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**COMMITTEE ON HERBAL MEDICINAL PRODUCTS
(HMPC)**

**REFLECTION PAPER ON MARKERS USED FOR QUANTITATIVE AND QUALITATIVE
ANALYSIS OF HERBAL MEDICINAL PRODUCTS¹ AND TRADITIONAL HERBAL
MEDICINAL PRODUCTS**

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¹ Throughout the reflection paper and unless otherwise specified, the term “herbal medicinal product” includes “traditional herbal medicinal product”.

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TABLE OF CONTENTS

1. EXECUTIVE SUMMARY	3
2. INTRODUCTION (BACKGROUND)	3
3. PROBLEM STATEMENT.....	3
4. CONCLUSIONS.....	4
5. DEFINITIONS	5
6. REFERENCES (SCIENTIFIC AND / OR LEGAL)	6

1. EXECUTIVE SUMMARY

This reflection paper applies to markers which are intended for quantitative and qualitative analytical control purposes of herbal medicinal products. The quality of herbal medicinal products should be guaranteed and demonstrated in accordance with the existing requirements as set out in Annex I of Directive 2001/83/EC, as amended, Annex I of Directive 2001/82/EC, as amended and with current EU/ICH guidelines on quality. In view of the specific and complex nature of herbal medicinal products, markers can provide an option to ensure and demonstrate adequate and consistent quality of these products. The purpose of this reflection paper is to consider issues related to markers and to suggest criteria to be taken into account to select markers.

2. INTRODUCTION (background)

Active substances (herbal substance(s) and/or herbal preparation(s)) in herbal medicinal products consist of complex mixtures of phytochemical constituents. The situation is further complicated when two or more herbal substances and/or herbal preparations are combined in a herbal medicinal product. A limited number of herbal substances and herbal preparations possess constituents which are generally accepted to contribute substantially to their therapeutic activity. These are defined as '*constituents with known therapeutic activity*'. However, for the majority of herbal substances and herbal preparations, the constituents or groups of constituents responsible for the therapeutic activity are not known. In some cases, certain constituents or groups of constituents may be generally accepted to contribute to the therapeutic activity but are not responsible for the full therapeutic effect. Such constituents or groups of constituents are useful for control purposes and are defined as '*active markers*'. *Analytical markers* are constituents or groups of constituents that serve solely for analytical purposes.

In accordance with the EMEA herbal quality guidelines (see Section 6 'References'), where a herbal medicinal product contains herbal substances and/or herbal preparations with '*constituents with known therapeutic activity*' then these constituents should be used for identification and quantification. Where constituents with known therapeutic activity are not present then markers should be used for identification and quantification of herbal medicinal products. European Pharmacopoeia (Ph. Eur.) monographs on herbal substances², herbal preparations³ and specific monographs in the herbal field need to be taken into consideration where applicable.

3. PROBLEM STATEMENT

At the moment there is only limited guidance relating to selection and quality requirements for markers. As such the choice and quality documentation provided on markers varies between applicants/manufacturers, even for very similar products.

The following issues have been identified:

- It is not always clear which constituents are characteristic of the herbal substance or characteristic constituents can be present in very low amounts.
- Markers can be unstable or difficult to define chemically.
- Markers are not always single compounds.

² The term "herbal substance" should be considered as equivalent to the term "herbal drug" as defined in the European Pharmacopoeia.

³ The term "herbal preparation" should be considered as equivalent to the term "herbal drug preparation" as defined in the European Pharmacopoeia.

- Proposed markers may not be characteristic of the herbal substance.
- Markers characteristic of the herbal substances are not always commercially available.
- Markers characteristic of the herbal substance may not be suitable as a marker for the herbal preparation or a finished product thereof (e.g. depending on loss during the manufacturing procedure or due to masking by other components in the product). This would require the selection of another marker.

4. CONCLUSIONS

In the view of the specific and complex nature of herbal medicinal products markers can provide an option to ensure and demonstrate the quality of these products. However, because limited guidance exists in this particular field, the following principles should be taken into account as far as possible:

- Selection of markers should be justified.
- Markers should be suitable for their intended purpose (e.g. identification, quantification, analytical control, stability).
- Markers should connect steps of production process and quality control measures.
- Markers are used for both quantitative and qualitative purposes. The proposed markers provide an important tool to link the active substance(s) (herbal substance(s) and/or herbal preparation(s)) to the herbal medicinal product irrespective of whether they have any therapeutic activity or not⁴. In general, the same marker(s) is (/are) used from herbal substance to the end of shelf life of the finished product. Exceptions need to be justified.
- Acceptance limits for content of a proposed marker should be specified and justified.
- Since the herbal substance or herbal preparation in its entirety is regarded as the active substance, a mere determination of the stability of the marker will not suffice. The stability of other substances present in the herbal substance or in the herbal preparation, should, as far as possible, also be demonstrated (e.g. by means of appropriate fingerprint chromatograms). It should also be demonstrated that their content remains comparable to the initial fingerprint.

For quantitative analysis, the following steps should be considered:

- If constituents with known therapeutic activity are present, their contents need to be determined quantitatively.
- If constituents responsible for the therapeutic activity are not known but an active marker is known, this active marker should be selected for quantitative analysis unless otherwise justified.
- 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:
 - a) Priority should be that the selected marker enables a specific assay for the active substance.
 - b) The marker should serve as a means of calculating the quantity of active substance (herbal substance or herbal preparation, respectively) in the finished product (herbal medicinal product).

⁴ However, the presence of the set markers within the established limits does not ensure by itself batch-to-batch uniformity.

- c) The selection of markers for quantitative analysis enables quantitative analysis of each active substance in the finished product.
- In the case of combination products, if it is not possible to select a separate marker for each active substance, joint analysis may be carried out, if justified appropriately.
- A suitable marker is a single substance or a group of substances.

For qualitative analysis, the following steps should be considered:

- The choice of markers used for identification should be justified.
- A suitable marker is a single substance or a group of substances.

5. DEFINITIONS

Characteristic constituents are chemically defined substances or groups of substances that are specific for a medicinal plant and can be used for identification purposes.

Constituents with known therapeutic activity: are chemically defined substances or groups of substances which are generally accepted to contribute substantially to the therapeutic activity of a herbal substance, a herbal preparation or a herbal medicinal product.

Herbal medicinal products: any medicinal product, exclusively containing as active substances one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

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.

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).

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.

There are two categories of markers:

Analytical markers are constituents or groups of constituents that serve solely for analytical purposes.

Active markers are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a herbal substance/preparation or herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal substance/preparation and/or herbal medicinal product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between competent regulatory authorities and applicants.

Traditional herbal medicinal products: are medicinal products for human use that fulfil the conditions laid down in article 16a (1) of Directive 2001/83/EC, as amended.

6. REFERENCES (SCIENTIFIC AND / OR LEGAL)

‘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, EMEA/CVMP/815/00 current version)

‘Guideline on quality of herbal medicinal products/traditional herbal medicinal products’ (CPMP/QWP/2819/00, EMEA/CVMP/814/00 current version)

Guideline on quality of combination herbal medicinal products / traditional herbal medicinal products (EMEA/HMPC/CHMP/CVMP/214869/2006)