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Reflection paper on stability testing of herbal medicinal products and traditional herbal medicinal products[1]

Final

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[1] Throughout the reflection paper and unless otherwise specified, the term 'herbal medicinal product'(HMP) includes 'traditional herbal medicinal product'.

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1. Introduction (background)

This reflection paper addresses the need for specific requirements for establishing the stability of herbal medicinal products (HMPs). The quality, including the stability, of HMPs 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 committees of the European Medicines Agency have published several quality guidelines related to stability testing, which focus mainly on chemically defined substances. In view of the complex nature of HMPs, 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 HMPs and to provide additional guidance where necessary.

2. Problem statement

Evaluating the stability of HMPs presents a number of challenges when compared to chemically defined substances. In particular:

- Active substances (herbal substances and/or herbal preparations) in HMPs 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 HMP.
- In many cases where combinations of herbal substances and/or herbal preparations are present in HMPs, they have similar constituents and this gives rise to even more analytical challenges.
- In addition, many herbal substances/herbal preparations are known to be unstable.

Taking into account these special features of HMPs, adequate quality concepts have been established. As part of a total control strategy for herbal substances, herbal preparations and HMPs, 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 (1, 2). Notwithstanding the appropriateness of this approach, its realisation is often associated with analytical problems and high costs.

In summary, HMPs 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

Industry attributes great importance to having stability guidance specific to HMPs 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 HMPs.

4. Conclusions

The Interested Parties have provided examples and comments covering the range of possible stability scenarios which are specific for herbal preparations and HMPs. It was agreed that these data are used

as basis for guidance in form of questions and answers. Some examples are more general whereas other examples are focused on specific problems. Stability related questions and answers have been included in the **Questions & answers on quality of herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/41500/2010)**. New questions and answers can be added if necessary.

Definitions

Herbal medicinal products: 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 markers: are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.
Analytical markers: are constituents or groups of constituents that serve for analytical purposes.

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 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.

References to guidelines

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

2. ‘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).

3. ‘Guideline on quality of combination herbal medicinal products/traditional herbal medicinal products’ (EMEA/HMPC/CHMP/CVMP/214869/2006, current version)

4. ‘Guideline on stability testing: stability testing of existing active substances and related finished products’ (CPMP/QWP/122/02, current version)