4 June 2015
EMA/HMPC/130616/2015
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on 'Reflection paper on microbiological aspects of herbal medicinal products and traditional herbal medicinal products' (EMA/HMPC/95714/2013)

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

	Organisations and/or individuals
1	Association of the European Self-Medication Industry (AESGP)
2	European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

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1. General comments - overview

Stake holder	General comment (if any)	Outcome (if applicable)
General comment EUCOPE	In general we consider the requirements regarding microbiological contamination as described in the current Ph. Eur. 5.1.8. (Microbiology) and 2.8.18 (Aflatoxine) as well as the specific monographs in Ph. Eur. sufficient to ensure the required quality of herbal medicinal products. Further tests and validations beyond these requirements should only be necessary as long as Ph. Eur. specifications cannot be met. Even though this reflection paper takes the peculiarities of herbal medicinal products into consideration, we see it very critical that there are many text passages describing requirements far beyond those of the European Pharmacopoeia without further explanations.	Partially accepted. In this reflection paper consideration is given as to how suitable microbial quality of herbal substances, herbal preparations, and HMPs can be achieved by preventative measures, manufacturing processes and by applying decontamination processes. The aim of the reflection paper is to provide an overview of the critical aspects to be taken into account to ensure suitable microbial quality. The focus is on current regulatory aspects, but aspects of GACP and GMP are discussed as well. A paragraph is added in the *Introduction* in order to clarify this.
General comment AESGP	AESGP in principle welcomes the new document on microbiological aspects of herbal medicinal products and traditional herbal medicinal products as it provides guidance on how to assess the microbiological status of a preparation/ product in case actual problems do occur. However, the reflection paper describes an extensive number of imaginable situations which are normally part of GMP and thus within the responsibility of the manufacturer and the inspecting authorities, and not part of the documentation used for the application of a marketing authorisation/registration. **The European Pharmacopoeia (Ph.Eur.) provides acceptance criteria as well as established procedures (chapter 5.1.8 or 2.6.31, respectively, for herbal medicinal products) which are used in practice. For this reason the considerations laid**	Partially accepted. See outcome to general comment from EUCOPE.

Stake holder	General comment (if any)	Outcome (if applicable)
	down in this reflection paper should only be used as an argument in case actual problems do occur in practice, e.g. in case the acceptance criteria given in Ph.Eur. chapter 5.1.8 are exceeded. The reflection paper should not be used as a basis to develop more rigid requirements for microbiological quality of herbal medicinal products, since concrete concerns about the microbiological quality of herbal medicinal products do not exist. **Final comment:** **We are of the opinion that the reflection paper provides useful guidance in case actual problems do occur in practice or in case concrete concerns about the microbiological quality of herbal medicinal products do exist. However, with regard to the daily practice of manufacturers, we are convinced that the acceptance criteria and established procedures provided by the Ph.Eur. are sufficient.** **The reflection paper must not be regarded as a basis to develop more rigid requirements for microbiological quality of herbal medicinal products which might result in specific validation of production or extraction procedures, extensive analytical testing on potential changes of the products' composition, increased routine testing e.g. on mycotoxins or additional validation of decontamination procedures.**	

2. Specific comments on text

Line number	Interested party	Comment and rationale; proposed changes	Outcome
55	EUCOPE	It is not clear whether this reflection paper also does not apply to sterile injections containing preparations of herbal preparations (e.g. mistletoe or birch leaves). If so, this should be clearly addressed and justified. A justification would be helpful to avoid, that manufacturers of injections containing herbal preparations have to consider this reflection paper during each marketing authorization or inspection. If the scope of this reflection paper includes sterile injections containing herbal preparations it would be helpful to get more information to which extent the content of this paper has to be taken into consideration with respect to incoming plant material (herbal substance) and in-process-controls, since the finished product has to be sterile anyway. If the scope of this reflection paper includes sterile injections containing herbal preparations the whole “endotoxine” area has to be added.	Accepted. It is already stated in the *Introduction* that sterile products are out of scope. The wording is slightly amended in order to clarify this.
66-67	AESGP	Comment: The sentence states that *“the content of live bacteria, fungi and their spores should be determined and limited in herbal substances/ preparations and HMPs”*. This requirement must however not go further than the provisions of the Ph.Eur. Proposed change: “The content of live bacteria, fungi and their spores should be determined and limited in herbal substances/ preparations and HMPs **in accordance with the provisions of Ph.Eur. chapters 2.6.31 and 5.1.8**.”	Accepted. Wording has been changed.
68-72	AESGP	Comment: Pathogenetic micro-organisms have to be absent according to Ph.Eur. chapter 5.1.8. Examples should not be listed here as this could imply additional requirements. Proposed change: Delete the brackets which list the species.	Accepted. Examples have been deleted and text reworded.

