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

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT 'REFLECTION PAPER ON MARKERS USED FOR QUANTITATIVE AND QUALITATIVE ANALYSIS OF HERBAL MEDICINAL PRODUCTS AND TRADITIONAL HERBAL MEDICINAL PRODUCTS' (EMEA/HMPC/253629/2007)

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

	Name of Organisation or individual	Country
1	Medicinal Products Agency (MPA)	Sweden
2	Österreichische Agentur fûr Gesundheit und Ernährungssicherheit GmbH (AGES PharmMed)	Austria
3	European Scientific Cooperative On Phytotherapy (ESCOP)	United Kingdom
4	Forschungsvereinigung der Arzneimittel-Hersteller e.V. (FAH)	Germany
5	Ayurvedic Trade Association	United Kingdom
6	Association of the European Self-Medication Industry (AESGP)	Belgium

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20)
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Table 2:Discussion of comments

All received comments have been discussed in close collaboration with the EDQM.
GENERAL COMMENTS - OVERVIEW
1) Definition of markers: for the correct specification of an extract and the correct declaration it has to be decided whether a chosen marker has only analytical purposes or contributes to the therapeutic activity. In practice this differentiation is only in rare cases clear. Scientific publications on constituents of medicinal plants should contain data on pharmacological activity at the moment. Therefore most of the constituents are reported to be pharmacologically active, a further conclusion whether this activity implies a 'therapeutic activity' is usually impossible. Furthermore, the interpretation of the amount of contribution to the therapeutic activity of a substance may change depending on research. **Outcome: This comment remains on a general level. No actions.** 2) Definitions in the European Pharmacopoeia: the definitions in the European Pharmacopoeia cause discrepancies: for most of the herbal substances and extracts a lower limit of a constituent is defined. Herbal substances or extracts containing less than this limit are considered to be of less value and therefore not suitable for pharmaceutical use. Is therefore the conclusion justified that the mentioned constituents contribute to the therapeutic activity and that therefore these constituents should be considered as active markers? But in this case the extracts have to be per definition quantified extracts, where the amount of the active marker has to be set to a defined range. In that cases, where no range is defined (e.g., Valerian dry extract, Passionflower dry extract), are these constituents then analytical markers only? Why is an extract containing less of this analytical marker not suitable for pharmaceutical use? **Outcome: If selected marker(s) has (/have) been based solely on the sufficient quality of plant material, it is difficult to know directly if this selected marker(s) is(/are) suitable or not on its(/their) analytical purposes relating to the herbal preparation, herbal medicinal product and stability study purposes, respectively.** **Proposal:** We propose therefore: 1) Information of the responsible expert groups of the European Pharmacopeia, ask for postponement of development of monographs on extracts. 2) Immediate initiative for discussions with the responsible expert groups of the European Pharmacopeia. **Outcome: To be taken into consideration.** 3) Amendment of the reflection paper: Inclusion of a list of active markers of the most common herbal substances Statement how to interpret limits of constituents in the definitions of a monograph of the European Pharmacopoeia **Outcome: Reference: See Community herbal monographs and list entries.**

We appreciate the HMPC reflection paper on markers because it takes the specific character of herbal medicinal products into account as well as their analytical particularities. It is a useful document for qualitative and quantitative analysis and in line with the definitions and recommendations of the EMEA guidelines on specifications and of quality of herbal medicinal products (CHMP/QWP/2820/00 rev. 1 and CHMP/QWP/2819/00 rev. 1, respectively). Thus it may contribute to create harmonised assessment criteria and to ensure consistent quality of herbal medicinal products. **Outcome: This comment remains on a general level. No actions.**
From our limited knowledge of the complexities of quantitative and qualitative analysis it seems to us that the proposals are broadly sensible. However it seems that in view of the rather low level of knowledge about the selection and use of markers for single herbal ingredients and the still lower level of knowledge about the practicalities of selection and use of markers for multi-ingredient herbal preparations that the regulators should at this stage be careful to offer preliminary guidance and avoid wording that implies that the guidance must be rigidly followed. **Outcome: This comment remains on a general level. No actions.**
We welcome this reflection paper as it will contribute to an appropriate quality standard for herbal medicinal products taking into account their complex nature as well as their analytical particularities. **Outcome: This comment remains on a general level. No actions.**

