9 October 2017
EMA/CHMP/349510/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the draft 'Questions and answers on benzyl alcohol' (EMA/CHMP/508188/2013)

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

Stakeholder no.	Name of organisation or individual
1	AESGP - Association of the European Self-Medication Industry
2	EFPIA – European Federation of Pharmaceutical industries and Associations
3	ESNEE - European Study of Neonatal Exposure to Excipients
4	Medicines Evaluation Board, the Netherlands
5	NPPG - Neonatal and Paediatric Pharmacists Group
6	Professor DK Theo Raynor, University of Leeds
7	SciencePharma (Poland)
8	Teva Pharmaceuticals Ltd

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Currently information for the package leaflet regarding benzyl alcohol is only required if benzyl alcohol is used in medicinal products for parenteral administration and it only refers to reactions in infants and children up to 3 years old (see Excipients Guideline as of July 2003). The warnings originated from various reports - mostly from the early 1980s - about serious adverse events in premature neonates after intravascular administration of solutions containing large amounts of benzyl alcohol relative to the patients' size to flush intravascular catheters. In the current revision EMA proposes a reduction of the threshold value to zero and additional and revised information for the package leaflet, not just for medicinal products for parenteral administration but for all other routes of administration as well. While we appreciate the EMA's decision to adjust the previous recommendations for parenteral administration, the new additional provisions for other patient groups and other routes of administration (oral / topical) do not seem justified. The missing differentiation between cutaneous application and topical administration to other tissues leads to warnings required for all topical routes of administration, regardless of the type of tissue. *The intended warnings exceed even those for oral administration and even for parenteral application in number and extent.* It should be made clear that the application will be a prospective one. However to ensure a smooth implementation of any possible changes, an adequate transition period should apply.	Partially agreed. See amended final label Implementation requirements are prospective with a time for implementation of up to 3 year after publication of the revised Annex (see last section of the draft EC guideline: https://ec.europa.eu/health/human-use/legal-framework/developments/2017_pc_guidelines_excipient_en

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2	EFPIA companies welcome the opportunity to provide feedback on the draft 'Questions and Answers on Benzyl alcohol and benzoic acid in the context of the revision of the guideline on Excipients in the label and package leaflet of medicinal products for human use'	Noted.
2	The limitation of the duration of use of topical benzyl alcohol to not more than week does not correlate with the intention of the label revision as expressed in lines 67-69 (The current recommendations are incomplete and too strict…). The Q&A document does not justify why "adolescents and adults" are included in the new proposed label text as no new safety information is presented for this patient population which would justify a labelling change. Benzyl alcohol is widely used as a solvent and especially as preservative in Medicinal products but also in cosmetics and medical devices. There are a relevant number of dermatological products approved for chronic diseases in Europe, which contain benzyl alcohol. Most of them have been on the market for a long time and have proven to be safe even in children. No new scientific information is presented (references given are dated 1982 to 2005) which would justify a label change regarding maximum treatment duration for topical products. In need to be considered that systemic exposure to Benzyl alcohol even after topical use under maximum therapeutic conditions ("worst case scenario") would remain substantially below the level of main concern expressed in line 61 (i.e. 100-200 mg/kg/day has been linked to "gasping syndrome") and the current label text for parenteral products (>90 mg/kg/day is specified as level of contraindication for infants and children up to 3 years old). Maximum systemic exposure to Benzyl alcohol can be extrapolated to	Agreed. Warnings for the topical route have been simplified in the final label.

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	<30mg/kg/day even assuming a “worst case scenario” of 100% percutaneous absorption, topical application of 1g drug product per kg body weight (“whole body treatment”) in young children, and a Benzyl alcohol content of up to 3% (if used as preservative in cosmetics; Handbook of Pharmaceutical Excipients) in topical drug products. Under routine clinical therapeutic use conditions, systemic exposure to benzyl alcohol is substantially lower (e.g. dependent on the Benzyl alcohol concentration in the drug product and the size of the treatment area dependent on the medical indication). From a safety perspective there are no grounds that justify the limitation of treatment duration for topical products to one week. A binding limitation of treatment duration to one week would directly impact a substantial number of existing long term treatments and as such exclude a large group of patients from treatments which have proven benefit. Regulating this excipient in pharmaceuticals also induces major inconsistencies with cosmetics and food. Based on the above EFPIA requests reconsideration of the durational constraint and proposes to remove it from the guidance. It is advised not to include such binding warnings in the excipients guideline.	
4	The Medicines Evaluation Board in the Netherlands considers that it should be clear from the revised Guideline on the “Excipients in the label and package leaflet of medicinal products for human use” and its related Questions and Answers that the guideline/Q&As is only intended to provide information to stakeholders on excipients with a relevant safety concern in cases where the acceptability of the excipient in the proposed quantity/concentration has been adequately justified by the company in the MA-dossier i.e. has been found	This will be taken into consideration for the updated version of the main guideline.

