9 October 2017
EMA/CHMP/579645/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the draft 'Information in the package leaflet for fragrances containing allergens' (EMA/CHMP/273718/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Novartis Pharma AG
2	WALA Heilmittel GmbH
3	Medicines Evaluation Board in The Netherlands (MEB)
4	F. Hoffmann-La Roche. Ltd
5	Reckitt Benckiser Healthcare (UK) Ltd
6	AESGP
7	BPI e.v.

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Novartis appreciates to comment on this draft information. The new proposed wording includes a section for all topical route of administration, which should be reconsidered for topical Otic products. Some Otic products do contain for example benzyl alcohol, but as stated in the proposal this is already addressed separately in the existing guidance. The proposal should be further clarified if it only refers to situation where allergen (e.g. Benzyl alcohol) is only included in a fragrance as a primary purpose. Rationale: Topical Otic products are administrated for local actions only, and are unlikely to contain a fragrance even if some of the allergen outlined in the proposal are included in the composition.	Not accepted. 1) Otic products The guideline “Excipients in the label and package leaflet of medicinal products for human use” states: “Topical medicinal products can be taken to include those medicinal products applied externally to the skin, respiratory products delivered to the lung by inhalation and any medicinal product delivered to the oral, nasal, rectal or vaginal mucosae, i.e. where the delivery may be local or transdermal. Hence, otic products are included as far as this refers to otic products which are applied externally to the skin of the ear. 2) Fragrance The provisions apply to the 26 fragrance allergens irrespective for which purpose they are added. 3) Benzyl-alcohol Benzyl alcohol is listed as one of the 26 fragrance allergens but can also be used as an excipient. When benzyl alcohol is used as an excipient (in addition to a fragrance or not), the label of this excipient applies.
2, 7	<u>Use of fragrances in medicinal products</u> The *Committee for Human Medicinal Products (CHMP)* wrongly assumes	

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	that fragrances are added to medicinal products exclusively to improve their smell. It therefore considers fragrances as ingredients that are not absolutely necessary and can be replaced or even omitted. The mask of unpleasant smells of certain substances, however, is also relevant to improve the compliance of patients. It is true that some fragrances may endanger allergic patients or may produce sensitization. From this point of view, the Committee's demand for labelling is comprehensible. It is only feasible, however, if the fragrances are added in measurable quantities of a single substance. In many natural remedies (e.g., herbal or anthroposophical medicinal products), however, essential oils and herbal extracts containing them are not used because of their pleasant scent, but because they have stabilizing effects due to their antimicrobial properties [1]. They replace synthetic substances that might pose an even higher risk of sensitization. Since there is no adequate single substitute for the respective essential oils as a multicompound mixture, it is hardly practicable to dispense of any of them. Question: Is the information on allergen fragrances in the package leaflet also required for essential oils added as excipients because of their stabilizing effects? 1. Reichling J, Schnitzler P, Suschke U and Saller R. Essential oils of aromatic plants with antibacterial, antifungal, antiviral, and cytotoxic properties - an overview. Forschende Komplementärmedizin 2009; 16(2): 79-90.	Response to the question: The provision does not differentiate for which purpose the fragrance allergens have been added since the risk of allergic reaction is irrespective of the purpose why the fragrance allergens have been added.
2, 7	Zero threshold for fragrances in essential oils is not manageable The meaningfulness of labelling fragrance excipients from a zero threshold in medicinal products is unrealistic, unless only a single allergen fragrance compound is intentionally added to the medicinal product. For essential oil	Not accepted. It can be assumed that topical medicinal products – unlike cosmetics - are applied to lesional skin with an impaired barrier function. Hence, there is a higher risk of allergic

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	excipients in medicinal products, the Committee's demand for labelling single fragrance allergen compounds substances is not manageable. A natural essential oil generally consists of a complex mixture of more than 100 different compounds the concentration of which is sometimes so low that it cannot be analytically detected in the final medicinal product. The composition of essential oils may also vary considerably, even for essential oils that are in compliance with the European Pharmacopeia. Moreover, an absolute 'zero' does not exist, since substances can be only detected when above the limit of detection. The requirements for such analytical procedures should be suitable and proportionate. However, it is generally not known, if the labelling of fragrances varies between medicinal products and pharmaceutical companies due to differences in the sensitivity of their analytical methods. Against this background it becomes obvious that zero-tolerance limits for fragrance ingredients are scientifically out-of-reach, and reasonable thresholds above trace amounts should be defined instead. Furthermore, the methodology to detect and characterize all components of essential oils is not developed yet, let alone proven for routine. Thus, a zero threshold would mean that even traces or analytically undetectable amounts of all fragrance allergens according *Annex III* of the *Regulation 1223/2009* on cosmetic products must be labelled. This might force marketing authorization holders (MAH) to declare even fragrance ingredients that might not occur in their final products just to rule out any risk of allergy or sensitization. Moreover, warnings like "may contain traces of ..." that, regrettably, are widespread in food industry, increase uncertainty instead of providing valid information for people suffering from an allergy. As a result, allergic patients might be deprived of a medicinal	reactions. Zero threshold means below the detection limit. If the respective fragrance allergen can be detected in the medicinal product, it should be labelled.

