Peak areas and retention times are included in the report

Valerian film-coated tablets

Batch no:P004 **Batch size:568.0 kg**

Date of manufacturing: 28.10.2010 Date of analysis:26.11.2010

(Active substance Batch-No: 112, manufactured September 2010)

Parameter	**Acceptance criteria**	**Result**
Appearance	yellow film-coated tablets, oblong/, app. 8.2 x 17.2 mm	conforms
Average mass	785.1 mg ± 5% (745.85 – 824.36 mg) Ph. Eur. 2.9.5	795.7 mg
Uniformity of mass	Ph. Eur. 2.9.5	+ 2.38 - 2.89% conforms
Disintegration	≤ 30 min Ph. Eur. 2.9.1	23 min
Loss on drying	≤ 6%	3.7%
TLC-fingerprint (valerian root)	corresponds	corresponds*
HPLC-fingerprint (valerian root)	corresponds	corresponds*
Assay of native dry extract	400 mg (380 – 420 mg)	405.4 mg*[1]
Assay sesquiterpenic acids		0.49%
Microbiological quality	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* : absence (25 g) *E. coli*: absence (1 g)	 < 10 < 10 < 10 absent absent

*TLC and HPLC chromatograms should be provided
[1]The assay is determined via the batch specific sesquiterpenic acid in the extract batch used.

TLC chromatogram for the parameter identity

HPLC chromatogram for the parameter assay

Peak areas and retention times are included in the report

Valerian film-coated tablets

Batch no:P005 Batch size:562.1 kg

Date of manufacturing: 28.10.2010 Date of analysis:26.11.2010

(Active substance Batch-No: 113, manufactured July 2010)

Parameter	**Acceptance criteria**	**Result**
Appearance	yellow film-coated tablets, oblong/, app. 8.2 x 17.2 mm	conforms
Average mass	785.1 mg ± 5% (745.85 – 824.36 mg) Ph. Eur. 2.9.5	796.5 mg
Uniformity of mass	Ph. Eur. 2.9.5	+ 2.32 - 3.27% conforms
Disintegration	≤ 30 min Ph. Eur. 2.9.1	19 min
Loss on drying	≤ 6%	4.1%
TLC-fingerprint (valerian root)	corresponds	corresponds*
HPLC-fingerprint (valerian root)	corresponds	corresponds*
Microbiological quality	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* : absence (25 g) *E. coli* : absence (1 g)	 < 100 < 10 < 10 absent absent
Assay of native dry extract	400 mg (380 – 420 mg)	397.9 mg*[1]
Assay sesquiterpenic acids		0.49%
Microbiological quality	complies with Ph. Eur. 5.1.8 B TAMC ≤ 104 TYMC ≤102 bile-tolerant gram-negative bacteria: ≤ 102 *Salmonella* : absence (25 g) *E. coli* : absence (1 g)	 < 100 < 10 < 10 absent absent

*TLC and HPLC chromatograms should be provided

[1]The assay is determined via the batch specific sesquiterpenic acid in the extract batch used.

TLC chromatogram for the parameter identity

HPLC chromatogram for the parameter assay

Peak areas and retention times are included in the report

3.2.P.5.5 Characterisation of impurities

Not applicable

3.2.P.5.6 Justification of specification(s)

Description	Description of dosage form (film-coated tablets) is given (colour, tablet mass, diameter, height).
Uniformity of mass	Testing of uniformity of mass (Ph. Eur. 2.9.5) is in accordance with Ph. Eur.
Disintegration	Testing of disintegration time (Ph. Eur. 2.9.1) is in accordance with Ph. Eur.
Loss on drying	Acceptance criterion for testing of loss on drying is based on batch and stability data
Identity	Via TLC and HPLC: the methods are specific for Valerian root preparations and correspond to the Ph. Eur. monograph for the aqueous extract. The methods are validated. The HPLC fingerprint (from assay) supports identity.
Assay	The HPLC method for assay is validated; the limit for assay of extract in the drug product is set in accordance with the requirements of the Guidelines CPMP/QWP/2819/00 Rev. 2, CPMP/QWP/2820/00 Rev. 2: At release, 400 mg Valerian root dry extract/tablet ± 5% (= 95 - 105%) of the declared value; at shelf-life ± 5% of the initial value. Content of analytical markers sesquiterpenic acids: The validated analytical range is given. The batch-specific result is reported on the Certificate of analysis.
Purity tests	Residual solvents: not applicable, no relevant solvent is used. Microbiological quality is tested in accordance with Ph. Eur. 2.6.31; the limits are set in accordance with Ph. Eur. 5.1.8 category B.

