5 April 2016
EMA/HMPC/669906/2015
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on 'Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products' (EMA/HMPC/71049/2007 Rev. 2)

Table 1: Organisations and/or individuals that commented on the draft second revision of the 'Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products' as released for public consultation on 9 April 2015 until 15 July 2015.

	Organisations and/or individuals
1	Association of the European Self-Medication Industry (AESGP)
2	European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
3	European Herbs Growers Association (EUROPAM)
4	i.DRAS GmbH, Germany

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	In principle we appreciate the revision of the guideline which provides helpful information to the applicants with regard to the compilation of the quality dossier. However, we fear that the content of the mock-up in Appendix 2 and the details given go beyond the requirements laid down in pharmacopoeias or guidelines. We understand that the mock-up is regarded as an example which intends to give support to applicants and to demonstrate by the practical example of Valerian extract how a real dossier is compiled. However, the requirements shall not be more stringent than existing guidelines and pharmacopoeia rules. When reference is made to other regulatory guidance documents, from our point of view the HMPC Notes for guidance should be quoted with the first priority followed by other relevant documents, because the HMPC Guidelines are specifically tailored to herbal medicinal products and take into account their particularities. We are aware of the fact that due to the different types of products and ways of production of herbal medicinal products, it is difficult to define a uniform type of documentation.	Comment has been noted.
EUCOPE	EUCOPE welcomes the opportunity for interested parties to submit their comments on the revision of 'Guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products'. This document gives helpful guidance on how to present the application for registration of THMPs in a CTD. However, we see some critical points that we want to address in the following: The Guideline already describes in chapter 3 and 4 the legal basis and all relevant regulatory documents that have to be taken into consideration for the compilation of a CTD dossier for THMPs. Appendix 1 gives especially valuable guidance for the structure and content of Module 3 – Quality part of a CTD, also referring to the applicable regulatory framework. The Appendix 2 contains a mock-up dossier which, however, goes beyond the requirements as	The text 'does not necessarily represent all requirements' has been deleted.

Interested party	Comment and Rationale	Outcome
	stated in Appendix 1 and in some aspects even contradicts Appendix 1. Furthermore, there are inconsistencies with the requirements described in the Notice to Applicants: Volume 2b, Medicinal products for human use, Presentation and format of the dossier CTD. The interpretation of the wording 'does not necessarily represent all requirements' can be misunderstood insofar that the documentation of the mock-up might not be complete and even more information is needed. As we have the concern that the mock-up dossier may be used as a benchmark during assessment of applications, we consider Appendix 2 not suitable to be part of such a guideline and kindly request the deletion of this section. Please find in Table 3 some examples for additional requirements and discrepancies between Appendix 2 and - NtA: Volume 2b, Notice to Applicants, Medicinal products for human use, Presentation and format of the dossier CTD - Guideline: EMA/HMPC/71049/2007/Rev.2 Guideline on the use of the CTD format in the preparation of a herbal medicinal - Appendix 1 in EMA/HMPC/71049/2007/Rev.2, and further comments that Appendix 2 is not suitable to be part of this guideline.	
EUROPAM	As an association dedicated to the production of medicinal plants, EUROPAM likes to focus comments on raw materials (herbal substances), their cultivation/wild collection and their first processing steps only. EMA should consider that a lot of conditions in field production/wild collection are – mainly due to environmental influences - more variable and need sometimes more flexibility in order to react to extreme situations. We are mainly concerned about the details listed in the valerian example in Appendix 2 and would encourage adding a statement that this example should be seen only as an example not to be followed in a strict sense. This form contains information that is not useful in registration but can be handled more efficiently under GACP. Therefore we believe that the commitment	The disclaimer clarifies that the Appendix 2 is only an example.

Interested party	Comment and Rationale	Outcome
	concerning a full compliance GACP qualification should be considered as the most important point. Generally the information demanded should focus on the information related to a possible risk and should avoid any irrelevant details in order to facilitate the administration of the production. For that reason EUROPAM recently proposed a list of information essential in terms of 'risk related information' in order to harmonize and simplify batch certificates (Novak, J: EUROPAM statement on requirements for a batch certification of medicinal and aromatic plants (MAPs), Journal of Applied Research on Medicinal and Aromatic Plants, 1 (2014) 70-71. http://dx.doi.org/10.1016/j.jarmap.2014.05.001) Although this publication focuses on batch certificates, some information could possibly be a good guidance for a CTD example. Globally for the herbal substance the user should indicate the following information: • Origin • Cultivation or wild collection • Harvest/collection period • Vegetative stage • Conventional or organic cultivation • Post harvest/post collection processes (specify in particular drying system and condition if applicable) • Storage condition	

Specific comments on text

Section number and heading	Interested party	Comment and rationale	Outcome

Comments on guideline text

3.2.S.2.5 Process validation and/or evaluation	AESGP	3.2.S.2.5 Process validation and/or evaluation Herbal preparation Not required acc. to GL 70278/2012-Rev1 '…information on validation of non-sterile active substances is not required in the dossier …'. For non-sterile chemical entity drug substance processes, results of process validation studies are not normally included in the dossier. Please also see our comments in Appendix 2 (3.2.S.2.5).	**Not endorsed** GL text 'applicable' does not necessarily mean that data have to be included in the dossier.
2.4. Non-clinical overview	AESGP	**Comment** *'When missing data on genotoxicity in section 5.3 of the monograph are mentioned they should be appropriately complemented.'* Instead of the wording 'appropriately complemented', the relevant HMPC Guideline for genotoxicity testing should be cited, if own data on genotoxicity testing have to be provided. **Proposed change** When missing data on genotoxicity in section 5.3 of the monograph are mentioned ~~they should be appropriately complemented~~ and own tests have to be provided, the testing strategy should follow the relevant HMPC Guideline (EMEA/HMPC/107079/2007).	**Not endorsed** Comment was considered and it was agreed that reference to GL EMEA/HMPC/107079/2007 as well as to ICHS2(R1) (EMA/CHMP/ICH/126642/08) has to be included in the dossier, but following the purpose of the 'Guideline on the use of CTD format for Registration Applications' the wording 'appropriately complemented' is considered to be more comprehensive and therefore is preferred.

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2.4. Non-clinical overview	AESGP	**Comment** *'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.'* If the HS/HP is identical to that already listed in the monograph, and the applicant wants to refer to the non-clinical / genotoxicity data mentioned in the monograph, there should be no need for 'demonstration', i.e. any analytical comparison as example. Even if the own HP differs slightly from that mentioned in the monograph, reference to the monograph rather than a 'demonstration' should be possible if this is in agreement with the 'Guideline on selection of test materials for genotoxicity testing' (EMEA/HMPC/67644/2009). **Proposed change** ~~Furthermore~~ For reference to genotoxicity data cited in the monograph, the applicant will need to demonstrate that the proposed product contains a HS/HP which correspond to the HS/HP listed in the monograph if that HS/HP is out of the 'representative range' of herbal substances/preparations according the 'Guideline on selection of test materials for genotoxicity testing' (EMEA/HMPC/67644/2009).	**Not endorsed** Text consistent with existing 'Regulatory Q&A on herbal medicinal products' (R8; EMA/HMPC/345132/2010 Rev.21 Corr). In the guideline EMEA/HMPC/67644/2009 'representative range' is considered to be what is covered by the 'bracketing/matrixing' concept. Limits for such a range are not defined in the GL. This concept is not appropriate in the context of the need to show comparability of one extract to another similar one.
2.4. Non-clinical overview	AESGP	**Comment** *'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.'* See above. For minor deviations regarding the extract characteristics there should be no need for an analytical comparison if these differences are within the scope and 'representative range' of	**Not endorsed** See above

Section number and heading	Interested party	Comment and rationale	Outcome
		the bracketing & matrixing guideline (EMEA/HMPC/67644/2009). **Proposed change** If the extract solvent and/or concentration is/are different from those given in the assessment report/monograph and out of the 'representative range' of EMEA/HMPC/67644/2009, 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.	
2.5. Clinical overview	AESGP	**Comment** *'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.'* If the HS/HP/THMP is identical to that of the list entry, there should be no need for any 'demonstration' because this will already be obvious by the declaration, manufacture and composition of that HS/HP/THMP. **Proposed change** However, the applicant must ~~demonstrate~~ state in this section of the dossier that the proposed HS/HP/THMP complies fully with the European Union list entry.	**Not endorsed** The request to change the wording is comprehensible, however, the change is not endorsed in order to keep consistency with the wording under 2.4 and 2.5 (see above; '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.')
2.5. Clinical overview	AESGP	**Comment** *'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.'*	**Not endorsed** No definition for 'significant' or 'nonsignificant' differences exists.