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	product they would have well tolerated. Therefore, the demand for labelling fragrances as allergens from a zero threshold is only valid for single intentionally added fragrance substances. As far as essential oils used as excipients in medicinal products are concerned, we suggest that only the respective essential oil (and not every single potential allergen fragrance that could be present) is labelled on the packaging and mentioned in the package leaflet. This option has already been realized for *camphor* and *menthol* in the German excipients guideline (= *Besonderheitenliste des BfArM)*[1]. 1. Besonderheitenliste des Bundesinstituts für Arzneimittel und Medizinprodukte (BfArM) / Version 1-12, März 2016, auf Basis der Excipients-Guideline (CPMP/463/00 Final, Juli 2003), der Arzneimittel-Warnhinweisverordnung sowie umgesetzter nationaler Stufenplanmaßnahmen.	
2, 7	The same thresholds as in cosmetics The EC has named 26 fragrance allergens that must be labelled on cosmetic and detergent products, if their concentration exceeds 100 parts per million (ppm) in a rinse-off product and 10 ppm in a leave-on product. The Committee's demand of a zero threshold for these fragrances in medicinal products is based on the assumption that medicinal products are possibly used on damaged or at least more sensitive skin. There are, however, many topical medicinal products that are not applied to damaged skin, like chest balms for the treatment of cough and bronchitis, ointments for rheumatic disorders, ointments for painful muscular tensions etc. Since the guideline on *Excipients in the label and package leaflet of medicinal products for human use* says: ...excipients may only show an	Not accepted. A distinction between topical medicinal products for application on damaged skin and those for application on undamaged skin is not realistic. A medical doctor is not always involved (OTC-products) and topical medicinal products may also be used for a longer period of time (chronic diseases).

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	effect above a certain 'dose' [1]. Consequently, for medicinal products that are not intended to be used on damaged skin, the same threshold for allergen fragrances as for cosmetic products should be applied. Furthermore, the information in the package leaflet of medicinal products ensures a higher patient safety. Medicinal products that are not to be applied to damaged skin already have a respective warning like a contraindication and/or precaution of use. Therefore, lower thresholds or even a zero threshold for medicinal products are not at all justifiable. A distinction has to be made between topical medicinal products for application on damaged skin and those for application on undamaged skin. Since a large part of the population suffers from skin diseases (e.g., acne, eczema), it can be assumed that cosmetics are applied to damaged skin to a great extent. Some cosmetic products are explicitly used on damaged skin, e.g. care products against sunburn. Therefore, the required safety evaluation of cosmetics already considers the application on damaged skin. Contrary to cosmetics, medicinal products are used for a limited period only. A longer treatment should only take place after a doctor has been consulted. This information is included in the package leaflet. The risk of sensitization is thus much lower and a doctor is always involved in the risk-benefit assessment of the treated patients. Therefore, the thresholds valid for cosmetics can be applied equally to medicinal products used on damaged skin. Lower thresholds do not make any sense. Since the existing validated methods for analyzing fragrances in cosmetics could then also be used for medicinal products, the implementation would be faster and more robust.	

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	1. Guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev.1). July 2003.	
2, 7	Additional information without advantages Regarding medicinal products, article 54(c) of *Directive 2001/83/EC* requires that all excipients need to be declared on the labelling, if the medicinal product is an injectable or a topical, or an eye preparation. Article 59 (1)(a) 2nd indent requires a full statement of the active substance and excipients in the package leaflet. Article 59 (1)(c) states that the package leaflet must include a list of information that is to be read before the medicinal product is used. Therefore, consumers of topical medicinal products are already aware of all ingredients of the medicinal product like single fragrance, essential oils or natural extracts, regardless of their concentration. The compounds additional information in the package leaflet proposed adds little value for the affected patients. People suffering from an allergy already find all information they need on the package and in the package leaflet so they can decide if they want to use the medicinal product with fragrances/ essential oils as potential allergens or not. Furthermore, the fact that medicinal products are generally available in pharmacies further increases the safety of patients, as they can get advice of the pharmacist about potential fragrance allergens contained.	Not accepted. The excipients guideline currently allows the use of the summarizing term "fragrance": Proprietary flavours or fragrances may be declared in general terms (e.g. 'orange flavour', 'citrus fragrance/perfume'); any known major components or those with a recognised action or effect should be declared specifically. The present approach clearly names 26 fragrance allergens that have to be labelled.
2, 7	Safety and tolerability Safety and tolerability of medicinal products are ensured through extensive	Not accepted. The evaluation of cutaneous tolerance of topical medicinal