Specification is supported by batch and stability data.

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

For the identity the reference materials used are tested/reported as described in the current Pharmacopoeia (monograph: “Valerian dry aqueous extract”).

Acetoxyvalerenic acid *R*

Valerenic acid *R*

Valerian standardised dry extract *HRS*

Corresponding working standards are established according to general analytical practice.

Details of the establishment are provided here by the Applicant.

Documentation on valerenic acid used for the quantitative analyses of the native extract in the finished product and during stability testing (3.2.P.8.3) is enclosed:

Valerenic acid (primary reference substance)

Nomenclature

Origin

Properties

Characterisation (Identity, Purity, Content)

Comment

References (Citations)

Validation (HPLC)

References (complete Papers)

Exemplary Certificate of Analysis with Attachments

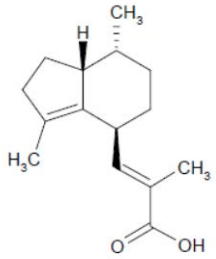
1. Nomenclature

Common name: Valerenic acid

Systematic name (CA): [4S-[4α(E),7β,7aα]]-3-(2,4,5,6,7,7a-hexahydro-3,7-dimethyl-1H-inden-4-yl)-2-methyl-2-propenoic acid

CAS-No: 3569-10-6

Structure:



Formula: $C_{15}H_{22}O_2$

Molecular weight: 234.34

2. Origin

Valerenic acid was isolated from valerian root. Extraction process was performed with heptane. The solvents acetone, methanol and water were used for chromatographic purification and crystallisation procedure.

3. Properties

3.1. Appearance:colourless, fine crystalline

3.2. Solubility:poorly soluble in water, soluble in acetone

4. Characterisation (Identity, Purity, Content)

4.1. Identity

Identity is determined by the following analytical methods concerning relevant literature (see 6.).

4.1.1. Elemental analysis

4.1.2 ^{1}H NMR spectrum (in $CDCl_3$)

4.1.3. ^{13}C NMR spectrum (in $CDCl_3$)

4.1.4 UV spectrum

4.1.5. Melting point

Chromatograms/spectra provided here.

4.2. Purity

Purity is determined by means of HPLC and titration. The content of the reference standard valerenic acid is determined as result of the assay minus the water content and the content of residual solvent content. Furthermore the ash is determined.

4.2.1 Chromatographic conditions of the HPLC method

Method:	HPLC; Reversed Phase, UV-detection
Column:	RP-18, 5 µm, 300 mm
Mobile phase:	A: methanol:water 70:30 + 3 ml phosphoric acid conc. B: methanol + 3 ml phosphoric acid conc.
Flow rate:	1.2 ml/min
Test solution:	approx.1.4 mg valerenic acid are weighed into a 20 ml volumetric flask + filled up to volume with ethanol 60%(V/V)
Injection volume:	30 µl
Detection:	UV 220 nm
Calculation:	area per cent method

Documents for validation see 7.1 and 7.3.

4.2.2. Titration

Titration is performed in anhydrous medium with tetrabutylammonium hydroxide solution (0.1 mol/l) using potentiometric end point detection.

One ml of 0.1 M tetrabutylammonium hydroxide is equivalent to 23.434 mg of $C_{15}H_{22}O_2$.

4.2.3. Water content

Karl-Fischer Method, according to Ph. Eur. 2.5.12.

4.2.4. Residual solvent (methanol)

^{1}H NMR spectrum (in DMSO-d_6)

4.2.5. Ash

According to Ph. Eur. 2.4.16 (with reduced amount of substance).

5. Comment

Identity and content of the reference substance are unequivocally substantiated by the documentation presented.

All batches are analysed according to the described procedure.

6. References (Citations)

R. Bos, Dissertation Univ. Groningen, NL, S. 51 (1997).

W. Karrer, E. Cherbuliez, C. H. Eugster, „Konstitution und Vorkommen der organischen Pflanzenstoffe“, Ergänzungsband 1, Birkhäuser Verlag Basel und Stuttgart 1977; 537 (Nr. 3609).