SPECIFIC COMMENTS ON TEXT

2. INTRODUCTION (background)

Line no.[1] + paragraph no.	Comment and Rationale	Outcome
	Since the 'herbal substance' in a 'herbal medicinal product' is sensibly taken in EU law to be the 'active substance' it is useful to remember that **all** the constituents of that herbal substance contribute to its activity. Even a constituent that is chemically relatively inert will have some chemical and also some physical activity. It is also important to remember also that the role of herbal substances used in herbal medicine is to enliven the natural balance or intelligence or wholeness of the body. The complex nature of the herbal substance, its wholeness, results in the balancing effect being at a more fundamental level than when the constituent(s) with the most obvious effect on the body's system, in which the symptoms of most immediate concern occur, are used alone. Therefore the presence of and 'activity' of all the constituents are important. This is a sensitive issue because allopathic medicine has so strongly emphasised single active ingredients and has as a result suffered, and	Not possible to consider changes to the definitions because they already exist in other relevant quality guidelines previously adopted and currently in use.

[1] Where applicable

	continues to suffer, so many difficulties with side effects. Since here we are considering **herbal** medicine it is necessary to carefully avoid the allopathic mindset and its associated terminology. **Proposal:** Therefore the wording of this section might be enhanced if the effects of the constituent(s) with the most obvious effect on the body's system, in which the symptoms of most immediate concern occur, is referred to as perhaps the 'headline or front line' therapeutic activity. Then 'Active markers' and 'Constituents with known therapeutic activity' can be defined as those *having headline or front line activity*. Ideally 'Analytical markers' might be defined *as constituents or groups of constituents that are chosen for analytical convenience only rather than through any assessment of their status in the therapeutic effect of the substance as a whole.*	
3. PROBLEM STATEMENT		
Line no. + para no.	**Comment and Rationale**	**Outcome**
bullet point 3	Markers are not always single compounds. **Comment:** This is *per se* not considered as a problem but a challenge. Even the Ph. Eur. use mixtures of compounds as markers.	For practical reasons this is acceptable. The underlined headline has slightly been modified ('problems' replaced by 'issues').
bullet points 2 and 5	The 2nd bullet point states that "markers can be unstable or difficult to define chemically": unstable markers are poor analytical tools and should not be used for the determination of the batch related content during stability tests. This should be made clear in the paper. The 5th bullet point states that "markers characteristic for the herbal substances are not always commercially available". In practice such markers are isolated and characterized. As it may be difficult to define these substances chemically (as stated under the 2nd indent) it should be sufficient to characterize a marker peak from a chromatogram without isolation and structure elucidation and to quantify it by calibration with another commercially available reference substance. Furthermore, analytical markers are not necessarily derived from the secondary metabolism of a plant (e.g. flavonoids), but might be selected	Agreed but should be obvious. No changes introduced. When justified and authorised, primary metabolites may be possible to use as markers.

	also from primary metabolism (e.g. specific amino acids, carbohydrates etc.). This might be useful in cases where suitable markers from secondary metabolism are not known or not available or occur in very low amounts not suitable for quantification (e.g. scopoletin in nettle root). An additional problem has been identified for combination products. In this case, markers can be characteristic for several herbal substances or a characteristic marker of one herbal substance can also be present in another herbal substance in low amounts.	Agreed but should be obvious. No changes introduced.
4. CONCLUSIONS		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
paragraph 1, bullet point 6	Does this point also concern herbal substances and herbal preparations where a marker with therapeutic activity is known? **Proposal:** Add a sentence about this.	Constituents as markers: see section 2 'Introduction' in the reflection paper.
	The selected marker substances should be well defined with regard to information on reference standards. **Proposal:** Add point under conclusion.	No need to add a new bullet point. It should be obvious to provide information on reference standards relating to selected markers.
paragraph 2, bullet point 3 c)	The following point is not clear: The selection of markers for quantitative analysis enables quantitative analysis of each active substance in the finished product. **Proposal:** The point needs clarification.	No need for changes.
paragraph 1, bullet point 4, the last sentence	All exceptions need to be justified. **Proposal:** Exceptions need to be justified.	Agreed.

