16 September 2010
EMA/HMPC/435996/2009
Committee on Herbal Medicinal Products (HMPC)

Overview of comments on draft 'Reflection paper on level of purification of extracts to be considered as herbal preparations (EMEA/HMPC/186645/2008)'

Final

Table 1: Organisations that commented on the 'Reflection paper on level of purification of extracts to be considered as herbal preparations' as released for consultation on 6 November 2008 until 15 April 2009

Organisation, country	
1	Association of the European Self-Medication Industry (AESGP)
2	Bundesverband der Pharmazeutischen Industrie (BPI), Germany
3	European Scientific Cooperative on Phytotherapy (ESCOP)
4	Indena S.p.A., Italy
5	PhytoLab GmbH & Co. KG, Germany

	Organisation or individual	**Contact details (e-mail address, telephone number, name of contact person)**
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2	BPI	BPI Bundesverbad der Pharmazeutischen Industire e.V. Friedrichstraße 148 10117 Berlin www.bpi.de Pharmaceutical Affairs/ CAM Tel.: (0 30) 2 79 09-113 Fax: (0 30) 2 79 09-313 e-mail: tbrueckner@bpi.de Contact person: Thomas Brückner
3	ESCOP	ESCOP Secretariat Argyle House Gandy Street EXETER, Devon EX4 3LS United Kingdom e-mail: secretariat@escop.com Tel: + 44 1392 424 626 Fax: + 44 1392 424 864 Contact person: Mr. S.Y. Mills
4	INDENA S.p.A.	Indena S.p.A. Viale Ortles 12 20139 Milan ITALY e-mail: ernesto.martinelli@indena.com Tel: + 39 0257496634 Fax: + 39 0257496642 Contact person: Mr. E.M. Martinell
5	PhytoLab GmbH & Co. KG	PhytoLab GmbH & Co. KG Dutendorfer Str. 5-7 91487 Vestenbergsgreuth GERMANY www.phytolab.com Contact person: Dr. Hartwig Sievers Tel. +49 9163 88-154 Fax +49 9163 88-349 e-mail: hartwig.sievers@phytolab.de

Table 2: Comments

General comments

Interested party	Comment and Rationale	Outcome
ESCOP	From our point of view, the decision to which category a product belongs, has to be made on a case-by-case basis. However, as a general principle we are of the opinion that all refined extracts including defined fractions of closely related constituents (e.g. silymarin, aescin) belong to the category of "herbal preparations". Only isolated single chemically defined substances which may represent a final step of purification do not belong to this category. As a consequence, the guidelines for herbal preparations and herbal medicinal products (e.g. quality, specifications etc.) apply for refined extracts including defined fractions of closely related constituents. In contrast, for isolated substances from plants which are regarded as chemically defined substances, the general quality guidelines for chemically defined active substances are applicable.	Agreed. (see lines 74-75 of the Reflection paper) The purpose of the Reflection paper has been missed. The key issue was to identify different categories of extracts which can fall under the definition of refined extracts, to be quoted as herbal preparations, in contrast to other products, such as for example mixtures of highly refined extracts in which the herbal matrix of natural concomitants has been removed, to be quoted as a mixture of isolated herbal constituents or mixtures of related herbal constituents.

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
	AESGP	Our comments are as follows: The text (line 33) states that herbal medicinal products have a number of characteristics that clearly differentiate them from	Agreed The following remark has be added in the Reflection paper: “It should be noted that herbal substances and

[1] Gaedcke F. Contribution to the discussion of the “Reflection paper on level of purification of extracts to be considered as herbal preparations” (EMEA/HMPC/186645/08).

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		chemically defined medicinal products. In addition, it should be noted that herbal substances, preparations including extracts are complex mixtures of substances, including those substances issued from natural transformation, which all together form the 'active substance'. For example: A rather high concentrated extract of milk thistle fruits specified to contain 65% of silymarin according to Pharm.Eur. is variable in its inner composition and contains between 20-45% of silycristin and silidianin, 40- 65% silibinin A and B and 10-20% isosilibinin A and B. Curcuminoids extracted and purified from Tumeric is not a single chemically defined constituent but a complex of 3 similar substances in ratio which can vary in a certain range, as follows: 95.0-100.0% curcuminoids calculated as sum of: 70-80% curcumin 15-25% desmethoxycurcumin 2.5-6.5% bidesmethoxycurcumin Using the above-mentioned example of milk thistle, Gaedcke [1] shows that the primary extract contains the whole spectrum of constituents of the herbal drug. Lipophilic purification leads to "70 % silymarin" containing less concomitant substances than the primary extract. Further purification leads to a defined herbal fraction "silymarin" (still a mixture of closely related constituents) and finally to the pure compound silibinin. Further purification leads to a defined herbal fraction "silymarin" (still a mixture of closely related constituents) and finally to the pure	herbal preparations are complex mixtures of natural constituents which all together form the 'active substance'. This includes those constituents that may arise from natural transformations," Examples included in the Reflection paper For the case of curcuminoids the method of refining has to be known to allow the assessment of the level of purification and the status of "herbal preparation" Agreed, the paper of Gaedecke addresses very well the issue, as considered by HMPC, and gives many suggestions for criteria useful for clarification of categorisation, but some questions still remain. These regard some particular refined extracts, where more than one constituent is present and the natural proportion is not always maintained. In this case the borderline has to be established on a