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	acceptable by the regulatory authorities in view of an overall benefit to risk evaluation of the medicinal product and adequate pharmaceutical development. In order to clearly inform the readers of the guideline/Q&As on this important aspect, this statement should be included at the top of the guideline/Q&As. It is noted that this statement particularly applies to pediatric medicines.	
4	It is not clear whether the Q&A will be a stand-alone document or should be read in addition to the current Guideline. In case the Q&A is intended to be a stand-alone document, an explanatory note to clarify the structure of the Table in Section 6 should be included. If it is to be read in conjunction with the current Guideline, this should be clearly mentioned.	Accepted. Clarification has been added on EMA webpage. The Q&A is a background document which is published for optional consultation.
4	(Line 71) The table in section 5 is useful to compare the information in the current document with the proposed text. However in the final document the table in section 5 may cause confusion. There is a risk that the information in this table will be used instead of the proposed information, especially because the table refers to "*current* information in the package leaflet". Therefore, it is advised to delete the table in section 5 in the final document.	Agreed. Title of the table has been clarified
4	(Line 72-73) The purpose of the last column of the Table included in Section 6 "Comments (for health care professionals)" is not clear. It is not clear when information is to be included in the SmPC, or when the information is included for the benefit of applicants and competent authorities. Any information considered relevant for health care professionals should be included in the SmPC, and hence reference to	The mention in brackets "(for healthcare professionals)" was added by mistake. The comments column is intended for applicants and competent authorities as stated in the "explanatory notes" of the guideline. Regarding references to SmPC, the information in the column "comments" is only a suggestion which is added when relevant in order to ensure consistency of important

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	the SmPC should be included. It is suggested to replace the last column by two other columns; one for information to be included in the SmPC and a second column for additional comments for the benefit of applicants and competent authorities.	safety information between the package leaflet and the SmPC. Wording of the SmPC should follow the SmPC guideline and can be adapted to product specific considerations. This is not the the scope of this guideline.
4	(Line 72-73) In some cases proposed wording for the package leaflet is provided while corresponding information to be included in the SmPC is missing. As the information in the package leaflet is derived from the information in the SmPC all relevant information should also be mentioned in the SmPC.	Rejected. The scope of the guideline is the package leaflet only. Where relevant, additional suggestion for the SmPC are added (see above).
4	In the title of this document and in the title of the guideline is mentioned '...Excipients in the label and package leaflet...' However also advice regarding the information to be included in the SmPC is given. Therefore, we propose to change "in the label and package leaflet" into 'in the product information'.	Rejected. The scope of the guideline is the package leaflet only. Where relevant, additional suggestion for the SmPC are added. (see above).
5	Overall the proposal to provide guidance on the use of benzyl alcohol in medicines used in children is to be welcomed. We support the proposals listed.	Acknowledged.
6	I am pleased to respond to this consultation to update labelling, based on a review of the safety of excipients. **Focus of comments** The focus of my response is on the readability of the proposed labelling wording – it is essential that patients are able to understand these safety messages, and hence be able to act upon them. This is in the context of between a third and half	The provided information is appreciated. We believe that the amendments made to the wording address the concern of readability.

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	of people having difficulty understanding health information.[1] **Evidence base** The proposals for amending the wordings are based on good practice in information writing and design, as described in a systematic review of the evidence[2], and the EMA guideline on readability.[3] A key principle is to use wording which reflects the lay language health professionals would use when talking to patients. That is the language they understand. However, although based on good practice, the understanding of such information can only be assured through user testing with the target audience, lay people.[4] **Statement of Interest** Professor Raynor is co-founder and academic advisor to LUTO Research which provides patient information development and testing services to the pharmaceutical industry and other health information providers. **References** 1. Raynor DK. Health literacy –is it time to shift the focus from patient to prescriber? BMJ 2012; 344: 7 http://www.bmj.com/content/344/bmj.e2188 2. Raynor DK, Blenkinsopp A, Knapp P et al. Systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines. Health Technology Assessment 2007; 11 : 1-178 http://www.hta.ac.uk/execsumm/summ1105.htm	

