12 March 2013
EMA/HMPC/768094/2012
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. 1)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	The Association of the European Self-medication Industry (AESGP)
2	Dr. Willmar Schwabe GmbH & Co. KG

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	AESGP appreciates having the opportunity to submit comments on this document and would be grateful if these comments can be taken into consideration.	
2	The possibility to submit comments is highly appreciated. We are looking forward to the outcome of proceedings.	

2. Specific comments on text

Line no.	Stake holder no.	Comment and rationale; proposed changes	Outcome
Line 113 (Page 6/15) 2.3 QOS	1,2	Comment: Test for radioactive contamination is currently not mandated, Ph. Eur. Herbal Drugs 1433 states “In some specific circumstances, the risk of radioactive contamination is to be considered”. Proposed change (if any): The QOS should summarise the data on potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, ~~radioactive contamination,~~ fumigants, etc.	Partly Accepted. The text was updated as follows: The QOS should summarise the data on potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, fumigants, etc. In some specific circumstances, the risk of radioactive contamination is to be considered”.
Line 113 (Page 7/15) 2.6 Non-clinical Summaries	1,2	Comment: Order of statements changed to emphasise THMP standard not requiring tabulated summaries because the substances are well-known and documented in monographs or in public domain data, editorial changes. Proposed change (if any): ~~Tabulated clinical and non-clinical summaries in Module 2 shall be provided.~~ Tables *are generally not required* ~~may not be necessary~~ for well-known substances *in a THMP procedure based on monograph or public domain data,* ~~but a proper~~	Tabulated non-clinical summaries are generally **not required** for well-known substances when a monograph or a list entry has been established. When the applicant is requested to supplement the data supporting the monograph with additional safety data (e.g. tests on genotoxicity, reproductive toxicity and carcinogenicity) these data **shall be presented** in the tabulated non-clinical summaries in this section. When there is no monograph nor a list entry, tabulated non-clinical summaries in Module 2 **shall be provided**.

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		~~justification for not providing them will be required.~~ *In exceptional cases where study data are provided for lack of monograph or public domain data, a tabulated non-clinical summary in Module 2 can be requested.*	
Line 113 (Page 7/15) 2.7 Clinical Summaries	1,2	Comment: Order of statements switched to emphasise THMP standard not requiring tabulated summaries because the substances are well-known and documented in monographs or in public domain data and editorial changes. Proposed change (if any): ~~Tabulated clinical and non-clinical summaries in Module 2 shall be provided.~~ Tables ~~may not be necessary~~*are generally not required* for well known substances *in a THMP procedure based on monograph or public domain data. In exceptional cases where study data are provided for lack of monograph or public domain data, a* ~~, but a proper justification for not providing them will be required.~~*tabulated clinical summary in Module 2 can be requested.*	Tabulated clinical summaries are generally **not required** for well-known substances when a monograph or a list entry has been established. When supplementing data 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, a tabulated summary **shall be presented** in this section 2.7.
Line 128 4.2. Study reports	1,2	Comment: Taking into consideration the usually very restricted amount of data provided by applicant initiative or	

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		on request, a summary should not be mandated. Proposed change (if any): If applicable. If data are available or have been requested they should be provided. ~~and summarised in Module 2.6 for which the corresponding expert report would be included in Module 2.4.~~	Not endorsed (as original text provides greater clarity on requirements).
Line 132 5.3 Clinical Study Reports	1,2	Comment: Taking into consideration the usually very restricted amount of data provided by applicant initiative or on request, a summary should not be mandated. Proposed change (if any): If applicable. If data are available or have been requested they should be provided. ~~and summarised in Module 2.7 for which the corresponding expert report would be included in Module 2.5.~~	Not endorsed (as original text provides greater clarity on requirements).
Line 226, 232	1,2	Comment: Undertaking letters between suppliers and manufacturer are part of the contract between the product manufacturer and the supplier in the context of GMP and therefore are not part of the registration dossier	Accepted.

