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4 **Concept paper on use of recovered/recycled solvents in**
5 **the manufacture of herbal preparations for use in herbal**
6 **medicinal products / traditional herbal medicinal products**
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27 **1. Introduction**

28 This concept paper concerns the standards to be applied to recycled/recovered solvents used for
29 extraction of herbal substances in the manufacture of herbal preparations for use in herbal medicinal
30 products (HMPs) / traditional herbal medicinal products (THMPs).

31 The quality of herbal medicinal products should be guaranteed and demonstrated in accordance with
32 the existing requirements as set out in Annex I of Directive 2001/83/EC, as amended, with specific
33 herbal quality guidelines such as 'Guideline on quality of HMPs/THMPs' (EMA/CPMP/QWP/2819/00 Rev.
34 2) (EMA/CVMP/814/00 Rev. 2), 'Guideline on specifications: test procedures and acceptance criteria for
35 herbal substances, herbal preparations and HMPs/THMPs' (EMA/CPMP/QWP/2820/00 Rev. 2)
36 (EMA/CVMP/815/00 Rev. 2), 'Guideline on quality of combination HMPs/THMPs'
37 (EMA/HMPC/CHMP/CVMP/214869/2006) and, in addition, with current EU/ICH general quality
38 guidelines for medicinal products that are applicable to HMPs/THMPs.

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

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

47 **2. Scope**

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

51 **3. Problem statement**

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

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

59 **4. Discussion**

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

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

70 Recovery of Materials and Solvents

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

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

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

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

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

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

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

108 **5. Recommendation**

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

112 A guideline on standards to be applied to recycled/recovered solvents used for extraction herbal
113 substances should describe the information to be provided in Module 3 section 3.2.S.2.3 Control of
114 Materials.

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

116 **6. Timetable**

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

120 **7. Resource requirements for preparation**

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

123 **8. Impact assessment (anticipated)**

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

128 This will therefore provide benefits to applicants in the preparation of their applications.

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

132 **9. Interested parties**

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

135 **10. Definitions**

136 **Herbal medicinal products:** any medicinal product, exclusively containing as active substances one
137 or more herbal substances or one or more herbal preparations, or one or more such herbal substances
138 in combination with one or more such herbal preparations.

139 **Herbal preparations:** are obtained by subjecting herbal substances to treatments such as extraction,
140 distillation, expression, fractionation, purification, concentration or fermentation. These include
141 comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and
142 processed exudates.

143 **Herbal substances:** all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an
144 unprocessed, usually dried form but sometimes fresh. Certain exudates that have not been subjected
145 to a specific treatment are also considered to be herbal substances. Herbal substances are precisely
146 defined by the plant part used and the botanical name according to the binomial system (genus,
147 species, variety and author).

148 **Specification:** A list of tests, references to analytical procedures, and appropriate acceptance criteria,
149 which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of
150 criteria to which a herbal substance/preparation or herbal medicinal product should conform to be
151 considered acceptable for its intended use. "Conformance to specifications" means that the herbal
152 substance/preparation and/or herbal medicinal product, when tested according to the listed analytical
153 procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that
154 are agreed to between competent regulatory authorities and applicants.

155 **Traditional herbal medicinal products:** are medicinal products for human use that fulfil the
156 conditions laid down in article 16a (1) of Directive 2001/83/EC, as amended.

157 **11. References**

158 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products'
159 (EMA/CPMP/QWP/2819/00 Rev. 2), (EMA/CVMP/814/00 Rev. 2)

160 'Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal
161 preparations and herbal medicinal products/traditional herbal medicinal products'
162 (EMA/CPMP/QWP/2820/00 Rev. 2), (EMA/CVMP/815/00 Rev. 2)

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

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

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