European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON HMPC 'GUIDELINE ON THE ASSESSMENT OF CLINICAL SAFETY AND EFFICACY IN THE PREPARATION OF COMMUNITY HERBAL MONOGRAPHS FOR WELL-ESTABLISHED AND OF COMMUNITY HERBAL MONOGRAPHS / ENTRIES TO THE COMMUNITY LIST FOR TRADITIONAL HERBAL MEDICINAL PRODUCTS / SUBSTANCES / PREPARATIONS'

EMEA/HMPC/104613/2005

Table 1: Organisations that commented on the document as released for consultation

	Organisation
1.	AESGP
2.	ESCOP
3.	Kooperation Phytopharmaka

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Table 2: Discussion of comments

Line no or section and paragraph no	Comment and rationale	Outcome
3. Legal basis, **p. 4**	- 1st paragraph: Community herbal monographs cover herbal substances and / or preparations, not final products.	No changes; wording is taken from article 16h (1) b of CD 2001/83/EC, as amended.
3. Legal basis, **p. 4**	- 7th paragraph: It is suggested to write "active substance" or "herbal substance"; the term "constituents of medicinal products" is unclear. Further to the factors listed, it is highlighted that different periods of time may be necessary for establishing well-established use of different active substances. In any case, however, the period of time required for establishing a well-established medicinal use of a herbal substance/ herbal preparation must not be less than one decade from the ***first*** systematic and documented use of that active substance as a medicinal product in the Community.	Endorsed; wording changed. Already addressed in the text; no changes.
4.1 Guidance on monographs for well-established herbal medicinal products; elements of the clinical documentation, **p. 5-8**	In general, this section mixes activities of HMPC and national authorities. On the one hand, the assessment of clinical safety and efficacy within the preparation of monographs (WEU/TU) and of the 'list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products' are described, on the other hand the assessment of filed dossiers are mentioned (e.g. 4.1). To stay close to the activities of the HMPC as laid down in the EC Directives, the requirements for the dossier may be left out in this document.	Endorsed. Text modified and clarification introduced.

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4.1 Guidance on monographs for well-established herbal medicinal products; elements of the clinical documentation, **p. 5**	- 1st paragraph: It is suggested to delete: "In addition to published controlled clinical trials" as it can be misleading. It is suggested to amend the following sentence: *"the assessment of safety and of efficacy may be based on **controlled or** non-controlled clinical studies, epidemiological studies such as cohort or observational studies etc."*	Not endorsed: Text is clear. Not endorsed; see above.
4.1 Guidance on monographs for well-established herbal medicinal products; elements of the clinical documentation, **p. 6**	Levels of evidence, Ia: For ethical reasons, further studies than randomised controlled trials should be included. Levels of evidence, IIb: The meaning of "quasi" should be explained. Levels of evidence, III: observational studies and surveillance studies should be included. Grading of recommendations, C: It is suggested to delete: **"**Indicates absence of directly applicable studies of good quality."	No changes, as this refers to and is taken from a WHO reference. Observational studies are a specific subset of epidemiological studies. The term "surveillance studies" is not clearly defined. If it is not a Phase IV clinical trial, this study type is covered by "epidemiological study".
4.1 Guidance on monographs for well-established herbal medicinal products; elements of the clinical documentation, **p. 6**	- 5th paragraph: It is suggested to delete the sentence: "It should be noted that all types of evidence have to be checked for their scientific quality and consistency. No type of evidence is a priori scientifically valid or not." as it contradicts the overall recommendations on the levels and grades addressed above in terms of scientific quality and consistency.	No changes. The type of evidence is descriptive and does not imply that the study / information is of good scientific quality.

