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

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

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Please always indicate clearly whether comments refer to the guideline text or to the newly added Appendix 2.

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

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

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Executive summary

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

Revision 1 pertained to the presentation and content of Module 3 on Quality (chemical, pharmaceutical and biological information) of dossiers for THMPs to help applicants 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 applicants 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 to help applicants with their submissions a mock-up has been included as Appendix 2. It serves as an example for applicants of the format providing clarification on the exact location of relevant parts of the documentation. The chosen mock-up does not necessarily represent all quality requirements.

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 THMPs 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 Appendix 1 is also applicable to HMPs applications for marketing authorisation.

3. Legal basis

According to Article 16c(1) of Directive 2001/83/EC as amended, the application for traditional use registration of herbal medicinal products shall be accompanied by:

a) The particulars and documents:

(i) Referred to in Article 8(3)(a) to (h), (j) and (k);

(ii) The results of the pharmaceutical tests referred to in the first[2] indent of Article 8(3)(i);

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

(iv) In case of combinations, as referred to in Article 1(30) or Article 16a(2), the information referred to in Article 16a(1)(e) relating to the combination as such; if the individual active 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.

[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).

c) Qualitative and quantitative particulars of all the constituents of the medicinal product[5], including the reference to its international non-proprietary name (INN) recommended by the WHO, where an INN for the medicinal product exists, or a reference to the relevant chemical name.

ca) Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.[6]

d) Description of the manufacturing method.

e) Therapeutic indications, contraindications and adverse reactions.

f) Posology, pharmaceutical form, method and route of administration and expected shelf-life.

g) Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, 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

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

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

[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).

1.1. Comprehensive Table of contents	Applicable
1.2. Application form	Applicable
1.3. Product Information	Applicable
1.3.1. SPC, Labelling and package leaflet	Applicable
1.3.2. Mock-up	Applicable (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), applicants 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 applicants 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 applicants 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
1.9. Information relating to Clinical Trials	Not applicable

121 *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	For HSs/HPs, a description of the desired product and product-related substances and a summary of general properties, characteristics features and characterization data, as described in S.3.1, should be included. The QOS should summarise the data on potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, fumigants, etc. In some specific circumstances, the risk of radioactive contamination is to be considered.

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

Summary Appendixes 2.3.R. Quality Overall Summary Regional Information	
2.4. Non-clinical overview	For THMPs, in Module 2.4, as referred to in Article 16c(1)(d) the following is required: a bibliographic review of safety data together with an expert report, and where required by the competent authority, upon additional request, data necessary for assessing the safety of the medicinal product. It is advised that the expert report on safety data takes into consideration the agreed format for the organisation of the nonclinical overview in the CTD. The list of relevant references for non-clinical data can be included at the end of module 2.4. Where a European Union herbal monograph or European Union list entry has been established: Where an assessment report (and therefore a European Union herbal monograph or European Union list entry) exists that is relevant to the proposed HS/HP, applicants should discuss this fact in the dossier taking into consideration that they refer to HS/HP and aspects related to the finished traditional herbal medicinal product. Several data, which would be necessary according to the Directive 2001/83/EC might not be needed according to specific guidance documents (e.g. “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)). This should be discussed and clarified within the nonclinical expert report. When missing data on genotoxicity in section 5.3 of the monograph are mentioned they should be appropriately complemented. Furthermore the applicant will need 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. If the extract solvent and/or concentration is/are different from those given in the assessment report/monograph, comparability has to be demonstrated by using appropriate analytical data. 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.
2.5. Clinical overview	2.5.4 Overview of Efficacy For THMPs, in Module 2.5, as referred to in Article 16c(1)(c) the following is required: bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the EU. Where a European Union herbal monograph or European Union list entry has been established that is relevant to the proposed HS/HP, applicants should discuss this fact in this section of the dossier. 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 applicants 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 applicants 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/THMP complies fully with the European Union list entry. Where no European Union list entry exists but a relevant monograph does exist, applicants 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. The same plant species and plant part listed in the monograph must be used in the proposed HS/HP. The posology should correspond to that stated 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. A corresponding product should have: • the same active ingredients, irrespective of the excipients • the same or similar intended purpose • the equivalent strength and posology • the same or similar route of administration If no comparable product is currently marketed, reference to scientific reference handbooks, official compendia for prescriptions or official pharmacopoeias of Member States can be considered, if the HS/HPor combination can be found in these references. Evidence on the traditional use of single active substances of a fixed combination will not be sufficient to establish a traditional use of a combination product but may be used to supplement the traditional use data. In addition to the period of use, the plausibility of pharmacological effects or efficacy of the medicinal product must be addressed in this section. Plausibility of a traditional indication may include, but is not limited to clinical data, pharmacological studies, case reports, bibliographic or expert evidence. 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. Evidence of widespread, long-standing use without significant safety problems emerging should form the basis of a typical safety report. Deficiencies in safety information should also be clearly addressed. The report should ideally consider the following aspects of safety: • the nature of the patient population and the extent of patient exposure/world-wide marketing experience to date • common and non-serious adverse events • serious adverse events • methods to prevent, mitigate or manage adverse events • reactions due to overdose

	• long-term safety if relevant data is available • special patient populations e.g. children and pregnant or lactating women • relevant animal toxicology and product quality information If risks have been identified, the report must explain why a positive benefit/risk-balance for a traditional use is justified. For example, if there are reports of serious adverse events, this must be balanced by sufficient evidence of appropriate benefit. In summary, 5 pivotal pieces of information must be discussed in this section of the dossier a) time in medicinal use b) therapeutic indication c) strength/type of HS/HP d) posology e) specific information on safe use and evidence of safety
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 Biopharmaceutics and associated analytical	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 Union list entry has been established that is relevant to the proposed HS/HP, tabulated summaries are not required. When supplementing data concerning the plausibility of pharmacological

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	effects or efficacy of the THMP as well as information on the safety of use are addressed in section 2.5, a tabulated summary should be presented in this section 2.7. When there is no monograph or list entry, tabulated clinical summaries in Module 2.7 should be provided.