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		Proposed change (if any): Delete the reference to “undertaking letters”.	
Line 330-332	1,2	Comment: The section “Results comparing the phytochemical composition…” is incomprehensible and we propose to delete this section. Proposed change (if any): A brief summary describing the development of the ***herbal substance*** and ***herbal preparation*** where applicable should be provided, taking into consideration the proposed route of administration and usage. ~~Results comparing the phytochemical composition of the herbal substance and herbal preparation where applicable used in supporting bibliographic data and the herbal substance and herbal preparation where applicable, described in 3.2.S.1.2 should be discussed, where appropriate.~~	Partly accepted. The text was updated as follows: The comparability of the phytochemical composition of the herbal substance/herbal preparation used in supporting bibliographic data and the herbal substance/herbal preparation described in 3.2.S.1.2 should be discussed as appropriate.
Line 345 Line 349-350	1,2	Comment: Providing chromatographic profiles in section 3.2.S.3.1 Elucidation of structure is not necessary since they should be provided in section 3.2.S.4 Control of Drug Substance. On changes of analytical methods affecting chromatographic profiles, variations would be required. In order to avoid redundancies and reduce workload, we propose to	Not accepted. In this section, the phytochemical characterisation consisting of chromatographic profiles (TLC, HPLC, GC) is important to define the herbal drug and herbal preparation, especially for the toxicological studies and clinical studies. This characterization is sometimes made with additional

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		delete references to chromatographic profiles in section 3.2.S.3.1. Proposed change (if any): • ***Herbal substance*** Information on the botanical, macroscopical, microscopical, phytochemical characterisation, and biological activity, if necessary, should be provided. For a non-compendial herbal substance, iconography of the plant and the part of the plant, and of the microscopical characters should be provided. ~~Chromatographic profiles (TLC, HPLC, GC) should be provided.~~ Alternatively: Chromatographic profiles (TLC, HPLC, GC) should be provided **if applicable**. • ***Herbal preparation*** Information on the phyto- and physicochemical characterisation and biological activity, if necessary, should be provided. ~~The definition of the herbal preparation by a typical chemical profile (chromatographic profiles: TLC, HPLC, GC) should be provided.~~ Alternatively: Chromatographic profiles (TLC, HPLC, GC) should be provided **if applicable**.	chromatographic profiles (e.g. HPLC profiles in addition to TLC profile retained for routine testing).
Line 371-378	1,2	Comment: For a herbal preparation, potential contaminants	Partly accepted. The text was updated as follows:

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		such as pesticides and fumigants residues, toxic metals, mycotoxins (e.g. aflatoxins, ochratoxin A) should only be discussed in cases where the herbal substance itself is the active pharmaceutical ingredient or, where applicable, as a result of analysis of the herbal substance used for production of the herbal preparation. Concerning radioactive contamination or ochratoxin A determination see comment to line 113 or line 413. Proposed change (if any): • **Herbal preparation** *In the case where the herbal substance itself is the active pharmaceutical ingredient or, where applicable, as a result of analysis of the herbal substance used for production of the herbal preparation p*otential contaminants originating from the herbal substance production and post-harvesting treatments such as pesticides and fumigants residues, toxic metals, ~~mycotoxins (~~aflatoxins *(and* ochratoxin A *for herbal drugs subject to contamination*), ~~microbial contamination and radioactive contamination~~ as well as potential adulterants should be discussed. *Microbial contamination and p*ossible impurities originating from the process or from degradation should be listed and discussed with an indication of their	• ***Herbal substance*** Potential contaminants originating from the herbal substance production and post-harvesting treatments such as pesticides and fumigants residues, toxic metals, aflatoxins, (and ochratoxin A for herbal drugs subject to contamination), microbial contamination as well as potential adulterants should be discussed. The risk of radioactive contamination is to be considered. Degradation products should be studied if relevant, e.g. potential degradants formed on storage or those that might arise as a result of decontamination treatments. • Herbal preparation Potential contaminants originating from the herbal substance production and post-harvesting treatments such as pesticides and fumigants residues, toxic metals, aflatoxins, (and ochratoxin A for herbal drugs subject to contamination), microbial contamination as well as potential adulterants should be discussed. The risk of radioactive contamination is to be considered. Possible impurities originating from the process or from degradation should be listed and discussed with an indication of their origin (e.g. potential degradants formed on storage or those that might arise as a result of decontamination treatments). The presence of potential residual solvents should be discussed.

