European Medicines Agency

London, 6 November 2008
Doc. Ref. EMEA/HMPC/186645/2008

COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

DRAFT

REFLECTION PAPER ON LEVEL OF PURIFICATION OF EXTRACTS TO BE CONSIDERED AS HERBAL PREPARATIONS

DRAFT AGREED BY HMPC DRAFTING GROUP ON QUALITY	June 2008 October 2008
DISCUSSION BY HMPC	September 2008
ADOPTION BY HMPC FOR RELEASE FOR CONSULTATION	6 November 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	15 April 2009

Comments should be provided to hmpc.secretariat@emea.europa.eu or by fax +44 20 75 23 70 51

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

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

1. INTRODUCTION (BACKGROUND)

The directive 2001/83/EC as amended provides definitions for herbal medicinal product (HMPs), herbal substances and herbal preparations.
According to these definitions a herbal medicinal product is 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. Traditional herbal medicinal products (THMPs) may contain also vitamins and minerals, provided that the action of the vitamins or minerals is ancillary to that of the herbal active ingredients.
Despite the fact that several chemical moieties are obtained by extraction and purification from plant material, it has been clarified that products containing chemically defined isolated constituents or a mixture thereof are not HMPs.
HMPs have a number of characteristics that clearly differentiate them from chemically defined medicinal products and therefore specific guidelines have been established, which covers particular aspects that general guidelines do not address.
On the other hand the same basic legislation applies to both HMPs and other medicinal products[1]. An additional simplified registration procedure has been established for THMPs.

2. PROBLEM STATEMENT

The definition for herbal preparations covers not only simply processed preparations, but also purified and concentrated preparations such as, for instance, refined extracts. Unwanted matter may be removed after extraction and, in the case of standardised and quantified extracts, purification procedures may be applied with the aim of increasing the content of constituents of known therapeutic activity or specific active markers.
In some cases the purification of a herbal extract is so substantial that it is questionable whether the resulting preparation may still be considered as a highly purified herbal preparation or whether it should be regarded as an isolated herbal constituent or a mixture of closely related herbal constituents (e.g. sennosides, aescin, etc.).
The purpose of this reflection paper is to generate a discussion on establishing criteria to distinguish the borderline between what may be considered as a herbal preparation and what might be classified as isolated herbal constituent..

3. DISCUSSION (ON THE PROBLEM STATEMENT)

The quality of a medicinal product is independent of its use, and therefore all general principles of quality and quality guidance documents also apply to HMPs.
Due to their complex nature, specific herbal quality guidelines provide further information on how the quality issues should be addressed in the case of herbal substances/herbal preparations/HMPs.
For isolated constituents from herbal origin (e.g. morphine) adherence to the general quality guidelines for chemically defined active substances is required.
A consensus is needed on how to categorise herbal extracts that are highly refined, in order to enhance transparency for applicants and authorities to ensure appropriate and consistent quality of medicinal products from herbal origin available within the Community.
Industry attributes great importance to the clarification of borderline issues and on when to apply the existing quality guidance documents to herbal products. Queries on the matter have already been raised with the competent authorities, in order to assist applicants in applying for the most appropriate authorisation/registration procedure.
The HMPC recommends the development of guidance on the level of purification of extracts to be considered as herbal preparations, to provide clarification on which existing guidance documents should be applied to different herbal refined extracts.
The guidance shall apply to herbal medicinal products both for human and veterinary use and to traditional herbal medicinal products for human use.

[1] Directive 2001/83/EC, as amended

It is expected that the matter concerns mainly standardised extracts (e.g. sennosides, silymarin) and to a less extent quantified extracts (e.g. from *Ginko biloba, Hypericum perforatum*).
In addition it might be useful to identify different categories of refined and/or enriched extracts, which will help in the assessment even if the final evaluation has to be made on a case by case basis.
Examples of categories may include

- Mixtures of chemically defined substances (e.g. alkaloids, saponins) with similar chemical structure extracted from herbal material which are difficult to separate.
- Chemically defined compounds extracted from herbal material and partially purified, e.g. 85%, but where the "impurities" in such highly refined extracts are other known plant constituents
- Isolated class of constituents, e.g. total alkaloids, maintaining the natural variability for which identification of the main constituents in the mixture is possible.
- Enriched extracts for which the pattern of characteristic constituents has to be determined.
- Standardised extract with a high content of constituents with known therapeutic activities (e.g. sennosides) or purified mixtures of a certain class of constituents obtained by specific processing methods (e.g. precipitation of sennosides with calcium salts).
- Mixture of similar constituents of the same class of constituents together with other similar constituents having the same activity in the natural proportion that may have subject to chemical treatment, e.g. acid hydrolisis..

.

4. CONCLUSIONS

It is considered of primary importance that Interested Parties provide information and comments covering the range of possible different categories, to provide a platform for discussion and that will be used for the development of guidance on this subject. The key issue is whether it is possible to establish criteria to distinguish herbal preparations from purified herbal constituents to be regarded as isolated chemical substances.
The possibility of establishing criteria to define this borderline should be explored depending on complexity of the mixture and the different levels of purification.
Depending on the comments received, the most appropriate guidance will be developed.

5. DEFINITIONS

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 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

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. European Pharmacopoeia General Monograph "Extracts" 04/2008:0765
4. European Pharmacopoeia General Monograph "Substances for pharmaceutical use" 01/2008:2034
5. European Pharmacopoeia General Chapter "Control of impurities in substances for pharmaceutical use" (5.10) 01/2008:51000
6. Summary of Requirements for Active Substances in the Quality Part of the Dossier (CHMP/QWP/297/97 Rev 1)
7. Guideline on 'Chemistry of New Active Substances' (CPMP/QWP/130/96 Rev. 1).
8. Guideline on 'Impurities Testing: Impurities in New Drug Substances' (CPMP/ICH/2737/99-ICH Q3A (R2))
9. Guideline on 'Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances' (CPMP/ICH/ 367/96-ICH Q6A)
10. Guideline on 'Specifications and control Tests on the Finished Product' (3AQ11A)