4.3. Module 3[9]

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

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

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

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

	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)	<u>For herbal substances</u> The name, address, and responsibility of each supplier, including contractors, and each proposed site or facility involved in production/collection and testing of the herbal substance should be provided, where appropriate. <u>For herbal preparations</u> The name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation should be provided, where appropriate.
3.2.S.2.2. Description of Manufacturing Process and Process Controls (name, manufacturer)	<u>For herbal substances</u> Information should be provided to adequately describe the plant production and plant collection, including: • Geographical source of medicinal plant • Cultivation, harvesting, drying and storage conditions

	• Batch size 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 • 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, macroscopical, microscopical, phytochemical characterisation, and biological activity if necessary, should be provided. For herbal preparations Information on the phyto- and physicochemical characterisation, and biological activity if necessary, should be provided.
3.2.S.3.2. Impurities (name, manufacturer)	For herbal substances • Potential contaminants originating from the herbal 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	Applicable

(name, manufacturer)	
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,	<u>For herbal medicinal products</u> A brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of

dosage form)	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	Applicable

Evaluation (name, dosage form)	
3.2.P.4 Control of Excipients (name, dosage form)	Applicable
3.2.P.4.1. Specifications (name, dosage form)	Applicable
3.2.P.4.2. Analytical Procedures (name, dosage form)	Applicable
3.2.P.4.3. Validation of Analytical Procedures (name, dosage form)	Applicable
3.2.P.4.4. Justification of Specifications (name, dosage form)	Applicable
3.2.P.4.5. Excipients of Human or Animal Origin (name, dosage form)	Applicable
3.2.P.4.6. Novel Excipients (name, dosage form)	Applicable
3.2.P.5. Control of Drug Product (name, dosage form)	Applicable
3.2.P.5.1. Specification(s) (name, dosage form)	Applicable
3.2.P.5.2. Analytical Procedures (name, dosage form)	Applicable
3.2.P.5.3. Validation of Analytical Procedures (name, dosage form)	Applicable
3.2.P.5.4. Batch Analyses (name,	Applicable

dosage form)	
3.2.P.5.5. Characterisation of Impurities (name, dosage form)	Applicable
3.2.P.5.6. Justification of Specification(s) (name, dosage form)	Applicable
3.2.P.6. Reference Standards or Materials (name, dosage form)	Applicable
3.2.P.7. Container Closure System (name, dosage form)	Applicable
3.2.P.8. Stability (name, dosage form)	Applicable
3.2.P.8.1. Stability Summary and Conclusion (name, dosage form)	Applicable
3.2.P.8.2. Post-approval Stability Protocol and Stability Commitment (name, dosage form)	Applicable
3.2.P.8.3. Stability Data (name, dosage form)	Applicable
3.2.R. Regional information	Applicable
3.3. Literature References	Applicable

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

4.4. Module 4: Non-clinical study reports

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

4.1. Module 4 Table of Contents	Applicable
4.2. Study Reports	If applicable. If data are available or have been requested they should be provided and summarised in Module 2.6 for which the corresponding expert report would be included in Module 2.4.
4.3. Literature References	For THMPs bibliographic references regarding safety data as referred to in Article 16c(1)(d) should be presented in Module 4. Such references should be indexed following the agreed format for the organisation of Module 4. 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.

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. These may include European Union herbal monographs, other official monographs, scientific reference handbooks, company sales data, official compendia for prescriptions, official pharmacopoeias of Member States or relevant pharmacovigilance data. If there are relevant clinical studies e.g. observational studies included in order to support the plausibility of pharmacological effects or efficacy and the evidence of long standing use, these data should also be presented in line with the structure of Module 5. For THMPs, in some cases the agreed CTD format for the clinical study reports may not be applicable because clinical data are missing.

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' (CPMP/QWP/2819/00 as revised, EMEA/CVMP/814/00 as revised).

'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products'.

(CPMP/QWP/2820/00 as revised, EMEA/CVMP/815/00 as revised).

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

'Guideline on non-clinical documentation for herbal medicinal products in applications for marketing authorisation (bibliographical and mixed applications) and in applications for simplified registration'.

(EMEA/HMPC/32116/2005).

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

'Guideline on selection of test materials for genotoxicity testing for traditional herbal medicinal products/ herbal medicinal products' (EMEA/HMPC/67644/2009).

'Guideline on the clinical assessment of fixed combinations of herbal substances/herbal preparations' (EMEA/HMPC/166326/2005).

'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]).

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

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

[10] Guidance on module 3 as described in this Appendix 1 is also applicable to herbal medicinal products (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.

3.1 Table of Contents of Module 3

A Table of Contents for Module 3 should be provided.

3.2 Body of data

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

3.2.S Drug substance[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***

[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.

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

3.2.S.2 Manufacture (name, manufacturer)

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

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

- ***Herbal substance***

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

- ***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 (e.g. spray dried products…).

The decontamination process validation should be included if necessary.

Reference guidelines:

- Process Validation.

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

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

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

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

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

For the ***herbal substance*** and the ***herbal preparation,*** 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***

In cases where the herbal substance is the active pharmaceutical ingredient, description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications.

- ***Herbal preparation***

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

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

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

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

Reference guideline: *Plastic Primary Packaging Materials.*

3.2.S.7 Stability (name, manufacturer)

- ***Herbal substance***

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

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

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

Reference guidance:

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

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

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

- Stability Testing of New Drug Substances and Products.

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

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

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

- Evaluation of Stability Data.

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

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

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

Reference guidelines:

- Stability Testing of New Drug Substances and Products.

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

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

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

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

Reference guidance:

- Stability Testing of New Drug Substances and Products.

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

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

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

- Validation of Analytical Procedures: Text and Methodology.

3.2.P Drug Product (name, dosage form)

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

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

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

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

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

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

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

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

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

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

Reference guidance:

- Development Pharmaceutics.

- Pharmaceutical Development.

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

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

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

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

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

For combination products, the compatibility of drug substances with each other 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, based on testing a minimum of two or three batches of the finished product, a shelf-life and label storage instructions applicable to all future batches of the finished product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf-life.

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

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

Reference guidance:

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

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

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

- Stability Testing of New Drug Substances and Products.

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

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

- In-Use Stability Testing of Human Medicinal Products.

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

- Evaluation of Stability Data.

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

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

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

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

Reference guidelines:

- Stability Testing of New Drug Substances and Products.

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

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

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

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

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

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

References guidelines:

- *Stability Testing of New Drug Substances and Products.*
- *Stability Testing of Existing Active Substances and Related Finished Products.*
- *Stability Testing for Application for Variations to a Marketing Authorisation.*
- *In-Use Stability Testing of Human Medicinal Products.*
- *Validation of Analytical Procedures: Text and Methodology.*

3.2.A Appendices

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

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

3.2.A.3 Excipients

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

3.2.R Regional information

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

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

For EU:

- Process validation scheme for the herbal medicinal product

  Reference guideline: Note for Guidance on Process Validation

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

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

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

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

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

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

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

3.3 Literature references

Key literature references should be provided, if applicable.

References relevant for Module 3

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

The guidelines referenced below are available on the EMA Website:

http://www.ema.europa.eu

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

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

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

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

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

B - List of references to quality guidelines

General guidelines

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

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

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/214869/06
Reflection paper on Stability Testing of Herbal Medicinal Products and Traditional of Herbal Medicinal Products.	EMA/HMPC/3626/09
Regulatory Questions & Answers (Q&A) on Herbal Medicinal Products.	EMA/HMPC/345132/2010 Rev. 1

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 applicants 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 and does not necessarily represent all quality requirements.