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		According to Article 16c of Directive 2001/83/EC, a corresponding product, as referred to in paragraph 1(c), is characterised by having the same active ingredients, irrespective of the excipients used, the same or similar intended purpose, equivalent strength and posology and the same or similar route of administration as the medicinal product applied for. In this respect minor differences regarding DER or extraction solvents used should not ban any references to the monograph as well as the mandatory conduction of any analytical comparisons if this is mentioned with the term 'to demonstrate'. **Proposed change** 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 <u>if significant differences regarding the pharmaceutical characteristics between the preparations / substances exist.</u>	
2.5.5 Overview of Safety	AESGP	**Comment** *'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…'*	**This section was deleted.**

Section number and heading	Interested party	Comment and rationale	Outcome
		It should be taken into account that many of this pharmacovigilance data can only be listed if the product has already been on the market. Therefore, 'If not based on own pharmacovigilance data so far available by published or other bibliographical data' should be added.	
2.5.5 Overview of Safety	AESGP	**Comment** *'For example, if there are reports of serious adverse events, this must be balanced by sufficient evidence of appropriate benefit.'* The term 'serious adverse events' means any event, including those which are not connected to a herbal product (e.g. an adverse event caused by a concomitant therapy during a clinical trial). As a consequence for some herbals, this would lead to the need to frequently re-evaluate the benefit/risk-balance. **Proposed change** For example, if there are reports of serious adverse ~~events~~ reactions**,** this must be balanced by sufficient evidence of appropriate benefit.	**This section was deleted.**
4.2. Module 2: Common Technical Document Summaries 2.7. Clinical Summaries	EUCOPE	**Comment** According to ICH guidelines any supplementary data e.g. from literature sources can be provided in the 2.5 Clinical Overview. To present the 2.7 Clinical Summary only makes sense if the results/data from clinical studies shall be presented. Furthermore, the differentiation between tabulated and written summaries only exists in the non-clinical part. According to ICH guidelines, there is no Tabulated Clinical Summary (just Clinical Summary). The paragraph shall therefore be modified accordingly. **Proposed change** When supplementing data from clinical studies concerning the plausibility of pharmacological effects, ~~or~~ the efficacy of the THMP ~~as well as information~~	**Partially endorsed** **Proposed change** When supplementing data from (clinical) studies ~~concerning the plausibility of pharmacological effects or efficacy of the THMP as well as information on the safety of use~~ are addressed in section 2.5, the 2.7 ~~tabulated~~ clinical summary should be presented in tabulated format ~~in this section 2.7~~.

Section number and heading	Interested party	Comment and rationale	Outcome
		~~on~~ or the safety of use are addressed in section 2.5, the 2.7 ~~tabulated~~ clinical summary should be presented ~~in this section 2.7~~.	
3.2.S.2.1. Manufacturer(s)	AESGP	**Comment** *'For herbal substances* *The name, address and responsibility of each producer or supplier, including contractors, and each proposed site or facility involved in production/collection and testing of the herbal substance should be provided, where appropriate.'* The listing of the herbal substance suppliers in the dossier causes an inadequate burden to both MAHs and NCAs which will even increase in the future. Each change (e.g. addition of a new supplier) requires the filing of a variation. Since the vast majority of herbal marketing authorisations and registrations are national, a large number of variations will be necessary, which requires extensive resources for both MAHs and NCAs. It is a GMP requirement that only qualified suppliers may be used by the manufacturer of the herbal preparation. The compliance of herbal substance suppliers is controlled by regular inspections of the authorities responsible for GMP supervision. Therefore, we believe that the level of control of the herbal substance suppliers is adequate on the GMP/QA level and that an inclusion of suppliers in the MA or registration dossier does not provide additional benefit. Anyway, a change of herbal substance suppliers or inclusion of a new one is not a variation item included in the variation guideline. Therefore it is classified as Ib variation (cost and time consuming). **Proposed change** Delete this part. ~~*For herbal substances*~~	**Not endorsed** Information about suppliers required acc. to Annex 1 Dir. 2001/83/EC.

Section number and heading	Interested party	Comment and rationale	Outcome
		~~*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.*~~	
4.3. Module 3, 3.2.S.2.2. Description of Manufacturing Process and Process Controls	EUCOPE	**Comment** For herbal substances: Batch size and the term batch are not applicable to plant parts or deliveries of the whole plant, because a harvest is not homogenous due to natural variability of the individual plants and plant parts, respectively. The term batch requires a homogenous state of a material and a closed system considering GMP requirements. In contrast to this the total amount of a harvest may be divided into several deliveries used by several manufacturers of HMPs. So the term 'lot' should be used for a delivery of an herbal substance to be used as starting material for extraction and/or manufacturing of the finished product. Furthermore one lot of the herbal substance may be divided into distinct amounts for production of different batches of the herbal preparation. The herbal preparation is the first state in the process of a HMP where the term batch is applicable. In cases where a lot of the herbal substance is used as the active ingredient the term batch is first applicable to the distinct amount subjected to a process of homogenisation. **Proposed change -** Replace the term 'batch' by 'lot' <u>For herbal preparations:</u> **Proposed change** Please add 'Quantification or quantified extract' to the list	**Endorsed** **Proposed change** 'For herbal substances… • ~~Batch~~ <u>Lot</u> size • …' '<u>For herbal preparations</u> Information should be provided to adequately describe the manufacturing process of the herbal preparation as follows, including data on the herbal substance as described above: • Description of processing (including flow diagram) • Solvents, reagents • Purification stages • Standardisation<u>/Quantification</u> • Batch size'

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4.3. Module 3, 3.2.P.2.2.2. Overages (name, dosage form)	EUCOPE	Overages of active ingredients are not applicable for HMPs.	**Not endorsed** See 'Questions & answers on quality of herbal medicinal products/traditional herbal medicinal products' (Q14; EMA/HMPC/41500/2010 Rev.5); stability overages would be acceptable for standardised extracts if justified. The guideline is not restricted to THMP concerning Module 3. In addition, the 'Note for guidance on development pharmaceutics' (CPMP/QWP/155/96) gives the following information under the point overage: 'Overages are primarily employed to cover losses during the manufacture of active substance or key excipients, …'
Comments on Appendix 1			
3.2.S.2.5. Process Validation and/or Evaluation (name, manufacturer)	EUCOPE	Validation of extract manufacture is not necessary acc. to GL 70278/2012-Rev1 '…information on validation of non-sterile active substances is not required in the dossier …'. For non-sterile chemical entity drug substance processes, results of process validation studies are not normally included in the dossier.	**Not endorsed** See above

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3.2.S.4.1., 3.2.S.4.2.	EUCOPE	In both 3.2.S.4.1 and 3.2.S.4.2 reference to the Ph. Eur. should only be made with the following wording: 'current Ph. Eur.' This refers to both herbal substance and herbal preparation.	**Not endorsed** Rather include a general remark that reference to Ph.Eur. means reference to current Ph.Eur. unless otherwise indicated.
3.2.S.5 Reference standards or materials (name, manufacturer)	EUCOPE	The supplier's name and standard reference number should not have to be provided here. This is subject to the QA system.	**Not endorsed** Reference standards have to be characterised in the dossier.

