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

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE USE OF THE CTD FORMAT IN THE PREPARATION OF A REGISTRATION APPLICATION FOR TRADITIONAL HERBAL MEDICINAL PRODUCTS[1]

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

	Name of Organisation or individual	Country
1	Association of the European Self-Medication Industry (AESGP)	Belgium
2	Biohorma/Bioforce IRG	The Netherlands
3	Kooperation Phytopharmaka	Germany

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

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW		
It would be useful to have a mock application for traditional herbal medicinal products in CTD format as an example. *This was not in the scope of the guideline however it can be consider at a future stage.*		
The GUIDELINE ON THE USE OF THE CTD FORMAT for THMP is welcomed. However, we suggest to give some more precise details of the structure and content of this guideline		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
SCOPE, page 3/13, article 2	The current guidance applies to all THMP independently of the fact whether the active substance is subject to a Community list/monograph or not. However, it should be made clear in the scope of the guidance that for a THMP containing a substance with list entry or monograph, only guidance on module 3 should be taken into account. Modules 4 and 5 can be omitted, as reference to the list entry/monograph is sufficient, and therefore the guidance does not apply. To our knowledge this guideline entirely applies only to THMP with an active substance which is not included in the European Community list. Therefore, we suggest to give an other definition in the SCOPE. *This guideline is applicable to applications for traditional use registration of traditional herbal medicinal products for human use having as active substance a substance which is subject of a Community herbal monograph or a substance for which such a monograph is not available.*	*Clarification has been introduced under Module 4 and 5 sections regarding list entries as follows:* *According with Article 16f(2), if an application for traditional use registration relates to a herbal substance, preparation or combination, the data specified in Article 16c(1)(b)(c)and (d) do not need to be provided.*

[2] Where applicable

1.5	Section 1.5: so far, no sub-section corresponds to the presentation of information justifying why the product meets the requirements for traditional use registration.	*Clarification is introduced in the introduction section as follows:* *If no specific heading exists, the information should be provided under the relevant module as described below.*
1.8	According to the Guidelines on Pharmacovigilance for Medicinal Products for Human Use (Vol. 9A), the pharmacovigilance obligations apply to all medicinal products authorised in the EU. Consequently, Information regarding the Pharmacovigilance has to be submitted for THMP within Module 1.8. *Applicable*	*Pharmacovigilance obligations apply to all medicinal products, however, the specific dossier requirement to provide a Pharmacovigilance system does not apply to THMP as Article 16c(1)(a) does not include a reference to Article 8(3)(ia).*
2.4	For bibliographical applications the Notice to Applicants on the CTD format gives advice that references are listed in the serially chapters 2.5.7 and 2.7.5; there is no advice which serial number is valid for the references of module 2.4 and 2.6. Because a dossier on a traditional THMP (as also other product categories) in most cases is based at least on supporting bibliographical data, advice should be given where to place the references in non-clinical data. *Bibliographical references for non-clinical data shall be listed at the end of module 2.4 and (in a new defined chapter "2.6.8: references" OR at the end of module 2.6).*	*CTD structure is an internationally agreed format and therefore no new subheadings can be introduced. However, clarification has been included in module 2.4 as follows:* *The list of relevant references **for non-clinical data** can be included at the end of module 2.4*
2.4 and 2.5	Can it be possible to get precisions about what is an "expert evidence" (see 2.5) versus "expert report" (see 2.4)?	*The wording from legislation is used..*

2.5	Within this module, the available data on the plausibility of efficacy as well as the data on the tradition of use shall be submitted. Considering the structure and content of the CTD, there is no information where to place these data in this module. We recommend to give advice where to place the data. We suggest to submit the data on the plausibility o**r** efficacy in the section on the efficacy, eventually also in the section on the pharmacology; the data on the tradition of use, which might cover extensive tables, may be placed within the section on the efficacy or in an annex following the references. *Bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Community: Data shall be placed within the section on the efficacy or in an annex.* *The plausibility of pharmacological effects or efficacy of the medicinal product of use should be addressed in the section of the efficacy (2.5.4, eventually also in the section on the pharmacology 2.5.3; the safety has to be addressed in the section on the safety 2.5.5.* Plausibility in traditional medicinal products has to be shown by the traditional use of the product and not by submitting clinical trials therefore we suggest to use the following, less confusing wording: *"In addition, the efficacy of the medicinal product (from traditional sources) or the plausibility of pharmacological effects as well as information on the safety of use should be addressed in this section.* We would like confirmation that the justification for the period of use and assessment of the plausibility of pharmacological effects or efficacy of the medicinal product should only be introduced in "2.5 Clinical overview"?	*This can be acceptable, however, the guidance will not be modified as it was intended to give applicants the flexibility of providing the relevant data under the most appropriate subheading depending on the medicinal product in question.* *The wording from Directive will be kept.* *This is confirmed.*

2.6 and 2.7	Exemption of providing tabulated clinical and non clinical summaries for “well known substances” seems conflicting as, in our opinion, all THMP should be regarded as “well known substances”. Moreover, the wording “very old” is subjective and does not correspond to an established definition. The templates according to Notice to Application Volume 2B are not easily applicable for herbal medicinal products. To tabulate all the written data in accordance with these templates generates more work without resulting in additional information, or improved understanding of the original information. This view is supported by the experience from the Canadian authorities which came, after two years of practice with such templates, to the conclusion that these tables are not practical for herbal products and have since withdrawn this requirement. *Non-clinical and clinical written summaries have to be provided for THMP; it is recommended to consider that tabulated summaries shall not be provided* *We therefore propose to use Modules 2.6 and 2.7 to present the bibliographic review of safety. This would be written summary of the available non-clinical and clinical literature that supports the safety of the product submitted for registration. Module 2.4 and 2.5 would therefore no longer contain the bibliographic review allowing the Expert reports contained within these modules to more accurately reflect the CTD format of the Non-clinical overviews.-*	*The following correction has been included in the guideline:* *Tabulated clinical and non-clinical summaries in Module 2 shall be provided. Tables may not be necessary for ~~very old,~~ well known substances, but a proper justification for not providing them will be required*