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	3. European Medicines Agency. Guideline on the readability Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use. EMA 2009 http://ec.europa.eu/health/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf 4. Raynor DK. User testing in developing patient medication information in Europe. Research in Social and Administrative Pharmacy, 2013 http://www.rsap.org/article/S1551-7411(13)00044-2/abstract	
7	It is recommended to provide differentiated information for the PIL and/or SmPC depending on exposures to benzyl alcohol, based on maximal single and/or daily dose of the product (and taking into account the risk of accumulation of benzyl alcohol). It is considered that it would be more informative to both patients and healthcare professionals, enabling them to better estimate the actual risks connected with the use of a particular medicinal product. According to section 4 “What are the safety concerns?” the “gasping syndrome” has been observed when benzyl alcohol was administered intravenously in the range of 100 to 200 mg/kg/day. Therefore, for very low exposures to benzyl alcohol (even taking into account the risk of accumulation) there should be no need to fully restrict the use of relevant products in neonates. It is acknowledged that the discussed document concerns benzyl alcohol used as an excipient. However, the same toxicological effects due to benzyl alcohol should be observed irrespective of the source of this substance. Therefore, if warnings are expected for products containing even minute amounts of benzyl alcohol used as an excipient, the same should be consequently considered if this	Partially agreed. The warnings for the PL have been amended (less strict). However as there is insufficient data to recommend a low threshold, zero is maintained by precaution, i.e. the information should appear in the PL if benzyl alcohol is present (whatever its quantity) Impurities are not in the scope of the guideline but if they are a concern (e.g. because above quality specifications) their safety will be addressed during the assessment and if necessary the product information will be updated accordingly for that specific product. The quantity of the excipient is required in order to be able to assess the cumulative risk of benzyl alcohol if contained in multiple medications.