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Comments on Appendix 2			
Disclaimer	AESGP	Appendix 2 contains a mock-up dossier which however, from our point of view, goes beyond the requirements as stated in Appendix 1 and in some aspects even contradicts Appendix 1. **Proposed change** Clarification should be added that Appendix 2 is not mandatory from a regulatory or scientific point of view but serves as a technical example.	**Not endorsed** Already addressed in the disclaimer.
Disclaimer	AESGP	**Comment** The interpretation of the wording 'does not necessarily represent all quality requirements' can be misunderstood insofar as the documentation of the example might not complete and more information is needed. **Proposed change** The product specific characteristics must be considered, so depending on the product more or less information is necessary.	**Partially endorsed** The sentence has been changed.
3.2.S.1.1	EUCOPE	Nomenclature of Guideline is not used: 'crude plant material' versus 'definition of herbal substance'.	**Endorsed** The wording 'crude plant material' has been changed to 'Definition of herbal substance'
3.2.S.1.1 Laboratory Code	EUCOPE	**Comment** The indication of the laboratory code is not relevant for registration purposes but rather GMP-relevant information. **Proposed change** Delete Laboratory Code	**Not endorsed** The laboratory code can be indicated if available, it is not mandatory

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3.2.S.1.1 Laboratory Code	AESGP	**Comment** The indication of the laboratory code is not relevant for registration purposes but rather GMP-relevant information. **Proposed change** Delete Laboratory Code	**Not endorsed** See above
3.2.S.1.2	i.DRAS	**Comment** In this chapter only the structure of relevant analytical markers / active markers / constituents with known therapeutic activity should be mentioned for the herbal substance and herbal preparation. **Proposed change (if any)** Information concerning other constituents should be moved to chapter 3.2.S.3.1	**Not endorsed** According to current guidelines a description of the relevant analytical markers / active markers / constituents with known therapeutic activity and additionally information of other constituents are required. In chapter 3.2.S. 3.1 additional information regarding special aspects of the analytical principles as applied should be given.
3.2.S.1.2	AESGP	**Comment** Information on other constituents is not relevant. This commonly available information (Assessment report HMPC, Hager, etc.) should not be the usual content of a dossier. **Proposed change** Delete lines 65-80.	**Not endorsed** See above
3.2.S.1.3	EUCOPE	Information regarding herbal substance is not requested by NtA and Guideline, it is suggested to omit the chapter ‘herbal substance’.	**Not endorsed** The structure corresponds with the CTD-Guideline; however, it should be noted that information is only needed for the herbal preparation

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3.2.S.1.3	AESGP	**Comment** In case of a herbal extract, the general properties are already included in the specification. Thus, it is not necessary to give this information twice. **Proposed change -** Delete lines 98-99 or refer to the specification.	**Not endorsed** According to the CTD-Guideline Appendix 1 organoleptic and physico-chemical description of other relevant properties of the herbal preparation are requested.
3.2.S.2.1.1	AESGP	Testing laboratories for both herbal substance and herbal preparation should not have to be given in the dossier. The comprehensive CoA which contains all results of release testing should suffice.	**Not endorsed** Indication of the Laboratories responsible for testing corresponds to the NTA and Directive 2001/83/EC.
3.2.S.2.1.1 & 3.2.S.2.1.2	i.DRAS	**Comment** Usually, the herbal substance / the herbal preparation is tested and a certificate of analysis is created, but it is not 'released' **Proposed change (if any)** It is sufficient to mention the manufacturer and the testing laboratory	**Endorsed** Changed to 'manufacturer/site where batch testing takes place'.
3.2.S.2.2.1	AESGP	**Comment** There is no correlation between the batch size of the herbal substance and the quality. The batch size can vary according to natural circumstances of the herbal substance, so this information is not necessary. **Proposed change -** Please delete this line.	**Not endorsed** The range of the batch size is necessary; it is also referred to the Classification-Guideline B.I.a.3 (variation procedure).
3.2.S.2.2.1	EUROPAM	*The batch size of the herbals substance Valerian root is between 2,000 and 20,000 kg.* Under practical conditions, the batch size is very variable and should not be regulated here since it is not linked to quality.	**Not endorsed** See above
3.2.S.2.2.1	AESGP	**Comment** The declaration of the origin should be more adapted to the needs of the plant (climate, raining etc.) without too many details. Stating single countries does not	**Not endorsed** The geographical source is required according to NTA, CTD-guideline and

Section number and heading	Interested party	Comment and rationale	Outcome
		seem appropriate. The country itself is not considered relevant information concerning the quality. Furthermore, the size of e.g. European countries like Bulgaria, Germany or Poland is different from Brazil or China. Moreover it should be recognised that some flexibility is necessary in case of potential failure of crops, political problems etc. Thus, the origin should be given in a more general way. **Proposed change** Information 'Europe' should be sufficient, perhaps with examples: 'The herbal substance Valerian root originates from e.g. Germany, Poland, The Netherlands, Bulgaria.'	also the Classification-Guideline B.I.a.2 (variation procedure). Q & A to be drafted.
3.2.S.2.2.1	EUCOPE	Detailed information about the origin in form of political borders (countries) is not suitable since macro- and microclimate is determining the growth and the performance of a plant. Listing of regions according to the UN world population prospect (revision 2012) 'Classification of countries by major area and region of the world' should be sufficient.	**Not endorsed** See above
3.2.S.2.2.1	EUROPAM	*Origin: The herbal substance Valerian root originates from Germany, Poland, The Netherlands, Bulgaria.* Although it was possibly the intention to give in the example a wide range of countries for more flexibility, there is no objective reason to exclude any other country that is capable to produce Valerian root in good quality. **Proposal -** delete 127-128 Origin.	**Not endorsed** See above
3.2.S.2.2.1	AESGP	**Comment** Information about cultivation/collection is too detailed. The condition of growing can strongly vary from one location to another. Only in case such details are correlated to the quality can respective information be requested.	**Not endorsed** See above

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3.2.S.2.2.1	EUROPAM	*Cultivation/Collection: Cultivation. Valerian is planted on sandy ground in spring time. Weed control is carried out by hoeing; if necessary herbicides are used.* Information too detailed and may often include textbook knowledge reducing a form of flexibility that is not influencing quality. **Proposal -** delete 129-130	**Not endorsed** See above
3.2.S.2.2.1	AESGP	**Comment** The stage of the plant's growth cycle at harvest is more informative than the season, especially if the plant originates from geographical sources of different climate zones. **Proposed change** 1) Replace 'harvest' by 'harvest time' 2) As an alternative the vegetative stage of the plant as a parameter for harvest time could be indicated.	**Not endorsed** 'Harvest' includes 'harvest time and vegetative stage'. It is pointed out that information given in the Appendix 2 is exemplarily, alternative wording can also be accepted to adequately describe the plant production and plant collection.
3.2.S.2.2.1	EUCOPE	**Comment** The stage of the plant's growth cycle at harvest is more informative than the season especially if the plant originates from geographical sources of different climate zones. **Proposed change** 1) Replace 'harvest' by harvest time; 2) As an alternative please indicate the vegetative stage of the plant as a parameter for harvest time.	**Not endorsed** See above
3.2.S.2.2.1	EUROPAM	*Harvest: In late autumn.* It is more appropriate to indicate the stage of plant development since time of year may be different under different climates. **Proposal** Defining plant growth stage or delete 131.	**Not endorsed** See above

