9 October 2017
EMA/CHMP/349506/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the draft 'Questions and answers on benzoic acid and benzoates' (EMA/CHMP/508189/2013)

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

Stakeholder no.	Name of organisation or individual
1	EFPIA – European Federation of Pharmaceutical industries and Associations
2	Medicines Evaluation Board, the Netherlands
3	NPPG - Neonatal and Paediatric Pharmacists Group
4	Professor DK Theo Raynor, University of Leeds
5	SciencePharma (Poland)
6	URSAPHARM Arzneimittel GmbH

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	EFPIA companies welcome the opportunity to provide feedback on the draft 'Questions and Answers on Benzoic acid and Benzoates in the context of the revision of the guideline on Excipients in the label and package leaflet of medicinal products for human use'	Acknowledged
1	In the Background information of the Q&A it is mentioned that the EC guideline "Excipients in the label and package leaflet of medicinal products for human use" (CPMP/463/00) will be revised. We would like to have better clarity on what the revision of the guideline will include as well as when exactly this is planned for. It is difficult to look at the different Q&A documents in isolation from the main guideline (specifically if certain main definitions could change in the future). Also from a company's perspective it will be very useful to have more visibility on how and when Q&A documents will be released. This will help to ensure the involvement of the right experts at the right time (for example Q&As for certain type of excipients are released together).	Accepted. This information can now be found on the EMA webpage on excipients in the product information.
1	In the current version of the Questions and Answers document parabens are excluded. We understand that this may be due to the fact that there is already a "Reflection paper on the use of methyl- and propylparaben as excipients in human medicinal products for oral use", however, we suggest that this is specified in the Q&A and link is provided to the Reflection paper.	Not accepted. The reflection paper on parabens is a standalone document.
1	We agree with the need to cover the paediatric population, which can be affected differently than adults. The guideline should however clarify that these statements are relevant only to products indicated	Not accepted. According to directive 2001/83/EC (amended by directive

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	in the concerned subpopulation(s) in order to avoid confusion for patients, parents, and prescribers, which could result in off-label use. **Proposed change (if any):** • Please add the following sentence "Information pertaining to a certain sub-population e.g. paediatric population should be added only to the product information of medicinal products indicated in the concerned sub-population(s). For clarity, please add a column in the table indicating the subpopulation(s) to which the safety information is applicable.	2010/84/EU) adverse reactions include also medication errors and uses outside the terms of the marketing authorisation. Information on subpopulations is included directly in the text for the PL, instead of an additional column to limit the complexity of the table.
1	**Implementation** Sufficient time should be allowed for implementation of the changes in the labelling of the impacted products. A two years implementation deadline is usually allowed for implementation of revised QRD templates. The two-year period for implementation should be initiated once the final European Commission guideline "**Excipients in the label and package leaflet of medicinal products for human use"** is adopted. In addition, it should be possible to combine the changes with other upcoming variations impacting the product information within the two years implementation period.	Flexibility for implementation of the new labels will be accepted as long as they are done in a timely manner within an appropriate regulatory framework.
2	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	Accepted. A sentence will be added in the Annex explanatory notes of the 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 paediatric medicines.	
2	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.	See above.
2	**(Line 81-82)** 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.	Partially accepted. The heading of the table has been changed.
2	**(Line 83-84)** The purpose of the last column of the Table included in Section 6 "Comments (for health care professionals)" is not clear. In some occasions it is mentioned that the information should be stated in the SmPC. However, it is not always mentioned to include the information given in the SmPC. In case reference to SmPC is missing, it is assumed the information given is a general clarification not to be included in the SmPC. However, the heading of the column states	Partially accepted. Mention of HCP has been removed from the column heading. Consistency of information between SmPC and PL is legally required and already reminded in the guideline. SmPC wording and section recommendations are specific to product assessment and therefore out of the scope of this

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	"comment (for HCPs)". In our opinion the information given in this column is in several cases relevant for health care professionals, and hence reference to include this information in the SmPC should be included. Furthermore, inclusion of information which is considered relevant for health care providers in the SmPC seems logical. One cannot expect health care professionals to read a Q&A document for additional clarification. 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.	guideline.
2	**(Line 83-84)** 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.	See above.
2	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'.	See above.
3	Overall the proposal to provide guidance on the use of benzoic acid and benzoates in medicines used in children is to be welcomed. We agree with the proposals suggested.	Acknowledged.
4	I am pleased to respond to this consultation to update labelling,	Principles accepted. See final Q&A.

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	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 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	

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	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 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	
5	In respect to the risk of jaundice, it is recommended to provide differentiated information for the PL and/or SmPC depending on the content of benzoic acid/ benzoates (exposures to benzoic acid/benzoates based on maximal single and/or daily dose of the product). It is considered that it would be more informative to both patients and healthcare professionals enabling them to better estimate the actual risk connected with the use of a particular medicinal product. A similar approach is applied in Questions and Answers on Ethanol. A proposal for parenteral or oral products connected with low exposures of patients to benzoic acid/benzoates: *This medicine contains very small amount of benzoic acid/benzoates. When taking the daily dose, this (ese) ingredient(s) is (are) not likely to exert any*	Partially accepted. Quantitative information will be mentioned in both SmPC and PL. Negative statements should be avoided to limit information to the essential.

