European Medicines Agency

London, 7 January 2009
Doc. Ref. EMEA/HMPC/3626/2009

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

DRAFT

REFLECTION PAPER ON STABILITY TESTING OF HERBAL MEDICINAL PRODUCTS AND TRADITIONAL HERBAL MEDICINAL PRODUCTS[1]

DRAFT AGREED BY HMPC DRAFTING GROUP ON QUALITY	February 2008 October 2008 December 2008
ADOPTION BY HMPC FOR RELEASE FOR CONSULTATION	15 January 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	15 May 2009

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KEYWORDS	HMPC; herbal medicinal products; traditional herbal medicinal products; herbal substances; herbal preparations; extracts; quality; stability

[1] Throughout the reflection paper and unless otherwise specified, the term "herbal medicinal product" includes "traditional herbal medicinal product".

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1. INTRODUCTION (BACKGROUND)

This reflection paper is concerned with the specific requirements for establishing the stability of herbal medicinal products. The quality, including the stability, 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 guidance on quality. The EMEA committees have published several quality guidelines related to stability testing, which focus mainly on chemically defined substances. In view of the complex nature of herbal medicinal products, it is considered that further guidance is needed in order to ensure that stability of these products is addressed appropriately. The purpose of this reflection paper is to consider issues relating to the application of the existing stability guidance on herbal medicinal products and to provide additional guidance where necessary.

2. PROBLEM STATEMENT

Active substances (herbal substances and/or herbal preparations) in herbal medicinal products consist of complex mixtures of constituents and in most cases the constituents responsible for the therapeutic effects are unknown. The situation is further complicated when two or more herbal substances and/or herbal preparations are combined in a herbal medicinal product. Combinations of herbal substances and/or herbal preparations with a similar composition of constituents give rise to even more analytical challenges. In addition, many herbal preparations consisting of such mixtures are known to be unstable. Taking into account these special features of herbal medicinal products, adequate quality concepts have been established. As part of a total control strategy for herbal substances, herbal preparations and herbal medicinal products, a set of test criteria including qualitative and quantitative parameters has been recognised as quality indicating. With regard to stability tests, chromatographic fingerprints as well as appropriate methods of assay via marker substances represent the fundamental part of this concept, laid down in shelf-life specifications (a,b). Notwithstanding the appropriateness of this approach, its realisation is often associated with analytical problems and high costs.

In summary, herbal medicinal products have a number of characteristics that clearly differentiate them from chemically defined medicinal products and therefore specific stability guidance needs to be established, which covers particular aspects that existing specific herbal guidelines and general guidelines on stability do not address.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Taking into account the significant number of questions that may arise when establishing stability concepts for different herbal preparations and herbal medicinal products, some examples are given to clarify the issues of this paper. Industry attributes great importance to having stability guidance specific to herbal medicinal products and, in particular, on when to apply a reduced set of stability tests. Queries on such matters are frequently raised with the competent authorities, in order to assist applicants in choosing appropriate stability protocols. These queries mainly relate to applications for registrations of traditional herbal medicinal products which often consist of combinations of a number of active substances. Although many scenarios will need to be assessed on a case-by-case basis, some examples may have general applicability and could provide a basis for general stability guidance for herbal medicinal products.

For example:

1)
A medicinal product is manufactured by a continuous production process comprising the production of the active substance and the production of the finished product. Are stability studies necessary for both the active substance and the finished product?

2)
A herbal tea consists of a mixture of cut herbal substances packaged in a multi-dose bag. Are comprehensive stability studies necessary for both the active substances and the finished product?

3)
A herbal tea consists of a essential oil containing cut herbal substance (e.g. peppermint leaves). The change in the assay from the initial value is higher than 20%, but the essential oil content at the end of the shelf-life is in line with the Ph. Eur. Monograph.

4)
An analytical marker is stable in the herbal substance (Pharmacopoeia monograph) and in solid dosage forms, but unstable in some liquid dosage forms (e.g. Acteoside as analytical marker of ribwort plantain [*Plantago lanceolata* L.]).

4. CONCLUSIONS

It is considered of primary importance that Interested Parties provide examples and comments covering the range of possible stability scenarios which are specific for herbal preparations and medicinal products. This will provide a platform for discussion that will be used for the development of guidance on this subject. The key issue is whether it is possible to establish criteria to give detailed guidance on the application of existing stability guidance to herbal preparations and herbal medicinal products. Depending on the comments received, the most appropriate guidance will be developed.

5. DEFINITIONS

Herbal medicinal product: any medicinal product, exclusively containing as active ingredients 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 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).
Herbal preparations: preparations 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.
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 that marker has been quantitatively determined in the herbal substance(s) or herbal preparation(s) themselves.

There are two categories of markers:

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

Analytical marker: are constituents or groups of constituents that serve for analytical purposes.

Specifications: 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 preparation / herbal substance or herbal medicinal product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the herbal preparation / herbal substance 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 the appropriate governmental regulatory agency and the applicant.

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 TO LITERATURE, GUIDELINES ETC

a) 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products' (CPMP/QWP/2819/00, EMEA/CVMP/814/00, current version).
b) '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).
c) 'Guideline on quality of combination herbal medicinal products/traditional herbal medicinal products' (EMEA/HMPC/CHMP/CVMP/214869/2006, current version)
d) 'Guideline on stability testing: stability testing of existing active substances and related finished products' (CPMP/QWP/122/02, current version)