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3.2.S.2.2.1	AESGP	**Comment** The use of potable water is not always necessary and possible. Product-specific processing steps should be taken into consideration when deciding which quality of water is required.	**Not endorsed** Potable water is mentioned because its quality is acceptable in general. However, the use of water from another source requires the evidence of equivalent quality.
3.2.S.2.2.1	EUROPAM	*Roots are washed with potable water ...* Some production steps (like e.g. washing) are regulated by regional and/or national regulations. GACP is taking this situation into account (here for washing 12.1 would be applicable: 'Primary processing includes washing, cutting before drying, fumigation, freezing, distillation, drying, etc. Where applicable, all of these processes must conform to regional and/or national regulations and should be carried out as soon after harvesting as possible.') Proposal: adjust this paragraph to GACP 12.1	**Not endorsed** See above GACP is an important part to define a consistent quality of the herbal substance, however it is not sufficient to reference only to GACP.
3.2.S.2.2.1	AESGP	**Comment** Detailed information on the drying temperature should only be necessary if it is correlated to the quality.	**Not endorsed** To determine consistent quality information about the drying temperature is necessary. Especially for Valerian root it is known from literature that valerenic acids are heat sensitive and therefore it is important to define the drying temperature and state this in the example documentation.
3.2.S.2.2.1	EUROPAM	*...and dried at not more than 45°C.* The temperature of the drying medium (air) is not the temperature of the product. Product temperatures may be much lower, especially at the beginning of drying, by evaporation cold.	**Not endorsed** See above To determine the product temperature seems to be not feasible for this drying

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		Proposal (1) '...and dried at not more than 45°C product temperature.' (2) Mentioning of drying temperature only if it influences product quality.	process. If the temperature influenced the product quality – e.g. herbal substances containing essential oil – sufficient data would be required.
3.2.S.2.2.1	AESGP	**Comment** Detailed information on the packaging is not necessary. Thus, reference to 3.2.S.6 is obsolete. Also according to the main text, information on the packaging of the herbal substance is not required in 3.2.S.6. **Proposed change -** delete reference to 3.2.S.6.	**Not endorsed** A short description of the packaging used for the herbal substance seems to be useful and is also in accordance with the GACP guidance.
3.2.S.2.2.1	EUCOPE	No info on the packaging of the herbal substance should have to be given if the herbal substance is not the active pharmaceutical ingredient. Thus, it is not necessary to refer to 3.2.S.6	**Not endorsed** See above
3.2.S.2.2.1	EUCOPE	It is suggested that the presentation of GACP-confirmations is omitted or placed into chapter 3.2.R as this is not requested by NtA and Guideline and can be quite bulky.	**Not endorsed** GACP confirmation could also be presented in chapter 3.2.R if preferred
3.2.S.2.2.1	EUCOPE	GACP questionnaires should not be part of the dossier, since this is a QA issue and thus subject to inspections.	**Not endorsed** See above
3.2.S.2.2.1	AESGP	**Comment** The provided GACP documentation is considered to be too detailed since this information is partly given in other sections of the dossier and is therefore redundant (e.g. name and address of supplier) or subject to contractual agreements. The GACP questionnaire should not be part of the dossier. A general confirmation of the applicant's qualified person that only GACP compliant suppliers are used should suffice for the dossier. The supervision of the GACP compliance should be subject to GMP inspections by the relevant authorities. As stated above, to avoid a high amount of variations, detailed information on the herbal substance suppliers should be avoided in the dossier.	**Not endorsed** GACP confirmation could also be presented in chapter 3.2.R if preferred. Form presented just is an example. Other presentations/information can also be accepted.

Section number and heading	Interested party	Comment and rationale	Outcome
		Proposed change Delete lines 142-143 with the subsequent table and perhaps add a remark here: 'if GACP conditions are confirmed, only a brief description of conditions should be provided'. In case this is not possible, please see our comments on the GACP Documentation as follows: **Comment on cultivation / collection from wild habitats** cultivation: kind of soil and surrounding: only information with an influence of the quality of the product should be required. Collection from wild habitats: wild harvesting on private land: every land has an owner, it can be a private person or a community, it has to do with rights of using and not with the quality. Every collection is organised, the level of organisation is specific for the article or the area, but it is essential to respect the existing systems and experiences, if there is no influence to the quality. **Proposed change** - The declaration of type of soil and surrounding should be only required if they have an influence on the quality. **Comment** With regard to the note 'Pesticides should be declared' we would like to state that in case of cultivation, it cannot generally be said which pesticides have been used. Pesticides are usually used only when needed and specifically case by case. Depending on the respective weeds, insects or fungi, the use of pesticides is adapted to the corresponding needs - taking into account the legal provisions and waiting periods. Therefore the use and choice of suitable pesticides has to be flexible and adapted to the respective circumstances. **Proposed change** Concerning the pesticides a confirmation referring to the current monograph 'Pesticide Residues' (Ph. Eur. 2.8.13) and Regulation (EG) 396/2005 should be sufficient.	

Section number and heading	Interested party	Comment and rationale	Outcome
		Comment on <u>natural drying</u> - We are wondering whether the meaning of 'on the fields' is 'on the soil'. It should be differentiated between direct contact to the soil or not. **Comment on <u>artificial drying -</u>** We are wondering whether the electrical source of energy has any relevance in the practice. **Comment on <u>state of the material after drying or during storage</u>** - This information is checked in the quality unit and directly indicates the level of the quality product. The quality of the herbal substance can only be influenced via the following processing steps like sorting, cleaning etc. **Comment on <u>foreign matter</u> -** The definition of the European Pharmacopoeia 2.8.2 should be considered: Herbal drugs should be free from moulds, insects and other animal contaminants. Foreign matter is material consisting of any or all of the following: 1/ Foreign organs: matter coming from the source of the plants but not defined as the drug. 2/ Foreign elements: matter not coming from the source plant and either of vegetable or mineral origin. **Comment on 'same' quality**: We do not understand that the suppliers assure deliveries with the 'same' quality. **Proposed change** The word 'same' should be replaced by 'according to the specification'.	
3.2.S.2.2.1	EUROPAM	The following GACP-Documentation is proved by the herbal substance supplier: The documentation is too detailed. Line 140 (The supplier observes the GACP rules) would be sufficient. **Proposal** - delete GACP-Documentation, alternatively consider the use of the EUROPAM statement on requirements for a batch certification of medicinal and aromatic plants (MAPs), Journal of Applied Research on Medicinal and Aromatic Plants, 1 (2014) 70-71. http://dx.doi.org/10.1016/j.jarmap.2014.05.001	**Not endorsed** See above

Section number and heading	Interested party	Comment and rationale	Outcome
3.2.S.2.2.2	AESGP	**Comment** In practice, it is more common to state a range than a fixed batch size. **Proposed change -** Thus, an example with a range would be more appropriate.	**Endorsed** Batch size of the herbal preparation: 350 kg (300 – 400 kg).
3.2.S.2.2.2	EUCOPE	The batch size of the herbal preparation should be declared with range and tolerance.	**Endorsed** See above
3.2.S.2.2.2	AESGP	**Comment** The calculation formula is not considered relevant. The quantities of excipients are calculated by standard procedures like the rule of mixing and percentages. **Proposed change -** delete line 163.	**Not endorsed** The formula often does not reflect the correct calculation procedure and is therefore needed.
3.2.S.2.2.2	EUCOPE	The flow chart should not contain numerical information like acceptance criteria.	**Not endorsed** IPC should always be part of the flow chart of the manufacturing process to be able to understand the process-strategy.
3.2.S.2.3	AESGP	**Comment** 'Water for preparation of extracts' is described in Ph. Eur. monograph 2249. This monograph regulates the requirements. If drinking water is used as starting material, quality has to be in accordance with Directive 98/83/EC. If this is confirmed by the supplier this should be sufficient to prove Ph. Eur. conformity. **Proposed change** Please delete 'specification and batch results for drinking water'.	**Endorsed**
3.2.S.2.3	AESGP	**Comment** The specification and results for one batch 'Water for extraction' do not correspond to information given in line 175-176. **Proposed change** Specification and results should be in line with the Ph. Eur. monograph 'Water for preparation of extracts - Aqua ad extractas praeparandas'.	**Endorsed**

