5 June 2014

Submission of comments on 'Questions and Answers on Benzyl alcohol 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/508188/2013)

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 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’ |  |
|   | 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 <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 excipients 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.  |  |

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)* |
| --- | --- | --- | --- |
| 51-53 |  | 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.”Proposed wording : please reconsider the assessment and the selection of the NOAEL  |  |
| Line 72 (pages 5/8 and 6/8) |  | 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 in cutaneous dosage forms.Proposed change: Clarify the meaning of “zero” |  |
| 72 (row 5, row 9) |  | 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 (if any): “Should not be used in pre-term or full-term **~~neonates~~** **newborn babies** unless strictly necessary because of the risk of severe toxicity including abnormal **~~respiration~~** **breathing** (“gasping syndrome”).” |  |
| 72 (row 6) |  | 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 (if any): “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)~~.**” |  |
| 72 (row 10) |  | 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 above. Comment 1: The application of this caution to all age groups is not 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 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 wording: replace text by. *Do not use in babies under 4 weeks of age*, *Use with caution in children up to 2 years old* |  |

Please add more rows if needed.