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

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON QUALITY OF COMBINATION HERBAL MEDICINAL PRODUCTS / TRADITIONAL HERBAL MEDICINAL PRODUCTS

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

	Name of Organisation or individual	Country
1	Association Européenne des Specialités Pharmacetiques Grand Public (AESGP)	
2	Forschungsvereinigung der Arzneimittel-Hersteller e.V (FAH)	Germany
3	Herbal Forum (HF)	United Kingdom

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW
The guideline provides useful information and pragmatic interpretations of the existing documents for herbal and traditional herbal combination products, taking into account the specific character of herbal substances/ preparations as complex mixtures and the difficulties to perform identification test and assays in combination products. - The level of justification and the experimental data, which are demanded when certain tests cannot be performed, can be quite extensive - A number of modifications of the text are proposed (see below) - Some more precise wording and minor corrections in the text are proposed (see below)
The guideline does not adequately address the additional challenges posed by the complex composition of combination products. Any potential easement/reduction in the analytical demands on finished products is more than counterbalanced by the requirement for increased analytical and validation demands elsewhere in the manufacturing chain and is dependant on expensive expert analytical reports and/or testing to demonstrate or prove that all of the analytical techniques in the European Pharmacopoeia would not be able to identify/assay each of the actives in the product. - The alternative to finished product testing, i.e. in process testing and validation, would be expensive to introduce and result in a longer, more complicated and more costly manufacturing process. - Any reduction in the amount of finished product testing is dependant on the absence of active markers or constituents with known therapeutic activity in the product. Given that most reference books contain information on key therapeutic constituents for herbs, very few herbs would qualify for this derogation and therefore there will be, in practice, no easement.
SPECIFIC COMMENTS ON TEXT
GUIDELINE

Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
Throughout the guideline (including decision trees)	Replace “finished product” by “herbal medicinal product”	(1) Agreed. The text is modified accordingly.

[1] Where applicable

EXECUTIVE SUMMARY		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Line 18	Delete "each".	(2) Not agreed. Each critical step needs to be documented in detail.
2 SCOPE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Lines 53 and 56	Replace "multi-ingredient products" by "multi-active substance products"	(3) Partly agreed. Suggestion to replace by : "products containing multiple active substances".
4 MAIN GUIDELINE TEXT		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Throughout the text	Replace "quantification" by "quantitative determination" as "quantified is linked to the classification of extracts according to the Ph. Eur, production and specifications of extracts.	(4) Agreed. The text is modified accordingly.
Lines 97-99	"It should be stressed that notwithstanding the guidance given, ~~all~~ usual analytical methods for identification and assay should be investigated first, e.g. the methods described in the Ph. Eur. General Chapter 2 "Methods of analysis"	(5) Partly agreed. Suggestion to change to: "all analytical methods usually applied for identification and assay should be investigated first, e.g. the methods described in the Ph. Eur. General Chapter 2 "Methods of analysis"
Line 104	Delete "fully"	(6) Agreed. The text is modified accordingly.
Line 110	Replace "consisting" by "consistent"	(7) Agreed. The text is modified accordingly.

Line 113	Delete “strict and “	(8) Agreed. The text is modified accordingly.
Lines 117-118	~~“Each~~ Critical steps of the manufacturing process ~~should be regarded as critical~~ has to be defined “.	(9) Not agreed. When strategies alternative to testing in the finished product are considered, each step in the manufacturing process is considered as critical.
Line 119	“and appropriate procedures to ensure correct addition of ~~ingredients~~ active substances and/or excipients should be in place as routine control”.	(10) Agreed. The text is modified accordingly.
Lines 122-123 and lines 182-185	“Where a joint assay is performed, the active substance specification should include a minimum value for the common marker (additional, if different from the pharmacopoeial marker) ~~limit for the common marker~~”	(11) Partly agreed. The requirements with regard to assay limits depend on the active substance. Reference is made to the existing quality guidelines for herbal medicinal products. Suggestion to change to : Where a joint assay is performed, the active substance specification should include a limit for the common marker (additional, if different from the pharmacopoeial marker) to ensure its recovery in the herbal medicinal product.
Lines 134 and 174 Decision trees #1 #2	“where constituents with known therapeutic activity or active markers of the herbal substance/preparation are not known, but analytical markers are known”	(12) Not agreed. Analytical markers may be known, and may be used, on a case by case basis.
Lines 138-140 and lines 189-191	“Where the herbal substance/preparation cannot be identified in the finished product, appropriate justification ~~and documentation~~ that ~~all~~ usual analytical methods, e.g. the methods described in the Ph. Eur. General Chapter 2 “Methods of analysis”, have been investigated should be provided”. Justification needs to be documented anyhow/ the term “all usual analytical methods” is not correct and should be replaced by “usual analytical methods” which already implies consideration of “all”, or e.g. “all analytical methods usually applied in pharmaceutical quality control”.	(13) Partly agreed. See (5). Documentation is needed.
Lines 144,	Delete “fully”.	(14)