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		origin (e.g. the study of the possible modifications occurring with decontamination treatments as ionizing radiation). The presence of potential residual solvents should be discussed.	
Line 393-394	1,2	Comment: Fatty or essential oils used as active substances are in many cases so called “atypical actives”. Data about the herbal substance are often very scarce. This circumstance should be taken in mind. Proposed change (if any): In the case of fatty or essential oils used as active substances of herbal medicinal products, a specification for the herbal substance *should be provided, as appropriate or* ~~is required~~ unless justified.	Not accepted. The text comes from the Quality guideline.
Line 405406	1,2	Comment: According to Ph.eur. *“The date on which monographs are to be implemented is fixed by a Resolution of the European Committee on Pharmaceuticals and Pharmaceutical Care (Partial Agreement) of the Council of Europe, following a recommendation by the Commission. This date is usually 1 year after adoption and about 6 months after publication.”*	Partly accepted. The text was updated as follows: For the herbal substance and the herbal preparation, the following should be provided as appropriate: - Where the European Pharmacopoeia applies, reference to the relevant monograph, - Where monographs other than those in the European

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		According to the Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (2010/C 17/01) February 2010: *"There is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that compliance with the updated monograph is implemented within* ***six months*** *of its publication and reference is made to the 'current edition' in the dossier of an authorised medicinal product."* A requirement to include a photocopy of the pharmacopoeial monograph instead of current practice to reference to current Pharmacopoeia would collide with requirements to update to current Pharmacopoeia monograph within 6 months without variation and force the applicant to submit variations on Pharmacopoeia updates instead. Proposed change (if any): For the ***herbal substance*** and the ***herbal preparation,*** according to the case, should be provided: - A ~~photocopy of~~*reference to* the pharmacopoeial monograph, with, if necessary, the description of the additional tests,	Pharmacopoeia are referred to, a copy of the monograph, - In all cases, details of any additional tests, - Where an in-house specification is referred to, a detailed description of all analytical procedures.

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		- Or for an in-house monograph, a detailed description of the retained analytical procedures.	
Line 409-410	1,2	Comment: Analytical validation for non-pharmacopoeial procedure (e.g.pesticides, heavy metals, aflatoxins) should be provided for the herbal substance or the herbal preparation depending on where the testing takes place. Proposed change (if any): Analytical validation information, including experimental data for non-pharmacopoeial procedure used for testing the ***herbal substance*** and/*or* the ***herbal preparation*** should be provided.	Not accepted. The word “or” is not used in the following paragraphs in the same way – and could lead to misunderstandings.
Line 413	1,2	Comment: According to current Ph.Eur. 2.8.22 Ochratoxin A determination is only required for herbals at risk of contamination (“Herbal drugs that are subject to contamination by ochratoxin A are tested by a validated method.”). Proposal to differentiate the wording for aflatoxin and ochratoxin to reflect this difference. Proposed change (if any): For impurities, quantitative analysis of pesticides residues must be validated on a suitable herbal	Accepted.

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		matrix (according to the indication given in European Pharmacopoeia in 2.8.13)5. For aflatoxin *determinations* (~~s~~and ochratoxin A determinations *for herbal drugs subject to contamination*), the suitability of the European Pharmacopoeia methods (2.8.18 and 2.8.22, respectively) to the herbal matrix tested must be performed. For microbiological examination, the suitability of the method must be performed (according to the indication given in 2.6.31).	
Line 421	1,2	Comment: According to NtA “results of batch analyses” should be provided in this section, and not “certificates of analysis” Proposed change: Adapt wording to wording according to NtA and line 423/424: …, at least the results of the analysis of one batch per site should be given.	Accepted.
Line 454	1,2	Comment: For the herbal substance, a description of the container closure system(s) should only be provided in cases where the herbal substance itself is the active pharmaceutical ingredient. In the majority of cases where the herbal substance is a starting	Accepted.