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4.1 Guidance on monographs for well-established herbal medicinal products; elements of the clinical documentation, **p. 7**	- Elements of the clinical documentation, 2nd paragraph: "All" data is not practicable.	No changes. The wording is "all relevant clinical data".
4.1 Guidance on monographs for well-established herbal medicinal products; elements of the clinical documentation, **p. 7**	- Elements of the clinical documentation, 5th paragraph: From our point of view, observational studies of good quality should be acceptable, too, to support a well-established medicinal use of the preparation. For this reason we suggest to add to this paragraph: *"In general, at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study) or observational study of good quality is required to substantiate efficacy."* From our point of view, clinical studies are necessary but exemptions for well-established use can be made by the HMPC on a case-to-case basis when sound medical experience in humans is available. For this reason we suggest to the following wording (and to use in only one paragraph: *"In general, at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study) of good quality is required to substantiate efficacy. In the absence of a controlled clinical trial a case-to-case assessment taking into account possible benefits, risks and types of diseases should be accepted if clinical experience with the herbal medicinal product is well documented and supportive, conclusive (human) pharmacological data of good quality are available."*	No changes. Observational studies are covered by the term epidemiological study. Not endorsed. The term "may be accepted" is more appropriate to the situation of a "case-by-case-assessment".

Line no or section and paragraph no	Comment and rationale	Outcome
4.1 Guidance on monographs for well-established herbal medicinal products; elements of the clinical documentation, **p. 7**	- Elements of the clinical documentation, 6th paragraph: The sentence on paragraph 5 should not be separated from the next paragraph, which describes an alternative approach: *"In the absence of a controlled clinical trial a case-by-case assessment"*. The use of both of these approaches is common practice as clinical studies are not always available. These approaches can be considered equivalent and equally acceptable. Both figure in the Levels of Evidence scheme on page 6. According to this scheme all levels of evidence including level IV belong to the area of well-established medicinal use and are mentioned under "4.1 Guidance for well-established products". Example 1: Clinical efficacy can be regarded as proven for Primulae radix (see also HMPWP core-data Primulae radix) Example 2: Although clinical studies do not exist for anthraquinone laxatives, efficacy is proven (see also draft HMPC monographs on Senna, Aloes and Frangula covering the well-established medicinal use only). In order to make clear that both these approaches can be used alternatively, we suggest to merge paragraph 5 and 6 and to reword as follows: *"In general, at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study)* ***or observational study*** *of good quality is required to substantiate efficacy. In the absence of a controlled clinical trial* ***or observational study*** *a case-by-case assessment taking into account possible benefits, risks and types of disease* ***should be accepted****, if* ~~*extensive*~~ *clinical experience with the herbal medicinal product is well documented and supportive, conclusive (human) pharmacological data of good quality are available. Evidence of grade C/level IV supported only by pre-clinical data are not sufficient to make the clinical efficacy of a product recognised."*	Changed to one paragraph. According to general criteria of EBM, the best evidence should be sought. In this sense the different types of evidence are not "equal". This is reflected in the current wording. The situation how to assess a HMP in absence of clinical studies is already reflected in the guideline by describing the case-by-case assessment; the examples described might be the outcome of such an assessment. Paragraphs merged. Extent of use is part of the criteria for acceptance of WEU. No changes.

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	Controlled clinical trials are not available in *every* case. For this reason the case-by-case assessment should not be used as an exemption, but as a useful alternative. E.g. in case of Primulae radix (see also HMPWP core-data Primulae radix) clinical efficacy can be regarded as proven. Furthermore, in case of anthraquinone laxatives, clinical studies do not exist; nevertheless efficacy is proven (see also draft HMPC monographs on Senna, Aloes and Frangula covering a well-established medicinal use only). We would like to suggest to make reference to published scientific monographs (e.g. ESCOP, WHO) or scientific material on the efficacy and the safety of herbal substances/herbal preparations as compiled by Kooperation Phytopharmaka.	
4.1 Guidance on monographs for well-established herbal medicinal products; elements of the clinical documentation, **p. 8**	- Elements of the clinical documentation, 9th paragraph: The term "degree of scientific interest" should be explained. We are wondering whether this could mean that if during a certain period no new research is published on a plant, "down-regulation" of the respective monograph from well-established to traditional use might take place.	Wording taken from the Annex to CD 2001/83 EC; clarification added.
4.2. Guidance on monographs and on the list of traditional herbal substances/preparations, **p. 8**	- 2nd paragraph: It reads that "the basis requirements encompass that the product is not harmful". This is not totally correct as such and needs to be completed as follows: "*the basis requirements encompass that the product is not harmful* ***under normal conditions of use***"	Endorsed.