Section number and heading	Interested party	Comment and rationale	Outcome
3.2.S.2.4	i.DRAS	**Comment** The manufacturing process of the herbal preparation Valerian root dry extract is described as a standard process. However, spray drying is mentioned as example for non-standard process on page 28, point 3.2.S.2.5 Process validation and/or evaluation (name, manufacturer) **Proposed change (if any)** - The contradiction should be clarified	**Endorsed** Appendix 1 has been adapted.
3.2.S.2.4	AESGP	**Comment** As to the companies' experiences, it is unusual that the temperature during the extraction and concentration steps are critical steps, since the temperature is set and then regulated by the equipment. **Proposed change -** Delete line 188-189.	**Not endorsed** In the current example these two conditions are defined to be critical.
3.2.S.2.4	AESGP	**Comment** If relevant, justification for the range of temperature should be given in section 3.2.S.2.6 Manufacturing Process Development. **Proposed change -** Delete line 191.	**Not endorsed** See above
3.2.S.2.5	AESGP	**Comment** According to the scope of GL 70278/2012-Rev. 1, information on validation of non-sterile active substances is not required in the dossier. **Proposed change** The process validation for herbal preparations based on historical data may be omitted in case of standard process.	**Endorsed**
3.2.S.2.5	EUCOPE	According to the scope of GL 70278/2012-Rev. 1 information on validation of non-sterile active substances is not required in the dossier.	**Endorsed** See above
3.2.S.2.5	i.DRAS	**Comment** According to EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, page 1: '…information on validation of non-sterile active substances is not required in the dossier', therefore for non-sterile herbal preparations validation data are not required in the	**Endorsed** See above

Section number and heading	Interested party	Comment and rationale	Outcome
		dossier. (refer also to page 28, point 3.2.S.2.5 Process validation and/or evaluation (name, manufacturer) of this guideline) **Proposed change (if any)** - The contradiction should be clarified	
3.2.S.2.6	AESGP	**Comment** Especially in case of traditional extracts, data on Manufacturing process development is not available. Manufacturing parameters are often based on experience or empiric data.	**Not endorsed** According to NTA and the Guideline CPMP/QWP/2819/00 Rev. 2 a brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable should be provided.
3.2.S.2.6	AESGP	**Comment** This section is considered redundant because this information is already given in chapters 3.2.S.1.2 and 3.2.S.4.1. **Proposed change** Delete lines 206-211.	**Not endorsed** Although a monograph exists for the herbal substance, the basic idea of the development should be explained briefly. It is pointed out that Appendix 2 is a specific example of a documentation which does not cover all possibilities. In general, a link to information given in section 3.2.S.1.2 and 3.2.S.4.1. could be sufficient.
3.2.S.3.1	AESGP	**Comment** Information on Structure and other Characteristics is already given in section 3.2.S.1.2 Structure and 3.2.S.4.1 Specification. Doubling of information should be avoided in order to have a clearly structured dossier. **Proposed change** Delete lines 226-257 or reference to section 3.2.S.1.2 Structure and/or 3.2.S.4.1 Specification.	**Not endorsed** See above

Section number and heading	Interested party	Comment and rationale	Outcome
3.2.S.3.1	AESGP	**Comment** In this example the herbal substance consists of the dried root of *Valeriana officinalis* L. The flowers are not used for the manufacture of the herbal preparation. Countries of origin are already given in chapter 3.2.S.2.2. **Proposed change** - Delete lines 236-238	**Not endorsed** The text is a general description of the whole plant which is required according to the CTD-Guideline.
3.2.S.3.1 3.2.S.7.3	AESGP	**Comment** In accordance with the Ph.Eur. and the specification of section 3.2.S.4.1 and 3.2.S.4.4.1, the TLC fingerprint is sufficient in order to characterise the herbal substance and the herbal preparation. **Proposed change** Delete 'and HPLC' and delete lines 714, 715, 723, 724, 731, 732, 739, 746,752	**Not endorsed** In this example the TLC and HPLC fingerprints are characteristic for the herbal substance resp. herbal preparation and it should therefore be referred to both methods.
3.2.S.3.1 3.2.S.7.3	EUCOPE	**Comment** To characterize the herbal substance and herbal preparation, the TLC fingerprint is sufficient corresponding to Ph. Eur. and to the specification of section 3.2.S.4.1 and 3.2.S.4.4.1. **Proposed change -** Delete 'and HPLC' Delete line 714, 715, 723, 724, 731, 732, 739, 746,752	**Not endorsed** See above
3.2.S.4.1.1	AESGP	**Comment** It should be mentioned that the testing is done according to the current Ph.Eur. monographs to avoid unnecessary variations in case of an updated Ph.Eur. monograph. As Valerian root and the Valerian root dry aqueous extract comply with Ph.Eur., the parameter mentioned in Ph.Eur. should not be provided in the dossier to avoid unnecessary variations in case of an updated Ph.Eur. monograph **Proposed change** The herbal substance Valerian root is tested in accordance with the actual valid Ph. Eur. monographs 'Valerian root' (0453) and 'Herbal drugs'(1433). Acceptance	**Endorsed** See modified table

<table>
<tr><th>Section number and heading</th><th>Interested party</th><th>Comment and rationale</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>
criteria for microbiological quality should be based on ‘maximum acceptable count’ in order to have a direct correlation with the determined values.

Release specification
According to the current Ph. Eur. Monograph ‘Valerian root’ (0453) with the following additional parameters:

<table>
<tr><td>Test for pesticide residues *</td><td>Ph. Eur. 2.8.13</td><td>EN 12393 / 12396-3
3.2.S.4.2.1</td></tr>
<tr><td>Test for heavy metals *</td><td>lead: ≤ 5 ppm
cadmium: ≤ 1.0 ppm
mercury: ≤ 0.1 ppm</td><td>Ph. Eur. 2.4.27
3.2.S.4.2.1</td></tr>
<tr><td>Microbiological quality</td><td>in accordance with Ph. Eur. 5.1.8 A
TAMC: ≤ 10^7
TYMC: ≤ 10^5
E. coli: ≤ 10^3
Salmonella: absence (in 25 g)</td><td>Ph. Eur. 2.6.31 / Ph. Eur. 2.6.12</td></tr>
<tr><td>Test for aflatoxins</td><td>Aflatoxin B1: ≤ 2 µg / kg
Aflatoxins B1, B2, G1, G2: ≤ 4 µg / kg</td><td>Ph. Eur. 2.8.18
3.2.S.4.2.1</td></tr>
</table>
*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 current 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
</td><td></td></tr>
</table>

<table>
<tr><th>Section number and heading</th><th>Interested party</th><th>Comment and rationale</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>According to actual valid Ph. Eur. Monograph ‘Valerian dry aqueous extract’ (2400) with the following additional parameters:

<table><tr><td>Particle size</td><td>min. 95 % = 0.315 mm</td><td>3.2.S.4.2.2</td></tr><tr><td>Microbiological quality</td><td>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)</td><td>Ph. Eur. 2.6.31 / Ph. Eur. 2.6.12</td></tr></table></td><td></td></tr>
<tr><td>3.2.S.4.1.1</td><td>EUCOPE</td><td>In contrast to Annex 1, in Appendix 2 microbiological testing of herbal substances is fixed to Ph. Eur. Cat 5.1.8 although this category is not applicable to herbal substance <u>for extraction</u>.
The acceptance criteria for both TYMC and TAMC acc. to the Ph. Eur. are 5 x 10^7 and 5 x 10^5, respectively. This refers in analogy to the acceptance criteria in the microbiological testing for herbal preparation and herbal product (quality and stability).
Only ‘current Ph. Eur.’ should be given here when a test refers to a Ph. Eur. method. This refers to all specifications and testing procedures in the dossier (for quality and stability for herbal substance, herbal preparation and finished product wherever applicable).</td><td>Partially endorsed
As it is justified in chapter 3.2.S.4.5.1 the specification from Ph. Eur. 5.1.8 A was applied analogously.
The maximum acceptable count from Ph. Eur. has been added to the table.</td></tr>
<tr><td>3.2.S.4.1.1
(Line 271-272)</td><td>AESGP</td><td>See Line 278 – 279 No 2)</td><td>Not Endorsed
Specifications were rephrased throughout the document.</td></tr>
<tr><td>3.2.S.4.1.1
(Line 271-272)</td><td>EUCOPE</td><td>See Line 278 – 279, No. 2)</td><td>Not Endorsed
Specifications were rephrased throughout the document.</td></tr>
</table>

Section number and heading	Interested party	Comment and rationale	Outcome
3.2.S.4.1.2 (Line 278-279)	AESGP	**Comment** 1) The odour is missing in the example. 2) Acceptance criteria of identity should be expressed as analytical requirement. **Proposed change** 1) add 'with characteristic valerian smell' 2) replace 'TLC according …' by 'TLC complies with the description according …'	**Endorsed**
3.2.S.4.1.2 (Line 278-279)	EUCOPE	1) The odour is missing in the example 2) Acceptance criteria of identity should be expressed as analytical requirement **Proposed change** 1) Complete 'with characteristic valerian smell' 2) Replace 'TLC according' by 'TLC complies the description according'	**Endorsed**
3.2.S.4.1.2	AESGP	**Comment** The Ph. Eur. monograph on Valerianae radix specifies a minimum content of sesquiterpenic acids. Thus, the analytical method described in the Ph. Eur. monograph is used for determination of content (assay). This method is considered to be validated, but the European Pharmacopoeia does not publish the validation data. Furthermore, all herbal substance batches are acceptable that fulfil the requirements concerning the minimum content and no upper limit for content is specified. Therefore, the footnote should only apply in case individual analytical methods are developed which have – of course – to be validated. **Proposed change** *Specification is in the validated range (if non-pharmacopoeial test methods are used)	**Not endorsed** In the Ph. Eur. general notices under implementation of pharmacopoeial methods it is clearly stated: When implementing a pharmacopoeial method, the user must assess whether and to what extent the suitability of the method under the actual conditions of use needs to be demonstrated according to relevant monographs, general chapters and quality systems. In this example the Ph. Eur. has been used. Proposed wording could be acceptable when a non Ph. Eur. is applied.

Section number and heading	Interested party	Comment and rationale	Outcome
3.2.S.4.1.2	AESGP	**Comment** Usually the word 'comply' is used in case of ranges like a specification. In case of analytical data as a reference, the word 'comparable' should be used. The usual terminology of 'start' is 'initial fingerprint'. **Proposed change** Replace 'TLC complies with the chromatogram at the start' by 'TLC is comparable to the initial fingerprint'	**Endorsed** See above
3.2.S.4.1.2	EUCOPE	**Comment** Usually the word 'comply' is used if you have ranges like a specification. For analytical data as a reference, you should use the word comparable. The usual terminology of 'start' is 'initial fingerprint'. **Proposed change** Replace 'TLC complies with the chromatogram at the start' by 'TLC is comparable to the initial fingerprint'.	**Endorsed** See above
3.2.S.4.1.2, 3.2.S.7.3	AESGP	**Comment** Acceptance criteria should be 90-110% instead of 90.0-110.0% to be in accordance with the Guideline on quality of herbal medicinal products/traditional herbal medicinal products. **Proposed change** - Replace '90.0-110.0%' by '90-110%'.	**Endorsed**
3.2.S.4.1.2 3.2.S.7.1	AESGP	**Comment** 'Shelf-life specification' is the commonly used term for this issue. **Proposed change** - Replace 'retest specification' by 'shelf-life specification'	**Not endorsed** For the herbal preparation the retest period is more appropriate wording as specification relates to the release value and not to the declared one.
3.2.S.4.1.2 3.2.S.7.1	EUCOPE	**Comment** 'Retest specification' is not the right term in this respect. The stability guideline describes a shelf-life for a finished product and a retest-period for an active	**Not endorsed** See above

Section number and heading	Interested party	Comment and rationale	Outcome
		substance. The term 'retest specification' does not exist and would be wrong since a retest always follows the release specification. **Proposed change** Replace 'Retest specification' by 'Specification for stability testing (to define the retest-period)'.	
3.2.S.4.2.1 3.2.S.4.2.2	AESGP	**Comment** It should be mentioned that the testing is done according to currently valid Ph.Eur. monographs to avoid unnecessary variations in case of an updated Ph.Eur. monograph. **Proposed changes** The analytical methods used for the identity and purity testing of the herbal substance Valerian root are in accordance with the actual valid Ph. Eur. monographs 'Valerian root' (0453) and 'Herbal drugs' (1433). and The analytical methods used for the identity and purity tests on the herbal preparation Valerian root dry extract are in accordance with the current Ph. Eur. monograph 'Valerian dry aqueous extract' (2400) and 331 'Extracts, Dry extracts' (0765)	**Not endorsed** See above
3.2.S.4.2.1	AESGP	**Comment** Reference to Ph. Eur. 2.8.13 is confusing as no method is given in the European Pharmacopoeia. **Proposed change** - Delete reference to Ph. Eur. 2.8.13.	**Not endorsed** Ph. Eur. 2.8.13 contains also general information concerning the qualitative and quantitative analyses and is therefore referenced.
3.2.S.4.2.2	EUCOPE	It is recommended to omit exemplary chromatograms from this chapter. As changes of the corresponding methods in Ph. Eur. do not need to be notified via variation as long as the specification states that the herbal preparation is tested according to the currently valid edition of the Ph. Eur., the marketing authorisation holder would need to update this chapter in case of change in methods. This is not	**Endorsed**

Section number and heading	Interested party	Comment and rationale	Outcome
		in line with the idea of stating 'testing according to currently valid Ph. Eur.'. The proof of testing according to currently valid Ph. Eur. is presented in chapter 3.2.S.4.4. Therefore it is suggested to omit the exemplary chromatographs.	
3.2.S.4.3.1	AESGP	**Comment** Usually validation is carried out on different reasonable matrices. A justification is not necessary as it is self-explanatory which validation has to be chosen (e.g. a herbal root drug is used; therefore the validation on the root matrix is reasonable). Otherwise a product specific validation could be requested at the worst. This requirement exceeds the adequate scope of work. **Proposed change** Validation data are provided including information on the herbal matrix…	**Not endorsed** Justification is needed if matrix is not the same as applied for.
3.2.S.4.4	AESGP	**Comment** The requirement of batch analysis data of two batches per supplier is not in line with Annex 1 of the GL in question. Herein the results of analysis of at least one batch per site should be given when there are several sites of production for the herbal substance. **Proposed change** Delete 'three' in line 479. The boxed text should be changed as follows: 'Herbal substance: two certificates of analyses are provided here; when there are several sites of production for the herbal substance, the results of analysis of at least one batch per site should be given. Herbal preparation: two certificates of analyses are provided here'.	The complete box together with the text was deleted.
3.2.S.4.4	EUCOPE	**Comment** The requirement of batch analysis data of two batches per supplier is not in line with Annex 1 of the Guideline in question. Herein the results of analysis of at least one batch per site should be given when there are several sites of production for the herbal substance.	The complete box together with the text was deleted.