2.6.2 to 2.6.5	According to the 3. Legal basis, a) (iii), the application for traditional use registration of HMP shall be accompanied by "The summary of product characteristics, without the data specified in Article 11(5) [pharmacological properties]".So, the paragraphs 2.6.2 to 2.6.5 of the module 2 should not apply to the traditional herbal medicinal products. According to section 2.4 of the present draft, only "a bibliographical review of safety" with corresponding documents is described as being required for THMP. *It is proposed to mention "Not applicable" for sections 2.6.2 to 2.6.5 of the CTD*	*If the bibliographic review of safety data includes studies that can be summarised into any of the indents of Module 2.6, this should be done.* *Clarification has been included as an introductory paragraph under 4.2 as follows:* *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.*
2.7.1 to 2.7.2	The following sections can be considered as non applicable: • 2.7.1 Summary of Biopharmaceutics and associated analytical methods • 2.7.2. Summary of Clinical Pharmacology Studies *It is proposed to mention "Not applicable" for sections 2.7.1 and 2.7.2*	*If the bibliographic review includes studies that can be summarised into any of the indents of Module 2.7, this should be done.* *Clarification has been included as an introductory paragraph under 5.3 as follow:* *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.*
3.2.S.1.3	The expected content should be clarified.	*As explained in the guideline, the term 'Applicable' means that the guidance provided in Notice to Applicants (NtA), Volume 2B - Common Technical Document (CTD) should apply. Therefore information regarding 'Physico-chemical properties' should be provided as per Module 3.2.S.1.3 of the NtA Volume 2B.*
3.2.S.2.1	The requirement stating that "*the name, the 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*" is exactly based on statement of the "Guideline on the Chemistry of New Active Substances (CPMP/QWP/130/96, Rev1)". Such requirement applied to herbal substances faces difficulties, indeed impossibilities as: • considering herbal substances produced/collected out of western Europe (especially in developing countries), it may be	*Proposed changed not accepted. There are no reasons for deviation from the requirements set out in Annex I to Directive 2001/83/EC, as amended.*

	difficult or impossible to get information on each area/site of production (herbal growers)/collection (collectors); • often, based on limited ordered quantities of herbal substance, the supply through wholesalers is necessary with impossibilities to get traceability of all the supply chain; • each change of supplier would mean submission of a variation. Such maintenance is burdensome. As it is not possible to anticipate at each time such herbal supply difficulties, there is a risk of stock rupture for the manufacturer if a change of supplier is not possible within a short period of time. *It is proposed to modify the sentence as follows: "the name, the 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 possible".*	
3.2.S.2.2	In our opinion, information about "batch size" is relevant for herbal preparations but not for herbal substances. In the context of plant production and moreover in the one of plant collection, the information "batch size" does not really makes sense in reality. Additionally, it is extremely difficult, if not impossible, to obtain this kind of information. *It is recommended to delete the requested "batch size" regarding the herbal substance.*	*The information on batch size is relevant in case that the herbal substance is subject to processing (e.g. drying, cutting etc.) as it could influence the manufacturing process. Batch size ranges should be defined as appropriate*
3.2.S.4	*It is confusing that under 3.2.S.4 "Control of Drug Substance", data for herbal substance(s) AND herbal preparations should be provided.* *As an alternative, we propose to insert the data for herbal substance(s) under 3.2.S.2.3 "Control of Material" as the herbal substance is a starting material in the production of a herbal preparation.* *From a logical point of view we would prefer to insert the specifications, analytical methods, validations of methods and certificates of analyses for the herbal substance in 3.2.S.2.3. In doing so, the structure of the dossier would become clearer; introducing and characterising all the substances which are used during manufacture before describing this process in Module 3.2.S3.*	*The same principle of providing information both for herbal substance(s) and herbal preparations under the same section applies throughout module 3.2.S. This structure was defined for Module 3 for herbal medicinal products.*

Modules 4 and 5	Modules 4 and 5 contain numerous sections which are “not applicable”. Are those sections to be provided with the documentation or is it possible only to provide what is “applicable”?	*4.1.: A ToC should be provided* *4.2.: If there are any study available they should be included in this module under the appropriate indent. For example, if there is only one study on in-vitro genotoxicity available, it should be placed under 4.2.3.3.1. All other indents should appear as ‘not applicable’ in the ToC.* *Same applies for Module 5.*
4.3 and 5.4	The statement “such references should be indexed following the agreed format for the organisation of Module 4/5” is unclear. According to the Notice to Applicants on the CTD format, there is a precise regulation where bibliographical references shall be placed (modules 4.3 and 5.4). Is it meant that the references should be annexed to the appropriate section they refer to? Please clarify. *We suggest to delete the sentences “Such references should be indexed following the agreed format for the organisation of Module 4/5”*	*Bibliographical references should be included in modules 4.3 and 5.4 in alphabetical order as per Notice to Applicants. In addition, an index following the agreed format for module 4/5 should also be provided here.* *Not agreed.*
Module 5	For an THMP substance or product specific data as well as bibliographical data will support the tradition of use. Advice should be given, if these data are included in the alphabetical order in chapter 5.4 on the references or if they shall be submitted in a separate chapter within 5.4 or module 5 generally . *Please clarify.*	*All clinical literature references should be placed in module 5.4, and there should not be a separate section for traditional use.* *However the relevant references to justify the long standing use of the medicinal product should be mentioned in Module 2.5.*