156, 186 and 201	Complete justification has to be provided always otherwise the justification is not valid. The intention of using "fully" is not clear as it would imply other situations were incomplete justification may be acceptable	Agreed. The text is modified accordingly.
Lines 144-146 and 156-158	"The identification test should be supported by ~~documented evidence on the manufacture of the finished product batch and~~ process validation". The meaning of "documented evidence of the finished product batch" is unclear. Appropriate batch records have to be filed (documented) anyhow as a GMP requirement and process validation is the main tool to provide evidence on validity of the manufacture process.	(15) Not agreed. Strict adherence to GMP with filing of appropriate batch records (that need to be filed for all medicinal products) are absolute requirements and conditions when considering strategies alternative to testing in the finished product. This justifies the emphasis placed on it in the guideline as "documented evidence on the manufacture of the finished product batch (batch records)". The applicant specifies and justifies which information is submitted in the application, and which documentation is available upon inspection by competent authorities.
Lines 152-155	"If IPC testing of the herbal substance/preparation is not possible, it is required that the herbal substance/preparation is identified <u>based on its</u> ~~according to the active substance~~ specifications immediately before the introduction of the active substance in the manufacture of the finished product".	(16) Partly agreed. Suggestion to change to: "If IPC testing of the herbal substance/preparation is not possible, it is required that the herbal substance/preparation is identified according to its specifications immediately before the introduction of the active substance in the manufacture of the finished product"
Lines 185-187	Delete "The approach taken should be fully justified by the applicant. Each approach should be supported by careful process validation and documentary evidence should be available"	(17) Not agreed. Each approach taken should be justified by the applicant, and should take into account the combination herbal medicinal product that is subject of the application. As required for all medicinal products, GMP, process validation and batch records documenting each step in the manufacturing process of the finished product and including results of IPC testing should ensure that, in combination with suitable testing criteria, a product of good and consisting quality is obtained.
Lines 195-200	"The manufacturing process ~~development~~ studies (e.g. analytical profiles during the stepwise addition of the herbal substances/preparations, ~~degradation studies during the manufacture of the finished product) and other studies [e.g. stability studies of the active substance(s)]~~ are pivotal in this regard and should underpin the proposed approach to ensure the quality and composition of the finished product e.g. assay of the active substance as IPC" .	(18) Not agreed. Although traditional herbal medicinal products trace back to known formulations etc, the manufacturing process development studies are pivotal to justify the choice of manufacturing process and to identity the critical process parameters relevant for subsequent process validation. Furthermore, having no knowledge about degradation during the manufacture of the herbal medicinal product or no stability data on the

	For Traditional Herbal Medicinal Products regularly no developmental studies have been /need to be performed.	active substance itself are in complete contradiction with the requirement to ensure the quality and composition of the herbal medicinal product.
Lines 201-202	Delete "Tests should be supported by documented evidence on the manufacture of the finished product batch"	(19) Not agreed. See (15)
Line 219	Replace "see also" by "according to"	(20) Agreed. The text is modified accordingly.
DEFENITIONS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Lines 242-245	Suggestion to delete "The control of the environment or equipment may also be regarded as a part of an in process control" because this is part of GMP and does not belong to the documents to be submitted within the marketing authorisation / registration dossier.	(21) Not agreed. The ICH definition of 'in process control' (IPC) is maintained in the guideline. As required for all medicinal products, GMP, process validation and batch records documenting each step in the manufacturing process of the finished product and including results of IPC testing should ensure that, in combination with suitable testing criteria, a product of good and consisting quality is obtained. The applicant specifies and justifies which information is submitted in the application, and which documentation is available upon inspection by competent authorities.
DECISION TREE #1		
Line no. + para no.	**Comment and Rationale**	**Outcome**
First ◊	"Active substance for which constituents with known therapeutic activity or active markers are known <u>in the herbal medicinal product</u>"	(22) Not agreed. The addition of "in the herbal medicinal product" is not necessary here. The criterion is whether it's an active substance for which constituents with known therapeutic activity or active markers are known, or not.
DECISION TREE #2		

Line no. + para no.	Comment and Rationale	Outcome
First ◊	"Active substance for which constituents with known therapeutic activity or active markers are known in the herbal medicinal product"	(23) Not agreed. See (22).
Second ◊	"An individual assay can be performed for the active substance in the herbal medicinal product"	(24) Agreed. The text is modified accordingly.
Second last □	"Appropriate manufacturing process design & validation to ensure the declared composition e.g. documented assay of the active substance as in process control (IPC)"	(25). Agreed. The text is modified accordingly.