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		compound silibinin (i.e. chemically defined and having a very high degree of purity).	case by case basis but aspects for grounds of categorisation should be properly addressed.
	AESGP	Pure chemical entities (produced by complete chemical synthesis, semi-synthetically or by isolation from plants or animal parts) contain single and 'pure' components whose chemistry and structure, including their stereochemical aspect are known. For example: Hyoscine (scopolamine), content 98.5-101% with 0.5% related substances Caffeine, content 98.5-101.5% with 0.5% related substances Conclusion As a general rule, even substantially refined and concentrated herbal preparations should not be regarded as isolated herbal constituents because their complete chemical characterisation is not possible. For this reason all levels of purification of primary extracts have to be classified as "herbal preparations" with the exception of "isolated single chemically defined constituents" representing the final step of purification. Consequently, all guidelines for herbal preparations and herbal medicinal products (e.g. quality, specification, stability, declaration etc.) should cover these purified preparations. Even highly concentrated preparations should be in general subject to the specific herbal guidelines.	Agreed Partially agreed. Highly concentrated preparations should be regarded as herbal preparations, but in case of highly refined extracts where is the borderline? In some cases the complete chemical characterisation of the main component(s) is possible and only a small part of the extract is not fully identified. Therefore it can be regarded as the "impurities fraction" (sometimes unidentified because of the high cost of the analytical procedures). The purpose of the reflection paper is to establish criteria to discriminate between highly purified extracts which can still be considered as herbal preparations and other preparations which should be considered as isolated constituents with a relatively high amount of

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		In contrast, isolated herbal constituents have to be regarded as chemically defined constituents with the consequence that the general quality guidelines for chemically defined active substances are applicable.	unidentified impurities. For instance, highly purified herbal constituents, which are mixed after purification should be regarded as a mixture of isolated constituents.
1. Problem statement	BPI	Comments The problem statement raises a problem that does not seem to be one because the definitions in 2001/83/EC are clear. If the characteristics described there apply, the corresponding guidelines have to be applied. Only if the requirements of chemically defined substances are fulfilled, the guidelines for chemically defined substances have to be applied. But this has to be decided on a case by case decision. The characteristics of an herbal preparation (herbal origin, further processing steps: extraction, distillation, expression, fractionation, purification, concentration and fermentation) allow to declare such preparations as herbal preparation and characterize an herbal preparation as such. This is important because only in this case all components are regarded as parts of the active substances and not as impurities.	The statement that the decision has to be made case by case is already present in the draft reflection paper published for public consultation (see lines 74-75) and it is maintained in the revised version (see lines 10, 81, 92 and 155). The purpose of the Reflection paper has not been fully understood. The key issue was to identify different categories of extracts which can fall under the definition of refined extracts, to be quoted as herbal preparations, in contrast to other products, such as for example mixture of highly refined extracts in which the herbal matrix has been removed, to be quoted as a mixture of isolated herbal constituents. The borderline between highly concentrated extracts and mixtures of isolated chemically defined constituents resulting from very highly refining procedures, involving for instance chemical treatments, has to be clarified (see also answer to the remark of ESCOP).
	BPI	2. Isolated herbal constituents as chemically defined active ingredients In order to approach to the questions raised it seems to be	

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		useful to remember what means the term "Chemically defined active ingredients (APIs)". There is actually a large set of guidelines and related papers regulating the chemical characterisation and specifications of new and known drug substances (Guidelines on chemistry, specifications, impurities etc). A lot of pharmacopoeial monographs worldwide deal with the corresponding quality aspects. Chemically defined active ingredients in most cases are obtained by chemical synthesis and purification procedures yielding single components with a very high degree of purity of> 95% or even higher. The chemistry and structure of the active ingredient has to be proven unambiguously, including stereochemical aspects. The impurities that may be expected from the manufacturing process and by the way of synthesis have to be strictly qualified and quantified analytically and toxicologically. Possible degradation products must also be identified and quantified resulting in very tight specifications of the content of the active substance, its impurities and degradation products. Thus, knowledge of the mass balance has to be achieved that is very close to 100% Some chemically defined active ingredients historically have been obtained using extraction procedures and by isolation from plants. Wherever possible isolation was substituted by chemical synthesis later on, not only for economical or ecological reasons but in order to fulfil the requirements of a strict characterisation	Not agreed. For some chemically defined active ingredients, especially of natural/biological origin, this degree of purity is not applied (e.g. antibiotics).