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4.2. Guidance on monographs and on the list of traditional herbal substances/preparations, **p. 8**	- 3rd paragraph: It reads that "Plausibility of a traditional indication may include, but is not limited to clinical data, pharmacological studies or case reports." According to Directive 2004/24/EC, the main criterion for plausibility of a traditional indication is the demonstrated long-standing use. Older clinical data, pharmacological studies or case reports may be used in addition, if available. Claiming, however, that plausibility "is not limited to clinical data" would not be in line with the Directive. For this reason we consider the following wording appropriate: *"Besides demonstration of long-standing use, plausibility of a traditional indication may in addition include pharmacological studies, older clinical studies or case reports."* Reference is given to the evidence of use, which must be "continuous and consistent". We are wondering whether this means the necessity to prove the use of the product for each of the 30 years. For reasons of clarity we suggest to say "has been in use throughout a period of 30 years".	Clarification added; evidence on the period of use and plausibility of the indication must be, both, assessed. Even if a substance has been used in a product over 15/30 years, a positive opinion may not be possible, if the indication is not plausible, e.g. because the posology is too low to expect any effect. "continuous" taken out, because the period of use may have been interrupted.
4.2. Guidance on monographs and on the list of traditional herbal substances/preparations, **p. 10**	- Last paragraph: According to this paragraph (referral by Member State) the assessor evaluates available information and as far as possible explains and justifies the proposed therapeutic indication, strength, posology and specific information on safe use. From our point of view it would be useful to publish this kind of information also within the published draft monographs compiled by the HMPC.	Relates to the rules of procedures for drafting monographs/lists/assessment reports.
5. Clinical safety, **p. 10**	- 2nd paragraph: The meaning of "similar criteria" should be clarified.	No change.

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6.1 Active substances, **p. 11**	- Well-established herbal medicinal products: Preparations described in a Pharmocopoeia are sufficiently specified.	No change; this will depend of the type of pharmacopoeia monograph i.e. specific monograph or "framework" monograph.
6.1 Active substances, **p. 11**	- Traditional herbal medicinal products: We would like to note that the extraction solvent may not be completely identical as in many cases no information is given in the (older) literature, and certain modifications should be permitted in order to "modernize" traditionally used preparations. For example, in the draft monograph on Valerianae radix, several traditional preparations are listed having a range of solvents. Therefore, we would like to suggest the following amendment to the guideline text: "*This will include the plant/part of the plant, the type of herbal preparation* ***(e.g. extract, tea)*** *and, for extracts, the* ***extraction solvent*** ~~*primary solvent*~~ ***(e.g. ethanol) in comparable polarity ranges****"*	Not endorsed; the definition is given in Article 16c (2) of CD 2001/83/EC, as amended. For new / modernised extracts, the procedure described in Article 16c (4) may be used in the framework of national applications for the simplified registration. Monographs/lists can only comprise existing active substances that fulfil all criteria.

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6.3 Additional considerations for Well-established and traditional herbal medicinal products, **p. 12**	- 1st paragraph: The last line of the paragraph suggests that other pharmaceutical forms, which are not included in the traditional herbal directive, are possible. It would be useful to have some examples of such pharmaceutical forms, which would not be considered traditional ones. The following rewording of the 1st paragraph is suggested (for clarity): *"For well- established and traditional herbal medicinal products additional information on the biopharmaceutical characterisation may be necessary if there are concerns relating to safety or if a specific pharmaceutical form is not well-established or a traditional one."*	Examples might include coated capsules with modified release or specific devices for inhalation or preparations for topical use as described in the two paragraphs that follow. Not endorsed, because biopharmaceutical data might be necessary for the assessment of efficacy in marketing authorisation.