EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 January 2013
EMA/HMPC/13658/2013
Committee on Herbal Medicinal Products (HMPC)

Concept paper on use of recovered/recycled solvents in the manufacture of herbal preparations for use in herbal medicinal products / traditional herbal medicinal products

Discussion by HMPC Drafting Group on Quality	September 2012 December 2012
Adoption by Committee on Herbal Medicinal Products (HMPC) for release for consultation	15 January 2013
Start of public consultation	15 February 2013
End of consultation (deadline for comments)	15 May 2013
Agreed by HMPC Quality Drafting Group	
Adopted by HMPC	

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

Keywords	HMPC; herbal medicinal products; traditional herbal medicinal products; herbal substances; herbal preparations; herbal extracts, recycled/recovered solvents

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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1. Introduction

This concept paper concerns the standards to be applied to recycled/recovered solvents used for extraction of herbal substances in the manufacture of herbal preparations for use in 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.

Recycled/recovered solvents are widely used for extraction of herbal substances in the manufacture of herbal preparations for use in HMPs / THMPs. The quality of the recycled/recovered solvents is a critical factor in controlling the quality of the resulting herbal preparations and ensuring batch to batch reproducibility.

The purpose of the proposed guideline is to identify the criteria to be taken into account when establishing standards/specifications for recycled/recovered solvents in the manufacture of herbal preparations and to provide guidance on the documentation needed to demonstrate that they are adequately controlled 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

Recycled/recovered solvents are widely used for extraction of herbal substances in the manufacture of herbal preparations for use in HMPs / THMPs. The quality of the recycled/recovered solvents is a critical factor in controlling the quality of the resulting herbal preparations and ensuring batch to batch reproducibility.

Existing guidelines provide only limited guidance on the standards/specifications to be applied to recycled/recovered solvents. As a result, the supporting documentation provided varies between applicants/manufacturers, even for similar products.

4. Discussion

The majority of herbal preparations used in HMPs / THMPs are herbal extracts. Whilst many herbal extracts are prepared using water a substantial number involve the use of organic solvents, primarily alcoholic extracts (ethanol, methanol), but also acetone, ethyl acetate etc may be employed. Furthermore, in many cases, solvents are used during the processing, such as preliminary defatting of the herbal substance, for example, with hexane or during purification, refining steps when solvents such as dichloromethane may be employed.

Current guidance on GMP for active pharmaceutical ingredients (APIs) sets out basic requirements for active substances and recognises that the use of recovered solvents is acceptable with the caveats that approved procedures for the recovery exist and that the recovered materials meet specifications suitable for their intended use.

Recovery of Materials and Solvents

- Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or co-mingling with other approved materials.
- Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.
- The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

The European Pharmacopoeia likewise recognises that for extracts where the organic solvent is removed, recovered or recycled solvent may be used, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before re-use or admixture with other approved materials.

However, existing guidelines provide only limited guidance on the standards/specifications to be applied to recycled/recovered solvents and this does not address the particular nature of herbal preparations and their complexity. As a result, the supporting documentation provided varies between applicants/manufacturers, even for similar products.

Further consideration should be given to documentation needed to demonstrate that the recycled/recovered solvents meet acceptable standards for the manufacture of herbal preparations. This should include discussion of issues relating to the methods used for recovery, stage at which solvents are recovered (e.g. in-process or final stage evaporation), acceptability of pooling of solvents from different extraction procedures, and should address the potential for cross-contamination as well as the validation data required to support the usage. In some cases, special provisions may need to apply, for example where solvents are used to remove unwanted, potentially toxic constituents, pooling of recovered solvents with other solvents may not be acceptable.

Recovery operations should be described in detail and handling of solvent mixtures should be addressed. Details of any processing (e.g. rectification) to improve the quality of the recovered solvent should be described. Recovered solvents need to be adequately controlled such that constituents from previous extractions or impurity levels, including potential contaminants such as pesticides, fumigants, mycotoxins, do not concentrate up or increase over time. Suitable specifications should be applied to the recovered solvents.

In cases where the herbal preparation is a liquid extract/tincture and the extraction solvent remains as part of the preparation and is not removed (cf. dry extracts/soft extracts), the use of recovered/recycled solvent (mainly ethanol) should be avoided unless fully justified and appropriate standards are applied.

A guideline on the standards to be applied to recycled/recovered solvents used in the manufacture of herbal preparations should describe in detail the documentation that the applicant should provide in order to demonstrate that the solvents are adequately characterised and meets quality standards appropriate for their intended use.

5. Recommendation

As there is very little information on standards to be applied to recycled/recovered solvents used for extraction of herbal substances in the existing guidelines, the HMPC recommends the development of a respective guideline.

A guideline on standards to be applied to recycled/recovered solvents used for extraction herbal substances should describe the information to be provided in Module 3 section 3.2.S.2.3 Control of 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 standards to be applied to recycled/recovered solvents used for extraction of herbal substances in the manufacture of herbal preparations is expected to benefit industry. When recycled/recovered solvents used for extraction need to be used, this guideline will clarify the information to be submitted in Module 3 (section 3.2.S.2.3 Control of Materials).

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

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).

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.

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)

European Pharmacopoeia General Monograph "Extracts" 04/2008:0765

ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (CPMP/ICH/4106/00)