E. Gottlieb, V. Kotlyar, A. Nudelman, J. Org. Chem. 1997, 62, 7512 - 7515.
Please refer to Section 3.3 - Literature references.

7. Validation

Data are provided here according to the Guideline on validation.

8. Exemplary Certificate of Analysis with Attachments

An exemplary Certificate of Analysis is enclosed. Identity and Content are substantiated doubtlessly.

Certificate of Analyses – Valerenic acid (primary reference substance)

Batch: xxxxxx-yyy-zzz Manufacture date: 08.08.2013

Identity

4.1.1 Elemental analyses	C 76.48%, H 9.41% (calc.: C 76.88%, H 9.46%, O 13.65%)
4.1.2 ^{1}H-NMR spectrum	corresponding to literature
4.1.3. ^{13}C NMR spectrum	corresponding to literature
4.1.1 UV spectrum	λ_{max} = 217 nm
4.1.5 Melting point	134.5 – 135.5 °C

Purity

4.2.1 HPLC	100.0%
4.2.2 Titration	99.7%
4.2.3 Water	<0.1%
4.2.4 Methanol	0.12%
4.2.5 Ash	<0.1%

Content

99.9%

Attachment to "4.1.2 NMR spectroscopy of valerenic acid

Approximately 19 mg valerenic acid (Batch No. Wo04-277-24) were dissolved in 0.6 ml $CDCl_3$, placed in a 5 mm tube and investigated spectroscopically (^{1}H- and ^{13}C-NMR) by means of a Bruker Avance 200 NMR instrument (resonance frequency 200 MHz for protons and 50 MHz for ^{13}C). Tetramethylsilane (^{1}H, Σ= 0 ppm) or $CDCl_3$ (^{13}C, Σ = 77.0 ppm) were used as internal standard for the chemical displacement. The experimental parameters are given in the spectra.

The chemical shifts of valerenic acid (Batch No. Wo04-277 24) corresponds to literature reference provided here in the dossier.

Attachment to "4.1.2 ^{1}H NMR spectrum (in $CDCl_3$)

^{1}H NMR spectrum provided here

Attachment to "4.1.3. ^{13}C NMR spectrum (in $CDCl_3$)"

^{13}C NMR spectrum provided here

3.2.P.7 Container closure systems

Container closure system of the drug product

Ten film-coated tablets are sealed into a press-through pack (blister strip). The blister strips consist of a colourless polymer foil and aluminium foil and are packed into a cardboard box together with the pack insert.

Container material

The blister strip consists of PVC/PVDC and aluminium foil.

PVC/PVDC foil for blister packaging

Description	Colourless PVC foil coated with PVDC foil (40 g/m^2)
Requirements:	The material complies with the Ph. Eur. chapter 3.1.
General properties	Colourless/bluish transparent foil No damages Inspection is performed visually
Identity	Identity is confirmed by NIR (Ph. Eur. 2.2.40) or IR (Ph. Eur. 2.2.24)
Thickness	Thickness (PVC 250 µm, PVdC 23 µm) specified by the foil supplier is confirmed according to SOP2525 following DIN 53370

Aluminium foil for blister packaging

Description:	Glossy on one side, hard and smooth; the non-glossy side is lacquer coated, printed and lacquer finished, the glossy side has a lacquer coat suitable for hot welding with polyvinyl chloride (PVC)
Thickness of Al-foil:	20 µm
Material:	Aluminium 99.9%
Outside:	Text (cellulose nitrate print colour base) 1.5 g/m^2, one side covered with heatseal lacquers made of polyurethane and/or polyester (7 µm), the other side with primer printing lacquer 2 g/m^2.
Requirements:	The materials comply with the valid European requirements EC Regulation No 1935/2004, EC Regulation No 2023/2006, Directive 94/62/EC and EMA Guideline EMA/410/01

Description/Drawing of the container closure system are provided here.

Applicant provides here detailed specifications of the packaging, the in house specification, certificates of analyses and IR spectra.

The manufacturer of the blisters confirms their suitability for the proposed use. A corresponding certificate is provided here.

