5 June 2014

Submission of comments on '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’ (EMA/CHMP/508189/2013)

Comments from:

| Name of organisation or individual |
| --- |
| EFPIA - Pär Tellner (par.tellner@efpia.eu) |

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)*(To be completed by the Agency)* |
| --- | --- | --- |
|  | 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’ |  |
|  | 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). |  |
|  | 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. |  |
|  | 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 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.
 |  |
| **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. |  |

1. Specific comments on text

| Line number(s) of the relevant text*(e.g. Lines 20-23)* | Stakeholder number*(To be completed by the Agency)* | Comment and rationale; proposed changes*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome*(To be completed by the Agency)* |
| --- | --- | --- | --- |
| Lines 81 (page 4/7) 83 (page 5/7) |  | 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 in cutaneous dosage forms.Proposed change: Clarify the meaning of “zero”  |  |
| Line 83  |  | Comment: See general comments. Proposed change (if any): For clarity, please add a column in the table indicating the subpopulation(s) to which the safety information is applicable. |  |
| 83 (row 2, row 4) |  | 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 (if any): “May increase jaundice (yellowing of the skin and eyes) in pre-term and full-term jaundiced **~~neonates~~** **newborn babies**.” |  |
| Line 83 (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 (if any): Please clarify to which sub-population(s) this warning is directed i.e. pregnant/breast-feeding women and/or neonates.  |  |

Please add more rows if needed.