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)

Crude plant material: 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.2.2.2 - 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:

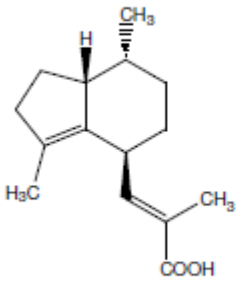
- Essential oil 0.5 - 1 % (formic, acetic, butyric, isovalerianic acids, borneol bornyl acetate, bornyl isovalerianate, α-pinene, camphene, myrtenol, α-terpineol, β-jonone, caryophyllene)
- Sesquiterpenes (valerenic, acetoxy-valerenic, hydroxy-valerenic acids and valerenal)
- Iridoids including valepotriates (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

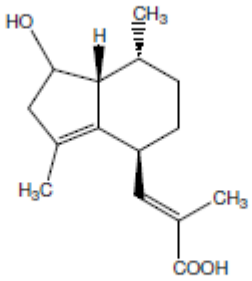
The characteristic constituents used as analytical markers in control tests are the sesquiterpenic acids: acetoxyvalerenic acid, hydroxyvalerenic acid and valerenic acid.

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 4mL/kg of essential oil (dried drug).

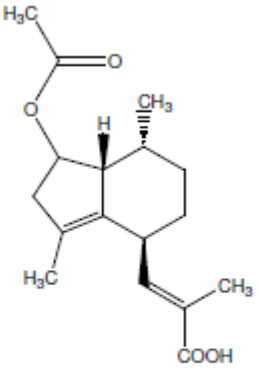
The chemical structures of the valerenic acids are given below:



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

Responsible for release of the herbal substance:

Name of the manufacturer
Address

3.2.S.2.1.2 Herbal preparation

Manufacturer of the herbal preparation:

Name of manufacturer
Address

Laboratory for testing of the herbal preparation:

Name of testing laboratory
Address

Responsible for release of the herbal preparation:

Name of 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 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):

Name of the herbal substance: Valerian root	
Code: 052014	
Name of Supplier /Exporter	
Country / Address:	
Name of the herbal substance - Commercial name: Valerian root - Latin name: *Valeriana officinalis* L.	
Origin of herbal substance - Country : Germany, Poland, The Netherlands, Bulgaria - Area/Region: "..."- - Cultivated: Yes~~/No~~ - Collected in wild habitats: ~~Yes /~~ No	
Cultivation - Annual: + / Perennial: + - Kind of soil: sandy - Surroundings: agriculture	Collection from wild habitats - Wild harvesting on private land: - From one area (organized): - From different areas and brought to a

- Fertilisers: Yes /~~No~~: Mineral: + /Organic: + - Plant gene manipulated: ~~Yes~~ / No - Others: ---	collecting point: - Type of soil: - Surroundings: - Others:
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 - 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: ---	Artificial drying - 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: ~~Yes~~ / 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.

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.

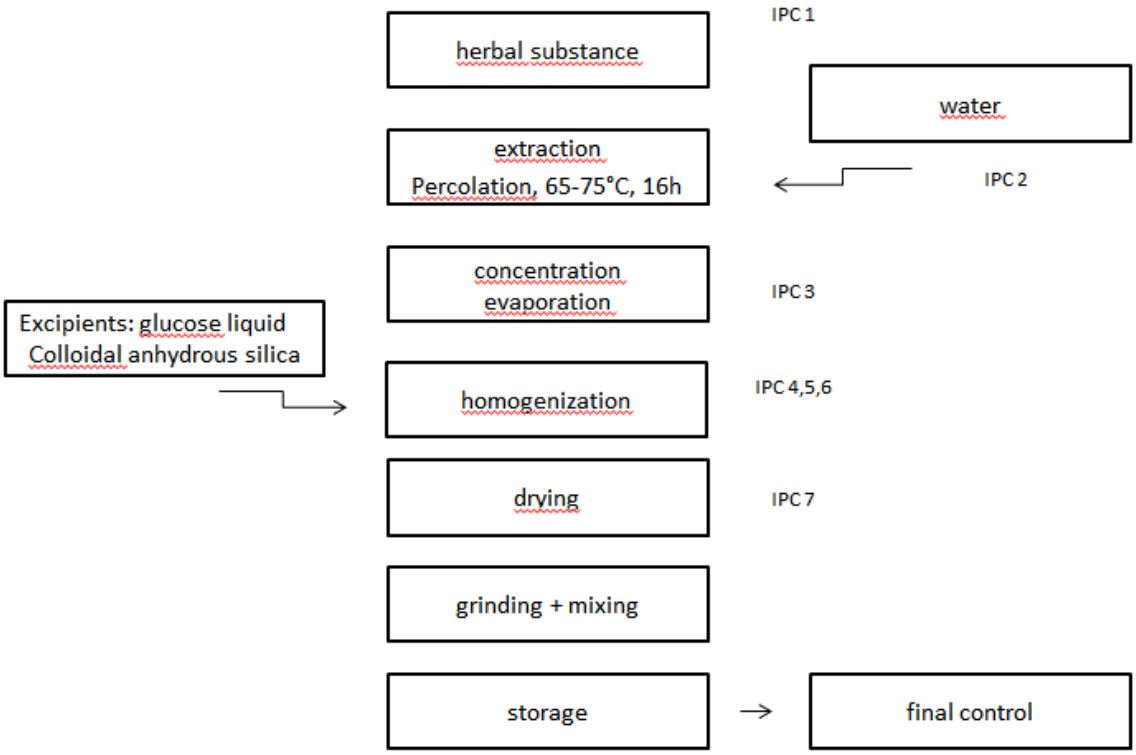
Calculation formula for the quantities of excipients is provided here.

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:

parameter	limit	result
odour („Geruchsschwellenwert TON“) *	2 bei 12°C 3 bei 25°C	odourless
taste („Geschmacksschwellenwert TFN“)	--------	neutral
clouding	1,0 NTU	< 0.2 NTU
sediment (qualitativ)	---------	none

absorbance coeff. 436 nm	1/m	0,5	< 0.1 m^{-1}
conductivity (25°C) *	µS/cm	1000	537
pH-value at measured temperature *		6,5 – 9,5	7,27
acid capacity until pH = 4,3	mmol/l	-----	4.31
oxygen (O_2)	mg/l	-----	0,47
total hardness of water	°dH	10-25	17.0
carbonate hardness	°dH	-----	12.1
calcium (Ca)	mg/l	50-150	99.5
magnesia (Mg)	mg/l	10-20	13.2
sodium (Na)	mg/l	50	10.2
potassium (K)	mg/l	5	1.73
iron (Fe)	mg/l	0.05	< 0.05
manganese (Mn)	mg/l	0.03	< 0.02
ammonia- ion (NH_4^+)	mg/l	0.1	< 0.02

nitrite- ion (NO_2^-)	mg/l	0.1	< 0.005
nitrate- ion (NO_3^-)	mg/l	10	1.44
chloride- ion (Cl^-)	mg/l	50	12.9
sulphate-ion (SO_4^{2-})	mg/l	150	79.2

total organic carbon (TOC)		no abnormal variation	< 0.47 mg/l
permanganate-index	mg O_2/l	2.5	1.58

parameter	limit	Result
total aerobic bacteria: at 22°C breeding temp. at 36°C breeding temp.	 max. 100 / 1 ml max. 100 / 1 ml	 0 0
E.coli: Enterococci Coliformic germs:	0 / 100 ml 0 / 100 ml 0 / 100 ml	negative negative negative

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.