Applicant provides here certificates of compliance

3.2.P.8 Stability

3.2.P.8.1 Stability summary and conclusion

The shelf-life specification is listed in Section 3.2.P.5.1. Test methods are listed in Section 3.2.P.5.2 and their validation reports are listed in Section 3.2.P.5.3.

Results of ICH stability testing of 3 production scale batches stored in blisters, as described in Section 3.2.P.7., are reported.

Storage conditions: I: 25°C ± 2°C, 60% RH ± 5% RH

II: 30°C ± 2°C, 65% RH ± 5% RH

III: 40°C ± 2°C, 75% RH ± 5% RH

The following table shows the batches, conditions and the test period:

Batch tested	F0230	F0235	F0301
Date of manufacturing	May 2010	September 2010	March 2010
Start of stability test	July 2010	October 2010	May 2010
Batch size	720,000 film-coated tablets	720,000 film-coated tablets	720,000 film-coated tablets
Documented testing period	I: 36 months	I: 36 months	I: 36 months
	II: 12 months	II: 12 months	II: 12 months
	III: 6 months	III: 6 months	III: 6 months

The start of the stability study is within three months after manufacture.

Storage condition I: Over a period of three years no significant changes were observed. All values corresponded to the shelf-life specification.

Storage condition II: Over a period of twelve months no significant changes were observed. All values corresponded to the shelf-life specification.

Storage condition III: Over a period of three months no significant changes were observed. All values corresponded to the shelf-life specification. However, after six months the TLC-fingerprints were not conforming and out of specification results were noted for disintegration time and loss on drying.

Based on the data of real-time testing a shelf-life of 3 years is justified, the finished product should not be stored above 30°C.

In-use stability is not necessary for this packaging.

Stability protocol

The stability indicating parameters of the shelf-life specification are used as a basis of this stability protocol.

Long term storage conditions: 25°C/60% RH

Parameter	Initial	3 months	6 months	9 months	12 months	18 months	24 months	36 months
Appearance	yellow-coloured, oblong without cracks	X	X	X	X	X	X	X
Disintegration	≤ 30 min	X	X	X	X	X	X	X
Loss on drying	≤ 7%	X	X	X	X	X	X	X
TLC-fingerprint (valerian root)	corresponds to initial TLC chromatographic profile	X	X	X	X	X	X	X
HPLC-fingerprint	corresponds to initial HPLC-chromatographic profile	X	X	X	X	X	X	X
Content of dry extract of valerian root	Initial value +/- 5%/film-coated tablet	X	X	X	X	X	X	X
Microbiological quality	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* : absence (25 g) *E. coli* : absence (1 g)	X						X

Long term storage conditions: 30°C/65% RH

Parameter	Initial	3 months	6 months	9 months	12 months
Appearance	yellow-coloured, oblong without cracks	X	X	X	X
Disintegration	≤ 30 min	X	X	X	X
Loss on drying	≤ 7%	X	X	X	X
TLC-fingerprint (valerian root)	corresponds to initial TLC chromatographic profile	X	X	X	X
HPLC-fingerprint	corresponds to initial HPLC-chromatographic profile	X	X	X	X
Content of dry extract of valerian root	Initial value +/- 5%/film-coated tablet	X	X	X	X
Microbiological quality	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* : absence (25 g) *E. coli* : absence (1 g)	X			X

Long term storage conditions: 40°C/75% RH

Parameter	Initial	3 months	6 months
Appearance	yellow-coloured, oblong without cracks	X	X
Disintegration	≤ 30 min	X	X
Loss on drying	≤ 7%	X	X
TLC-fingerprint (valerian root)	corresponds to initial TLC chromatographic profile	X	X
HPLC-fingerprint	corresponds to initial HPLC-chromatographic profile	X	X
Content of dry extract of valerian root	Initial value +/- 5%/film-coated tablet	X	X
Microbiological quality	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* : absence (25 g) *E. coli* : absence (1 g)		X

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

The stability tests are finalised. According to GMP-rules, on-going stability tests will be performed.

3.2.P.8.3 Stability data (name, dosage form)

On the following pages tabulated summaries from the above mentioned batches are provided. The corresponding TLC-fingerprints of every test point are attached for each batch.

