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Committee on Herbal Medicinal products (HMPC)

Concept paper on the development of a Reflection Paper on modern manufacturing techniques used for herbal preparations

Agreed by Quality Drafting Group	June 2023
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Start of public consultation	15 August 2023
End of consultation (deadline for comments)	15 November 2023

Comments should be provided using this template. The completed comments form should be sent to hmpc.secretariat@ema.europa.eu

Keywords	Herbal medicinal products, traditional herbal medicinal products, herbal preparations, extracts, modern manufacturing techniques, comparability between preparations.[1]

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. Introduction

The manufacturing of herbal preparations has always been considered close to traditional/conventional techniques, which involve the use of extraction solvents of different polarities such as ethanol-water mixtures for generally obtaining extracts for further processing. Only little information regarding the manufacturing processes is given in relevant monographs of the European Pharmacopeia (Ph. Eur.) and few key parameters describe classic solvent extracts in the product information (SmPC/labelling/package leaflet) and in EU herbal monographs in line with the Guideline on declaration of herbal substances/preparations in HMPs/THMPs (EMA/HMPC/CHMP/CVMP/287539/2005 Rev.1). Furthermore, some recommendations on the comparability between preparations obtained with the traditional methods are available in Regulatory Questions & Answers on HMPs (EMA/HMPC/345132/2010).

However, the traditional methods do not necessarily cover all preparations which may be available on the market and in traditional or well-established medicinal use.

Modern, improved and non-conventional manufacturing techniques may complement the existing traditional methodology and optimise processes.

2. Problem statement

Modern technologies for the extraction of plants, which are already used in small scale or research applications or to wider extent in the food or cosmetic industry, are not widely used yet at industrial level for the production of HMPs and therefore rarely subject in applications for marketing authorisation/registration or herbal-specific guidance. However, the role of modern manufacturing techniques must also be considered for its opportunities and effects on critical quality attributes of HMPs. The new manufacturing processes include modified extraction methods such as ultrasound-assisted, microwave-assisted, enzymatic-assisted, pulsed electric field, supercritical or subcritical fluid and deep eutectic extraction.

Modern techniques could present various advantages over the conventional approaches, such as higher extraction efficiency, reduction in the use of organic extraction solvents, the usage of non-hazardous solvents, a reduction in the extraction time and the consumption of less energy. They also offer extended tools to obtain extracts of selective composition, i.e. for the targeted extraction or exclusion of specific fractions from the total spectrum of plant compounds for better purity, consistency and standardisation of resulting herbal extracts.

In addition to their advantages, these methods may also have some disadvantages linked to various issues of technical reliability, consistency, homogeneity, stability, validation, qualification, documentation, transferability or scale up.

The emergence of modern manufacturing techniques may impact the quality dossier content and assessment needs for HMPs, including aspects of the correspondence/comparability of herbal preparations. Scientific discussions at HMPC on newly available data on supercritical CO_2-extracts indicate the need for guidance to be able to address herbal active substances not obtained with conventional solvent extraction in general and regarding comparability between preparations obtained by different manufacturing techniques.

3. Discussion (on the problem statement)

It is considered of primary importance that interested parties provide comments covering the range of modern manufacturing techniques applied to herbal preparations in their current manufacturing

practice. Examples used at the industrial level are of particular interest and will be considered in the development of a reflection paper on this subject. The key issue is to discuss the opportunities and challenges in the application of these modern manufacturing techniques to HMPs and the expectations when they are included in the marketing authorisation/registration dossier. Furthermore, considerations regarding comparability between various preparations obtained by modern methods as well as those obtained by traditional manufacturing methods should also be covered.

Input by industry and academia will help to discuss the relevance of key parameters associated with certain technologies beyond the conventional ones used for classical solvent extraction, such as solvent and drug extract ratio (DER). Also, testing needs, analytical markers and minimum requirements to ensure and document consistent quality of preparations manufactured with modern technologies will need first a dialogue and basic understanding of principles to support harmonised approaches in case-by-case decisions.

Such dialogue appears necessary to embrace innovation and application of modern technologies without any derogations to established quality standards and conventions of Ph. Eur. and EU guidelines in order to ensure high and consistent quality of HMPs.

4. Recommendation

Given the modern manufacturing techniques and emerging trends, the aim is to raise the topic with interested parties and seek their cooperation in providing examples and comments on modern methods/technologies used in the manufacturing process of herbal preparations.

Based on the information provided by interested parties, the Quality Drafting Group of the HMPC will first develop a reflection paper to go into detail about the subject and then, when appropriate, develop more specific guidance or consider adapting existing guidance/ templates.

5. Proposed timetable

It is anticipated that drafting the reflection paper will start after the public consultation of the concept paper and take approximately 9-12 months before release for external consultation.

6. Resource requirements for preparation

Several rapporteurs will be involved in the drafting of the reflection paper. The draft is expected to be discussed at future meetings of the HMPC Quality Drafting Group. The contribution of the Quality Innovation Group (QIG), European Directorate for the Quality of Medicines and HealthCare (EDQM) experts or other experts from European Special Experts Community is foreseen if needed.

7. Impact assessment (anticipated)

The proposed reflection paper should support the industry in the development and application of modern manufacturing techniques regarding herbal preparations.

Benefits are expected for the industry in the preparation of their dossiers and for competent authorities in their assessment of these dossiers during the procedures. Furthermore, the possibility of including preparations obtained with modern technology in EU herbal monographs is expected to be facilitated.

Some existing guidelines or templates may later need to be amended or updated as a result of the reflection paper. The considerations may also contribute to the discussion on appropriate manufacturing techniques for HMPs in coordination with Ph. Eur. expert groups.

8. Interested parties

The interested parties include regulators, the pharmaceutical industry, academic groups, and Ph. Eur. expert groups.

9. References to literature, guidelines, etc.

Guideline on quality of herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/CHMP/CVMP/201116/2005 as revised)

Guideline on quality of combination herbal medicinal products/traditional herbal medicinal products (EMEA/HMPC/CHMP/CVMP/214869/06)

Ph. Eur. monographs on herbal drug extracts (information chapter) (5.23)

Ph. Eur. monograph on herbal drug extracts (0765)

Reflection paper on markers used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products (EMEA/HMPC/253629/2007)

Reflection paper on the level of purification of extracts to be considered as herbal preparations (EMA/HMPC/186645/2008)

Regulatory Q&A on herbal medicinal products (EMA/HMPC/345132/2010 as revised)

Questions & answers on quality of herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/41500/2010 as revised)