Justification for the range of temperature is given here.

3.2.S.2.5 Process Validation and/or Evaluation

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

The herbal preparation is produced under standard production conditions in a range of batch sizes. Based on the analytical results of five batches in a retrospective process validation, a batch size of 250-350 kg can be considered as validated.

Batch No.	Acceptance	1111	1112	1113	1114	1115

	criteria					
Date of release		10.08.2005	24.09.2005	27.10.2005	26.11.2005	12.12.2005
Batch Size		355 kg	280 kg	350 kg	250 kg	340 kg
DERnative	5-9:1	6,5:1	7,5:1	5:1	8,5:1	7:1
Characters		complies	complies	complies	complies	complies
Particle size	95 % < 0,315 mm	complies	complies	complies	complies	complies
Loss on drying	≤ 6 %	2,7	1,8	4,2	4,6	2,4
Fingerprint identity		complies	complies	complies	complies	complies
Assay (sesquiterpenic acids)	≥. 0,02 % (*m/m*)	0,03	0,05	0,04	0,025	0,035
Microbiological examination		complies	complies	complies	complies	complies
TAMC	≤ 10^4 CFU/g	136	< 10	116	< 10	223
TYMC	≤ 10^2 CFU/g	34	< 10	< 10	15	26
Bile-tolerant gram-negative bacteria	≤ 10^2 CFU/g	< 10	< 10	< 10	20	50
E. coli (1 g)	Absence (1 g)	absent	absent	absent	absent	absent
*Salmonella (*25 g)	Absence (25 g)	absent	absent	absent	absent	absent

The historical data demonstrate that the quality parameters conform with their acceptance criteria. The batch data support the proposed DER_{native}.The retrospective analysis of the five batches demonstrates that the extract quality is reproducible.

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 acetoxy-valerenic 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**).

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 manufacture 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, acetoxy-valerenic and hydroxy-valerenic 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).

Release specification

Valerian root release-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	TLC according to Ph. Eur. monograph "Valerian root"	Ph. Eur. 2.2.27
Foreign matter	≤ 5 % of stem bases and ≤ 2 % of other foreign matter	Ph. Eur. 2.8.2 3.2.S.4.2.2
Loss on drying	≤ 12.0 %	Ph. Eur. 2.2.32
Total ash	≤ 12.0 %	Ph. Eur. 2.4.16
Ash insoluble in hydrochloric acid	≤ 5.0 %	Ph. Eur. 2.8.1
Assay (essential oil)	≥ 4 mL/kg (dried drug)	Ph. Eur. 2.8.12
Assay (sesquiterpenic acids,, expressed as valerenic acid)	≥ 0.17 % (dried drug)	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 ppm cadmium: ≤ 1.0 ppm mercury: ≤ 0.1 ppm	Ph. Eur. 2.4.27 3.2.S.4.2.1
Microbiological quality	in accordance with Ph. Eur. 5.1.8 A TAMC: ≤ 10^7 TYMC: ≤ 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.

Release specification

Valerian root-dry-extract release-specification	**Valid from: 12.12.2010**	**Version number aaa**
Parameters	**Acceptance criteria**	**Test procedures**
Organoleptic test	brown, hygroscopic powder	visual
Particle size	min. 95 % = 0.315 mm	3.2.S.4.2.2
Loss on drying	≤ 6.0 %	Ph. Eur. 2.8.17
Identity test	TLC 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	in accordance with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤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. 2.6.12

*Specification is in the validated range

Retest specification

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	≤ 6.0 %	Ph. Eur. 2.8.17
Fingerprint test	TLC complies with the chromatogram at the start	Ph. Eur. 2.2.27
Assay (sesquiterpenic acids, expressed as valerenic acid)	90.0 – 110.0 %* of the initial value (dried extract) HPLC	Ph. Eur. 2.2.29
Microbiological quality **	in accordance with Ph. Eur. 5.1.8 B TAMC ≤ 10^4 TYMC ≤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).*

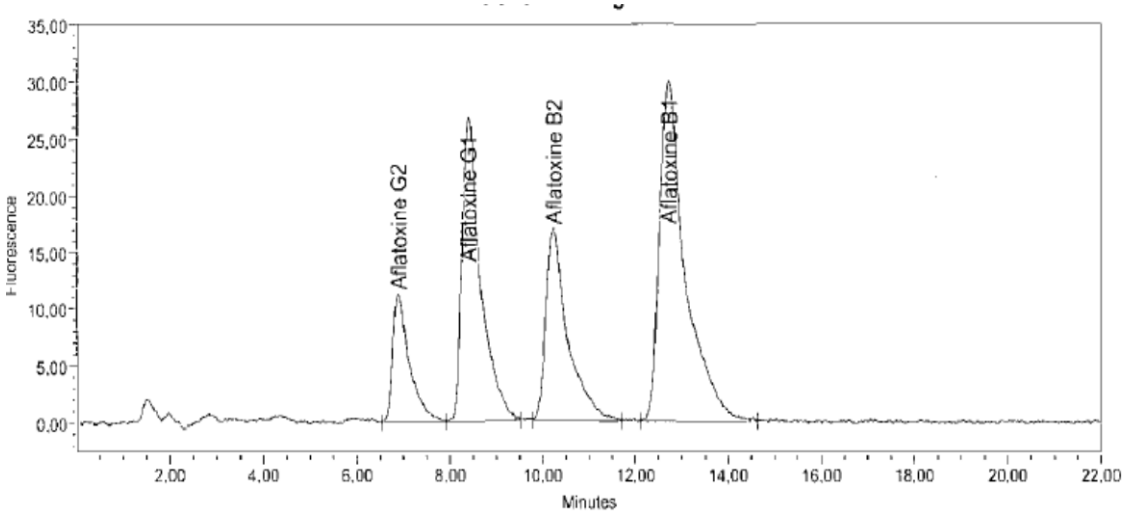
Test for aflatoxins — Internal HPLC procedure according to Ph. Eur. 2.8.18.