Product name: Valerian film-coated tablets

Batch: F0230

Storage conditions: Long-term, 25 °C ± 2 °C, 60 RH ± 5% RH

Parameter	**Acceptance criteria**	**0 months**	**3 months**	**6 months**	**9 months**	**12 months**
Appearance	yellow-coloured film-coated tablets, oblong, without cracks	complies	complies	complies	complies	complies
Disintegration	≤ 30 min	18	17	19	21	24
Loss on drying	≤ 7.0%	3.2	3.8	3.5	4.4	3.5
TLC/HPLC-fingerprint	corresponds to initial TLC/HPLC-chromatogram	initial	complies	complies	complies	complies
Assay	95 – 105% related to t_0 (sum of Sesquiterpenic acids calc. as valerenic acid)	391.8 mg 100.0% (1.386 mg)	390.3 mg 99.6% (1.381 mg)	383.7 mg 97.9% (1.363 mg)	399.8 mg 102.0% (1.408 mg)	410.6 mg 104.8% (1.453 mg)
Microbiological purity	complies with Ph. Eur. 5.1.8 B					
	TAMC ≤ 10^4	< 100				
	TYMC ≤10^2	< 10	not tested	not tested	not tested	not tested
	bile-tolerant gram-negative bacteria: ≤ 10^2	< 1				
	Salmonella : absence (25 g)	absent				
	E. coli : absence (1 g)	absent				

Product name: Valerian film-coated tablets

Batch: F0230

Storage conditions: Long-term, 25 °C ± 2 °C, 60% RH ± 5% RH

Parameter	**Acceptance criteria**	**18 months**	**24 months**	**36 months**
Appearance	yellow-coloured film-coated tablets, oblong, without cracks	complies	complies	complies
Disintegration	≤ 30 min	22	22	24
Loss on drying	≤ 7.0%	5.2	4.5	4.9
TLC/HPLC-fingerprint	corresponds to initial TLC/HPLC-chromatogram	complies	complies	complies
Assay	95 – 105% related to t_0 (sum of Sesquiterpenic acids calc. as valerenic acid)	386.5 mg 98.6% (1.371 mg)	408.6 mg 104.3% (1.433 mg)	388.5 mg 99.2% (1.348 mg)
Microbiological purity	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* : absence (25 g) *E. coli :* absence (1 g)	not tested	not tested	complies

Product name: Valerian film-coated tablets

Batch: F0230

Storage conditions: Intermediate, 30 °C ± 2 °C, 65% RH ± 5% RH

Parameter	**Acceptance criteria**	**0 months**	**3 months**	**6 months**	**9 months**	**12 months**
Appearance	yellow-coloured film-coated tablets, oblong, without cracks	complies	complies	complies	complies	complies
Disintegration	≤ 30 min	18	20	20	21	22
Loss on drying	≤ 7.0%	3.2	4.2	3.5	4.1	5.1
TLC/HPLC-fingerprint	corresponds to initial TLC/HPLC-chromatogram	initial	complies	complies	complies	complies
Assay	95 – 105% related to t_0 (sum of Sesquiterpenic acids calc. as valerenic acid)	391.8 mg 100.0% (1.386 mg)	385.3 mg 98.3% (1.367 mg)	389.0 mg 99.3% (1.378 mg)	395.2 mg 100.9% (1.395 mg)	404.8 mg 103.3% (1.422 mg)
Microbiological purity	complies with Ph. Eur. 5.1.8 B					
	TAMC ≤ 10^4	< 100				< 100
	TYMC ≤10^2	< 10				< 10
	bile-tolerant gram-negative bacteria: ≤ 10^2		not tested	not tested	not tested	
	Salmonella : absence (25 g)	< 1				< 1
	E. coli : absence (1 g)	absent				absent
		absent				absent

Product name: Valerian film-coated tablets

Batch: F0230

Storage conditions: Accelerated, 40 °C ± 2 °C, 75% RH. ± 5% RH

Parameter	**Acceptance criteria**	**0 months**	**3 months**	**6 months**
Appearance	yellow-coloured film-coated tablets, oblong, without cracks	complies	complies	complies
Disintegration	≤ 30 min	18	25	38
Loss on drying	≤ 7.0%	3.2	6.1	8.8
TLC/HPLC-fingerprint	corresponds to initial TLC/HPLC-chromatogram	initial	complies	not conform
Assay	95 – 105% related to t_0 (sum of Sesquiterpenic acids calc. as valerenic acid)	391.8 mg 100.0% (1.386 mg)	388.4 mg 99.2% (1.376 mg)	379.9 mg 97.0% (1.352 mg)
Microbiological purity	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* : absence (25 g) *E. coli* : absence (1 g)	 < 100 < 10 < 1 absent absent	 not tested 	 < 100 < 10 < 1 absent absent