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	substance is likely as an impurity (e.g. of some drug substances). However, this would lead to unnecessary confusion of both patients and healthcare professionals. A low limit for exposure to benzyl alcohol exempting the need of discussed warnings would solve the problem. On the other hand, for products causing a significant exposure to benzyl alcohol, a special warning for risk of co-administration with products containing benzoic acid / benzoates would be recommended.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
35-36	4	**Comment:** Structural formulas for benzyl alcohol and benzoic acid are given. Structural formulas are not included in the draft Q&A for benzoic acid and benzoates. This is inconsistent. Furthermore, the formulas are not considered relevant for the purpose of this Q&A. **Proposed change:** Remove structural formulas from section 2.	Accepted.
51-53	2	**Comment:** The reasoning behind the following text is unclear "Indeed, a subchronic oral reference dose of 1 mg/kg/day for adult was derived based on the NOAEL of 200 mg/kg found in a 13 weeks rat study. A chronic oral reference dose of 0.3 mg/kg/day for adult was derived based on the LOAEL of 200 mg/kg found in a 2 years carcinogenicity study." Scientific Committee on Food (EFSA) concluded in their report (referred to in this Q&A as reference 1) that: "The Committee considers that the studies on carcinogenicity in rats and mice did **not** show compound-related adverse effects at dose levels up to 200 mg/kg bw in the mouse and up to 400 mg/kg in the rat, in both cases the highest dose levels tested."	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please reconsider the assessment and the selection of the NOAEL	
Page 5-6 (table)	2	**Comment:** Please clarify “zero”. In case it means 0.0, the product should be definitely free of benzyl alcohol and benzoic acid and in that case, there is no need of any information on the package leaflet since the excipients is not allowed in cutaneous dosage forms. **Proposed change:** Clarify the meaning of “zero”	Not accepted. The meaning of the zero threshold is explained in the explanatory notes of the Guideline. Zero is not a quantitative value but a “convention” to indicate that the information should always appear in the PL when the excipient is present whatever its quantity.
Table	4	**Comment:** Regarding parenteral and rectal route of administration: a text proposal to include “*The amount of benzyl alcohol”* in the package leaflet is given. The corresponding proposal to include this information in the SmPC is missing (last column) and should be included.	Rejected. SmPC information should be consistent in both the package leaflet and the SmPC, no matters whether it is specifies in the “comments” or not, but the SmPC is a matter for the SmPC guideline and is out of scope of this guideline.
Table	8	**Comment:** We would suggest the wording for children 3 years old or younger to consult a physician for the proper dosing of any products that contain Benzyl Alcohol. **Proposed change (if any):** This product contains Benzyl Alcohol. For use of this	Accepted. The text has been modified along these principles.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		product in children of 3 years old or younger, you need to consult a physician for the proper dosing of this product.	
Page 5, D-2	5	**Comment:** "The amount of benzyl alcohol per each <volume/unit> is xx mg." - The word 'per' is a word not usually used by lay people – 'in' is the appropriate lay word to use. **Proposed change:** The amount of benzyl alcohol in each <volume/unit> is xx mg.	Partly accepted. Sentence changed for "This medicine contains xx mg benzyl alcohol in each <volume/unit>."
Table	4	**Comment:** According to the information in the lines 33 and 34 benzyl alcohol is metabolised into benzoic acid. What is the reason why the warnings mentioned in the Q&A of benzoic acid and benzoates are not included in the Q&A of benzyl alcohol?	Reported adverse effects of benzyl alcohol and benzoic acid are not identical.
Line 72; Column 5; rows 3 and 7	7	(comments to parenteral/rectal and topical administration) **Comment:** Amount of <benzyl alcohol> per <volume unit> should also be stated in the SmPC. **Proposed change:** The amount of benzyl alcohol per each <volume/unit> is xx mg.	Partly accepted. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Table	4	**Comment:** For topical administration patient populations (children, adolescents and adults) are mentioned in the text for the package leaflet. However, these populations are not mentioned in the proposed text for the package leaflet for medicines to be administered via other routes. What is the reason to mention only for topical administration these patient populations?	Agreed. Information has been modified
Page 5, D-5 and page 6, D-5	2	**Comment:** In the following sentence: “Should not be used in pre-term or full-term neonates unless strictly necessary because of the risk of severe toxicity including abnormal respiration (“gasping syndrome”).” The terms “neonates” and “abnormal respiration” are not patient friendly. **Proposed change:** “Should not be used in pre-term or full-term **newborn babies** unless strictly necessary because of the risk of severe toxicity including abnormal **breathing** (“gasping syndrome”).”	Partly accepted. See final wording.
Table	4	**Comment:** Neonates are mentioned in the text proposal for parenteral, rectal and topical route of administration. It is unclear why neonates are not mentioned in the text proposal for oral administration as oral	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		administration is possible for neonates.	
Table	4	**Comment:** Regarding the advice for pre-term or full term neonates in case of parenteral and rectal administration the word 'must' in the current excipient guideline has been changed into 'should'. If there is no specific reason for this change, we prefer the word 'must'.	Partly accepted See above.
Page 5, D-6	5	**Comment:** Should not be used in pre-term or full-term neonates unless strictly necessary because of the risk of severe toxicity including abnormal respiration ("gasping syndrome"). - The passive wording 'Should not be used' will be better understood by the active 'Do not use'. - The words 'pre-term' and 'full-term' are not words used by professionals when talking to patients. They would use the words 'new-born' and either 'babies born early' or 'premature'. In the latter case, it is appropriate to put the lay wording first, with the more technical term in brackets. - To maximise readability, there should be one main idea or message in each sentence. Hence this wording has been split into two sentences. - The words 'toxicity' and 'abnormal respiration' are	Principles accepted (see above).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		difficult words for lay people and have been replaced. **Proposed change:** Do not use in new born babies, and babies born early (premature babies), unless strictly necessary. This is because of the risk of severe side effects including breathing problems (called “gasping syndrome”).	
Line 72; Column 4; rows 5 and 9	7	(information on the “gasping syndrome”) **Comment:** Harmonisation of the information on the “gasping syndrome” for parenteral / rectal and topical routes of administration is recommended.	Acknowledged. However this information has been removed from the topical route.
Line 72; Column 5; row 9	7	(comments to “gasping syndrome” for topical administration) **Comment:** Information that cutaneous absorption of benzyl alcohol is significant is recommended to be included here to explain the risk of “gasping syndrome” when using topical products (currently the information provided here relates to intravenous administration only).	Acknowledged. However this information has been removed from the topical route.
Page 5, D-6	3	**Comment:** I don’t like the phrase ‘unless strictly necessary’ for Benzyl alcohol as it is too subjective. If it is necessary to use a product with Benzyl alcohol for a neonate then it should giver clearer guidance as to monitoring the	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		infant during and after administration.	
Page 6, D-2	2	**Comment:** In the following sentence: “Talk to your doctor or pharmacist if you have liver or kidney problems or if you are pregnant or breast-feeding as high volumes may lead to toxicity (metabolic perturbation)” The term “metabolic perturbation” is not patient friendly. **Proposed change:** “Talk to your doctor or pharmacist if you have liver or kidney problems or if you are pregnant or breast-feeding as high volumes may lead to toxicity”	Partly accepted
Page 6, D-2	2	**Comment:** Talk to your doctor or pharmacist if you have liver or kidney problems or if you are pregnant or breast-feeding as high volumes may lead to toxicity (metabolic perturbation) - This long sentence has been split into two with one main message per sentence. - Again ‘toxicity’ has been replaced with ‘side effects’. **Proposed change:** Talk to your doctor or pharmacist if you have liver or kidney problems or if you are pregnant or breast-feeding. This is because large amounts may cause side	Partly accepted