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:

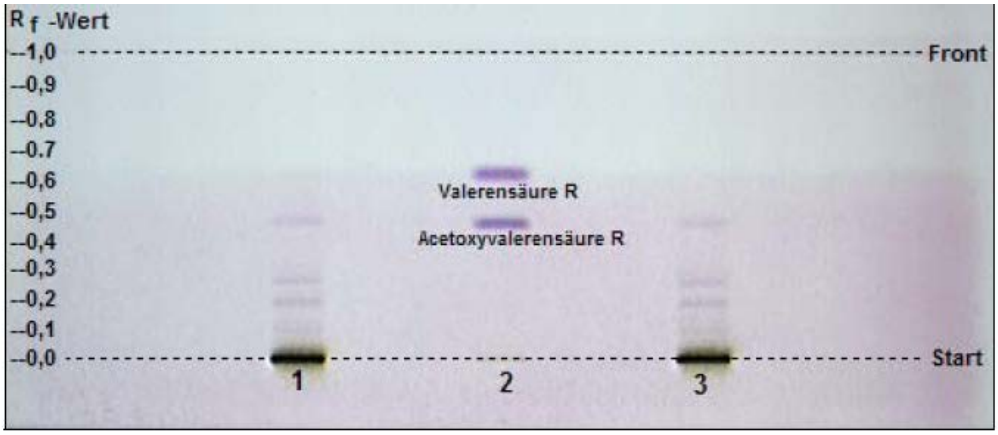


Microbiological quality — Ph. Eur. 5.1.8, method Ph. Eur. 2.6.31 / Ph. Eur. 2.6.12

3.2.S.4.2.2 Herbal preparation

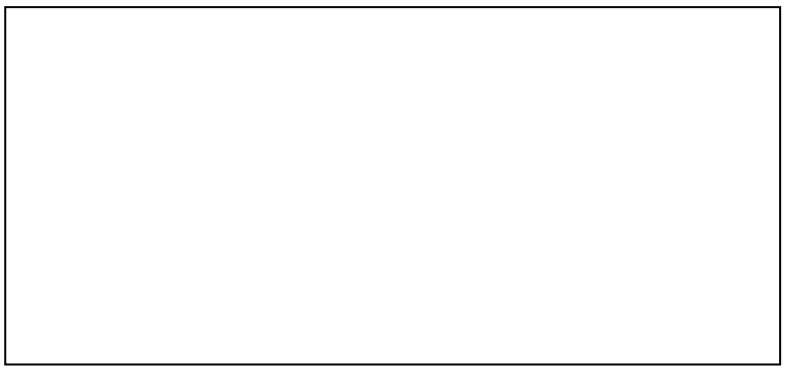
The analytical methods used for the identity and purity tests on the herbal preparation Valerian root dry extract are in accordance with the Ph. Eur. monograph “Valerian dry aqueous extract” (2400) and “Extracts, Dry extracts” (0765)

Organoleptic tests	brown, hygroscopic powder;
Particle size	particle size is at least 95 % ≤ 0.315 mm. 10.0 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“. Exemplary TLC chromatogram



Assay (HPLC) carried out in accordance to method described for the assay in the Ph. Eur. monograph “Valerian dry aqueous extract“

Exemplary HPLC chromatogram



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 B_2:

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

Three certificates of analyses are provided here, exceeding the minimum requirement of two batches per supplier (herbal substance) and two batches of dry extract.

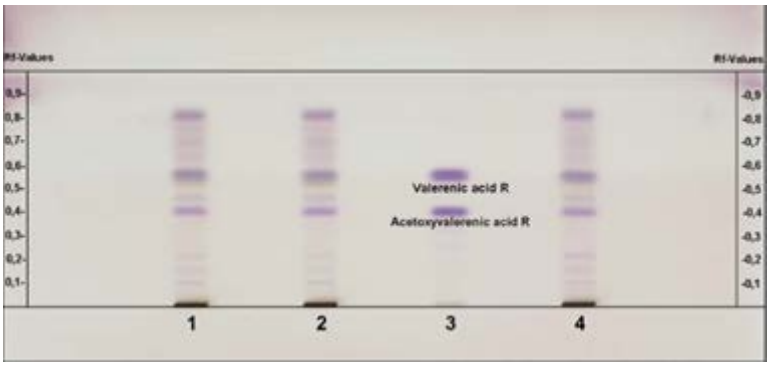
3.2.S.4.4.1 Herbal substance

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
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	1.5 0.3

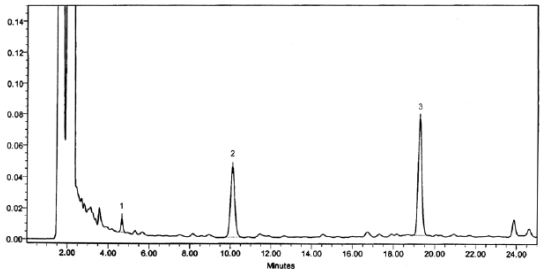
	mercury: ≤ 0.1 ppm	0.01
Microbiological quality	complies with Ph. Eur. 5.1.8 A TAMC: ≤ 107 TYMC: ≤ 105 E. coli: ≤ 103 Salmonella: absence (25 g)	 900000 40000 < 10 absent
Test for aflatoxins	Aflatoxin B1: ≤ 2 µg/kg Aflatoxin B1, B2, G1, G2: ≤ 4 µg/kg	< 0.5 < 1.0

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

Peak areas and retention times are also stated in the dossier.

Pesticide residues of batch 11223344

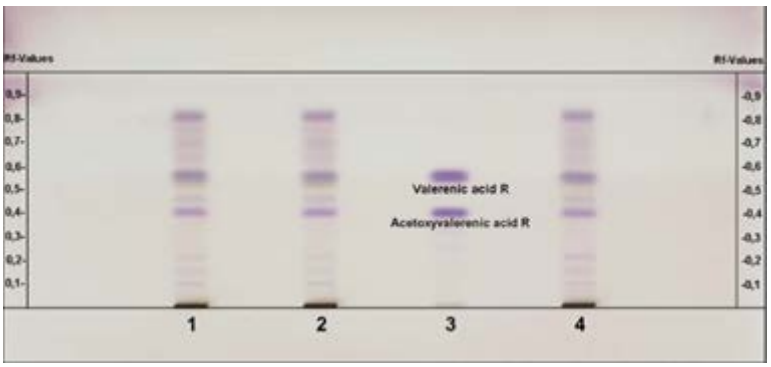
Substance	Limit (mg/kg)	Value
Acephate	0.1	n.d.
Alachlor	0.05	n.d.
Aldrin and Dieldrin (sum of)	0.05	n.d.
Azinphos-ethyl	0.1	n.d.
Azinphos-methyl	1	n.d.
Bromophos-ethyl	0.05	n.d.
Bromophos-methyl	0.05	n.d.
Brompropylate	3	n.d.
Chlordane, sum	0.05	n.d.
Chlorfenvinphos	0.5	n.d.

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.
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.