[2] Where applicable

paragraph 2, bullet point 3, the first sentence	-If selection of a constituents responsible for the therapeutic activity or an active marker is not possible for quantitative analysis, an analytical marker should selected bearing in mind the following principles: **Proposal:** -If selection of constituents responsible for the therapeutic activity or an active marker is not possible for quantitative analysis, an analytical marker should be selected bearing in mind the following principles.	Agreed.
paragraph 2, a new last point	**Proposal:** -A suitable marker is a single substance or a group of substances.	Agreed. New sentence introduced.
paragraph 1, bullet point 6	Indent 6 usefully points out that the stability of the herbal substance or herbal preparation, as a whole needs to be assessed. In this regard one should remember that: -While fingerprinting is useful the organoleptic sensory tests by a qualified herbal practitioner are indispensable and should be part of any QC system. -There are certain preparations in Ayurveda that are traditionally regarded as getting better with age. The regulators should allow for this possibility.	Relevant quality guidelines previously adopted and currently in use, need to be followed.
paragraph 1, bullet point 4	The 4th bullet states that in general, the “same marker(s) is (/are) used from herbal substance to the end of shelf-life of the finished product”. From our point of view, such a requirement is often not in accordance with pharmacopoeial monographs which determine only a sum of parameters/markers or a group of substances, respectively, which might no longer be available in the preparation of the finished product. For this reason we would like to propose the wording: "exceptions are acceptable and need to be justified".	No change introduced. The sentence “Exceptions need to be justified” includes the idea on accepting exceptions if appropriately justified.
paragraph 1, bullet point 5	According to the 5th bullet, “acceptance limits for the content of a proposed marker should be specified and justified”. From our point of view, it should be made clear that these acceptance limits might be changed if justified by practical experience. Furthermore, in case markers are proposed by pharmacopoeial monographs on herbal substances, additional tests of the proposed markers should not be necessary.	No changes introduced. It should be obvious that acceptance limits might be changed if justified by practical experience. Changes are possible to apply and introduce through an appropriate variation procedure.

paragraph 1, bullet point 6	The 6th bullet states that with regard to stability testing, “it should also be demonstrated that the proportional content of other substances remains comparable to the initial fingerprint”. In the case of herbal medicinal products (finished products such as tablets, capsules, etc.) and especially in the case of combinations products (two or more extracts) and combination with multivitamin preparations, it is often difficult to find a suitable chromatographic condition to have a selected marker compound resoluted from the other peaks. Therefore the request to demonstrate the stability of an extract in a complex finished product like a combination product by means of the demonstration of the stability of more than one marker compound or even through the stability of the fingerprint chromatogram is not realistic. It should be taken into account that excipients (e.g. oils, fats, lecithin, flavouring substances, etc) used for galenical formulations are multi-component substances which give signals in HPLC or GC chromatograms. Such excipients are also changing with time so that additional peaks may appear on a chromatogram interfering in the fingerprinting of the plant. Therefore, it should not be required that each peak of the fingerprint be assessed separately in comparison with the initial chromatogram. A comparable "picture” should be acceptable. A quantitative or semi-quantitative evaluation of individual peaks during stability testing is not realistic. For this reason, we suggest deleting the last sentence: "It should also be demonstrated that their proportional content remains comparable to the initial fingerprint" of this paragraph.	The word ‘proportional’ has been deleted.
paragraph 2	<u>Quantitative analysis</u> With regard to the quantitative analysis, we would like to include a further statement (under the 2nd indent): As markers are not always individual constituents, the determination of groups is possible. From our point of view, this should also include non-chromatographic methods e.g. the determination of total phenols by folin reagent. For the calculation it should be possible to refer to a defined "model" substance (e.g. epicatechin) by the term "calculated as" as it is usually done in Pharmacopoeia monographs. It should be made clear that for quantitative analysis (like for qualitative analysis), a suitable marker might also represent a group of substances. We would like to propose to include this option as an additional indent under "quantitative analysis".	Agreed. A new sentence “A suitable marker is a single substance or a group of substances” introduced.