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	measures taken by the MAHs and the authorities. According to *Directive 2001/83/EC*, for marketing authorization application, usually non-clinical and clinical data (including information on local tolerance), have to be submitted. According to the *Guideline on non-clinical local tolerance testing of medicinal products* [1], the complete evaluation of cutaneous tolerance of topical medicinal products is required; amongst others a repeated-dose cutaneous tolerance test as well as an evaluation of the sensitizing potential. Therefore, European competent authorities evaluate all data on local tolerance and sensitizing potential before they approve the marketing authorization or the variation of composition of an authorized medicinal product. If warnings or contraindications are required for patient safety because of the data submitted, these are included in the package leaflet. Thus, the proposed general reference to a possible sensitization and allergy-inducing effect in the package leaflet is not necessary. Furthermore, according to Article 1 of the *Directive 2001/83/EC*, each MAH has to run a pharmacovigilance system. The MAH thus continuously monitors the safety of authorized medicinal products and detects any changes of their risk-benefit balance. The pharmacovigilance system includes signal detection and evaluation of spontaneous reports by monitoring individual case safety reports and relevant scientific literature. Thus, potential incompatibility risks for patients are early identified and the product information is updated correspondingly. 1. Guideline on non-clinical local tolerance testing of medicinal products (EMA/CHMP/SWP/2145/2000 Rev. 1). 2015.	products prior to marketing authorisation does not necessarily mean that single substances which an allergenic potential must not be used. It is one aim of this revision to provide guidance which fragrances allergens have to be labelled. As stated in the document in the European population there is an estimated frequency of contact allergy to fragrances of 1–3%. This is one scientific rationale for the need to inform patients if one of the 26 fragrance allergens is contained in the topical medicinal product.

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2, 7	Do patients really benefit from additional information? There are disagreements about the allergic potential of some of the 26 fragrance allergens that have already been labeled in cosmetics according to current European regulation. Large-scale clinical studies demonstrate that some of them are more frequent sensitizers whereas other turned out to be extremely rare sensitizers that provoke only minor or no positive reactions at all [1,2]. Accordingly, the *Information Network of Departments of Dermatology (IVDK)* in Germany expresses some criticism about the approach of the SCCNFP (*Scientific Committee on Cosmetic and Non-Food-Products intended for Consumers*) and the conclusions it has drawn [3]. The IVDK is convinced that most of the selected fragrance ingredients are no relevant allergens [1]. Tests for fragrance allergy usually consist of two test mixtures (*FM I* and *FM II*), so the patients are only tested for 14 fragrance ingredients without further differentiation between the individual fragrances afterwards. In most cases, positive results of such test results lead to a corresponding entry in the patient's allergy passport and to the doctor advising the patient to generally avoid fragrances in the future. Thus, the proposed information in package leaflet adds little value to the affected patients. 1. Schnuch A, Uter W, Geier J, Lessmann H and Frosch PJ. Sensitization to 26 fragrances to be labelled according to current European regulation. Results of the IVDK and review of the literature. Contact Dermatitis 2007; 57(1): 1-10. 2. 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	Not accepted. The concerns of the IVDK are noted. However, the current approach to align with the provisions for the cosmetics (as a minimum) seems to be pragmatic. This does not prevent further and future discussion on which other allergens should be listed. However, such a discussion for individual allergens may take a longer time. Hence, the current approach is reasonable.