501 **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. monogr. "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
Microblological 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

502 TLC chromatogram for the parameter identity



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504 2 = Batch No: 55667788
505 3 = Acetoxyvalerenic- and valerenic acids
506 4 = Valerian root
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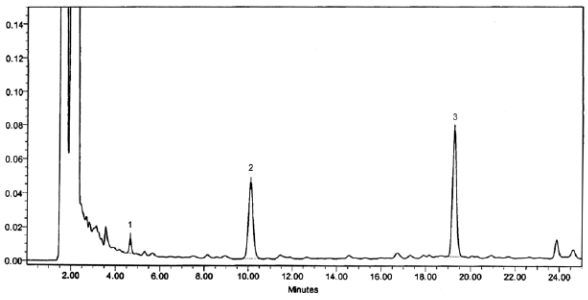
508 HPLC chromatogram for the parameter assay



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

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510 Peak areas and retention times are also stated in the dossier.

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512 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.
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.

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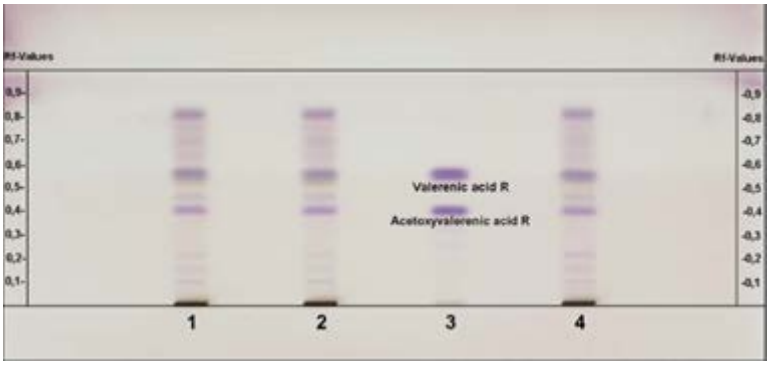
514 **Batch No: 11552277, Batch size: 2800 kg**

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	3.1 ≤ 2
Loss on drying	≤ 12.0 %	7.1
Total ash	≤ 12.0 %	10.0
Ash insoluble in hydrochloric acid	≤ 5.0 %	4.7
Assay (essential oil)	Ph. Eur. monograph "Valerian root" ≥ 4 mL/kg (dried drug)	8.9
Assay (sesquiterpenic acids, expressed. as valerenic acid)	Ph. Eur. monograph "Valerian root"	0.41

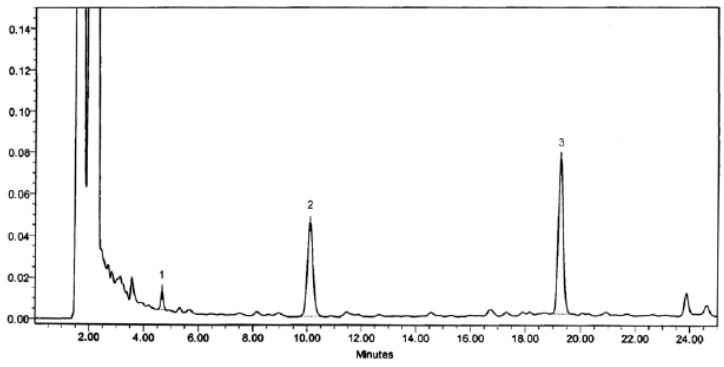
	≥ 0.17 % (dried drug)	
Test for pesticide residues	Ph. Eur. 2.8.13	complies (see addendum)
Test for heavy metals	lead: ≤ 5 ppm cadmium: ≤ 1.0 ppm mercury: ≤ 0.1 ppm	1.5 0.3 n.d.
Microblological quality	complies with Ph. Eur. 5.1.8 A TAMC: ≤ 10^7 TYMC: ≤ 10^5 E. coli: ≤ 10^2 Salmonella: absence (25 g)	 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: 11552277
3 = Acetoxyvalerenic- and valerenic acid
4 = Valerian root

HPLC chromatogram for the parameter assay



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

Peak areas and retention times are also stated in the dossier.

Pesticide residues of batch 11552277

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.
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.

526 **3.2.S.4.4.2 Herbal preparation**

527 **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

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529 TLC chromatogram for the parameter identity

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537 HPLC chromatogram for the parameter assay

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Peak areas and retention times are also stated in the dossier.

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

Peak areas and retention times are also stated in the dossier.

Batch-No: 213, Manufacture date 28.10.12, Release date 15.12.12, Batch size 360 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 %	5.1
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)	0.03
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

Peak areas and retention times are also stated in the dossier.

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 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 and validated sufficiently in accordance with the requirements of the EU-Guideline on validation.

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

Acetoxy-valerenic 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-No Y0000583 is used as primary reference standard for the assay of sesquiterpenic acids. At the time batch 3 is valid. The assigned content is 0.43 % of $C_{15}H_{22}O_2$. No further information is available at the EDQM.

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 and complies with Commission regulation (EU) No 1183/2012. The container is therefore suitable for storage of the herbal substance.

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 release 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
	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 retest specification 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 substancezones after storage for 12 months at 25 °C / 60 % RH.

The results of the long term testing are in accordance with the retest specification.

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.

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)	90.0 – 110.0 % 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 (25 g) 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 and HPLC chromatograms should be provided here.

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**

713

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

714

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**

715

Product: Valerian root dry extract	**9 months**	**12 months**

Batch: 211 Storage conditions: long-term 25 °C ± 2 °C, 60 % RH ± 5 % HPLC – fingerprint		

716

717 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	90.0 – 110.0 % 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 (25 g) E. coli: absence (1 g)	< 10 < 10 <100 absent absent	n.t.	n.t.	n.t.	< 10 < 10 <100 absent absent

718 n.t. = not tested
719

720 **TLC and HPLC chromatograms should be provided here.**

721

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**

722

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

723

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**

724

725 Batch 213 long term testing

Parameters	**Acceptance criteria**	**t_0**	**t_3**	**t_6**	**t_9**	**t_{12}** 726 727
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)	90.0 – 110.0 % 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 (25 g) 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 and HPLC chromatograms are provided here.

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**

733

734 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	4.9
Fingerprint (TLC)	complies with the chromatogram at the start	complies	oos
Assay calculated via sesquiterpenic acids (HPLC)	90.0 – 110.0 % 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.

735 n.t. = not tested
736

TLC and HPLC chromatograms are provided here.

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**

741 Batch 212 accelerated testing
742

Parameters	**Acceptance criteria**	t_0	t_3
Organoleptic test	brown, hygroscopic powder with valerian smell	complies	complies
Loss on drying	≤ 6.0 %	4.1	4.8
Fingerprint (TLC)	complies with the chromatogram at the start	complies	oos
Assay calculated via sesquiterpenic acids	90.0 – 110.0 % 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.

743 n.t. = not tested

TLC and HPLC chromatograms are provided here.

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**

747 Batch 213 long term 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	6.0
Fingerprint (TLC)	complies with the chromatogram at the start	complies	oos
Assay calculated via sesquiterpenic acids (HPLC)	90.0 – 110.0 % 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.

748 n.t. = not tested
749

TLC and HPLC chromatograms are provided here.	

