EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2017
EMA/HMPC/183134/2017 Rev. 1
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on "Guideline on the assessment of clinical safety and efficacy in the preparation of European Union herbal monographs for well-established and traditional herbal medicinal products" (EMA/HMPC/104613/2005 Rev. 1)

Table 1: Organisations and/or individuals that commented on the draft "Guideline on the assessment of clinical safety and efficacy in the preparation of European Union herbal monographs for well-established and traditional herbal medicinal products" (EMA/HMPC/104613/2005 Rev. 1) as released for public consultation on 1 September 2016 until 30 November 2016.

	Organisations and/or individuals
1	ESCOP - European Scientific Cooperative on Phytotherapy
2	EUCOPE - European Confederation of Pharmaceutical Entrepreneurs
3	AESGP – Association of the European Self-Medication Industry
4	Prof.Dr. Henning Blume, SocraTec C&S GmbH, Oberursel/Germany Prof.Dr.Theodor Dingermann, Institut für Pharmazeutische Biologie, Goethe-Universität Frankfurt a.M. Prof.Dr.Manfred Schubert-Zsilavecz, Institut für Pharmazeutische Chemie, Goethe-Universität Frankfurt a.M. and Zentrallaboratorium Deutscher Apotheker, Eschborn/Germany

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

Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
EUCOPE	EUCOPE welcomes the opportunity to submit comments on the "**Guideline on the assessment of clinical safety and efficacy in the preparation of European Union herbal monographs for well-established and traditional herbal medicinal products - Draft revision 1**". Based on experiences made over the last decade in developing European Union herbal monographs, we highly appreciate an update of the document appropriately. In the following we would like to give some general and some specific comments and we hope they will be taken into consideration **General comments** **Data Protection** The quality refinement of herbal extracts as well as intensive clinical research leading to herbal medicinal products of high quality, safety and evidence-based efficacy can only be obtained by high investments. The performance of clinical trials with Herbal Medicinal Products (HMPs) requires special study designs taking into consideration the particularities of this product category and is very time and cost intensive. Most clinical trials are performed with extracts which are produced using highly specific manufacturing processes. Results from clinical trials can normally not be transferred to other products even though the same plant and plant parts are used due to the uniqueness of the extract. Although data protection is legally granted - e.g. for new active substances a period of 8 years data protection + 2 years market protection or for a new indication of an already existing active substance based on new data of clinical	As per the provisions of Article 16h(3) of Directive 2001/83/EC, the HMPC shall establish Union herbal monographs for both well-established and traditional herbal medicinal products. The role of the monographs is to achieve harmonisation and thereby facilitate marketing authorisations/registrations in EU. The Union herbal monographs are thus intended to serve as a basis for bibliographical marketing authorisation or simplified registration. A consequence of article 10(1) of Directive 2001/83/EC is that medicinal products authorised based on own clinical data according to article 8(3) are entitled to a period of 8 years of protection of clinical data that were used in the authorisation procedure. Normally, as indicated above, the well-established use monographs will cover herbal substances/preparations which constituted the active substances in products authorised on the legal basis of well-established use (article 10a of Directive 2001/83/EC) and have been on the market for at least 10 years. Therefore, the EU herbal monographs will not normally include herbal medicinal products which benefit from data exclusivity for 8 years derived from article 10 (1) of the directive. However, if there is a marketing authorisation granted