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	Dermatology. Contact Dermatitis 2010; 63(5): 254-261. 3. Scientific Committee on Cosmetic and Non-Food-Products intended for Consumers (SCCNFP). OPINION on Fragrance allergy in consumers. 1999.	
2, 7	Cross-reference to the regulation on cosmetic products In Chapter 3 it is stated: *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. […]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. […]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 currently under discussion that the number of fragrance allergens subject to declaration in cosmetic products shall be increased from 26 to 90 [1]. According to the above wording, this decision would then also be immediately valid for the labelling of medicinal products. We object to incorporating provisions of cosmetics in guidelines for medicinal products like the excipient guideline without previous consultation with the pharmaceutical associations. Beside the currently discussed relevance of these fragrances as allergens, there are many other reasons why it is highly questionable if the patients benefit from the requested labelling. Currently, standardized testing kits for dermatological practices are only available of less than 50 of the 90 fragrance ingredients and essential oils	Not accepted. Justification: The final opinion of the Scientific Committee on Consumer Safety was published in 2012 (http://ec.europa.eu/health/scientific_committees/consultations/public_consultations/sccs_consultation_04_en.htm). However, no changes to the legal framework have been made in the meantime. If amendments are made concerning the fragrance allergens which need to be labelled in cosmetics this would also apply to the topical medicinal products. The scientific reasoning is the same as for the current 26 fragrance allergens. Further on, if the fragrance allergens are not contained in the medicinal products there is no need for labelling.

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	proposed for future declaration. This means that dermatologists are currently not able to find out whether their patients are allergic or not. Furthermore, in cases of essential oils used as excipients, the labelling of dozens of fragrances that could possibly be present, would only lead to confusion and uncertainty of the patients without providing any valid information. Moreover, the practical implementation is hard to achieve. The EU Commission's proposal to list a total of 90 fragrance substances in the ingredients list on the packaging, in addition to the full declaration of medicinal ingredients, is unmanageable, particularly for small packaging. In case of essential oil excipients it could become necessary to label dozens of fragrances, even if only traces or analytically undetectable amounts of them were possibly present. Anyway, expanding the declaration requirements for allergen fragrances as discussed is currently not possible and would entail enormous analytical development efforts. There is presently no established routine method for identifying and quantifying the full set of fragrance allergens. 1. Scientific Committee on Consumer Safety (SCCS) OPINION on Fragrance allergens in cosmetic products. June 2012.	
2, 7	The origins of the fragrances should be considered The *Scientific Committee on Consumer Safety (SCCS)* recommends to limit the use of the fragrances listed in tab. 13-5 regardless of their origin (pure synthetic substances or components of complex essential oils). Noteworthy, despite a confirmed fragrance allergy, users state that they generally tolerate natural cosmetic products very well.	Not accepted. From a scientific point of view it is the molecule itself which is critical for the allergenic potential irrespective of its origin (synthetic or natural). The proposed labelling refers to single substances and there is no scientific reason why an essential oil containing one of

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	We have tested the essential oil mixtures contained in our cosmetic products *Dr. Hauschka* on people with confirmed fragrance allergies by a reputable dermatological clinic: 20 essential oil mixtures used in cosmetic products by *Dr. Hauschka* were tested on 25 persons suffering from a fragrance-mix allergy. Only 3.4 % of these extremely sensitive persons developed an allergic reaction to the applied test concentrations of 5 %. Test concentrations of approx. 0.5 % resulted in no allergic contact reactions at all [1]. The origins of fragrances should be considered in the excipients guideline. The actual allergic potential of fragrances depends on whether they are pure synthetic substances or components of essential oils. Essential oils should be considered separately from single fragrances. To declare a specific essential oil as potential allergen, appropriate scientific literature should be available for proof. 1. Meyer U. Verträglichkeit natürlicher ätherischer Öle bei ausgewiesenen Duftstoff-Mix-Allergikern. [Tolerance of natural essential oils by persons known to be allergic to to a mix of fragrance mix]. Der Merkurstab 2004/Journal of Anthroposophic Medicine; 57(1): 59-61.	the 26 fragrance allergens should be exempted from labelling.
2, 7	Conclusion & Practical implementation We welcome the CHMP's efforts to further improve patients' protection and to provide them with information on fragrance ingredients that are used in medicinal products. At the same time, however, we doubt that the proposed information expansion on the packaging will provide real added value for affected patients but rather uncertainty. Medicinal products should not be treated as equivalents to cosmetics. Contrary to cosmetics, they are used for a limited period only. The risk of sensitization is thus much lower.	The comments as stated in the conclusion in the left column have already been addressed above.