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		effects (called “metabolic perturbation”)	
Page 6 (table)	1	Topical administration – Information for the package leaflet, 1st line: *“The amount of benzyl alcohol per each <volume/unit> is xx mg.”* **Comments:** Whereas the declaration is already required for medicinal products for parenteral administration (probably with regard to the dose-dependent side effects in neonates after intravascular administration), the EMA now recommends - without further explanation - that the amount per volume should be given in the package leaflet regardless of the route of administration. Since there are no indications that side effects similar to those in neonates after intravascular administration may occur if benzyl alcohol is used in medicinal products for cutaneous application in usual concentrations we do not consider it necessary to declare its amount in the package leaflet of such medicinal products. **Proposed change:** The declaration of the amount of benzyl alcohol per volume should be deleted.	Not accepted The declaration of the amount of benzyl alcohol per volume should not be deleted as it is an important piece of information for the physician.
Page 6 (table)	1	Topical administration – Information for the package leaflet, 2nd line: *“May cause allergic reactions.”*	Not accepted. Allergic reactions have been reported in association with benzyl alcohol. Therefore this information can be useful for

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Comments: Currently the warning on allergic reactions to benzyl alcohol in medicinal products only refers to the parenteral administration in infants and children up to 3 years old. There are no similar provisions for older patients or for other routes of administration. The proposal now recommends a warning about allergic reactions for all routes of administration, regardless of the patients' age and the amount of benzyl alcohol. However, no data or information to justify this proposal was presented to substantiate the requirement. There are no (new) reports on a significant number of allergic reactions. On the contrary, reports on human patch testing indicate that the incidence of allergic reactions is low. For example the OECD and the Cosmetics Ingredient Review (CIR) Expert Panel both concluded in their 2001 assessments: *"Benzyl alcohol gave positive and negative results in animals. Benzyl alcohol also demonstrated a* ***maximum incidence of sensitization of only 1 % in human patch testing****. Over several decades no sensitization with these compounds has been seen among workers."* [OECD SIDS Initial Assessment Report for 13th SIAM (Bern, 7th - 9th November 2001) Chemical Name:	the already sensitised patient.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Benzoates: Benzoic acid, Sodium benzoate, Potassium benzoate, Benzyl alcohol CAS No: 65-85-0, 532-32-1, 582-25-2, 100-51-6] *"It [benzyl alcohol] was not a sensitizer when tested in a maximization test at 10 % in petrolatum, and demonstrated a low incidence of sensitization in provocation studies."* [Cosmetic Ingredients Review Expert Panel, Final report on the safety assessment of benzyl alcohol, benzoic acid and sodium benzoate. International Journal of Toxicology, 20 (Suppl. 3):23-50. 2001] CIR even confirmed its assessment in 2011: *"In its previous safety assessment of benzyl alcohol, benzoic acid, and sodium benzoate, the Panel established a 5 % safe concentration limit for benzyl alcohol, benzoic acid, and sodium benzoate and a 10 % safe concentration limit for benzyl alcohol in hair dyes. On review of the current practices of use and concentration, it was clear that industry has adhered to those limits. Accordingly, reference to present practices of use and concentration is sufficient to assure safety."* [Cosmetic Ingredients Review Expert Panel, Amended final safety assessment of benzyl alcohol, benzoic acid and its salts and benzyl esters benzoate. http://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR574.pdf]	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: The proposed warning should be deleted unless substantiated.	
Page 6 (table)	1	Topical administration – Information for the package leaflet, 3rd line: *"Should not be used in neonates (premature and full-term) unless strictly necessary as benzyl alcohol has been associated with serious adverse events in neonates ("gasping syndrome")."* **Comments:** The draft paper proposes this warning for parenteral, rectal and topical administration, but not for oral administration. This is quite surprising since the reports on serious adverse events to which it refers are strictly limited to intravascular administration of solutions containing benzyl alcohol in very low weight neonates with an immature metabolism. None of the reports dealt with other routes of administration, i.e. oral or topical. Gershanik et al. (Reference No. 5) concluded that the accumulation of benzyl alcohol in premature neonates after intravascular administration that led to intoxication and gasping syndrome was either the result of the administration of high doses relative to the patients' size and / or of the reduced capacity of the immature organism to metabolise and eliminate benzyl alcohol and its metabolites. Brown et al. (reference no. 6) reported several fatal	Accepted.