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	undesirable effect. In respect to topical products, it should be noted that although the risk of jaundice may be very low, the product may still be irritant to the skin, eyes and mucous membranes. It is also recommended to clearly indicate that the information on risk of jaundice is not required when the particular product is not intended for use by neonates and/or when it is clear that the product is not likely to be administered to this risk group. On the other hand, for products causing a significant exposure to benzoic acid/benzoates, a special warning for risk of co-administration with products containing benzyl alcohol would be recommended.	
6	Please indicate: Will it be necessary to update the package leaflet information for a medicinal product that is not intended for use in pre-term and full-term neonates?	See above

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
45-47	2	**Comment:** This Q&A only concerns benzoic acid and benzoates as excipient. Therefore it is not necessary to mention the indication for sodium benzoate as active ingredient.	Accepted.
Lines 81 (page 4/7) 83 (page 5/7)	1	**Comment:** Does "Threshold = zero" mean 0.0 or ≤ 0.9? In case it means 0.0, the product should be definitely free of benzoic acid and benzoate 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. See the explanatory notes of the Guideline Annex explaining the meaning of the zero threshold.
Line 83	1	**Comment:** See general comments. **Proposed change:** For clarity, please add a column in the table indicating the subpopulation(s) to which the safety information is applicable.	Not accepted. See general comments.
83	2	**Comment:** A warning for the development of kernicterus is given. Taking into account the seriousness of kernicterus, it should be taken into consideration to mention in the	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		SmPC a stronger warning.	
Page 5, D-2 and D-4	4	**Comment:** The amount of <benzoic acid /benzoate salt> 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 <benzoic acid /benzoate salt> in each <volume/unit> is xx mg.	Accepted.
83 (row 2, row 4)	1	**Comment:** In the following sentence: "May increase jaundice (yellowing of the skin and eyes) in pre-term and full-term jaundiced neonates" The term "neonates" is not patient friendly. **Proposed change:** May increase jaundice (yellowing of the skin and eyes) in pre-term and full-term jaundiced newborn babies	Accepted.
Page 5, D-3	4	**Comment:** May increase jaundice (yellowing of the skin and eyes) in pre-term and full-term jaundiced neonates - The word 'pre-term' and 'full-term' are not words used by professionals when talking to patients. They would use the words 'new-born' and either	Partially accepted. The term newborn (up to 4 weeks) which is the most understandable across EU languages will be used consistently.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		'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. **Proposed change:** In new born babies and babies born early (premature babies).	
Line 83	1	(second row for parenteral, oral routes: "May increase jaundice ....." and "Increase in bilirubinaemia ..... in the brain tissue"). **Comment:** It is not clear whether the risk of jaundice in pre-term and full-term jaundiced neonates comes from the uptake of Benzoic acid and benzoates via oral or parenteral routes by the mother (pregnant or breastfeeding) or by the neonate. **Proposed change:** Please clarify to which sub-population(s) this warning is directed i.e. pregnant/breast-feeding women and/or neonates.	Accepted.
Line 83, column 5, row 3	5	(comments to topical route of administration) **Comment:** The amount of benzoic acid and/or benzoate salts per volume/unit should also be stated in the SmPC.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: The amount of <benzoic acid/benzoate salt> per each <volume/unit/dose> is xx mg.	
Page 5, D-5	4	**Comment:** May increase jaundice (yellowing of the skin and eyes) in pre-term and full-term jaundiced neonates because of its absorption through the skin. - To maximise readability, there should be one main idea or message in each sentence. Hence this wording has been split into two sentences. - In addition, the grammar has been simplified in the second part, and the word 'absorption' replace by the easier and more familiar word 'absorbed'. **Proposed change:** May increase jaundice (yellowing of the skin and eyes) in new born babies and babies born early (premature babies). This is because it is absorbed through the skin.	Partly accepted. See final Q&A.
Page 5, D-6	4	**Comment:** "May be irritant to the skin, eyes and mucous membranes." - The passive 'may be irritant' is less direct and understandable than the more direct 'May irritate'. - The term 'mucous membranes' is not likely to be	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		understood by at least 90% of lay people. **Proposed change:** May irritate the skin and eyes. It may also irritate inside places like the mouth, nose, genitals and back passage.	
83-84	2	**Comment:** Regarding Topical route of administration: a text proposal to include "*The amount of <benzoic acid /benzoate salt>"* in the package leaflet is given. The corresponding proposal to include this information in the SmPC is missing (last column) and should be included.	Partially accepted. As the threshold is zero, the quantitative information will be systematically included in the SmPC in accordance with the SmPC guideline.