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

765 # Drug product

766 ## 3.2.P.1 Description and composition of the drug product

767 **Dosage form**

768 The dosage form is a film-coated tablet containing 500 mg dry extract preparation (corresponding to
769 400 mg native dry extract) of valerian root. The shape is oblong and the colour yellow.

770 **Composition**

771 1 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 %	Coating agent	32.80	 Ph. Eur. Ph. Eur.

	Titanium dioxide 25 % Talc 14,8 %			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.

772 * Combined as Cellactose 80

773 **not contained in the finished product

774 **Container**

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

777 ## 3.2.P.2 Pharmaceutical development

778 ### 3.2.P.2.1 Components of the drug product

779 #### 3.2.P.2.1.1 Drug Substance

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

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

789 #### 3.2.P.2.1.2 Excipients

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

794 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

795 ### 3.2.P.2.2 Drug product

796 #### 3.2.P.2.2.1 Formulation Development

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

799 Doses are very accurate and administration is easy.

800 Every colouring is possible.

801 The taste of the herbal substances could be masked.

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

803 Therefore compliance will be good.

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

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

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

811 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 optimization 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 approx. 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

An overage of 20 % of the film-coating suspension is applied to compensate for losses during the spraying step. This is a commonly used amount for such film-coating excipients.

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***

873 * 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******

874 * water amount not contained in the final product

875 ** not contained in the final product

876 *** overage of 20% is included

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

877 ## 3.2.P.3.3 Description of manufacturing process and process controls

878 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

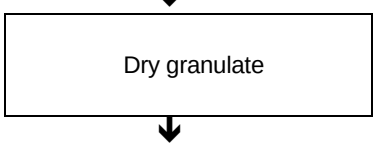
The film-coated tablets are sealed into a corresponding number of blisters; the blisters are packed into folding boxes together with the package insert = finished packs.

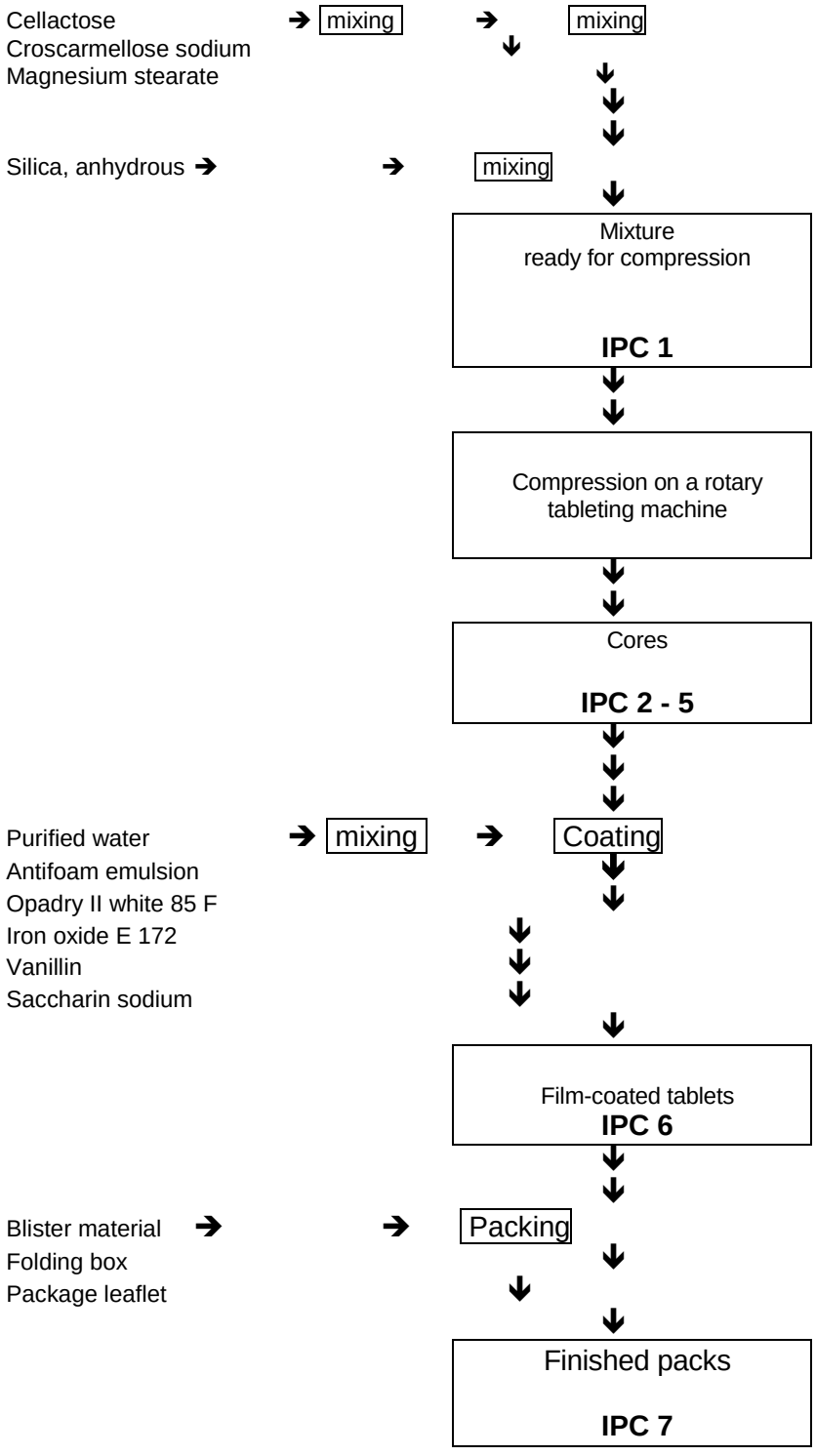
In-process controls and specification of blister strips: see IP 7.

Manufacturing flow diagram:

Component **Process / Product / IP controls**

Dry extract of valerian root (preparation) ➔ mixing
Cellactose compacting
Hydrogenated soya oil sieving
Croscarmellose sodium





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	resistance to	≥ 1x per hour	Ph. Eur. 2.9.8	70 - 190 N

	IPC 3 IPC 4 IPC 5	crushing disintegration uniformity of mass friability	1 x per batch ≥ 1x per hour 1 x per batch	Ph. Eur. 2.9.1 Ph. Eur. 2.9.5 Ph. Eur. 2.9.7	≤ 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

984 IPC for finished packs

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

985 ## 3.2.P.4 Control of excipients

986 ### 3.2.P.4.1 Specifications

987 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 %	 Ph. Eur.

Methyl cellulose 7.67 % Sorbic acid 0.31 %	Ph. Eur. Ph. Eur.
Purified water	Ph. Eur.*

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

989 Non-Pharmacopoeial excipients:

Substance	Specification
Iron oxide, E 172	RL 2009/35/EG i.V. mit VO (EG) Nr. 1333/2008 und der 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 1,0 % 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

990

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 45.0 g water into an appropriate size beaker. Add 20.0 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	corresponds to the	HPLC profile from assay

(HPLC)	example-fingerprint (see P.5.2)	
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 ≤ 104 TYMC ≤ 102 bile-tolerant gram-negative bacteria: ≤ 102 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
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:

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

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. 1.00 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 three 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 raw data are provided here.