Interested party	Comment and Rationale	Outcome
	trials one year can be granted – the use of data before the end of protection period is being observed. HMPC uses all published - so called bibliographical data - to establish new European Union monographs with respect to a well-established medicinal use (WEU). Generally, results of clinical studies are published and referenced in scientific discussions, especially trials, that have been performed in cooperation with scientific or academic institutions. A preliminary check on data protection of the published results used for the establishment of monographs is generally not performed by the Committee. This situation is not acceptable in light of preserving innovation. **An appropriate procedural step to evaluate existing data protection has to be implemented** in order to guarantee data protection and assure that results from clinical studies are legitimised to be used in herbal monographs. The situation will certainly be more vital, since it became mandatory for sponsors as of 21 July 2014 to publish clinical trial results in the European Clinical Trials Database (EudraCT), managed by the European Medicines Agency (EMA). This information will be fed into the publicly accessible European Union Clinical Trials Register and summary results of clinical trials will become available to the public. As this published data can be granted data exclusivity a preliminary data protection evaluation must be guaranteed before data is being used by HMPC to compile new well-established use monographs. To increase the disposition of manufacturer of herbal medicinal products to further invest in research and innovation of phytopharmaceuticals a better protection of their data has to be guaranteed. **We therefore suggest to include additional assessment on data protection (verification of published data regarding their status of protection) within the standard operating procedure of compiling**	in the EU, according to Article 8(3), for a product containing the same active substance as intended for the monograph, the HMPC would not normally use that data (even if published) if the data are still under protection. . This situation could only occur if a marketing authorisation, according to Article 8(3), has been granted during the 8 years preceding the adoption of the monograph. Also, if there are significant clinical studies which have led to a new indication for a well-established substance, the holders could explore the possibility for herbal medicinal products covered by herbal monographs to benefit from data exclusivity by reference to the requirements of Article 10(5) of Directive 2001/83/EC. This legal provision states that "where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication". This data exclusivity period is non-cumulative to other periods of protection and it refers exclusively to the data concerning the new indications. Such a data exclusivity period is an incentive for development of new indications whilst data protection would not otherwise apply. Clinical studies carried out in relation to the new indication and protected by data exclusivity would not normally be covered by the monograph within the 1-year period of

Interested party	Comment and Rationale	Outcome
	scientific data to support HMPC assessment work and of the establishment of European Union herbal monographs (WEU). <u>Protected data can only be used for the assessment and establishment of European Union herbal monographs if the data owner gives his consent!</u> Corresponding changes could be included e.g. in **1. Standard operation procedure: SOP/H/3189 (see Appendix 1)** Title: Compiling scientific data to support HMPC assessment work Procedure Step 9 - Archiving material used for HMPC assessment (Page 5) or additional step. **<u>Proposed change:</u>** Add as first sentence: "*Verification <u>of any existing data protection on published data. Does the published data refer to a herbal medicinal product with a certain extract that has been authorized as medicinal product during the past 8 years for the first time within the EU? Referring to the respective extract: Are the provisions of a well-established medicinal use fulfilled? Protected data have to be identified properly and can only be used for the establishment of European Union herbal monographs after owner's written consent on using the data for this purpose</u>*." Corresponding changes have to be added to the flow chart. **Standard operation procedure: SOP/H/3163 (see Appendix 2)** **Title: Establishment of Community herbal monographs and Community list entries and related documents** **Procedure Step 5 (Page 12) or additional step**	data exclusivity. Results of clinical trials do not form the basis for the establishment of traditional use monographs (see section 4.2 below) and the question of data protection of such data in case of traditional use monographs is thus not an issue. Revisions of SOPs are outside the scope of this guideline revision.

Interested party	Comment and Rationale	Outcome
	Proposed change: Add as first sentence: "*Verification of any existing data protection on published data. Does the published data refer to a herbal medicinal product with a certain extract that has been authorized as medicinal product during the past 8 years for the first time within the EU? Referring to the respective extract: Are the provisions of a well-established medicinal use fulfilled? Protected data have to be identified properly and can only be used for the establishment of European Union herbal monographs after owner's written consent for using the data for this purpose*." Corresponding changes have to be added to the flow chart. **This topic should be addressed in the revised Guideline.**	

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
Introduction	AESGP	Comment: The phrase "systematic use of published literature will be a contribution to avoid animal experiments in preclinical testing and reduce the number of new clinical trials in humans" is omitted in the revised guideline. Proposed change (if any): The recommendation to avoid animal testing should remain in the revised guideline as it is a broadly accepted approach.	Endorsed The sentence has been re-introduced into the document.

