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Committee on Herbal Medicinal Products (HMPC)

Concept paper on non-pharmacopoeial reference standards for herbal substances, herbal preparations and herbal medicinal products / traditional herbal medicinal products

Draft

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Comments should be provided using this template to hmpc.secretariat@ema.europa.eu

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1. Introduction (background)

This concept paper applies to non-pharmacopoeial reference standards for herbal substances, herbal preparations and herbal medicinal products (HMPs) / traditional herbal medicinal products (THMPs).

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, with specific herbal quality guidelines such as 'Guideline on quality of HMPs/THMPs' (EMA/CPMP/QWP/2819/00 Rev. 2) (EMA/CVMP/814/00 Rev. 2), 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and HMPs/THMPs' (EMA/CPMP/QWP/2820/00 Rev. 2) (EMA/CVMP/815/00 Rev. 2), 'Guideline on quality of combination HMPs/THMPs' (EMEA/HMPC/CHMP/CVMP/214869/2006) and, in addition, with current EU/ICH general quality guidelines for medicinal products that are applicable to HMPs/THMPs.

Reference standards play an essential role when ensuring and demonstrating adequate and consistent quality of herbal substances, herbal preparations and HMPs/THMPs. These reference standards 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 etc.

In the European Pharmacopoeia (Ph. Eur.) monographs on herbal substances and herbal preparations, pharmacopoeial reference standards are described for a specific purpose and they are only demonstrated to be suitable for the use indicated. Where pharmacopoeial reference standards are available they should be used as primary standards.

In cases, where pharmacopoeial reference standards are not available, non-pharmacopoeial reference standards should be established.

The purpose of the proposed guideline is to identify the criteria to be taken into account when using non-pharmacopoeial reference standards and to provide guidance on the documentation needed to demonstrate that they are adequately characterised and suitable for their intended purpose.

2. Scope

The concepts described in the proposed guideline will be applicable to registration applications for THMPs for human use and will also be applicable to marketing authorisation applications for HMPs for human and veterinary use.

3. Problem statement

Active substances (herbal substance(s) and/or herbal preparation(s)) in HMPs consist of complex mixtures of phytochemical constituents. To ensure adequate quality control, reference standards are necessary for their identification, purity testing and assay.

Existing guidelines provide only limited guidance on non-pharmacopoeial reference standards (e.g. on 'Specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and HMPs/THMPs'). As a result, the choice of these non-pharmacopoeial reference standards, their production and the quality documentation provided vary between applicants/manufacturers, even for similar products.

4. Discussion (on the problem statement)

A non-pharmacopoeial 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 etc.

Chemically defined substances are either commercially available or they have to be isolated and purified. However, in every case, as described in Ph. Eur. Chapter 5.12., detailed documentation on the structural elucidation and the purity should be provided, especially if the reference standard is intended for an assay. These substances can be used as primary or secondary standards.

A guideline on non-pharmacopoeial reference standards should describe in detail the documentation that the applicant should provide in order to demonstrate that the reference standard is adequately characterised and meets quality standards appropriate for its intended use.

5. Recommendation

As there is very little information on reference standards in the existing guidelines, the HMPC recommends the development of a respective guideline.

A guideline on non-pharmacopoeial reference standards for herbal substances, herbal preparations and HMP/THMPs should describe the information to be provided in Module 3 sections 3.2.S.5. and 3.2.P.6. 'Reference standards or materials'.

This guideline shall apply to THMPs for human use and to HMPs both for human and veterinary use.

6. Timetable

It is anticipated that a draft guideline could be available one year after publication of the concept paper. The draft guideline will be released for external consultation for six months. The guideline could be finalised within six months after external consultation.

7. Resource requirements for preparation

The Rapporteur and Co-Rapporteur should prepare a draft guideline. Members States are invited to provide comments via their Committee and/or Working Party Members.

8. Impact assessment (anticipated)

The development of this guideline on non-pharmacopoeial reference standards is expected to benefit industry. When non-pharmacopoeial reference standards need to be used, this guideline will clarify the information to be submitted in Module 3 (sections 3.2.S.5. and 3.2.P.6. 'Reference standards or materials'), taking account of the nature of the non-pharmacopoeial reference standard, its intended use, production, labelling and storage. This will therefore provide benefits to applicants in the preparation of their applications.

The guideline is also expected to help competent authorities when assessing applications by harmonising requirements and thus enabling a more consistent approach to assessment of the documentation.

9. Interested parties

During the consultation period on the draft guideline, comments from parties concerned with the use of THMPs and HMPs will be welcome.

10. 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).

Impurity:

(1) Any component of the herbal substance, which is not the entity defined as the herbal substance.

(2) Any component of the herbal preparation/herbal medicinal product that is not the entity defined as the herbal substance/ preparation or an excipient in the herbal preparation/herbal medicinal product.

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.

Reference standard: is a general term covering reference substances, reference preparations and reference spectra, used as a standard in an assay, an identification or a purity test.

Primary standard: A standard shown to have suitable properties for the intended use, the demonstration of suitability being made without comparison to an existing standard.

Secondary standard: A standard established by comparison with a primary standard.

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.

Unidentified impurity: an impurity which is defined solely by qualitative analytical properties, (e.g., chromatographic retention time).

11. References

- 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products'.

(EMA/CPMP/QWP/2819/00 Rev. 2), (EMA/CVMP/814/00 Rev. 2).

- 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products'.

(EMA/CPMP/QWP/2820/00 Rev. 2), (EMA/CVMP/815/00 Rev. 2).

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

- 'Reflection paper on markers used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products'.

(EMEA/HMPC/253629/2007).

- European Pharmacopoeia Chapter 5.12. 'Reference standards'.