Validation on the HPLC method assay

<u>Sesquiterpenic acids:</u>

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 ≤ 104 TYMC ≤102 bile-tolerant gram-negative bacteria: ≤ 102 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 ≤ 104	< 10
	TYMC ≤102	< 10
	bile-tolerant gram-negative bacteria: ≤ 102	< 10
	Salmonella : absence (25 g)	absent
	E. coli: absence (1 g)	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

(Act

ive 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 %	796.5 mg

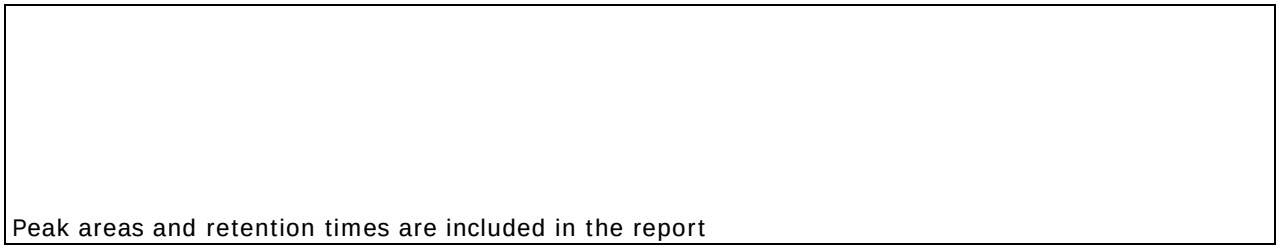
	(745.85 – 824.36 mg) Ph. Eur. 2.9.5	
Uniformity of mass	Ph. Eur. 2.9.5	+ 2.32 - 3.27 % conforms
Disintegration	≤ 30 min Ph. Eur. 2.9.1	19 min
Loss on drying	≤ 6 %	4.1 %
TLC-fingerprint (valerian root)	corresponds	corresponds*
HPLC-fingerprint (valerian root)	corresponds	corresponds*
Microbiological quality	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.

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

Characterization (Identity, Purity, Content)

Comment

References (Citations)

Validation (HPLC)

References (complete Papers)

Exemplary Certificate of Analysis with Attachments

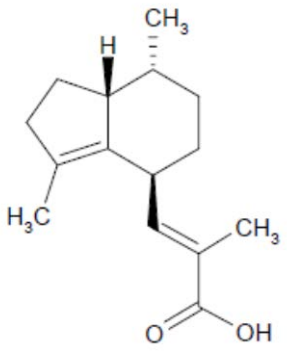
1. Nomenclature

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

An ethanolic-aqueous extract from Valerian root is dissolved in ethanol (50 % by weight in water) and extracted with heptane. The heptane is distilled off under vacuum. The oily residue is separated between 0.6 % potassium hydroxide in ethanol (50 % by weight in water) and heptane. After acidification of the potassium hydroxide solution with hydrochloric acid to pH 2, the valerenic acid is re-extracted with heptane.

The valerenic acid so obtained is purified by means of column chromatography over Sephadex LH-20 (mobile phase: acetone), crystallisation from acetone / water and finally recrystallization from methanol.

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.

1 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, S. 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

Approx. 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

10 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 2.3.P.5.2 and their validation reports are listed in Section 2.3.P.5.3.

Results of ICH stability testing of 3 production scale batches stored in blisters, as described in Section 3.2.P.7.2., 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 month	6 month	9 month	12 month	18 month	24 month	36 month
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

1390

1391 **Long term storage conditions: 30°C/65% RH**

Parameter	Initial	3 month	6 month	9 month	12 month
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	Initial value	X	X	X	X

extract of valerian root	+/- 5 % / film-coated tablet				
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 month	6 month
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		X

	TYMC ≤10^2 bile-tolerant gram-negative bacteria: ≤ 10^2 Salmonella : absence (25 g) E. coli : absence (1 g)		

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

The stability tests are finalized. According to GMP-rules, on-going stability tests will be performed on one batch per year.

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.

1401 Product name: Valerian film-coated tablets

1402 Batch: F0230

1403 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 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	not tested	not tested	not tested

1404 Product name: Valerian film-coated tablets

1405 Batch: F0230

1406 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

1407 Product name: Valerian film-coated tablets

1408 Batch: F0230

1409 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 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	not tested	not tested	 < 100 < 10 < 1 absent absent

1410 Product name: Valerian film-coated tablets

1411 Batch: F0230

1412 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	0 months	3 months	6 months

TLC – fingerprint and HPLC-chromatogram			
9 months	**12 months**	**18 months**	**24 months**

1413

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**

1414 1 = Reference solution

1415 2 = Test solution

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

1416

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

1417 1 = Reference solution

1418 2 = Test solution

1419 Product name: Valerian film-coated tablets

1420 Batch: F0235

1421 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

1422 Product name: Valerian film-coated tablets

1423 Batch: F0235

1424 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-	complies	complies	complies

	chromatogram			
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

1425 Product name: Valerian film-coated tablets

1426 Batch: F0235

1427 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

1428 Product name: Valerian film-coated tablets

1429 Batch: F0235

1430 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	382.9 mg	380.5 mg	385.4 mg

	(sum of Sesquiterpenic acids calc. as valerenic acid)	100.0 % (1.156 mg)	99.5 % (1.149 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

1431

Product: Valerian film-coated tablets Batch: F0235 Storage conditions: Long term, 25 °C ± 2 °C, 60 % r RH ± 5 % RH TLC – fingerprint and HPLC-chromatogram	**0 months**	**3 months**	**6 months**
6 months	**9 months**	**18 months**	**24 months**
Product: Valerian film-coated tablets	**36 months**		

Batch: F0235 Storage conditions: Long term, 25 °C ± 2 °C, 60 RH ± 5 % RH TLC – fingerprint and HPLC-chromatogram			

1432

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**

1433

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

1438 Batch: F0301

1439 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

1440 Product name: Valerian film-coated tablets

1441 Batch: F0301

1442 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)	368.0 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

1443 Product name: Valerian film-coated tablets

1444 Batch: F0301

1445 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

1446

Product: Valerian film-coated tablets Batch: F0301	0 months	3 months	6 months

Storage conditions: Long term, 25 °C ± 2 °C, 60 % RH ± 5 % RH TLC – fingerprint and HPLC-chromatogram			
9 months	**12 months**	**18 months**	**24 months**

1447

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**

1448

Product: Valerian film-coated tablets Batch: F0301 Storage conditions: Intermediate,	**0 months**	**3 months**

30 °C ± 2 °C, 65 % RH ± 5 % RH TLC – fingerprint and HPLC-chromatogram		
6 months	**9 months**	**12 months**

1449

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.