Section number and heading	Interested party	Comment and rationale	Outcome
		Proposed change Please adapt this passage according to Annex 1 to Guideline EMA/HMPC/71049/2007 rev. 2, delete the second part of the sentence: 'exceeding the minimum requirement of two batches per supplier (herbal substance) and two batches of dry extract.	
3.2.S.4.4 3.2.S.4.4.1 3.2.S.4.4.2	AESGP	**Comment** HPLC chromatograms are not meaningful from our point of view. Also from appendix 1, section 3.2.S4.4. batch analysis only TLC fingerprints are required.	**Not endorsed** In Appendix 1 is specified that chromatographic profiles are required.
3.2.S.4.4.1 3.2.S.4.4.2	EUCOPE	Presentation of HPLC chromatograms is not requested by Guideline / Appendix 1 and NtA. Deletion of information is suggested.	**Not endorsed** See above
3.2.S.4.4.1 3.2.S.4.4.2	AESGP	**Comment** Peak areas and retention times should not be stated in the dossier. Peak areas are part of the chromatogram. Retention times are usually given within description of the method. In combination with calculation formula and specified content (assay) all relevant information is presented in the quality dossier to reproduce the tests. We see a certain risk that this will lead to additional requirements regarding those parameters. However, a certain variation is usual. **Proposed change** Delete lines 498/510/523/546/572/596 completely or replace the wording by 'HPLC/GC chromatograms including peak areas and retention times should be presented.'	**Endorsed**
3.2.S.4.4.1	EUCOPE	**Comment** Peak areas and retention times are stated in the dossier although not required by any guidance document. **Proposed change** Omit the sentence: 'Peak areas and retention times are also stated in the dossier.'	**Not endorsed** See above

Section number and heading	Interested party	Comment and rationale	Outcome
3.2.S.4.4.1 3.2.S.4.4.2 3.2.P.5.4	i.DRAS	**Comment** The retention times should be mentioned, but there is no need to add peak areas because they depend of the instrument used Proposed change (if any): delete 'peak areas'	**Not endorsed** See above
3.2.S.4.4.1	AESGP	**Comment** The submission of an HPLC chromatogram for the parameter 'assay' is not required according to Annex 1 to guideline EMA/HMPC/71049/2007 rev. 2 and Certification of suitability to Monographs of the European Pharmacopoeia: CONTENT OF THE DOSSIER FOR HERBAL DRUGS AND HERBAL DRUG PREPARATIONS QUALITY EVALUATION. **Proposed change -** HPLC Chromatogram for the parameter assay may be omitted.	**Not endorsed** See above In Appendix 1 is specified that chromatographic profiles are required.
3.2.S.4.4.1	EUCOPE	**Comment** The submission of HPLC Chromatogram for the parameter assay is not required according to Annex 1 to guideline EMA/HMPC/71049/2007 rev. 2 and Certification of suitability to Monographs of the European Pharmacopoeia: CONTENT OF THE DOSSIER FOR HERBAL DRUGS AND HERBAL DRUG PREPARATIONS QUALITY EVALUATION. **Proposed change -** HPLC Chromatogram for the parameter assay may be omitted.	**Not endorsed** See above
3.2.S.4.5.1	AESGP	**Comment** From our point of view, the individual results of examinations on 'special impurities' do not constitute a part of the documentation of the dossier. Exemplary results are already included in part 3.2.S.4.4. For the justification of skip testing, the number of tests carried out show sufficient explanatory power. The benchmark for the evaluation of the data results from the relevant requirements of the pharmacopoeia. Since these requirements are met, the individual evaluation of the data does not lead to further relevant information. In any case, additional provision of data from 9 batches is not considered necessary.	**Not endorsed** Skip testing is a case by case decision. Further guidance is being developed.

Section number and heading	Interested party	Comment and rationale	Outcome
		Proposed change Delete lines 616-617, or, in case this is not possible: The provided results on three batches plus data of further batches support the once a year test frequency for pesticide residues and heavy metals. Data on further batches of herbal substance are provided here to justify the skip-testing for pesticides and heavy metals.	
3.2.S.4.5.1	EUCOPE	**Comment** Data on 5-10 batches are considered sufficient in order to perform a statistical evaluation. **Proposed change** Data on ~~further nine~~ 5-10 batches of herbals substances are provided here….	**Not endorsed** See above
3.2.S.4.5.2	AESGP	**Comment** In general acceptance criteria are given for pharmacopoeia methods. For other tests reasonable criteria have to be chosen. In most cases these criteria will be selected based on experience without experimental data for the respective herbal substance. (E.g. in case of newly developed extracts, historical batch data are not available). Moreover, if the specified microbiological quality of the herbal preparation is in line with finished product specification further justification of the acceptance criteria is unnecessary. **Proposed change** Please delete the sentence 'historical experimental data are provided here to set the acceptance criteria' or add '*If applicable*, historical experimental data are provided…'	**Not endorsed** Appendix 2 is a specific example, in general is up to the applicant to justify when it isn't applicable.
3.2.S.4.5.2	AESGP	**Comment** Pharmacopoeial methods are regarded as validated. Further validations of the TLC and HPLC methods are therefore not necessary (see line 368). **Proposed change** - Delete lines 626 -627.	**Partially endorsed**
3.2.S.5	AESGP	**Comment** It should be possible to use a 'working standard' in the same way as provided for	**Not endorsed**

Section number and heading	Interested party	Comment and rationale	Outcome
		the product (see line 1207). **Proposed change** - Please add 'working standard'	
3.2.S.5	AESGP	**Comment** In this case a reference standard Valerian dry extract HRS is used and these standards will be delivered by the EDQM. Information concerning the primary reference standard or other standard materials should be representative for upcoming batches. Batch number, specific content of this batch etc. are subject to change and should not be provided in the dossier. **Proposed change** Line 646 should be modified as follows: 'An exemplary batch of the reference standard/reference material is documented hereafter.' Delete line 647 and 649.	**Endorsed** Text has been amended.
3.2.S.6	AESGP	Here the contents of Appendix 2 are definitely contradictory to those in Appendix 1: Appendix 1 states that in cases where the herbal substance is the active pharmaceutical ingredient, a description of the container closure system should be provided. The herbal substance in Appendix 2 is NOT the active ingredient, nevertheless, information on the container closure system is provided.	**Partially endorsed** Appendix 1 has been adapted.
3.2.S.6	EUCOPE	Information on container closure system is not required by Guideline / Appendix 1, therefore it is suggested to omit the information on the container closure system of the herbal substance, as the herbal substance is not the active pharmaceutically ingredient.	**Partially endorsed** See above
3.2.S.6	AESGP	**Comment** The monograph '3.2.2. Plastic containers and closures for pharmaceutical use' refers to the packing of final pharmaceutical products but not to those of APIs. **Proposed change -** Delete line 658.	**Not endorsed** It is pointed out that Appendix 2 is a specific example of a documentation which does not cover all possibilities.
3.2.S.6	AESGP	**Comment** It should be sufficient to present specifications of the packaging manufacturers or	**Not endorsed** The mentioned specification of the