Product: Valerian film-coated tablets Batch: F0230 Storage conditions: Long term, 25 °C ± 2 °C, 60% RH ± 5% RH TLC – fingerprint and HPLC-chromatogram	**0 months**	**3 months**	**6 months**
9 months	**12 months**	**18 months**	**24 months**

Product: Valerian film-coated tablets Batch: F0230 Storage conditions: Long term, 25 °C ± 2° C, 60 % RH ± 5% RH TLC – fingerprint and HPLC-chromatogram	**36 months**

Product: Valerian film-coated tablets Batch: F0230 Storage conditions: Intermediate, 30 °C ± 2 °C, 65% RH ± 5% RH TLC – fingerprint and HPLC-chromatogram	**0 months**	**3 months**
6 months	**9 months**	**12 months**

Product: Valerian film-coated tablets Batch: F0230 Storage conditions: Accelerated, 40 °C ± 2 °C, 75% RH ± 5% RH. TLC – fingerprint and HPLC-chromatogram	**0 months**	**3 months**	**6 months**

Product name: Valerian film-coated tablets

Batch: F0235

Storage conditions: Long-term, 25 °C ± 2 °C, 60% RH ± 5% RH

Parameter	**Acceptance criteria**	**0 months**	**3 months**	**6 months**	**9 months**	**12 months**
Appearance	yellow-coloured film-coated tablets, oblong, without cracks	complies	complies	complies	complies	complies
Disintegration	≤ 30 min	16	15	17	17	19
Loss on drying	≤ 7.0%	2.4	2.8	3.5	2.9	3.5
TLC/HPLC-fingerprint	corresponds to initial TLC/HPLC-chromatogram	initial	complies	complies	complies	complies
Assay	95 – 105% related to t_0 (sum of Sesquiterpenic acids calc. as valerenic acid)	382.9 mg 100.0% (1.156 mg)	392.4 mg 102.5% (1.179 mg)	402.1 mg 105.0% (1.201 mg)	389.5 mg 101.7% (1.171 mg)	400.8 mg 104.7% (1.198 mg)
Microbiological purity	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella :* absence (25 g) *E. coli :* absence (1 g)	 < 10 < 10 < 10 absent absent	 not tested 	 not tested 	 not tested 	 not tested

Product name: Valerian film-coated tablets

Batch: F0235

Storage conditions: Long-term, 25 °C ± 2 °C, 60% RH ± 5% RH

Parameter	**Acceptance criteria**	**18 months**	**24 months**	**36 months**
Appearance	yellow-coloured film-coated tablets, oblong, without cracks	complies	complies	complies
Disintegration	≤ 30 min	21	23	25
Loss on drying	≤ 7.0%	3.1	3.9	3.5
TLC/HPLC-fingerprint	corresponds to initial TLC/HPLC-chromatogram	complies	complies	complies
Assay	95 – 105% related to t_0 (sum of Sesquiterpenic acids calc. as valerenic acid)	380.5 mg 99.4% (1.147 mg)	403.9 mg 104.3% (1.203 mg)	387.9 mg 101.3% (1.168 mg)
Microbiological purity	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* : absence (25 g) *E. coli* : absence (1 g)	 < 10 < 10 < 10 absent absent	 not tested 	 complies