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		and composition of the active ingredient(>95%). Only in some rare cases isolated herbal constituents are still used nowadays and consequently have to be treated as chemically defined active ingredients. The same is valid for some rare examples of mixtures of chemically defined active ingredients (e.g. ergoloid mesylates). Such mixtures might not be developed in the future under the roof of the present guidelines.	Agreed. This type of mixtures, which are not necessarily so rare has been included in the Reflection paper, as an example of non herbal preparations.
	BPI	3. Herbal preparations as active ingredients Herbal preparations/extracts are obtained by extraction of herbal substances (plant material) and consist of a multitude of constituents. Nevertheless they are considered to be an active ingredient in their whole composition. There are three groups of herbal preparations/extracts distinguished by a classification scheme of Pharm. Eur. namely standardised, quantified and other extracts. Pharm. Eur. defines also the possibility to refine extracts. Refining extracts may aim to reduce problematical constituents or to increase the content of therapeutical or pharmacological active constituents. Thus refined extracts theoretically would be possible for all types of extracts, but should always be accompanied by a scientific argumentation and justification acceptable for the registration authorities. In contrast to isolated herbal constituents and chemically defined active ingredients concentrated fractions/extracts may however not be characterised exhaustively concerning their exact composition of active constituents, the nature and amount of	Agreed

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		impurities and degradation products. For example a rather high concentrated extract of milk thistle fruits specified to contain 65%of silymarin according to Pharm.Eur. still is variable in its inner composition between 20-45% of silycristin and silidianin, 40- 65% silibinin A and B and 10-20% isosilibinin A and B. Possible impurities from the plant material during the concentration process may not be predicted or qualified and quantified. Therefore, the tight network of guidelines and pharmacopeial monographs covering herbal preparations makes exceptions concerning impurities and degradation products.	Agreed: this category is already present in the reflection paper.
		Conclusion As a rule, even substantially refined and concentrated herbal preparations may not be regarded as isolated herbal constituents as a complete chemical characterisation is not feasible. Such highly concentrated preparations should be in general subjected to the guidelines for herbals and the reasons for purification and concentration well scientifically justified case by case. Distinguishing a borderline between herbal preparations and isolated substances would also mean that substances / mixtures of closely related substances isolated from any herbal substances and having a high concentration would fall under the regulations for chemically defined active ingredients. Consequently · these substances / mixtures of close related substances should not be used to prepare any herbal medicinal product containing	Not agreed. The statement that all the refined extracts have to be regarded as herbal preparations is too simplistic. We agree that even substantially refined and concentrated herbal preparations in general may not be regarded as isolated herbal constituents. However there are cases where the herbal matrix of natural concomitants is no longer present in the final product. Moreover, in general, extracts subjected to chemical processes cannot be fully considered as herbal preparations, because these type of processes are not natural transformations and should be the subject of a case by case assessment.

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		any additional herbal active ingredient, · these substances / mixtures of close related substances should not be used to prepare any finished product of traditional medicinal use (2001/83 art.16a – i). A retrospective discussion of this topic seems to make no or only little sense, as the herbal preparations given as an example are all well established and registered since long times worldwide. The (wrong) classification of an highly concentrated herbal preparation as an isolated substance may cause new problems as the following example may highlight: An herbal medicinal product with eucalyptus oil (Ph.Eur.) and menthol (Ph.Eur.) can be seen as an herbal medicinal product and the corresponding herbal guidelines can be applied. If menthol was regarded as chemically defined active substance the medicinal product would not be classified as herbal medicinal product anymore and all the components of eucalyptus oil would have to be classified as impurities. Also a rationale for the combination of all components of the eucalyptus oil would have to be provided, which altogether would be a very wrong approach.	The purpose of the reflection paper is to identify also these cases. Not agreed This example is really the case. A mixture of eucalyptus oil and menthol is not a herbal medicinal product because menthol is a chemically defined isolated constituent, even if it is from herbal origin. In this case eucalyptus oil is not an impurity, but a herbal preparation and the medicinal product is a combination of a herbal preparation (eucalyptus oil) with a chemically defined API (menthol). The herbal quality guidelines apply to the eucalyptus oil and the guidelines for chemically defined APIs apply to menthol.
	INDENA	In our opinion, all examples of categories, listed in the reflection	