Section number and heading	Interested party	Comment and rationale	Outcome
		the in house specification of the extract manufacturer used for the testing on receipt. **Proposed change for addition to line 658** 'Specifications are provided here of the packaging manufacturers and/or the in house specification of the extract manufacturer used for the testing on receipt'.	manufacturer and the specification used for testing on receipt are different specifications with varied purposes, both should be provided.
3.2.S.7	AESGP	**Comment** We recommend to replace the word 'immediately' with 'in due time' in order to provide more flexibility to adjust this issue for specific characteristics of different herbal drugs. **Proposed change** The herbal substance complies with the release specification in due time before use in the manufacturing of the herbal preparation. Therefore no stability studies are performed.	**Not endorsed** Wording according to Guideline CPMP/QWP/122/02 rev 1 corr
3.2.S.7	EUCOPE	Guideline and NtA does not foresee information on herbal substance. Deletion of chapter 'herbal substance' is suggested.	**Not endorsed**
3.2.S.7.1	AESGP	**Comment -** See comment to line 281 **Proposed change** - Replace 'retest specification' by 'shelf-life specification'.	**Not endorsed** See above
3.2.S.7.1	EUCOPE	**Comment -** Please refer to comment in terms of line 281. **Proposed change** - Replace 'retest specification' by 'shelf-life specification'.	**Not endorsed** See above
3.2.S.7.1	AESGP	**Comment -** See lines 281-282 **Proposed change -** Replace 'comply' by 'comparable'.	**Not endorsed** See above
3.2.S.7.1	EUCOPE	**Comment -** see Line 281 - 282 **Proposed change -** Replace 'comply' by 'comparable'	**Not endorsed** See above
3.2.S.7.3	EUCOPE	**Comment** In line 701 to 702 an OOS-result is described in loss on drying. The OOS-Result in the data is given in the TLC. **Proposed change -** Loss on drying at T3 6,1. Set fingerprint at T3 to complies	**Endorsed**

Section number and heading	Interested party	Comment and rationale	Outcome
3.2.S.7.3	AESGP	**Comment** In lines 701-702 an OOS result in the loss on drying is described. The OOS result in the data is given in the TLC. **Proposed change -** Loss on drying at T3 6,1. Set fingerprint at T3 to comply…	**Endorsed**
3.2.P.2.2.2	AESGP	**Comment** The note for guidance on development pharmaceutics (CPMP/QWP/155/96) gives the following information under the point overage: 'Overages are primarily employed to cover losses during the manufacture of active substance or key excipients, i.e. manufacturing overages, and/or during shelf-life i.e. stability overage. These can be distinguished since in the former case there is unlikely to be increased dosage administered to the patient, whereas the stability overage will result in overdosing where batches of product may reach the patient soon after release.' In the case of the film-coating process of tablets such an overage in terms of the above mentioned guideline is not applied Therefore the statement 'not applicable' seems to be correct with view to the above mentioned guideline. **Proposed change -** Not applicable	**Endorsed**
3.2.P.3.2	EUCOPE	Listing of 'per film-coated tablet' basis is not required by Appendix 1. Deletion of information is suggested.	**Not endorsed** The information is useful.
3.2.P.3.3	EUCOPE	According to NtA only narrative description is necessary; redundant information should be omitted.	**Not endorsed** It is pointed out that Appendix 2 is a specific example a narrative description could also be accepted.
3.2.P.3.3	EUCOPE	It is suggested to omit the frequency of testing of the IPCs because this is part of the GMP manufacturing batch record.	**Not endorsed** The minimum frequency is useful to assess the strategy of manufacturing control.
3.2.P.3.5	AESGP	**Comment** It should not be given the impression that at the time of application, data of three	**Not endorsed** It is pointed out that Appendix 2 is a

Section number and heading	Interested party	Comment and rationale	Outcome
		full-scale production batches must be available. It is common practice that 2-3 pilot-scale batches are produced within the scope of the application procedure. Scale-up to production-scale is often performed post-authorisation. **Proposed change** Line 975 should be modified as follows: The results of the in-process controls on 2-3 pilot-scale/full-scale production batches are presented below.	specific example of a documentation which does not cover all possibilities. Providing data of pilot batches represents the minimum standard, however, in the present case 3 production batches are provided.
3.2.P.4.1	AESGP	**Comment** 'Iron oxide, E 172' is included in the USP as an official pharmacopoeia. **Proposed change** Therefore it should be deleted in the part 'Non-pharmacopoeial excipient'.	**Not endorsed** All colourants used should be in accordance with the European Directives and Regulations mentioned in the table; referring to the USP is not sufficient (or relevant).
3.2.P.5.1	i.DRAS	**Comment** During shelf life there is no need to test uniformity of mass, average mass is sufficient **Proposed change (if any) -** Delete this parameter from shelf life specification	**Not endorsed** It has to be differentiated between the shelf-life specification and the stability protocol, this parameter is part of the shelf-life specification but not of the stability protocol.
3.2.P.5.3	AESGP	**Comment** It is not necessary to provide raw data for validation information in the quality dossier. The validation report should show all relevant data, chromatograms and a summary of conclusion only. Otherwise the validation report is too extensive and confusing. **Proposed change** - Please delete 'raw data'.	**Partially endorsed** It is not sufficient to present only a validation report. The assessment of the validation should be possible on basis of the respective data and chromatograms.
3.2.P.5.4	EUCOPE	Information on active substance batch is not requested by Guideline or Appendix 1. Deletion of information is suggested.	**Not endorsed** Appendix 1 only addresses essential requirements. Stating the batches of

Section number and heading	Interested party	Comment and rationale	Outcome
			active substance used in the manufacturing of the finished product batches in the example-documentation is an obligatory information which is also mentioned in context of the batch-specific testing of the parameter the assay.
3.2.P.5.4	EUCOPE	Presentation of HPLC chromatograms is not requested by Guideline or Appendix 1. Deletion of information is suggested.	**Not endorsed** See above
3.2.P.6	AESGP	**Comment** This section is considered to be too detailed. The isolation/synthesis of the reference substance should be described more generally in order to avoid unnecessary changes. This is justifiable because the tests on identity, purity and content carried out on the reference standard are significant for its quality. **Proposed change** The text should be changed as follows: 'Valerenic acid was isolated from valerian root. Extraction process was performed with heptane. The solvents acetone, methanol and water were used for chromatographic purification and crystallization procedure.'	**Endorsed**
3.2.P.7	EUCOPE	Presentation of certificates of analysis and IR spectra is not requested by NtA, Guideline on plastic immediate packaging materials and Appendix 1. Deletion of requirement is suggested.	**Not endorsed** These documents need to be provided to demonstrate the suitability of the materials in the exemplary documentation; especially the IR spectra demonstrate the identity of the material.
3.2.P.8.2	AESGP	**Comments** We consider two stability batches sufficient. Only for critical dosage forms, such as sterile products, three stability batches can be required. See CPMP/QWP/122/02	**Not endorsed** It is pointed out that Appendix 2 is a specific example 2 batches could also be

Section number and heading	Interested party	Comment and rationale	Outcome
		Rev. 1 corr. **Proposed change** Replace '... of 3 production scale batches...' in '...of 2 production scale batches...'	accepted.
3.2.P.8.2	EUCOPE	2 stability batches are enough. Only for critical dosage forms, such as sterile products, 3 stability batches can be required. See CPMP/QWP/122/02 Rev. 1 corr. **Proposed change** Replace '... of 3 production scale batches...' in '...of 2 production scale batches...'.	**Not endorsed** See above
3.2.P.8.2	AESGP	**Comment** Mentioning GMP rules should not be part of the dossier. According to the GMP rules, the requested testing of one batch per year can be altered if justified (e.g. if no batch is produced; bracketing matrixing can be applied). Mentioning a determined batch number per year would lead to a need of variation in case of altering the number. The 'Guideline on Stability Testing: Stability testing of existing active substances and related finished products' states in chapter 2.1.8 Stability Commitment: 'Where the submission includes long-term stability data on three production batches covering the proposed shelf life, a post approval commitment is considered unnecessary.' **Proposed change** Delete the sentence 'According to GMP-rules, on-going stability tests will be performed on one batch per year.'	**Partially endorsed** Text has been amended.
3.2.P.8.2	EUCOPE	**Comment** Reference to GMP-rules in the dossier is not applicable in the registration dossier. **Proposed change** Omit the sentence 'According to GMP-rules, on-going stability tests will be performed on one batch per year'.	**Partially endorsed** See above