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Information in the package leaflet for fragrances containing allergens in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1) Draft

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Comments are requested only on the table "*Proposal for updated information in the package leaflet*" using column and row references.

Comments should be provided using this [template](#). The completed comments form should be sent to excipients@ema.europa.eu

Keywords	<i>Excipients, Package leaflet, Fragrances, Allergens</i>
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Executive summary

The EC designated 26 fragrances as allergens requiring labelling in cosmetic and detergent products if the concentration of the designated ingredient exceeds 100 parts per million (ppm) for a rinse-off product and 10 ppm for a leave-on product. Some of these allergens are also used in topically applied medicinal products. Hence, it was considered necessary to also request labelling for these 26 fragrances if contained in topically applied medicinal products. However, since topically applied medicinal products may be applied on a more sensitive skin (if damaged), a zero threshold should be applied instead.

It is noted that benzyl alcohol, which is among the 26 fragrance allergens, is also addressed separately in the excipients guideline [1].

Proposal for new information in the package leaflet

[Column and row references to be used for comments]

	A	B	C	D	E
1	Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
2	Fragrances containing allergens	Topical	Zero	This medicine contains fragrance with <allergen >*	In addition to the occurrence of allergic reactions in already sensitised patients, non-sensitised patients may develop sensitisation. * < >: fragrance allergen according to table 1
3				May cause allergic reactions.	
4					

Scientific background

1. Use in medicinal products

Fragrances are added in order to obtain an acceptable or even pleasant over-all odour to medicinal products in which some active ingredients carry an unpleasant smell, which may hinder its use by the patient.

Fragrances are used as excipients in some topically applied medicinal products e.g. various approved ointments and creams.

2. Safety concerns

In Germany, approximately 7% of the population experience an acute contact dermatitis within a year and about 15–20% of the population is sensitised to common allergens. With regard to fragrance allergens, the frequency of contact sensitisation in patients routinely patch tested for suspected allergic contact dermatitis was found to be 15% [2, 4].

In Regulation 1223/2009 on cosmetic products [Article 19 (1) g in combination with Annex III: labelling of substances of fragrances in cosmetics] and former Directive 76/768/EEC, amended, 26 fragrances are currently designated by the EC as allergens requiring labelling in cosmetic and detergent products if the concentration of the designated ingredient exceeds 100 parts per million (ppm) for a rinse-off product and 10 ppm for a leave-on product. Some of these allergens are also used in medicinal products.

The 26 fragrance allergens if contained in topically applied medicinal products may

- a) Cause severe allergic reactions in sensitised patients. Information of patients before the use of the medicinal product containing these allergens is the adequate prevention.
- b) Sensitise fragrance allergen naïve patients to these allergens (e.g. patients in particular prone to develop sensitisation).

3. Safety information relevant for the package leaflet

Fragrance allergens requiring labelling in cosmetics should also be labelled in the product information of topically applied drug products if contained in these. However, in contrast to cosmetics a zero threshold should be applied since topically applied medicinal products may be used on a more sensitive skin (if damaged). The International Nomenclature of Cosmetic Ingredients (INCI) is also considered to be applicable to medicines.

Inclusion of these allergens in the excipients guideline is therefore proposed as an appropriate approach to solve this issue.

The information on the allergens in the excipients guideline will be ensured by a cross-reference to Annex III of the Regulation 1223/2009 on cosmetic products. Table 1 in the appendix lists all the 26 fragrance allergens designated by the EC. These compounds were included in the formerly valid directive 76/768/EEC and are included in the currently valid EC regulation no. 1223/2009, as well.

For convenience of the reader a footnote will be added stating that the cross-reference refers to the version of the Annex III of the Regulation 1223/2009 on cosmetic products dated 30 November 2009. There fragrances are grouped and listed from #67 to #92. In addition, it will be stated that Annex III

reflects the advancement of science at the time of the adoption of the Regulation on 30 November 2009. Therefore, the reader should check whether amendments of the Annex III with regard to the 26 allergens have been introduced in the meantime.

It is pointed out that benzyl alcohol – although among the 26 fragrance allergens listed in Annex III (i.e. #45) of Regulation 1223/2009 on cosmetic products – is already addressed separately in the excipients guideline and by a specific Q&A.

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References – Bibliography

1. Guideline on excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev.1). July 2003.
2. Schnuch, A. et al., Bundesgesundheitsbl 2012; 55: p. 329–37.
3. Scientific Committee on Consumer Safety (SCCS) OPINION on Fragrance allergens in cosmetic products, [June 2012](#)
4. Uter, W., Geier, J., Frosch, P. and Schnuch, A., 'Contact allergy to fragrances: current patch test results (2005–2008) from the Information Network of Departments of Dermatology', Contact Dermatitis, 2010, 63: p. 254–261. doi: 10.1111/j.1600-0536.2010.01759.x

Appendix:

Table 1: European Union List of Fragrance Allergens Requiring Labelling on Cosmetic and Detergent Products [3]

Substance	CAS No
3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one	127-51-5
Amyl cinnamal	122-40-7
Amylcinnamyl alcohol	101-85-9
Anisyl alcohol	105-13-5
Benzyl alcohol	100-51-6
Benzyl benzoate	120-51-4
Benzyl cinnamate	103-41-3
Benzyl salicylate	118-58-1
Cinnamal	104-55-2
Cinnamyl alcohol	104-54-1
Citral	5392-40-5
Citronellol	106-22-9
Coumarin	91-64-5
d-Limonene	5989-27-5
Eugenol	97-53-0
Farnesol	4602-84-0
Geraniol	106-24-1
Hexyl cinnamaldehyde	101-86-0
Hydroxycitronellal	107-75-5
Hydroxymethylpentyl-cyclohexenecarboxaldehyde	31906-04-4
Isoeugenol	97-54-1
Lilial	80-54-6
Linalool	78-70-6
Methyl heptine carbonate	111-12-6
Oak moss	90028-68-5
Tree moss	90028-67-4