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

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OVERVIEW OF COMMENTS RECEIVED ON 'GUIDELINE ON THE CLINICAL ASSESSMENT OF FIXED COMBINATIONS OF HERBAL SUBSTANCES / HERBAL PREPARATIONS'

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

	Organisation
1.	Association of the European Self-Medication Industry (AESGP)
2.	The Herbal Forum
3.	Other EMEA Committees

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Table 2:Discussion of comments

General comment	Comment and rationale	Outcome / Proposed change
	The commenting organisation appreciates the new HMPC Draft "Guideline on the clinical assessment of fixed combinations of herbal substances/herbal preparations" as it provides guidance to the applicants on the documents to be submitted for fixed combinations. In particular, the organisation welcomes the clear differentiation between well-established and traditional herbal medicinal products as regards the extent of data to be submitted.	No modification introduced.
	The guideline states that the efficacy and the safety of the fixed combination "must be evident" from clinical trials or from bibliographic data submitted by the applicant. In addition, it is recommended that the proposed dosage of the fixed combination and the contribution of each active substance must be justified in the clinical overview/expert report. However, it is unclear which kind of clinical data is required and how the doses and the choice of each active substance should be justified. For traditional herbal medicinal products the evidence is based on "plausibility". For well-established herbal medicinal products, it is recommended that B/R assessment of the fixed combination is equal or exceeds the one of each of its active substances taken alone. Could the HMPC further describe which studies they expect to allow this conclusion? It is not believed that companies will perform factorial design clinical trials and compare efficacy and safety of the fixed combination to that of each active substance, especially because there are many active substances in herbal preparations.	Modification / explanation introduced.

	It is also suggested to specify what kind of studies should be performed to assess safety pre-MA. It is stated that if a fixed combination appears more harmful than any individual substance given alone, the applicant must provide clinical evidence that this is not the case. It is suggested to specify what kind of clinical evidence is expected. It is stated that epidemiological or post-marketing studies may be enough. We are not sure that epidemiological studies may give enough safety information for any kind of product (medicinal or herbal) pre-authorization, except for very severe adverse events (example: acute severe hepatic insufficiency due to Chinese herbal tea given for atopic dermatitis). Overall, the guideline does not specify the type of studies (done by the applicant or reported in the literature) necessary to conclude efficacy and safety of the fixed herbal combination in order to grant MA.	Similar aspect as the previous one. See above.

Line no or section and paragraph no	Comment and rationale	Outcome / Proposed change
General considerations, p. 3: subsection a)	This section contains general considerations, particularly on the extent of data to be submitted. For instance, a well-founded data analysis should be submitted for combinations corresponding closely to those, which are in widespread use, which "may be helpful in reducing the amount of clinical trials to be performed". From our point of view, providing additional clinical study results would be more or les an exceptional case whereas normally bibliographic data in the sense of a "bibliographic data analysis" will be sufficient. For this reason, we propose to move the text of footnote No. 3 into the normal text: *"Provided that the respective bibliographic data on the fixed combination and on its ingredients are thoroughly and reliably documented, this analysis may be* ~~***helpful in reducing the amount of clinical trials to be performed***~~ ***sufficient for the justification of the efficacy and safety of the fixed combination*** *and could facilitate the selection of doses for each substance and the proposed dose range of the fixed combination."*	Proposal endorsed. Footnote can be included in the main text.
General considerations, p. 4: second paragraph	The extent of justification of the rationale needs to be clarified. While a theoretical justification is needed, we believe that the clinical proof of the rationale should be simplified, as the complexity of the herbal combinations would hardly allow one to carry out three- or four-arm trials to prove additive or synergistic actions.	Modification introduced (see general chapter modification above).
General considerations, p. 5: Traditional herbal medicinal products	We agree with the statement given for traditional herbal medicinal products that *"the requirements relating to efficacy will be reduced to the level of plausibility"*. However, regarding well-established herbal medicinal products, it is thought that some clarification would be needed as regards the term *"valid therapeutic principles"* (page 4, second paragraph). From our point of view, "well-established therapeutic principles" would be more helpful.	Modification introduced.