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	S.p.A.	paper should be deemed herbal preparations. Consequently, the guidelines for herbal preparations and herbal medicinal products (e.g. quality, specifications etc.) will apply to all the categories. Examining deeper the example of category: - Chemically defined compounds extracted from herbal material and partially purified, e.g. 85%, but where "impurities" in such highly refined extracts are known plant constituents; we would like to suggest that the rationale for this kind of herbal preparation is the following: additional and costly purification efforts to obtain highly purified isolated products are sometimes not necessary, in that the other constituents belong to the starting herbal drug and/or to the starting herbal preparation itself. Furthermore, to avoid any misunderstanding with the meaning of "impurity" included into the above sentence of the HPMPC Draft, we propose to reword it as follows: -Chemically defined compounds extracted from herbal material and partially purified, e.g. 85%, where the remaining part are other constituents belonging to the starting herbal material.	Not agreed. This is a case by case decision Not agreed. The classification depends on the way of preparation and on the complexity of the extract and not on the costs of the purification. Agreed, but reduction of cost cannot be provided as a justification.
Line-79-81	PhytoLab GmbH & Co. KG	Chemically defined compounds gained by physical-chemical methods (extraction, but this would also apply to distillation or sublimation) should not be defined via a percentage range (in this example the arbitrary 85%): In the context of herbal/natural products it is more consistent to focus on the residues, or “impurities” (which in the example would be 15%). The chemically defined compound, as well as the residue should	Partially agreed. The focus on residues originating from the same plant source may be a good way forward, but it should be distinguished from the mixture of isolated herbal constituents after their separation or separate purification.

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		both originate from the same plant source: In addition the term "impurities" may be misleading in this context. Herbal materials are multi-component mixtures. On the contrary, only impurities from external sources (e.g. from the process, like solvents etc.) should be addressed as such.	As the whole herbal preparation is considered to be the "active substance", all constituents originating from the plant material (concomitant constituents) are considered to be part of the active substance and not impurities. However, if the active substance is classified as an isolated chemically defined compound, all related constituents originating from the herbal substance would be considered as impurities.
Line 116-118	PhytoLab GmbH & Co. KG	The definition of herbal preparations should also include substances such as natural camphor, which are naturally occurring or produced from natural sources by only simply procedures, such as crystallisation, distillation and/or sublimation. It must be stressed in this context that natural camphor is different from all other isolated natural compounds which are subject of Ph. Eur. Monographs (attachment 1) in that it is the only substance among them that may be found in nature in this pure form.	Not agreed. It has been already clarified that camphor, menthol and soy lecithin are not herbal preparations because their structure is completely identifiable (see EMEA/HMPC/151144/06 Corr Overview of Questions and Answers relating to Technical/Scientific Issues).

Attachment 1

Examples from Ph. Eur. Monographs describing natural compounds

	Name	Pharmacopoeia	Grade of purity (%)	Production
	Ascorbinic acid	Ph. Eur.	99.5-100.5	Synthetic
	Atropine sulphate	Ph. Eur.	99.0-101.0	Isolation
	Camphor, rac. D-camphor	Ph. Eur. Ph. Eur.	Min. 96.0 Min. 94.0	Isolation Synthetic
	Caffeine	Ph. Eur.	98.5-101.5	Mostly synthetic
	Chinine hydrochloride	Ph. Eur.	98.0-101.0	Isolation
	Cineol	Ph. Eur.	Min. 98.0	Isolation
	Codeine	Ph. Eur.	99.0-101.1	Mostly synthetic
	Colchicine	Ph. Eur.	97.0-102.0	Isolation / synthetic
	Digitoxin	Ph. Eur.	95.0-103.5	Isolation
	Digoxin	Ph. Eur.	96.0-102.0	Isolation
	Ephedrine	Ph. Eur.	99.0-101.0	Mostly synthetic
	Eugenol	Ph. Eur.	Min. 97.0	Isolation
	Hyoscyamine sulfat	Ph. Eur.	98.0-101.0	Isolation
	Menthol	Ph. Eur.	Min. 99.0	Isolation
	Morphyn-hydrochloride	Ph. Eur.	Min. 98.0	Isolation
	Nicotine	Ph. Eur.	99.0-101.0	Isolation
	Rutoside trihydrate	Ph. Eur.	95.0-101.0	Isolation
	Thymol	Ph. Eur.	Min. 99.0	Isolation / synthetic