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	Therefore, the thresholds valid for cosmetics should be applied equally to medicinal products. At least a distinction has to be made between topical medicinal products for application on damaged skin and those for application on undamaged skin. In addition, we object to incorporating provisions of cosmetics in guidelines for medicinal products like the excipient guideline without previous consultation with the pharmaceutical associations. The origins of fragrances should be considered in the excipients guideline. The actual allergic potential of fragrances depends on whether they are pure synthetic substances or components of essential oils. Essential oils should be considered separately from single fragrances. To declare a specific essential oil as potential allergen, appropriate scientific literature should be available. A natural essential oil consists of a complex mixture of over 100 different compounds. The components and nature of essential oils may vary considerably. The methodology to detect and characterize all components of essential oils is not developed yet, let alone proven for routine analysis. For essential oil excipients added in medicinal products, the Committee's demand for labelling single fragrance allergen compounds substances is completely unrealistic. A zero threshold would mean that even traces or analytically undetectable amounts of fragrance allergens must be labelled. This might force MAH to declare even fragrance ingredients that might not occur in their final products just to rule out any risk of allergy or sensitization. Warnings like "may contain traces of...” that, regrettably, are widespread in food industry, increase uncertainty instead of providing valid information for people suffering from an allergy.	

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	As far as essential oils used as excipients in medicinal products are concerned, we suggest that only the respective essential oil (and not every single potential allergen fragrance that could be contained in it) is labelled on the packaging and mentioned in the package leaflet. This option has already been realized for *camphor* and *menthol* in the German excipients guideline (= *Besonderheitenliste des BfArM)* [1] 1. Besonderheitenliste des Bundesinstituts für Arzneimittel und Medizinprodukte (BfArM) / Version 1-12, März 2016, auf Basis der Excipients-Guideline (CPMP/463/00 Final, Juli 2003), der Arzneimittel-Warnhinweisverordnung sowie umgesetzter nationaler Stufenplanmaßnahmen.	
7	Furthermore, it is difficult to know from a qualitative and quantitative point of view all the constituents of an essential oil. We cannot be sure to detect all allergenes contained in the fragrance. So, for safety reasons, it would be better to make the information of patients about allergic risk on essential oil itself, not considering the specific allergenes Even our companies producing medicinal prodcuts for hand desinfection are of the opinion that the “zero threshold” is not practical and even not justified. The suppliers of fragrances provide overview lists with the substances that are potentially allergenes according to the cosmetics guideline Nr. 1234/2009, Annex III, Nr. 67-92. For each allergene, the amount is based on a calculated analysis in %. The detection limit is 10 ppm. That means the list comprises already a variety of substances that cannot be detected analytically. Fragrances consists of a mixture of many components of natural (herbal) origin. 18 of the 26 allergene fragrances appear in essential oils or herbal extracts. Due to variations of the climatic conditions, the substances, even the components with allergic potential, underlay variations in their amount from batch to batch, even if the	Not accepted. The patient should be informed specifically if one the 26 fragrance allergens is contained in the topical medicinal product and not if an essential oil is contained. It is pointed out that the respective topical medicinal products can still contain the respective fragrance allergens, however, these have to be labelled according to the provisions. Zero threshold means below the detection limit. If the respective fragrance allergen can be detected in the medicinal product, it should be labelled.

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	substances are in a low concentration limit. In alcoholic hand desinfectants, the amount of perfumes are ≤ 0,1%. That means a strong dilution of the perfumes and the most allergenic substances are far below under the detection limit of 10 ppm. Even the experts of the SCCS regard the threshold of 10 ppm for leave-on products as safe and should even apply for desinfectants used on intact skin Literature: Scientific Committee on Consumer Safety (SCCS)-OPINION on Fractance allergenes in cosmetic products –SCCS/1459/11, 26-27 June 2012	
3	THE MEB has no comments	Acknowledged.
4	The efforts to update the current excipients guideline are appreciated, and proposed revisions are welcomed. This guideline should be updated as new evidence suggests the need for update.	
4	It is recommended to include a general requirement in the guideline that the quantity of the excipients per dose unit should be included for cases where toxicity depends on quantity of the excipient. Wording proposal could be as follows: This medicine contains xx mg <excipient> in each <volume/dosage unit>	Not accepted. Concerning the fragrance allergens allergic reactions and not toxicity is the clinical problem. Since allergic reactions may also occur with tiny doses the inclusion of the quantity of the excipient would not be helpful.
6	**Threshold set at zero.** A natural essential oil generally consists of a complex mixture of more than 100 different compounds the concentration of which is sometimes so low that it cannot be analytically detected in the final medicinal product. The composition of essential oils may also vary considerably, even for essential oils that are in compliance with the European Pharmacopeia.	Not accepted. Analytics should be done to know whether one or more of the 26 fragrance allergens are contained. There is a need to specifically mention the fragrance allergen if it is one of the 26 allergens. The proposed warning “may contain an allergen as identified for cosmetic