Product name: Valerian film-coated tablets

Batch: F0235

Storage conditions: Intermediate, 30 °C ± 2 °C, 65 RH ± 5% RH

Parameter	**Acceptance criteria**	**0 months**	**3 months**	**6 months**	**9 months**	**12 months**
Appearance	yellow-coloured film-coated tablets, oblong, without cracks	complies	complies	complies	complies	complies
Disintegration	≤ 30 min	16	18	21	25	30
Loss on drying	≤ 7.0%	2.4	2.8	3.5	4.0	4.4
TLC/HPLC-fingerprint	corresponds to initial TLC/HPLC-chromatogram	initial	complies	complies	complies	complies
Assay	95 – 105% related to t_0 (sum of Sesquiterpenic acids calc. as valerenic acid)	382.9 mg 100.0% (1.156 mg)	383.4 mg 100.1% (1.156 mg)	388.7 mg 101.5% (1.169 mg)	381.2 mg 99.6% (1.151 mg)	401.9 mg 105.0% (1.203 mg)
Microbiological purity	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative *bacteria: ≤ 10^2* *Salmonella absence (25 g)* *E. coli* absence (1 g)	 < 10 < 10 < 10 absent absent	 not tested 	 not tested 	 not tested 	 < 10 < 10 < 10 absent absent

Product name: Valerian film-coated tablets

Batch: F0235

Storage conditions: Accelerated, 40°C ± 2°C, 75% RH ± 5% RH

Parameter	**Acceptance criteria**	**0 months**	**3 months**	**6 months**
Appearance	yellow-coloured film-coated tablets, oblong, without cracks	complies	complies	complies
Disintegration	≤ 30 min	16	25	40
Loss on drying	≤. 7.0%	2.4	5.9	7.5
TLC/HPLC-fingerprint	corresponds to initial TLC/HPLC-chromatogram	initial	complies	not conform
Assay	95 – 105% related to t_0 (sum of Sesquiterpenic acids calc. as valerenic acid)	382.9 mg 100.0% (1.156 mg)	380.5 mg 99.5% (1.149 mg)	385.4 mg 100.5% (1.161 mg)
Microbiological purity	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* absence (25 g) *E. coli* absence (1 g)	 < 10 < 10 < 10 absent absent	 not tested 	 < 10 < 10 < 10 absent absent

Product: Valerian film-coated tablets Batch: F0235 Storage conditions: Long term, 25 °C ± 2 °C, 60% RH ± 5% RH TLC – fingerprint and HPLC-chromatogram	**0 months**	**3 months**	**6 months**
9 months	**12 months**	**18 months**	**24 months**

Product: Valerian film-coated tablets Batch: F0235 Storage conditions: Long term, 25 °C ± 2° C, 60% RH ± 5% RH TLC – fingerprint and HPLC-chromatogram	**36 months**

Product: Valerian film-coated tablets Batch: F0235 Storage conditions: Intermediate, 30 °C ± 2 °C, 65% RH ± 5% RH TLC – fingerprint and HPLC-chromatogram	**0 months**	**3 months**
6 months	**9 months**	**12 months**

Product: Valerian film-coated tablets Batch: F0235 Storage conditions: Accelerated, 40 °C ± 2 °C, 75% RH ± 5% RH. TLC – fingerprint and HPLC-chromatogram	**0 months**	**3 months**	**6 months**

Product name: Valerian film-coated tablets

Batch: F0301

Storage conditions: Long-term, 25 °C ± 2 °C, 60 RH ± 5% RH

Parameter	**Acceptance criteria**	**0 months**	**3 months**	**6 months**	**9 months**	**12 months**
Appearance	yellow-coloured film-coated tablets, oblong, without cracks	complies	complies	complies	complies	complies
Disintegration	≤ 30 min	15	15	16	18	19
Loss on drying	≤ 7.0%	3.8	3.9	4.1	3.9	4.4
TLC/HPLC-fingerprint	corresponds to initial TLC/HPLC-chromatogram	initial	complies	complies	complies	complies
Assay	95 – 105% related to t_0 (sum of Sesquiterpenic acids calc. as valerenic acid)	387.0 mg 100% (1.996 mg)	387.4 mg 100.1% (1.998 mg)	393.5 mg 101.7% (2.023 mg)	406.4 mg 105.0% (2.080 mg)	383.1 mg 99.0% (1.980 mg)
Microbiological purity	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella :* absence (25 g) *E. coli :* absence (1 g)	complies	not tested	not tested	not tested	not tested

