European Medicines Agency

London, 12 November 2009
Doc. Ref. EMEA/HMCP/651266/2009

OVERVIEW OF COMMENTS RECEIVED ON

GUIDELINE ON SELECTION OF TEST MATERIALS FOR GENOTOXICITY TESTING FOR TRADITIONAL HERBAL MEDICINAL PRODUCTS/HERBAL MEDICINAL PRODUCTS EMEA/HMPC/67644/2009

Table 1: Organisations that commented on the document as released for consultation in June 2009 until September 2009.

	Organisation	Country
1	Association of the European Self-Medication Industry (AESGP)	Brussels, Belgium
2	Kooperation Phytopharmaka	Bonn, Germany

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Table 2: Discussion of comments

Stakeholder No.	General Comment (if any)	Outcome
	AESGP AESGP in principle appreciates this new document which provides explanation concerning the bracketing/matrixing concept for genotoxicity testing. It might help to restrict genotoxicity to an appropriate extent of materials and also contribute to the overall reduction and/or replacement of animal testing.	Endorsed.
	Kooperation Phytopharmaka In principle we welcome the new draft guideline which might help to restrict genotoxicity to an appropriate extent and thus contribute to the overall reduction and/or replacement also of animal testing which is one of the objectives of the revised ICH S2(R) Note for Guidance on genotoxicity testing. For this reason we fully agree with the HMPC proposal to establish a bracketing/matrixing concept to the range of test materials. Such a concept has already been used in many cases by Kooperation Phytopharmaka within a joint project of Ames tests. In this project, for a large number of herbal preparations specific preparations of defined polarity have been selected, and the results obtained with these preparations have been transferred to further preparations.	Endorsed.

2. SPECIFIC COMMENTS ON TEXT

<table>
<tr><th>Line No of the first line(s) affected</th><th>Stakeholder No.</th><th>Comment and Rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td>130-131 and 145-146</td><td></td><td>
AESGP

Comments:
We have a minor comment on the tables which show ranges of solvents and demonstrate that two “extreme” and potentially a “mid-range” extract can be tested to cover the whole range. Herbal extracts are always characterised by the alcohol content of the extraction solvent and not by its water content. Although the water content might be useful to demonstrate the range of polarities it may be misleading in this case.

Proposed change (if any):
In this context we would like to propose to leave out the second column indicating the water content.

Row 130-131

Table 1 Melilot herb: Aqueous and ethanolic extracts
<table>
<tr><td colspan="2">Herbal preparations</td></tr>
<tr><td>Herbal substance for tea preparation</td><td></td></tr>
<tr><td>Dry extracts (3 - 5:1), water</td><td></td></tr>
<tr><td>Liquid extracts (1:1), ethanol 30 % V/V</td><td></td></tr>
<tr><td>Dry Extracts (5 - 7:1), ethanol 50 % V/V</td><td></td></tr>
<tr><td>Dry extracts (4 - 8:1), ethanol 25 % m/m</td><td></td></tr>
<tr><td>Dry extracts (4 - 8:1), ethanol 35 % V/V</td><td></td></tr>
<tr><td>Dry extracts (6 - 9:1), ethanol 90 % V/V</td><td></td></tr>
</table>
</td><td>Endorsed.</td></tr>
</table>

<table>
<tr><th>Line No of the first line(s) affected</th><th>Stakeholder No.</th><th>Comment and Rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>Row 145-146

Table 2 Passiflora herb: Aqueous and ethanolic extracts

<table>
<tr><td colspan="2">Herbal preparations</td></tr>
<tr><td>Herbal substance for tea preparation</td><td></td></tr>
<tr><td>Liquid extract (1:8); extraction solvent 25% ethanol</td><td></td></tr>
<tr><td>Liquid extract (1:8) ; extraction solvent 45% ethanol</td><td></td></tr>
<tr><td>Liquid extract (1:1) ; extraction solvent 25% ethanol</td><td></td></tr>
<tr><td>Liquid extract (1:1) ; extraction solvent 70% ethanol</td><td></td></tr>
<tr><td></td><td></td></tr>
</table>

Kooperation Phytopharmaka

We appreciate the examples given under point 4. Selection of test materials which might elucidate the reduced testing design and the “bracketing/matrixing” concept. The example of Melilot herb shows that two “extreme” and a “mid-range” extract can be tested and thus cover the whole range. We fully agree with this concept, however, in the respective table we propose to leave out the second column indicating the water content because this is misleading. Extracts are always characterised by the ethanol content of the extraction solvent and not by its water content.
In addition we suggest to integrate the methanolic extracts into the table according to their polarity: For this reason the 30% methanolic extract should be included behind the aqueous extract and the 50% methanolic extract between the 35 and 90% ethanolic extract. Thus the second paragraph (line 136-138) can be left out.</td><td>Endorsed.

Endorsed.

Endorsed.</td></tr>
</table>

Line No of the first line(s) affected	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		For this reason we propose to change table 1 as follows: *Herbal preparations* Herbal substance for tea preparation Dry extracts (3 - 5:1), water **Dry extracts (7 - 9:1), methanol 30 % V/V** Liquid extracts (1:1), ethanol 30 % V/V Dry Extracts (5 - 7:1), ethanol 50 % V/V Dry extracts (4 - 8:1), ethanol 25 % m/m Dry extracts (4 - 8:1), ethanol 35 % V/V **Dry extracts (4 - 8:1), methanol 50 % V/V** Dry extracts (6 - 9:1), ethanol 90 % V/V For the example Passiflora herb we also propose to leave out the second column indicating the water content because usually the extracts are characterised by the ethanol content of the extraction solvent. With regard to entire herbal substances (e.g. powdered herbal drugs) used in herbal medicinal products (line 154-159) we agree that preparations should be tested which cover the whole phytochemical profile, e.g. a polar solvent (water), an apolar solvent (heptane) and a mid-range solvent.	Endorsed. Endorsed.