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91-94	AESGP	Comment: From our point of view, using the term “degradation” does not take the particularities of herbal substances and products into account. In contrast to chemical entities, the term "degradation" does not necessarily mean a loss of activity. E.g. a transformation of a glycoside into its aglycone and the corresponding sugar unit is usually not relevant as long as the specification is met. Furthermore, particularly aqueous and aqueous/ethanolic systems such as liquid extracts, tinctures and liquid medicinal products demonstrate natural transformation processes. In these cases, naturally occurring variances of the composition of constituents are product-immanent. Finally herbal drug preparations (1434) can be obtained by different treatments, e.g. by extraction yet also by fermentation of herbal drugs, where enzymes from the plant as well as from microorganisms may contribute to achieve the desired product. Proposed change: The sentence “It is undesirable to have chemical degradation … or liquid dosage form)” should be deleted.	Partially accepted. Text amended.
94-95	AESGP	Comment: The physiochemical characteristics of plants are specified by the Ph.Eur. monographs. No further actions are necessary if the parameters of the monographs are kept. Evaluation of a potential change of activity is generally not applicable and not realistic. Proposed change: The sentence “Any potential reduction or change … must be evaluated” should be deleted.	Accepted.
128-129	AESGP	Comment: If the limits of aflatoxins and ochratoxin A are kept according Ph.Eur. 2.8.18 and specific monographs, no further evaluation is necessary. The enrichment of mycotoxins during the extraction process may occur, but evaluation of such a risk should not be made on a routine basis, only in case of suspicion. Aflatoxins and other mycotoxins can occur in case of inappropriate storage under humid conditions, particularly in case of roots, fruits or seeds. A general conclusion on the occurrence of	Partially accepted. Paragraph reworded.

Line number	Interested party	Comment and rationale; proposed changes	Outcome
		mycotoxins in the extract cannot be deduced. Proposed change: In case of suspect, this risk should be evaluated by validation of the extraction process.	
137-139	AESGP	Comment: As the way from herbal drug to herbal drug preparation includes many different processes (e.g. distillations), which are not all covered in the same way by GMP, we suggest the following change. Proposed Change: "The herbal substance should be manufactured in compliance with good agricultural and collection practice (GACP) and, from the starting material onwards, the herbal preparation should be manufactured in compliance with good manufacturing practice (GMP) **as distinguished in the Guide to GMP**."	Accepted. Text slightly modified.
137-141	EUCOPE	It should be clearly described when GACP requirements end and GMP requirement starts. What is the definition of "starting material" in this context? The requirements for essential oils should be in line with the HMPC document "Questions & answers on quality of herbal medicinal products/traditional herbal medicinal products" (EMA/HMPC/41500/2010 Rev. 3)". In Question 1 regarding essential oils it is stated, that early production steps could follow the GACP principles if the last steps were in line with GMP. Furthermore, similar standards can be accepted if justified (including risk assessment). This should be added in this section.	Accepted. A general reference to the EU guidelines for GMP is added.
183-184	AESGP	Comment: Requirements for testing excipients should not exceed the Ph.Eur. requirements. Proposed change: Microbial contamination of excipients used to produce the chosen dosage form should be	Partially accepted. Microbiological quality of excipients should be tested in accordance with Ph.Eur. and EU guidelines (e.g. ICH