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	This does not take into account what the general analytical LOD/LOQ positions might be and hence is based on the premise that if there is a chance the material is present it should be listed. Some thresholds should be set along with guidance for future complex mixtures with clarity as to what marker is to be used for any given essential oil. These oils by their very nature are usually of natural origin and the levels of material can fluctuate year on year, so even if <LOD one year it maybe >LOQ another. Furthermore, the methodology to detect and characterize all components of essential oils is not developed yet, let alone proven for routine. The meaningfulness of labelling fragrance excipients from a zero threshold in medicinal products is unrealistic, unless only a single allergen fragrance compound is intentionally added to the medicinal product. For essential oil excipients in medicinal products, the Committee's demand for labelling single fragrance allergen compounds substances is not manageable. If the threshold is to be set at zero then the only statement that should be considered is “may contain an allergen as identified for cosmetic products”. Because of the specific vigilance data for medicines exact levels of allergic reaction should be more readily accessible and so should be listed as a side-effect rather than as “may cause allergic reaction” which through vigilance data may not have been shown to be correct. Thus, a zero threshold would mean that even traces or analytically undetectable amounts of all fragrance allergens according Annex III of the Regulation 1223/2009 on cosmetic products must be labelled. This might force marketing authorization holders (MAH) to declare even fragrance ingredients that might not occur in their final products just to rule out any risk of allergy or sensitization. Moreover, warnings like "may contain traces of ...” increase uncertainty instead of providing valid information for people	products” is not helpful in this regard. It is the intention to inform the patient that a specific fragrance allergen is contained which complies with a warning. The intention is to specifically inform if one or more of the 26 fragrance allergens are contained in the medicinal product, which is valid information for the patients who are sensitised to these fragrance allergens. The excipients guideline currently allows the use of the summarizing term “fragrance”: Proprietary flavours or fragrances may be declared in general terms (e.g. 'orange flavour’, 'citrus fragrance/perfume'); any known major components or those with a recognised action or effect should be declared specifically.

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	suffering from an allergy. As a result, allergic patients might be deprived of a medicinal product they would have well tolerated. Therefore, the demand for labelling fragrances as allergens from a zero threshold is only valid for single intentionally added fragrance substances. As far as essential oils used as excipients in medicinal products are concerned, we suggest that only the respective essential oil (and not every single potential allergen fragrance that could be present) is labelled on the packaging and mentioned in the package leaflet. This option has already been realized for camphor and menthol in the German excipients guideline [1]. Article 54(c) of Directive 2001/83/EC requires that all excipients need to be declared on the labelling, if the medicinal product is an injectable or a topical, or an eye preparation. Article 59 (1) (a) 2nd indent requires a full statement of the active substance and excipients in the package leaflet. Article 59 (1) (c) states that the package leaflet must include a list of information that is to be read before the medicinal product is used. Therefore, consumers of topical medicinal products should already be aware of all ingredients of the medicinal product like single fragrances, essential oils or natural extracts, regardless of their concentration. 1. Besonderheitenliste des Bundesinstituts für Arzneimittel und Medizinprodukte (BfArM) / Version 1-12, März 2016, auf Basis der Excipients-Guideline (CPMP/463/00 Final, Juli 2003), der Arzneimittel-Warnhinweisverordnung sowie umgesetzter nationaler Stufenplanmaßnahmen	The present approach clearly names 26 fragrance allergens
6	**Topical vs Oral formulations:** The Cosmetics regulation does not differentiate whether the fragrance listing applies to topical creams or in flavours for oral products such as	From a pharmaceutical point of view, toothpaste is considered an oral-mucosal and not an oral pharmaceutical form.