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		cases of intoxication related to the intravascular administration of large amount of benzyl alcohol in premature infants. Post mortem examinations showed high quantities of accumulated benzyl alcohol and its metabolite that exceeded the capacity of the infants' metabolic capacity. The authors recommended the discontinuation of the use of benzyl alcohol in parenteral medicinal products for small premature infants. In its 2002 evaluation (mentioned by the EMA in section 4), the SCF reassessed the safety of benzyl alcohol as a carrier solvent for flavouring agents based on animal and human toxicity data. Hiller et al. (1986), Benda et al. (1986) and Jardine and Rogers (1989) compared human toxicity data from very low birth weight (premature) neonates before and after the discontinuation of the use of benzyl alcohol in intravasal flush solutions indicating an improvement in the number of severe adverse effects. The report by Gershanik et al. was also used by the EMA (reference no. 5: see above). Based on these reports the SCF concluded for benzyl alcohol as a carrier solvent for flavouring substances: *"Since the benzyl alcohol was administered acutely and intravenously in high doses, the effects observed in premature infants are considered irrelevant to the use of benzyl alcohol as a carrier solvent for flavouring*	

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		substances at the intended use level." Unfortunately this conclusion did not make its way into the EMA's assessment, although even EMA refers to the report by Gershanik et al. Additionally the result of the SCF's evaluation in 2002 was the same as in 1981. Based on animal data after oral administration the SCF confirmed its previous evaluation (1981) and the inclusion of benzyl alcohol in the group ADI of 0-5 mg / kg bodyweight for benzoic acid, the benzoate salts (calcium, potassium and sodium), benzaldehyde, benzyl acetate, benzyl alcohol and benzyl benzoate. *"The metabolism by man is well established. Although no specific toxicological studies are available it is acceptable to include benzyl alcohol in the group ADI of 5 mg/kg bw established for benzoic acid (representing total benzoates) by JECFA (1973). The Committee considers the use of this extraction solvent acceptable." (SCF 1981)* Unlike stated by the EMA, benzyl alcohol was not "added" to the group ADI in 2002, the 1981 allocation of the ADI was merely confirmed. **Proposed change:** The warning should be deleted for topically administrated medicinal products unless substantiated.	
Page 6, D-5	5	**Comment:**	Accepted. See final Q&A.

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		Should not be used in neonates (pre-term and full-term) unless strictly necessary as benzyl alcohol has been associated with serious adverse events in neonates ("gasping syndrome"). - The passive wording 'Should not be used' will be better understood by the active 'Do not use'. - The words 'pre-term' and 'full-term' are not words used by professionals when talking to patients. They would use the words 'new-born' and either 'babies born early' or 'premature'. In the latter case, it is appropriate to put the lay wording first, with the more technical term in brackets. - To maximise readability, there should be one main idea or message in each sentence. Hence this wording has been split into two sentences. **Proposed change:** Do not use in new born babies, and babies born early (premature babies), unless strictly necessary. This is because of the risk of severe side effects including breathing problems (called "gasping syndrome").	
Page 6 (table)	1	Topical administration – Information for the package leaflet, 4th line: *"Use with caution and preferably not more than a week in children (more than 4 weeks old), adolescents and adults."* **Comment:** This warning that refers to all patient groups	Accepted.

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		regardless of their age and the amount of benzyl alcohol restricts the use of medicinal products for topical administrations without substantiation. There are no reports that indicate serious adverse events in patients after cutaneous or otherwise topical administration of medicinal products containing benzyl alcohol. There are even no reports indicating serious adverse events after intravascular administration in patients other than in neonates with an immature metabolism. In fact, this warning even exceed the warnings for parenteral and rectal administration which only refer to neonates, pregnancy, breast-feeding and patients with liver or kidney problems, but do not restrict the duration of the administration in general. Therefore this restriction is absolutely unacceptable, especially in the light of the data presented below that indicate an absorption rate after cutaneous application clearly below 100 %. The EMA should therefore delete it completely. Furthermore, no new scientific information is presented (references given are dated 1982 to 2005) which would justify a label change regarding maximum treatment duration for topical products. Furthermore, systemic exposure to Benzyl alcohol even after topical use under maximum therapeutic conditions (“worst case scenario”) would maintain substantially below the level of main concern expressed in line 61 (i.e. 100-	