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		controlled and monitored **in accordance with the Ph.Eur. requirements.**	Q6A, EMEA "guideline on excipients" and GMP). Text has been modified.
188-191	AESGP	Comment: We fully agree that prevention of microbial contamination is better than reduction of microbial load in the final product. However, we suggest taking into consideration whether GMP requirements shall really be mentioned in this context.	Not accepted. GMP plays an important role in ensuring sufficient quality of the HMP.
197-199	AESGP	Comment: It is stated that *"if a decontamination treatment has been used, it is necessary to demonstrate that the constituents of the plant are not affected and that no harmful residues remain."* As e.g. steam treatment usually affects volatile constituents, it is important that the specification of the monograph is met after treatment. As herbal products contain many different substances, a demonstration that no harmful residues are built is not practicable. Proposed change: "If a decontamination treatment has been used, it is necessary to demonstrate that the constituents of the plant are not affected and that no harmful residues remain. **This can normally be fulfilled by demonstration that the specification of the monograph is met after treatment. "**	Partially accepted. This general requirement is cited from the Ph.Eur. monograph "Herbal Drugs". Also see outcome to comment l. 235-239 from EUCOPE.
221-223	EUCOPE	The wording is a little bit irritating. It is stated that decontamination should only take place in the case that no lack of quality exist. That makes no sense because material has to be decontaminated due to the fact that material is not appropriate for use.	Partially accepted. See amended text.
221-223	AESGP	Comment: The text states: *"A decontamination treatment should not be used simply as a precautionary measure and decontamination treatments should not be used where the herbal substances/preparations/HMPs have microbial contents unfit for human or animal consumption."*	Partially accepted. See amended text. The proposed text is not endorsed because the second paragraph of the point 2.2.1 the issue of the risk

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		From our point of view, a batch-specific decision is not practicable. Decision about decontamination treatment, however, should be made on a risk assessment for the product. Proposed change: Please add the following sentence: “A decision about decontamination treatment should be made on a risk assessment for the product.”	assessment is already addressed.
223-230	AESGP	Comment: With regard to pathogenic bacteria, microbial metabolites, endotoxins etc. it is fully sufficient, from our point of view, to perform testing in accordance with the requirements of the Ph.Eur. A more general requirement for testing must not be deduced. Proposed change: We suggest replacing lines 223 – 230 by the following: “In case decontamination treatment is used, the treated product has to fulfil the requirements of the Ph.Eur.”	Partially accepted. See outcome to general comments, comments l. 128-129 and EUCOPE comments l. 489-492.
235-239	EUCOPE	The decontamination method described in the specific Ph. Eur. monographs should be sufficient to demonstrate that the chemical profile of the products has not been affected. The chemical profile is obtained by chromatographic fingerprint according to the corresponding Ph. Eur. monograph. Additional validations are not reasonable, since contamination varies from batch to batch. It should be sufficient that the product applies with respect to compounds and microbial load to the specification.	Partially accepted. Normally, methods, with the main purpose of decontaminating the herbal substance/preparation, are not described in the specific Ph.Eur. herbal monographs. See amended text.
235-239	AESGP	Comment: Evaluation of the chemical profile after decontamination goes too far from our point of view. Proposed change: Please delete line 235 – 239 as far as lines 223 – 230 already state (see proposal above)	Partially accepted. See outcome to comment l. 235-239 from EUCOPE.

