18 Dec 2020

Submission of comments on *ICH Q3D (R2) Step 2b on elemental impurities – EMA/CHMP/353369/2013*

Comments from:

| Name of organisation or individual |
| --- |
| EFPIA  |

*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)* |
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|  | The guidance Appendix on cutaneous / transcutaneous limits for elemental impurities is considered to be of significant value.  |
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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)* |
| --- | --- | --- | --- |
| 13 |  | Is it possible to add the word “limits” to the header of table A2?Permitted Concentration **limits** of Elemental Impurities for Option 1 |  |
| Lines 17-18 (Table A.2.2) |  | The application of the rounded PDE values in appendix 2 or the calculated PDE values in appendix 3 could be clarified more clearly in the guideline in general. |  |
| Lines 46-69 |  | The oral PDE for gold was derived from a study after intraperitoneal administration. The parenteral PDE was set to be equivalent to the oral PDE based on the point of departure selection for the oral PDE and the high bioavailability after intramuscular administration. However, for derivation of the inhalation PDE it is stated that no data for inhalation or parenteral exposure were available and an additional assessment factor of 100 was applied. The difference in acceptability of route to route extrapolation for the different PDEs appears inconsistent and overly conservative for the inhalation PDE. Furthermore, the mentioned potential local tissue toxicity is not substantiated by referenced data. |  |
| 52 |  | Can you please add “A factor of 5 for F1 was chosen because rat was species investigated in the most relevant study”  |  |
| 65 |  | You are mentioning in the absence of parenteral data, but in our opinion intraperitoneal is parenteral.Proposed change (if any): We propose the following sentence “In the absence of relevant inhalation data  |  |
| 131 |  | “... the lowest level of silver resulting in argyria was 1 g metallic silver.”: Is the cumulative dose meant here? If yes, proposed change:“... the lowest **cumulative dose** of silver resulting in argyria was 1 g metallic silver.” |  |
| 261 and 460 ff |  | Line 261: “...the assessment relied on evaluating the available data for inorganic forms of the EI...”Please consider if further clarification is appropriate - also in the main guideline - that all PDEs are applicable only for inorganic forms of the elements.  |  |
| 441 |  | Comment: The text states that a “justified estimation of a WORST CASE” exposure / MDD should be provided. Worst case suggests the most extreme patient use should be accounted for. This may be overly precautionary and it may be more reasonable to allow for not ‘worst case MDD’ to be used but rather a MDD that covers ‘most routine patient use circumstances’.  | Proposed change (if any): Please change this text to allow for “a justified estimation of a MDD that cover most routine patient use circumstances.” |
| Minor comments regarding format: |  |  |  |
| e.g. 45, 48, 60, 110 |  | intra peritoneal: Proposed change to intraperitoneal (without blank) in whole document |  |
| 59 |  | “2/mg/kg”: Proposed change to: 2 mg/kg |  |
| e.g. 69, 146, 160 |  | “day” is partly abbreviated as “d”, mostly notProposed change: consistent use of “day” throughout the whole document, e.g. in Line 69:PDE = 322 μg/**day** / 100 = 3.22 μg/day |  |
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