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		200 mg/kg/day has been linked to “gasping syndrome”) and the current label text for parenteral products (>90 mg/kg/day is specified as level of contraindication for infants and children up to 3 years old). Maximum systemic exposure to Benzyl alcohol can be extrapolated to <30mg/kg/day even assuming a “worst case scenario” of 100% percutaneous absorption, topical application of 1g drug product per kg body weight (“whole body treatment”) in young children, and a Benzyl alcohol content of up to 3% (if used as preservative in cosmetics; Handbook of Pharmaceutical Excipients) in topical drug products. Under routine clinical therapeutic use conditions, systemic exposure to benzyl alcohol is substantially lower (e.g. dependent on the Benzyl alcohol concentration in the drug product and the size of the treatment area dependent on the medical indication). **Proposed change:** The proposed warning should be removed.	
Page 6, D-6	2	The following sentence: “Use with caution and preferably not more than a week in children (more than 4 weeks old), adolescents and adults” is not acceptable for EFPIA. See general comment. **Comment 1:** The application of this caution to all age groups is not	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		in line with literature. Based on the arguments of the immature metabolic system and the risk for gasping syndrome a cautionary statement for children from 1-24 months old can be understood. However, based on the results of the juvenile and repeated dose toxicity study results there is no reason to restrict the use of benzyl alcohol as an excipient in topical agent to one week. In addition, children, adolescents and adults are exposed daily to benzyl alcohol, as it is a natural constituent of a number of plants. It occurs, for example, in some edible fruits (up to 5 mg/kg). The toxicity of benzyl alcohol has been studied extensively, including acute, short-term and long-term toxicity, carcinogenicity, genotoxicity and developmental toxicity. In juvenile rats with a mature metabolic system (PND22, equivalent to a 2-year old child) it was shown that benzyl alcohol dosed up to 6 weeks (until PND64) has a similar NOAEL as adult animals treated for 13 weeks. Acceptable daily intakes were established by the World Health Organization at 5 mg/kg for Benzyl Alcohol. Therefore it would be more than logically to use the same recommendations as the WHO and EFSA for topical and oral pharmaceutical agents. As benzyl alcohol can produce nonimmunologic contact urticaria and nonimmunologic immediate contact reactions, characterized by the appearance of wheals, erythema, and pruritis, likely involving a cholinergic mechanism, it was concluded that these ingredients could be used	

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		safely at concentrations up to 5%, but that manufacturers should consider the nonimmunologic phenomena when using these ingredients in cosmetic formulations designed for infants and children. **Comment 2:** Additionally if the warning is maintained clearer instructions are needed for the caregiver. The term "preferably" is ambiguous as it does not provide clear guidance. **Proposed change:** Replace text by "*Do not use in babies under 4 weeks of age*, *Use with caution in children up to 2 years old"*	
Page 6, D-6	5	**Comment:** Use with caution and preferably not more than a week in children (more than 4 weeks old), adolescents and adults - This long sentence has been split into two sentences with one message in each. - 'Preferably' is not a helpful word for patients – it is not something they can take action on. **Proposed change:** Use with care in children (more than 4 weeks old), older children and adults. Talk to a doctor or pharmacist before using for more than a week.	Partly accepted. See final Q&A.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Page 6 (table)	1	Topical administration – Information for the package leaflet, 5th line: *"Mildly irritant to the skin, eyes and mucous membranes."* **Comment:** Currently the excipients guideline does not address irritation of the skin, the eyes and mucous membranes by benzyl alcohol at all. The draft paper now proposes a warning that all topically administered medicinal products containing benzyl alcohol are mildly irritant to the skin, the eyes and mucous membranes. In the above mentioned 2001 Final report on the safety assessment of benzyl alcohol, benzoic acid and sodium benzoate the CIR expert panel evaluated study data from the 1970s and 1990s, concluding that: *"Benzoic acid and benzyl alcohol are slightly irritating to the skin, ...* *Benzoic acid and benzyl alcohol are irritating to the eye..."* Although these data were already available no warning on irritating effects was considered necessary when the provision for the current version of the excipients guideline (as of 2003) were established nor was it added to the BfArM Besonderheitenliste which has been frequently updated. Please note that the concentrations used in the studies were rather high, around 10 %. The concentration of	Partly accepted. Wording has been simplified.

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		benzyl alcohol used as preservative in medicinal products for cutaneous administration is usually much lower (1-2 %). **Proposed change:** Add missing reference to (more recent) data to evaluate the actual irritating potential in concentrations common for medicinal products.	
Page 6, D-7	5	**Comment:** Mildly irritant to the skin, eyes and mucous membranes. - The term 'mucous membranes' is not likely to be understood by at least 90% of lay people. **Proposed change:** May cause mild irritation to the skin and eyes. It may also irritate inside places like the mouth, nose, genitals and back passage.	Acknowledged. However the information for the topical route has been simplified.
Line 72; Column 5; row 11	7	(comments to risk of irritation for topical administration) **Comment:** Information on significant cutaneous absorption of benzyl alcohol seems not to be relevant here.	Accepted.
Page 6 (table)	1	Topical administration – Comments (for health care professionals), 5th line: "Cutaneous absorption of benzyl alcohol is significant."	Accepted.