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		"In case decontamination treatment is used, the treated product has to fulfil the requirements of the Ph.Eur. or the release specification respectively."	
253-255	EUCOPE	Comment: We recommend to change the wording, because microorganisms won't proliferate at lower concentrations of alcohol than 60 % m/m (as it is already described in literature* and as were shown in own in-house tests). Even though germ reducing effects are weaker (resp. slower) while using lower alcohol concentrations, there is a pronounced germicidal effect on vegetative microorganisms and their proliferation is inhibited at alcohol concentrations down to 20 % m/m. Homeopathic mother tinctures often have ethanol concentrations of about 43 % (m/m) and long-term experience confirms that there are no microbial issues. When 15 % m/m of ethanol (corresponding to 18 % V/V) are added to casein soya bean digest broth and this preparation, which offers – except for the contend of ethanol – optimum conditions for microbial growth, is challenged with *Escherichia coli, Salmonella aboney, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans* or *Aspergillus brasiliensis*, efficient and continuous reductions of microbial counts can be observed. These examples demonstrate that alcohol has marked decontamination effects also at lower concentrations. Proposed change: Even though higher alcohol concentrations (60 to 80 %) have stronger decontamination effects than lower concentrations on not spore forming germs, a pronounced antimicrobial effect on not spore forming germs can be shown down to 20 % alcohol content and the proliferation of any spore ore not spore forming microorganism is inhibited. In any case every antimicrobial effect should be verified during validation processes.	Accepted. Wording has been changed.
253-255	AESGP	Comment: Alcohol has marked decontamination effects also at lower concentrations. When 15 % m/m of ethanol (corresponding to 18 % V/V) are added to casein soya bean digest broth and this preparation, which offers – except for the contend of ethanol – optimum	Accepted. Wording has been changed.

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		conditions for microbial growth, is challenged with *Escherichia coli, Salmonella aboney, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans* or *Aspergillus brasiliensis*, efficient and continuous reductions of microbial counts can be observed. Proposed change: ~~However, only~~**Medium to** higher alcohol concentrations (**≥ 20%**~~60 to 80%~~) have marked decontamination effects~~because, at lower concentrations of alcohol, the presence of water potentially facilitates the growth of the micro-organisms~~.	
261-265	AESGP	Comment: The classification of soft extracts as "ideal medium for microbial growth" is too much generalised to our view. Proposed change: "…the total microbial level may be increased after alcohol evaporation, as the~~aqueous soft extract is an ideal medium for microbial growth~~ **microbiological quality of stored extracts has to be observed according to 5.1.8."**	Partially accepted. See outcome to comment l. 265 from EUCOPE.
265	EUCOPE	An aqueous soft extract is not an ideal medium for microbiological growth.	Partially accepted. The text is amended to tone down the capability of soft extracts as a growth medium.
272	EUCOPE	In this line very specific requirements are given for the storage period (24h) and the temperature of the refrigerator (2-8°C) to prevent microbial growth. We would appreciate if other storage conditions would also be accepted as long as they have been proven to be reasonable by corresponding data.	Accepted. The text has been amended.
281-282	EUCOPE	Comment: Ethanol is bactericidal and fungicidal also at lower concentrations. When 15 % m/m of ethanol (corresponding to 18 % V/V) are added to casein soya bean digest broth and this	Accepted. Wording has been changed.

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		preparation, which offers – except for the contend of ethanol – optimum conditions for microbial growth, is challenged with *Escherichia coli, Salmonella aboney, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans* or *Aspergillus brasiliensis*, efficient and continuous reductions of microbial counts can be observed. Proposed change: Ethanol is bactericidal and *fungicidal* in aqueous mixtures at concentrations between 60 *20*-95% V/V but is ineffective against bacterial spores.	
281-282	AESGP	Comment: Ethanol is bactericidal and fungicidal also at lower concentrations. When 15 % m/m of ethanol (corresponding to 18 % V/V) are added to casein soya bean digest broth and this preparation, which offers – except for the contend of ethanol – optimum conditions for microbial growth, is challenged with *Escherichia coli, Salmonella aboney, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans* or *Aspergillus brasiliensis*, efficient and continuous reductions of microbial counts can be observed. Proposed change: Ethanol is bactericidal **and fungicidal** in aqueous mixtures at concentrations between ~~60~~**20**-95% V/V but is ineffective against bacterial spores.	Accepted. Wording has been changed.
285-286	AESGP	Comment: The occurrence of chemical changes by the use of ethanol does not mean the normal extraction process. Proposed change: Delete this sentence.	Accepted.
403-405	AESGP	Comment: In our view, this wording is rather complex, negative and not correct as in Europe, steam treatment is the most common technique to reduce microbial contamination of herbs. Proposed change:	Accepted.