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		material for a preparation, the same requirements as for other starting materials should apply, without the need to specify the container closure system(s). Proposed change (if any): *In cases where the herbal substance is the active pharmaceutical ingredient* ~~A~~ description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications.	
Line 471474	1,2	Comment: For the herbal substance, storage conditions statements should only be mandated in cases where the herbal substance itself is the active pharmaceutical ingredient. In the majority of cases where the herbal substance is a starting material for a preparation, the same requirements as for other starting materials should apply. Information about compliance with requirements for specification should be provided in 3.2.S.4 correspondingly. Proposed change (if any): ~~Herbal substances, which are used as starting material in the manufacturing process of a herbal preparation, shall comply with specification before use (e.g. before extraction).~~	Accepted.

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		In cases where the herbal substance is the active pharmaceutical ingredient storage conditions of the herbal substance by the producer and the supplier and by the active substance manufacturer should be stated.	
Line 520522	1,2	Comment: A listing of the quality of excipients should be provided in section 3.2.P.4.1. On changes of quality of excipients, variations would be required. In order to avoid redundancies and reduce workload, we propose to delete references to quality of excipients in section 3.2.P.1. Proposed change (if any): **Composition**, i.e.: list of all components of the dosage form and their amount on a per-unit basis (including overages, if any), the function of the components, ~~and a reference to their quality standards~~ ~~(e.g. compendial~~*diluents*~~monographs or manufacturer's specifications),~~	Not accepted. The text is from NTA of the "Presentation and format of the dossier CTD" for chemicals.
Line 524	1	Comment: Description of the type of container and closure should be provided in section 3.2.P.7. On changes of type of container and closure, variations would be required. In order to avoid redundancies and reduce workload, we propose to delete references	Not accepted. The text is from NTA of the "Presentation and format of the dossier CTD" for chemicals.

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		to type of container and closure in section 3.2.P.1. Proposed change (if any): **Type of container and closure** used for the dosage form and accompanying reconstitution diluent, if applicable.	
Line 555	1,2	Comment: This guideline on the use of the CTD format in the preparation of a registration application for traditional herbal medicinal products refers explicitly to THMPs. The compatibility of drug substances in a (traditional) combination product should be already given by the evidence on the long-standing traditional use over at least 30 years of a corresponding product. Proposed change (if any): *The compatibility of the drug substances with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g. water content, solubility, particle size distribution) of the drug substances that can influence the performance of the herbal medicinal product should be discussed.* ~~For combination products, the compatibility of drug substances with each other should be discussed.~~	Partly accepted. For combination products, the compatibility of drug substances with each other will have been demonstrated by the evidence of traditional use.

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Line 574	1,2	Comment: According to Guideline on Specification for Herbal Medicinal Products CPMP/QWP/2820/00 Rev 1 dissolution may be replaced by disintegration as widely practiced. Proposal to replace dissolution by disintegration. Proposed change (if any): Parameters relevant to the performance of the herbal medicinal product, such as dis*integration*~~solution~~, particle size distribution, rheological properties, biological activity should be addressed.	Partly accepted. For well-established use dissolution is required. The text was updated as follows: Parameters relevant to the performance of the herbal medicinal product, such as disintegration and/or dissolution, particle size distribution, rheological properties, biological activity should be addressed.
Line 612	1,2	Comment: Quality of active substance should be provided in 3.2.S. A listing of the quality of excipients should be provided in section 3.2.P.4.1. On changes of quality of active substance or excipients, variations would be required. In order to avoid redundancies and reduce workload, we propose to delete references to quality of all components in section 3.2.P.3.2 Proposed change (if any): A batch formula for the intended batch size (an application for variable and/or alternative batch size should be justified) should be provided that includes a list of all components of the dosage form	Not accepted. The text is from NTA of the “Presentation and format of the dossier CTD” for chemicals.

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		to be used in the manufacturing process *and* their amounts on a per batch basis, including overage~~,~~ ~~and a reference to their quality standards.~~	