Section number and heading	Interested party	Comment and Rationale	Outcome
Line 100- 101	AESGP	Comment: The reference to Article 10a and Annex 1 of Directive 2001/83/EC in regard to well established use (WEU) and THMPs is not fully correct because THMPs are not mentioned in Annex I yet and article 10a refers to WEUs only. Furthermore, the next paragraphs (lines 102 – 140) are referring to aspects of especially well established use products. Proposed change (if any): Therefore, we recommend deleting the phrase "registration of traditional herbal medicinal products" in line 101.	Endorsed The phrase has been deleted.
Throughout the document (lines 132-138; 192-196; 376; 381-386)		Comment: Due to uncertainties in the phrasings "similar to the product", "different from the product", "different herbal preparation", "same herbal preparation (although to the same plant material)" and "otherwise comparable preparations" clear distinctions and references are required. For example, based on the current notice to applicants (NtA) Volume 2A, Chapter 1 the term "similar" is used for applications of paragraph 4 of Article 10 only (similar biological products) which is not applicable to herbal medicinal products. This is also in agreement with the meaning of the term "similar" laid down in Directive 2001/83/EC article 10. If the term "same" is used (same active substance, same herbal preparation) we propose to refer to section E.3 of Commission Communication 98/C229/03 (*Official Journal C 229, 22/7/1998 p. 4-17*) like in the current NtA Volume 2A, Chapter 1. This would clarify that for example, excipients and "other excipients" present within the herbal preparation, or herbal medicinal product, are out of scope of this definition. If reference to the Commission Communication is made, it is	Partly endorsed Lines 132-136 in the guideline are quoted directly from Directive 2001/83/EC (Annex 1), and can as such not be changed. For clarity, reference to Annex 1 has been added to the text. Lines 192-196; For clarity, the text in brackets has been changed to (although the herbal preparation may originate from the same plant species). Lines 375-376: To align the guideline text with the terminology of well-established use in Annex 1, the word "comparable" has been replaced by "similar". Lines 381-386: It is agreed that in Annex 1, the terminology "same constituent" is also used concerning products with a well-established use. However, it is only used in the context of assessing "post-marketing experience with other products containing the same constituent". This has now been clarified and added to

Section number and heading	Interested party	Comment and Rationale	Outcome
		further obvious which pharmaceutical forms can usually be defined as the "same".As a definition of the "same" is first given on page 11 of 13 (in section 6.1) and this uncertainty affects several passages and pages, we recommend to include a reference to the above mentioned Commission Communication clarifying the term "same" at first mention (on page 5) at least as a footnote. Furthermore, we note that the concept of a definition for "same active substances" also applies to herbal medicinal products falling under the well-established use as well as those corresponding to the traditional use according to article 16a of Directive 2001/83/EC. Proposed change (if any): The paragraph on lines 381 – 384 explaining the term "same" should also be mentioned in chapter 6.2 (line 386) in regard to well established products – here preferably complemented by the relevant DER. This would be in agreement with the section "qualitative and quantitative composition" of HMPC WEU monographs. In addition, for herbal medicinal products falling under Article 10a of Directive 2001/83/EC annex I of this Directive specifies that in these cases a judgement must explain the relevance of any data submitted which concern a product different from the product intended for marketing authorisation/application.	the guideline in section 3 (original line139) and in section 6.1 (original line 381), respectively.
Lines 138 177 292	EUCOPE	**Comment:** The term "pivotal" is used in connection with full applications (Art 8.3) and may not be appropriate in the context of the well-	Endorsed. The word "pivotal" has been replaced by "relevant" or "essential", in the document.

Section number and heading	Interested party	Comment and Rationale	Outcome
		established use because the demonstration of efficacy is based on a broader range of clinical data beyond "pivotal studies". **Proposed change:** Delete "pivotal" in the corresponding lines.	
Line 170-220	AESGP	Comment: We regret that the reference to the guidance "The WHO General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine", WHO/EDM/TRM/2000[1] is removed. This WHO Guideline is still valid and describes the important ABC grading and evidence levels which are described in detail in the current version of this HMPC-Guideline. Proposed change (if any): Due to the fact that grading of recommendations regarding different evidence levels is an important aspect to be discussed and assessed in expert reports of marketing authorisations according to article 10a as well as registrations according to article 16a of Directive 2001/83/EC we recommend not to delete the reference to this document.	Not endorsed. The methodology of grading evidence as described by the WHO is not used in regulatory approval procedures for medicinal products in EU. Neither has it been used by HMPC in the development of EU herbal monographs. It should thus be deleted from the guideline.
Line 181	EUCOPE	**Comment:** The use of the term "clinical relevance" is not appropriate, since no general definition exists. This has to be defined for each therapeutic field individually under consideration of the circumstances of the specific patient population. The clinical assessor's evaluation of clinical relevance may therefore be	Not endorsed In a controlled clinical study, the efficacy results in the treated patient group are compared to the results in a control group (usually placebo). If a treatment is found to have a statistically significant effect, but the effect is so small that it has no practical meaning to the patient,