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		~~The use of steam is, in general, not advisable~~**If steam is used** to reduce the microbial contamination of plant material, ~~unless, following the process~~, the material ~~is~~ **should be** dried immediately as any residual water may affect the subsequent processing stages.	
422-424	AESGP	Comment: UHT treatment is an effective standard process during manufacture of extracts. We are of the opinion that assessment of each extract is not practicable. Proposed change: Please add: "In case heat treatment is used, it is sufficient that the treated product fulfil the requirements of the specification."	Partially accepted. The use of decontamination treatments should be justified during product development on a case-by-case basis. Text amended – see last paragraph of 2.2.1
449-460	AESGP	Comment: It should be mentioned that suitability of the methods for the respective herbal matrix should be demonstrated. Proposed change: Please add after line 460: "The suitability of media and methods should be demonstrated by use of reference test strains described in Ph.Eur Chapters mentioned above."	Accepted.
483-488	AESGP	General comment: The so-called "Special Ph. Eur. Provisions…" in Table 5.1.4.-1 are applicable for "oral dosage forms" which contain "raw materials from natural () origin". → Therefore "other" dosage forms are a **typing error** in this context and must read "oral" dosage forms. Comment: To our opinion lozenges should not need to fulfil the (more rigid) criteria of "oromucosal use" according to chapter 5.1.4. because these requirements cannot be kept e.g. by acacia (see individual Ph.Eur. monograph) or other substances of natural origin.	Partially accepted. The typing error is corrected. The example of lozenges is very specific and is not added in the text of this RP.

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		Proposed change: Please add: “Lozenges containing active substances or excipients of natural origin fulfil the requirements of orally used dosage forms according to Ph.Eur. chapter 5.1.4.”	
489-492	EUCOPE	The reflection paper considers more pathogens necessary to be tested for absence of specific bacteria than the European Pharmacopoeia. A justification should be provided. Furthermore more details concerning the implementation should be given: a) Is the testing of the additional pathogens required for each batch or should this testing only be performed during a special period of time? b) “Absence of specific bacteria” is referred to which amount of the sample? c) In this section (2.3. Testing of […]) it should clearly be described which kind of tests are required for “herbal substances”, “herbal preparations” and “herbal medicinal products”	Not accepted. In Ph.Eur. 5.1.8 it is stated that it *may* be necessary to consider other pathogens. Reference to Ph.Eur. is given in the text. A separate guidance document to be provided in the future.
520	EUCOPE	Hygroscopic substances don’t contaminate easier per se. It’s the amount of absorbed water that finally leads to low a_w-values.	Accepted. Text amended.
622-624	AESGP	Comment: It is stated that the “it should be demonstrated that the decontamination process does not alter the chemical composition … in the product“. As e.g. steam treatment might affect volatile constituents it is important that the specification of the monograph is met after treatment. Proposed change: Please add: “This can normally by fulfilled by demonstration that the specification of the monograph is met after treatment.”	Partially accepted. See outcome to comments l. 91-94, l. 94-95 and l. 197-199.

Literature

Axel Kramer & Ojan Assadian (Hrsg.): Wallhäußers Praxis der Sterilisation, Desinfektion, Antiseptik und Konservierung: Qualitätssicherung der Hygiene in Industrie, Pharmazie und Medizin, Georg Thieme Verlag Stuttgart, New York 2008.

Morton H.E.: The relationship of concentration and germicidal efficiency of ethyl alcohol. Annals of the N.Y. Academy of Sciences, 1950, 53, 191-196.

Pinon et al.: Growth, survival and inactivation of Pseudomonas aeruginosa and Staphylococcus aureus strains of various origin in the presence of ethanol. J. Cosmetic Science 2007, 29, 111-119