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

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1. Introduction

This reflection paper concerns the use of recycled/recovered solvents for extraction of herbal substances in the manufacture of herbal preparations for use in herbal medicinal products (HMPs)/ traditional herbal medicinal products (THMPs).

The purpose of this reflection paper is to highlight the criteria to be taken into account when considering the use of recycled/recovered solvents for extraction or other steps in the manufacture of herbal preparations and when establishing acceptance criteria/specifications for recycled/recovered solvents to ensure that they are adequately controlled and suitable for their intended purpose.

The aim is to provide clarification on the issues to be addressed and the documentation which should be submitted in order to assist applicants in developing dossiers for HMPs/THMPs.

For environmental reasons as well as safety considerations, organic solvents used during the manufacture of medicinal products have to be recovered and disposed of in a suitable manner depending on the solvents used. The recovery and re-use of solvents in the same process or in different processes is generally acceptable from a GMP standpoint (see discussion below).

However, in the case of solvents used in the manufacture of HMPs/THMPs, the re-use of recovered/recycled solvents raises particular concerns when the quality of the resulting extracts is considered.

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

2. Discussion

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

Recovery of Materials and Solvents (CPMP/ICH/4106/00)

- 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.

However, in the case of solvents used in the manufacture of HMPs, the re-use of recovered/recycled solvents raises particular concerns due to the complex nature of the herbal preparations used as APIs in herbal medicinal products.

The majority of herbal preparations used in HMPs/THMPs are herbal extracts. These include liquid preparations (liquid extracts and tinctures), semi-solid preparations (soft extracts and oleoresins) and solid preparations (dry extracts). With dry extracts the solvent is removed during the manufacturing

process and only residues of solvents will remain. However, in the case of liquid extracts the extraction solvents and/or solvents used during subsequent manufacturing steps remain as part of the herbal preparation. With soft extracts the solvent is partially removed during production.

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. In some manufacturing processes the herbal extract is prepared using a sequential approach where the plant material is extracted with solvent a number of times and at each step the solvent is recovered and re-used for the next step. 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.

The extent to which recycled/recovered solvents are used in the manufacture of herbal preparations is not documented but it is clear that the quality of recycled/recovered solvents is a critical factor in controlling the quality of the resulting herbal preparations and ensuring batch to batch reproducibility. Potential differences in quality between 'virgin' solvents and recycled/recovered solvents could lead to significant differences in the phytochemical composition of the resulting extracts and in certain cases could lead to higher levels of contaminants/impurities.

Recycled/recovered solvents are generally not used in the manufacture of liquid extracts and tinctures.

The European Pharmacopoeia recognises that for herbal extracts where solvents are recovered from the production process, such 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.

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

The following points should be addressed when the use of recovered or recycled solvents is being considered for herbal preparations:

(i) The acceptability of using recovered or recycled solvents for extraction of herbal substances

Where recycled/recovered solvents are used for extraction of herbal substances the solvents should preferably originate from the same production process rather than from extraction of different herbal substances.

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

(ii) Suitability of the methods used for recovery and the stage at which solvents are recovered

Mixed waste solvents are usually separated by distillation or rectification processes. However, in many cases mixtures of solvents cannot be recycled simply by distillation and the individual solvents must be separated by an appropriate technique such as separation by membrane filtration (e.g. pervaporation or organic solvent nanofiltration (OSN)) followed by rectification.

Azeotropic mixtures can be formed during distillation processes therefore the recovery procedures must be validated. It is difficult to validate the recovery procedures when recycled solvents in producing different products are used.

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. The stage at which the solvents are recovered, e.g. in process or final stage evaporation, may impact on the methods that can be applied and this should also be addressed.

(iii) The acceptability of pooling of solvents from different extraction procedures

This arises where solvents from different extraction procedures are combined i.e. not dedicating the use of a recovered solvent to the process from which they came.

Where recovered solvents will be used in processes from which they did not originate the potential for cross-contamination needs to be addressed and appropriate validation data generated to support the usage. In general the solvents used in different extraction procedures should be restricted to circumstances where lack of carry-over is proven or potential carry-over does not affect the composition of the new extract (e.g. when the recycled extraction solvent was previously used to process a single component of a subsequent mixture, or when a validated method to detect all possible residual constituents arising from the previous extraction process is available).

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.

In the case of certain herbal substances with volatile or other odoriferous constituents e.g. garlic, valerian, re-use of extraction solvents is limited to preparations of the respective herbal ingredient.

(iv) Appropriate controls for recovered or recycled solvent

Appropriate controls need to be applied to recovered or recycled solvent used for extraction of herbal substances. 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.

Recycled solvents such as ethanol or acetone coming from initial mixtures with water generally contain a high content of water which can be contaminated with impurities co-extracted during distillation. Such impurities would not be controlled adequately simply by a dry residue test and suitable methods would need to be applied to determine the nature of the impurities and the controls necessary.

Suitable specifications should be applied to the recovered solvents and should be submitted in the dossier with appropriate justification for the test methods and limits applied. All test methods should be appropriately validated.

Deviations from 'virgin' solvent specifications should be justified and supported by batch data as appropriate. Any differences in specification should be shown to have no adverse effect on the physico-chemical properties of the solvent or on the qualitative and quantitative impurity profile. In particular, water content and levels of volatile organic compounds should be addressed.

3. Conclusions

Where recycled/recovered solvents are used for extraction of herbal substances in the manufacture of herbal preparations for use in HMPs/THMPs.

The quality of the recycled/recovered solvents should be fully addressed as a critical factor which may affect the quality of the resulting herbal preparations and batch to batch reproducibility.

The use of recycled/recovered solvents should be discussed and justified in the dossier and the applicant should demonstrate that the solvents are adequately characterised and meet quality standards appropriate for their intended use.

Information on the methods used for solvent recovery should be submitted, together with evidence to demonstrate that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards. Suitable specifications should be submitted for the recycled/recovered solvents and deviations from 'virgin' solvent specifications should be justified and supported by batch data as appropriate.

4. References

- 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products'. (EMA/CPMP/QWP/2819/00), (EMA/CVMP/814/00).
- '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), (EMA/CVMP/815/00).
- 'Guideline on quality of combination herbal medicinal products / traditional herbal medicinal products'. (EMA/HMPC/CHMP/CVMP/214869/2006).

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