	Furthermore, it should be possible to refer to the sum of peaks of two or more individual substances in case transformation reactions take place between constituents, e.g. rosmarinic acid to caffeic acid or [6]-gingerol to [6]-shogaol. Furthermore, the option of group determinations (e.g. photometric determination of flavonoids, hydroxyanthracene derivatives etc.) should also be possible for mono-preparations.	Agreed. A new sentence "A suitable marker is a single substance or a group of substances" introduced.
	Reference marker compounds, reference standard extracts and working standard extracts are all suitable for the quantitative determination (establishement of calibration curves) of marker compounds in herbal drugs and herbal preparations. Although the precision and accuracy of these markers are the same, their costs are quite different. -Reference marker compounds are generally expensive as their cost usually depends on their purity. In addition to their cost (e.g. 5mg of each of the ginsensosides Rg1, Re, Rf, Rb, Rc, Rb2, Rd at a degree of purity labelled between 95%-99% are sold by a supplier for 1,455 euro), a pharmaceutical company is obliged to add the cost for a full characterisation as well as the determination of the exact purity as well as the water content. The amount of 5mg each can be used for a very limited number of calibration curves. -Pharmacopoeial reference standard extracts are not so expensive (286 euro/g) but to now available for a few plant (e.g. Asian ginseng extract). With such an amount, several calibration curves for the quantitative determination of the 6 main ginsenosides of P.ginseng (and of P.quinquefolius) in P.ginseng or P. quinquefolius extracts can be established. -Working standard extracts: they are much cheaper (e.g. 1 kilogram of P.ginseng extract costs about 400 euro). The pre-requisite is that the content of the marker(s) is (/are) established against either a reference standard extract or against a reference marker compound of established purity at least once a year. With such amount, thousands of calibration curves can be established. The paper should mention the possibility to use reference standards extracts or working standards extracts instead of pure marker compound.	This issue has not been included into this reflection paper. No limitations are mentioned in the draft reflection paper on markers relating on the reference marker compounds, reference standard extracts and working standard extracts. However, the reference standard has been defined in the "Guideline on specifications: Test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products (CPMP/QWP/2820/00 Rev 1)" as "A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. In the case of herbal medicinal products, the reference standard may be a botanical sample of the herbal substance, a sample of the herbal preparation e.g. extract or tincture or a chemically defined substance e.g. a constituent with known therapeutic activity, an active marker or an analytical marker or a known impurity. The reference standard has a quality appropriate to its use. The composition of reference standards of herbal substances and herbal preparations intended for use in assays should be adequately controlled and the purity of a standard should be measured by validated quantitative procedures."
	With regard to the principle mentioned under b and c it should be emphasized that a marker serves the purpose of a "batch specific control" of an active substance in a finished product.	No additional text introduced because both batch specific control and sufficient uniformity between batches needs to be demonstrated concurrently.

5. DEFINITIONS		
Line no.[3] + paragraph no.	**Comment and Rationale**	**Outcome**
definition 1	Characteristic constituents are chemically defined substances or groups of substances that are specific for a medicinal plant and can be used for identification purposes. **Proposal:** To be deleted because constituents with known therapeutic activity are not mentioned in text.	Not agreed. The term "characteristic constituents" can be found under section 3 'Problem statement', first point: "It is not always clear which constituents are characteristic of the herbal substance or characteristic constituents can be present in very low amounts."
definition 4	Herbal preparations: are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates. **Proposal:** Herbal preparations: are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation **including homogenisation**. These include **homogenised** comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.	No changes introduced. The definition of herbal preparations is given according to Article 1(32) of Directive 2001/83/EC as amended by Directive 2004/24/EC.
definition 5	Herbal substances: all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).	No changes introduced. The definition of herbal substance is given according to Article 1(31) of Directive 2001/83/EC as amended by Directive 2004/24/EC.

[3] Where applicable

	Proposal: Herbal substances: all mainly whole, fragmented, **comminuted** or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh **before homogenisation**. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).	
definition 6	Markers: are chemically defined constituents or groups of constituents of a herbal substance, a herbal preparation or a herbal medicinal product which are of interest for control purposes independent of whether they have any therapeutic activity. Markers serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the herbal medicinal product if the marker has been quantitatively determined in the herbal substance or herbal preparation. **Proposal:** Markers: are chemically defined constituents or groups of constituents of a herbal substance, a herbal preparation or a herbal medicinal product which are of interest for control purposes independent of whether they have any therapeutic activity. **Among other purposes m**arkers serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the herbal medicinal product if the marker has been quantitatively determined in the herbal substance or herbal preparation.	No changes introduced. The definition on markers is identical comparing to the corresponding definition in relevant quality guidelines previously adopted and currently in use.
	Markers are defined as *chemically defined constituents*. It is not obvious to us that they have to be chemically defined. Might it not be that their physical activity may be sufficient to define them? E.g. their activity in a chromatographic set-up.	Comment is not relevant for this reflection paper. The definitions are coming from the other relevant quality guidelines previously adopted and currently in use; therefore it cannot be changed.