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	toothpaste etc. The EMA draft document refers to topically applied products only, therefore it is important to understand why the scope is limited. Although it is likely that there is little if any data on the allergic potential of these materials in an oral administration, there should be a clear rationale for not including oral based products such as flavours that may contain the currently listed ingredients or others to be added soon.	The excipients GL defines topical as follows: Topical medicinal products can be taken to include those medicinal products applied externally to the skin, respiratory products delivered to the lung by inhalation and any medicinal product delivered to the oral, nasal, rectal or vaginal mucosae, i.e. where the delivery may be local or transdermal. Hence, any medicinal product delivered to the oral mucosae, i.e. where the delivery may be local or transdermal, is included.
6	**General comment concerning data support:** Linking the medicines guidance to this specific element of cosmetic legislation is of concern. The designation of the initial 26 materials as allergens is considered to be based on controversial data, and the current proposals to extend the allergen list by some 80 to 90 additional materials is again considered to be based on less than satisfactory data. **API vs INCI:** Importantly, in the expanded list there are now materials that are also registered as APIs in medicines (eg menthol, camphor, peppermint oil (INCI name = mentha piperita) etc). On this basis how would labelling (INCI vs INN etc) then be handled and what is the potential for confusion? With the discussion still ongoing about the additional 'allergens' the Cosmetics Industry is discussing whether such long lists can be 'dematerialised' in terms of online availability of the exact list, if agreed how would the medicines guidelines handle this?	Not accepted. The concerns are noted. However, the current approach to align with the provisions with cosmetics (as a minimum) seems to be pragmatic. This does not prevent discussion on which other allergens should be listed. However, such a discussion for individual allergens may take a long time. Hence, the current approach seems to be reasonable. The concentration will be higher in case the use as an active ingredient is intended, and the active ingredient will be evaluated as such then. The labelling as an excipient does not apply in such a case. This will be decided at a later point of time.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	2	**Comments:** Regrettably, there are no line numbers in the text which one can relate to.	
Page 4 Table row 2 and 3	4	**Comments:** Benzyl benzoates (from the List of Fragrance Allergens) can be rapidly hydrolysed into benzoic acid and benzyl alcohol, both are already included in the current excipients guideline, including the recommendation for topical formulation containing benzoic acid. Potential inconsistent wording between fragrance allergens and benzoic acid and benzyl alcohol will be introduced by incorporating the revisions into the existing guideline. The wording for benzoic acid and benzoates in the guideline is to be adapted, as appropriate.	Not accepted. The hydrolysis of an ester, such as benzyl benzoate, requires the presence of water (absent in ointments), and the hydrolysis depends on the pH of the vehicle. The use of strongly alkaline or acid pH values which could increase a risk of hydrolysis can be regarded as an exception for topical drug products, if used at all. Additionally, the whole formulation may lower any risk of hydrolysis (e. g. by dissolution of benzyl benzoate in the lipophilic phase of an emulsion since benzyl benzoate is practically insoluble in water but miscible with lipophilic phases such as fatty oils). Therefore, no general assumption concerning a hydrolysis of benzyl benzoate can be made. Furthermore, sufficient stability of excipients should be generally investigated during pharmaceutical stability, and only sufficiently stable excipients should be chosen for the final formulation of a drug product.
Page 4 Table row 2 and 3	4	**Comments:** Addition of benzyl alcohol in topical formulation in the current Excipients Guidance, where its parenteral use is already addressed, is supportable	No further explanation necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Page 4 Line 2, Column E	5	**Comments:** The MAH would like clarification regarding the following comment: *"In addition to the occurrence of allergic reactions in already sensitised patients, non-sensitised patients may also develop sensitisation"* It is unclear whether this is intended as a general comment or as proposed SmPC wording.	The comment column is not foreseen for implementation in the SPC/PL.
p. 4/8 Column C	2	**Comments:** An absolute 'zero' does not exist, since substances can be only detected when above the limit of detection. The thresholds valid for cosmetics should be applied equally to medicinal products. Contrary to cosmetics, medicinal products are used for a limited period only. The risk of sensitization is thus much lower.	Zero threshold means below the detection limit. If the respective fragrance allergen can be detected in the medicinal product, it should be labelled. See explanations given above in the document. It can be assumed that topical medicinal products – unlike cosmetics - are in general applied to lesional skin with an impaired barrier function. Hence, there is a higher risk of allergic reactions.
Table p. 4/8, column C (Threshold)	6, 7	**Comments:** Clarification of the threshold value is needed (zero is not clear because with zero allergen, no labelling is required; the labelling is necessary if allergens are > zero). Furthermore, add a unit (ppm or %). **Proposed change:** > zero (ppm or %)	Zero threshold means below the detection limit. If the respective fragrance allergen can be detected in the medicinal product, it should be labelled.