Section number and heading	Interested party	Comment and Rationale	Outcome
		subjective, especially as far as OTC indications are concerned which are typical for herbal medicinal products. This will lead to imbalances between the assessments of active substances/monographs in the same therapeutically area. **Proposed change:** Delete the sentence: *The clinical relevance of the documented efficacy of the product/substance must be assessed.*	the treatment effect is considered not clinically relevant. Consequently, the product cannot be considered clinically effective and should not be approved. The clinical relevance should be assessed by an experienced clinical assessor.
Lines 184-186	AESGP	Comment: Within this table in the line "statistical analysis data" a "quality score" is mentioned; such a score should be described or defined, as only in (some) meta-analyses or systematic reviews quality scores are involved. Proposed change (if any): We suggest using the Jadad Score, which often is used in meta-analyses.The Cochrane risk of biais tool may also be of use.	Comment is endorsed, but no change of the guideline text is considered necessary. In the AR template, the Jadad score is suggested to be used. Other tools may also be used.
Line 186 Table 1	ESCOP	The table lists several study characteristics that should be assessed by the rapporteur. We consider it important that the material used in clinical studies (e.g. an extract prepared from a medicinal plant) is well characterised including e.g. the part of a plant used, the drug extract ratio and the extraction solvent.	Comment is endorsed, but no change of the guideline text is considered necessary. It is obvious from lines 132-135, 193-196 and the revised section 6.1, that the nature of the herbal preparation must be carefully assessed.

Section number and heading	Interested party	Comment and Rationale	Outcome
Line 186 Table 1	EUCOPE	**Comment:** For the characterisation of a herbal medicinal product the description of the pharmaceutical form, dosage regimen and the route of administration is not sufficient. Especially to compare different preparations with each other it is important to get knowledge about their qualitative and quantitative composition. Therefore the drug extract ratio (DER) and the extraction solvent should always be described, other specifications would also be helpful. **Proposed change:** Add the following parameters to be described under "Herbal preparations": DER (Drug extract ratio) Extraction solvent Other specifications if applicable	See above.
Line 227-309	AESGP	Comment: consideration of WHO/EDM/TRM/2000[1] was skipped; please see our above comment under line 170-220. Furthermore, it is important to note that for traditional herbal medicinal products not only grade C recommendations but rather grade A/B recommendations - based on clinical studies which do not meet the requirement of a "controlled clinical study of good quality" - can provide the basis for the proposed indication as well as the proof that the medicinal product has an efficacy which is "plausible".	Not endorsed. See above (lines 170-220). Additionally, it should be emphasised that the mandatory text of the therapeutic indication for a THMP ends with: "the product is a traditional herbal medicinal products for use in specified indications exclusively based upon long-standing use". Furthermore article 16a 1. (e) of the Directive states that "… the pharmacological effects or efficacy are

Section number and heading	Interested party	Comment and Rationale	Outcome
		Proposed change (if any): the above mentioned WHO Guidance as well as the consideration of clinical studies (if available) supporting the evidence of "plausibility" should be mentioned here.	plausible on the basis of long-standing use and experience."
Line 247	AESGP	Comment: The phrase "plausibility of a traditional indication may include, but is not limited to clinical data, pharmacological studies or case reports" was omitted. Proposed change (if any): Taking into account our comments under line 227 we recommend to maintain this sentence which refers to "clinical data" substantiating "plausibility" of traditional products.	Not endorsed because, according to the Directive, clinical data pharmacological studies or case reports cannot substitute the experience of long-standing use. See above.
319-330	ESCOP	We appreciate the statement that, for example, treatment of BPH symptoms Is eligible for a traditional use claim "after serious conditions have been excluded by a medical doctor". This has been common practice in preparation of monographs during the past few years, but it has not yet been included in a guideline.	-
Line 310-343	AESGP	Comment: "For most of the herbal drugs / herbal preparations only a traditional use is acknowledged, even if data from clinical trials are available.	Not Endorsed. See above lines 227-309.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Proposed change (if any): If such data is available, we suggest evaluating the quality of these clinical studies by the same methods including the table as described in the chapter for the well-established use (line 184 ff).	
Line 319-330	AESGP	Comment: We very much appreciate the reference to collaborative care being included in the guideline (e.g. treatment of BPH symptoms).	-
Line 352-357	ESCOP	The draft mentions that the clinical safety assessment must address the specific situation e.g. of children. We are of the opinion that this must not result in restrictions on the use of herbal medicinal products in children where there is insufficient data from studies in specific age groups available. Otherwise, the consequence would be an imbalance between (traditional) herbal medicinal products and food supplements, which are in most cases not limited to use in adults.	Not endorsed. The usage in children is included in the monograph when adequate data are available on specific age groups.
Lines 352-357	AESGP	Comment: The draft mentions that the clinical safety assessment must address specific situations e.g. children. We appreciate this and are of the opinion that data extrapolation could be considered in case data are seen insufficient for some age groups. In any case this should not result in restrictions on the use for herbal medicinal products in children in case there is no sufficient data from studies in a specific age group.	See above.