Product name: Valerian film-coated tablets

Batch: F0301

Storage conditions: Long-term, 25 °C ± 2 °C, 60 RH ± 5% RH

Parameter	**Acceptance criteria**	**18 months**	**24 months**	**36 months**
Appearance	yellow-coloured film-coated tablets, oblong, without cracks	complies	complies	complies
Disintegration	≤ 30 min	21	19	23
Loss on drying	≤ 7.0%	4.8	4.9	5.0
TLC/HPLC-fingerprint	corresponds to initial TLC/HPLC-chromatogram	initial	complies	complies
Assay	95 – 105% related to t_0 (sum of Sesquiterpenic acids calc. as valerenic acid)	383.1 mg 99.0% (1.980 mg)	404.9 mg 104.6% (2.070 mg)	399.4 mg 103.2% (2.047 mg)
Microbiological purity	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* : absence (25 g) *E. coli* : absence (1 g)	not tested	not tested	complies

Product name: Valerian film-coated tablets

Batch: F0301

Storage conditions: Intermediate, 30 °C ± 2 °C, 65% RH ± 5% RH

Parameter	**Acceptance criteria**	**0 months**	**3 months**	**6 months**	**9 months**	**12 months**
Appearance	yellow-coloured film-coated tablets, oblong, without cracks	complies	complies	complies	complies	complies
Disintegration	≤ 30 min	15	17	19	20	21
Loss on drying	≤7.0%	3.8	3.9	4.8	4.9	5.2
TLC/HPLC-fingerprint	corresponds to initial TLC/HPLC-chromatogram	initial	complies	complies	complies	complies
Assay	95 – 105% related to t_0 (sum of Sesquiterpenic acids calc. as valerenic acid)	387.0 mg 101.5% (1.996 mg)	392.8 mg 101.2% (2.020 mg)	405.5 mg 104.7% (2.080 mg)	405.3 mg 104.7% (2.088 mg)	368 mg 95.1% (1.918 mg)
Microbiological purity	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* : absence (25 g) *E. coli* : absence (1 g)	complies	not tested	not tested	not tested	complies

Product name: Valerian film-coated tablets

Batch: F0301

Storage conditions: Accelerated, 40 °C ± 2 °C, 75% RH ± 5% RH

Parameter	**Acceptance criteria**	**0 months**	**3 months**	**6 months**
Appearance	yellow-coloured film-coated tablets, oblong, without cracks	complies	complies	complies
Disintegration	≤ 30 min	15	22	30
Loss on drying	≤ 7.0%	3.8	6.6	9.0
TLC/HPLC-fingerprint	corresponds to initial TLC/HPLC-chromatogram	initial	complies	not conform
Assay	95 – 105% related to t_0 (sum of Sesquiterpenic acids calc. as valerenic acid)	387.0 mg 100% (1.996 mg)	380.6 mg 98.3% (1.970 mg)	409.7 mg 105.8% (2.089 mg)
Microbiological purity	complies with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 *Salmonella* : absence (25 g) *E. coli* : absence (1 g)	complies	not tested	complies

Product: Valerian film-coated tablets Batch: F0301 Storage conditions: Long term, 25 °C ± 2 °C, 60% RH ± 5% RH TLC – fingerprint and HPLC-chromatogram	**0 months**	**3 months**	**6 months**
9 months	**12 months**	**18 months**	**24 months**

Product: Valerian film-coated tablets Batch: F0301 Storage conditions: Long term, 25 °C ± 2° C, 60 % RH ± 5% RH TLC – fingerprint and HPLC-chromatogram	**36 months**

Product: Valerian film-coated tablets Batch: F0301 Storage conditions: Intermediate, 30 °C ± 2 °C, 65% RH ± 5% RH TLC – fingerprint and HPLC-chromatogram	**0 months**	**3 months**
6 months	**9 months**	**12 months**

Product: Valerian film-coated tablets Batch: F0301 Storage conditions: Accelerated, 40 °C ± 2 °C, 75% RH ± 5% RH. TLC – fingerprint and HPLC-chromatogram	**0 months**	**3 months**	**6 months**

Appendices

3.2.A.1 Facilities and equipment

Not applicable

3.2.A.2 Adventitious agents safety evaluation

Not applicable

3.2.A.3 Excipients

Not applicable

3.2.R Regional information

Process validation scheme for the drug

Not applicable

Certificate(s) of Suitability

Not applicable

Materials of animal origin

Please find attached suppliers' TSE information on Cellactose 80:

Certificate with TSE information on Cellactose 80 is provided here.

3.3 Literature references

Annex 1-3

References are provided here.