p. 4/8	2	**Comments:** The origins of fragrances should be considered in the	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Column C		excipients guideline. Essential oils should be considered separately from single fragrances. For essential oil excipients added in medicinal products, the Committee's demand for labelling single fragrance allergen compounds substances is completely unrealistic. A natural essential oil consists of a complex mixture of over 100 different compounds. The methodology to detect and characterize all components of essential oils is not developed yet, let alone proven for routine analysis. **Proposed change:** As far as essential oils used as excipients in medicinal products are concerned, only the respective essential oil (and not every single potential allergen fragrance that could be contained in it) should be mentioned in the package leaflet.	See above in the document. The intention is to specifically inform if one or more of the 26 fragrance allergens is contained in the medicinal product, which is valid information for the patients who are sensitised to these fragrance allergens.
Table p. 4/8, column D	6, 7	**Comments:** From a qualitative and quantitative point of view, it is difficult to know all the constituents of an essential oil. The manufacturer can therefore not be sure to detect all allergens contained in the fragrance. So, for safety reasons, it would be better to make the patient information about allergic risks on essential oil itself, not considering the specific allergens. **Proposed change:** This medicine contains essential oil of X, which may cause	Not accepted. See above in the document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		allergic reactions.	
Table p. 4/8, column E	6, 7	**Proposed change:** Delete the sentence concerning fragrance allergens	Not accepted. It is important that in addition to mentioning the fragrance allergen, the patient should also be informed about the risk which is connected to the fragrance allergen, i.e., may cause allergic reactions.
p. 5/8 1. Use in medicinal products	2	**Comments:** The *Committee for Human Medicinal Products (CHMP)* wrongly assumes that fragrances are added to medicinal products only to improve their smell. In many natural remedies (e.g., anthroposophical or herbal medicinal products), however, herbal essential oils and herbal extracts are not used because of their pleasant scent, but because of their stabilizing effects. They replace synthetic substances that might have an even higher risk of sensitization. Since there is no adequate substitute, it is hardly practicable to dispense of them. **Proposed change:** Please clarify if the demand for labelling fragrances as allergens from a zero threshold is only valid for single allergen compounds intentionally added as fragrance substance.	The demand for labelling fragrances as allergens from a zero threshold is valid irrespective whether the single allergen is intentionally added as fragrance or whether it is contained in an essential oil.
p. 5/8 2. Safety concerns,	2	**Comments:** The paragraph is confusing, since it gives an incoherent account of wrong figures. Having checked the respective	Partly accepted. The wording has been slightly amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
line 2-4		references, we understand that 15 – 20 % of the German population has already been sensitized to some common allergen. About 7 % of the population experiences an acute contact dermatitis (ACD) within a year [1]. In 15 % of the patients routinely patch tested because of suspected ACD, positive reactions have been caused by fragrances of Fragrance Mix(FM) I or II and/or by *Peru balsam* (*Myroxylon pereirae* resin) [2]! Even if the number of allergies caused by Peru balsam is not subtracted, based on the 7 % of the populations that suffers from an ACD, only a total of about 1 % would suffer from ACD caused by fragrances. Since *Peru balsam* is a well-known allergen, the true number of contact dermatitis caused by fragrances is even considerably lower. Only about 10 % of the patients tested with FMI and FMII showed positive reaction to the allergens [2]. **Proposed change:** The false figures have to be corrected. In the European population, there is an estimated frequency of contact allergy to fragrances of on average 1 - 3 %. Furthermore, the total number of allergies to fragrances has remained stable during the last 10 years [3]. 1. Schnuch, A. et al., Bundesgesundheitsbl 2012; 55: p. 329–337. 2. 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.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		3. Scientific Committee on Consumer Safety (SCCS) OPINION on Fragrance allergens in cosmetic products. June 2012.	
3. Safety information […], p. 5/8 line 8 – p.p. 6/8 line 3	2	**Comments:** We object to incorporating provisions of cosmetics in guidelines for medicinal products like the excipient guideline without previous consultation with the pharmaceutical associations. **Proposed change:** Table 1 should not be automatically linked by a cross-reference to the cosmetic regulation. An extension of table 1 should be adopted only after a newly consultation period with the pharmaceutical associations.	Not accepted. See above in the document. In addition, there is no scientific sound reason why fragrance allergens need to be labelled in cosmetics (based on a scientific evaluation) but not in topical medicinal products, in particular if it is considered that topical medicinal products are in general applied to lesional skin.
p. 8/8, table 1	2	**Comments:** The origins of fragrances should be considered in the excipients guideline. The actual allergic potential of fragrances depends on whether they are pure synthetic substances or components of essential oils. **Proposed change:** Essential oils should be considered separately from single fragrances. To declare a specific essential oil as potential allergen in Table 1, appropriate scientific literature should be available.	Not accepted. Justification: See above in the document. From a scientific point of view it is the molecule itself which is critical for the allergenic potential irrespective of its origin (synthetic or natural). Not the essential oil but the single fragrance allergen should be labelled.