Section number and heading	Interested party	Comment and Rationale	Outcome
Line 227- Chapter 4.2 Guidance on monographs and on the list of traditional herbal substances/ preparations	EUCOPE	**Comment:** So far, chapter 5.1 (Pharmacodynamic properties) of the traditional use part of a European Union herbal monograph is left blank, since it is not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended. According to the report of the AESGP/MLWP hearing on 6 May 2014 (EMA/HMPC/540095/2014), pharmacodynamic data can be considered to be included in section 5.1. of a traditional use monograph on a case-by-case basis. This is especially the case if the pharmacological properties support the plausibility of the long-standing therapeutic use. This should be reflected in this Guideline. Although information on pharmacodynamic properties is not required, such information will be informative and helpful to healthcare professionals. Therefore available data of sufficient scientific quality should be provided. **Proposed change:** Addition of the sentence: *If pharmacodynamic data of adequate quality are available, they should be summarised in chapter 5.1. (Pharmacodynamic properties).*	Not endorsed. Data on pharmacodynamics properties are not required for THMPs in the simplified registration procedure. In analogy with data on preclinical safety, information on pharmacodynamics properties are not included in the monographs unless necessary for the safe use of the product. In agreement with the directive, plausibility of pharmacological effects or efficacy of THMPs is assessed on the basis of long-standing use, not on assessment of pharmacological studies (see above).
Line 412		**Comment:** Bridging to clinical information (related to efficacy and/or safety) which has been obtained from studies conducted with	Partly endorsed. Questions related to a potential need for biopharmaceutical characterisation of HMPs are

Section number and heading	Interested party	Comment and Rationale	Outcome
		another medicinal products is only acceptable if it can be demonstrated that the new product for which Marketing Authorisation is intended is "essentially similar" to that medicinal product which has been used in the clinical studies. In case of generic applications this evidence can be provided by assessing bioequivalence between the products. In principle same procedure is applicable in case of "well established use" procedures. From the scientific perspective relevant difference cannot be seen in this respect between chemically defined products and herbal medicinal products. Consequently same procedure and requirements should be applied for herbal medicinal products. This requirement is in particular essential as long as dosage forms with modified release properties are concerned. In such cases abridged applications without proof of bioequivalence are scientifically inacceptable. **<u>Proposed change:</u>** The introductory sentence "*Additional information on the biopharmaceutical characterisation may be necessary*" should be complemented by the following sentences: *"This is in particular essential in case of oral dosage forms with modified release characteristics. For such herbal medicinal products in-vivo studies characterising the systemic exposure and assessment of bioequivalence will normally be required."*	essentially linked to individual marketing authorisation applications on a case by case basis. This is outside the scope of the guideline. We thank the interested party for bringing this to attention. The sentence on biopharmaceutical characterisation on line 412 has been deleted from the guideline.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Literature [1] Blume H, Brauer KG, Dingermann T, Mutschler E, Steinhilber D, Abdel-Tawab M, Zuendorf I.: Gute Substitutionspraxis. DPhG-Leitlinien 2014. http://www.dphg.de/fileadmin/content/pdfs/dphg_leitlinie_gute_substitutionspraxis.pdf [2]Briefing Document/Position Statement for an Expert Meeting of the German Pharmaceutical Society [3]Resolution published from the Expert Meeting of the German Pharmaceutical Society	