General considerations, p. 5 : Traditional herbal medicinal products	Why is a risk/benefit assessment proposed for products, which are not required to demonstrate efficacy? Clarification of this point, and of any proposed methodology would be appreciated.	Even though the demonstration of efficacy is reduced to "plausibility", any risk has to be balanced against the plausible efficacy/potential benefit for the consumer. No modification introduced.
Indications, p. 6: Traditional herbal medicinal products	Further explanation of the intention of the first sentence of the first paragraphs of point 5.2 is needed, '*Similar considerations will be applicable to traditional herbal medicinal products'.* This sentence refers back to 5.1, which deals with Well-established herbal medicinal products, and it is not clear whether the intention is to apply all of its considerations to THMPs. In our view, some may not be entirely appropriate for traditional herbal medicinal products – for instance the requirement for exact details of the contribution and proportion pf each active substance in relation to the claimed effect. 5.2 First paragraph, third sentence, ' *If reference is made to a particular traditional system of therapy, this should be expressed in the wording of the indication.* Our understanding of *Article* l6g 2. of Directive 2004/24/EC is that it is not mandatory to name the particular traditional system of therapy, and we therefore suggest that in the Guideline the word 'should' be replaced with 'may'.	No modification introduced. If a specific traditional system of therapy is the main basis for the therapeutical concept of the fixed combination product, this should always be made transparent to the patient/consumer.
Composition and dosage regimen, p. 6: Well-established herbal medicinal products	As there are cases of herbal medicinal products in which combination partners are present in amounts of less than 10% of the single doses, but whose efficacy is proven by clinical studies, we would like to propose adding the following sentence at the end of the third paragraph: *"However, if the efficacy of the combination is proven, such a combination will be accepted."*	No modification introduced. Both aspects, i.e. the efficacy of the product and the rationale of the composition must be substantiated. The limit given (10%) is not a fixed limit. This is clearly expressed by the wording: ".. are unlikely …".

Composition and dosage regimen, p. 6: Traditional herbal medicinal products	As it stands, the text would not allow any modification of the traditional combination to account for new scientific evidence. We would plea for a more flexible handling of the combinations, in particular with regard to the multivitamin preparations containing herbals. The multivitamin part should be modifiable to account for changes in RDA and addition or elimination of some vitamins or minerals should be allowed to adjust the product to the modern scientific standards. Second sentence of section 6.2: As, according to Article 16c(1)a)iv), information on the combination as such is required (and no justification of the individual compounds), we think that this sentence should read as follows: *The assessment of 'plausibility' will take into account the extent of traditional use of the combination, traditional posology of the* ***combination*** ~~***individual active constituents***~~ *and, as far as applicable, …"*	No modification added. The modifications/deviations from tradition are addressed in article 16 (c) (2) and (3). No modification added. Both aspects have to be addressed.
Composition and dosage regimen, p. 6: Traditional herbal medicinal products	The definitions of 'Vitamin' and 'Mineral' are not given in Annexes I and II of the Food Supplements Directive. Therefore we find the intended meaning of the word '*reference*' in the second sentence of the second paragraph of this section to be less than clear. We trust that it is not intended to mean that only those vitamins and minerals listed in these annexes can be used in THM products. In our view this should not be the case – each vitamin or mineral should be assessed on its own merits. In relation to dosage levels, we are not clear from the last sentence in this section whether the reference to '*scientific committees of the Community'* is intended to mean that maximum levels will be based on EFSA's recommendations, - which in our view would be appropriate – or whether choices will be made from a number of different scientific committees.	No modification added. The terms "Vitamin" and "Mineral" are understood in the same way as they are understood in the food legislation. It is not intended to introduce a new definition of these terms. The choice will depend on the type of preparation / way of administration. For some preparations, e.g. ointments, limits that are valid for cosmetics may be applicable.