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		Comment: This statement is not justified and lacks scientific evidence. According to the evaluation in section 4 "What are the safety concerns?" animal toxicity data relating to the absorption rate after parenteral and topical administration are missing. For lack of specific data, the EMA simply assumes that benzyl alcohol is as just readily absorbed after parenteral and topical administration as it is absorbed after oral exposure. Yet, in 2011, CIR evaluated data from percutaneous absorption studies of benzyl alcohol and benzyl benzoates determining absorption values of 31.6 ± 4.2 % [unoccluded]; 56.3 ± 14.5 % [with plastic wrap]; 79.9 ± 7.4 % [under a glass chamber] for benzyl alcohol in rhesus monkeys. They also assessed a study that indicated a dose dependent increase of the percutaneous absorption of benzyl alcohol. [Cosmetic Ingredients Review Expert Panel, Amended final safety assessment of benzyl alcohol, benzoic acid and its salts and benzyl esters benzoate. http://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR574.pdf]: "The percutaneous absorption of [7-14C]benzyl alcohol and [7-14C]benzyl benzoate in vivo was evaluated using 4 female Rhesus monkeys (10 to 19 years old). Each chemical was applied (4 µg/cm^2, without or with occlusion [glass chamber - G or plastic wrap - P]) to a clipped 1 cm^2 area of abdominal skin; the vehicle was	

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		acetone (10 to 20 µl / cm^2). The animals remained in metabolism chairs/metabolism cages for 5 days. The amount of absorbed compound in the urine was determined by liquid scintillation counting. Mean values (± SEM, 4 animals) for urinary excretion of the administered dose were: 77.4 ± 4.3 % (benzyl alcohol) and 65.3 ± 13.4 % (benzyl benzoate). **Percutaneous absorption values (absorption, as % of applied dose) were as follows: benzyl alcohol (31.6 ± 4.2 % [unoccluded]; 56.3 ± 14.5 % [P]; 79.9 ± 7.4 % [G])** ... Over a 5-day period, the urinary excretion of radioactivity was 65.3 ± 13.4 % following dermal application of benzyl benzoate and 56.5 ± 7.7 % following dermal application of benzyl alcohol. When the acetone vehicle was replaced with a lotion (10 mg / cm^2), percutaneous absorption was increased. The increase was significant for benzyl benzoate ($P < 0.05$), but not for benzyl alcohol. There was no apparent correlation between the skin penetration of benzyl alcohol and benzyl benzoate and their octanol-water partition coefficients of 7.4 and 3.97, respectively.53" "The penetration of benzyl alcohol through split-thickness cadaver skin was evaluated using nonoccluded Franz diffusion cells. Benzyl alcohol (spiked with 14C radiolabel) in ethanol was applied to the skin at doses ranging from 0.9 to 10,600 µg/cm^2. After 24 h, the percentage of radioactivity that	

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		penetrated the skin increased gradually with dose, ranging from 19.8 ± 2.9 % (lowest dose) to 29.2 ± 3.0 % (highest dose). Also, less than 4 % of the administered radioactivity was retained in the tissues at 24 h, and evaporation accounted for the remaining percentage. Data from this study were also analyzed in relation to a finite dose diffusion/evaporation model. The results of this analysis indicated that the increase in benzyl alcohol absorption with dose was consistent with a 3-fold increase in diffusivity in the stratum corneum, as the concentration of benzyl alcohol increased from tracer levels to saturation.[55]" As expected, due to the skin's natural barrier function, the amount of benzyl alcohol absorbed through the (intact) skin is much lower than assumed by the EMA ("close to 100 %"). It is therefore unnecessary and disproportionate to assume a 100 % absorption rate for benzyl alcohol in medicinal products for cutaneous application, especially if the medicinal product contains low concentrations of benzyl alcohol and is not applied under occlusion. The statement "Cutaneous absorption of benzyl alcohol is significant." should therefore be deleted. Warnings for cutaneous application should not exceed the warnings for oral administration. If considered necessary, the EMA could distinguish between cutaneous application and topical	

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		administration to other tissues such as mucous membranes or eyes with respect to varying and higher absorption rates. **Proposed change:** The remark should be deleted unless substantiated.	