20 January 2021
EMA/42340/2021

Overview of comments received on ICH guideline Q3D(R2) on elemental impurities (EMA/CHMP/ICH/353369/2013)

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

Stakeholder no.	Name of organisation or individual
1	Gilead Sciences Ireland UC
2	Medicines for Europe
3	J&J Self Care and J&J Consumer and Janssen Pharmaceutica
4	EFPIA

Please note that comments will be sent to the **ICH Q3D(R2) Maintenance EWG** for consideration in the context of Step 3 of the ICH process.

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1. General comments – overview

Stakeholder no.	General comment (if any)
3	1) The revision to Q3D proposes concentration based limits for Ni and Co in dermal and transdermal medicinal products (CTCL) on top of a dermal PDE. The use of the proposed CTCL is not consistent with best practices for managing allergens e.g. in foods. Furthermore the establishment of such limits may inappropriately omit labeling which could help to inform, and therefore prevent, significant (potentially life-threatening) adverse events in patients who have a known hypersensitivity to Ni or Co. As such, the proposed CTCL limits represent a concern for the safety of sensitized patients. For foods the solution for managing the potential for severe allergic reactions of e.g. milk, egg, fish, crustacean shellfish, tree nuts, wheat, peanuts, soybeans) is to require labelling as a precautionary principal whenever there is any reason to believe that they can be present (https://ec.europa.eu/food/sites/food/files/safety/docs/labelling_legislation_guidance_allegens-2017-4864_en.pdf). For other potential allergens, voluntary labelling is the recommended practice (https://www.fda.gov/media/117410/download, Draft Guidance for Industry: Voluntary Disclosure of Sesame as an Allergen). Similar precautionary labelling requirements are in place for other allergens such as nickel and latex in medical products (https://www.fda.gov/media/85473/download; https://www.fda.gov/media/123272/download) and for various excipients in drug products (labelling excipient warning guideline). Within the context of elemental impurities in cutaneous drugs, it is strongly recommended to align with these best practices especially since these are probably more protective. Therefore it is proposed to remove the CTCL from the guideline and instead add a recommendation to label for the potential presence of Ni and Co when there is reason to believe that these elements are present. Please clarify how these limits will be implemented. If the intent is to apply these limits retrospectively (as was done for the original guidance) we request that an appropriate implementation period be included
4	The guidance Appendix on cutaneous / transcutaneous limits for elemental impurities is considered to be of significant value.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes
2	3	**Comments:** Confirm the rounding of Ag (Line 2) is as Note 1 (Line 4) and the Ag PDEs on Line 87. **Proposed change:** In Line 2 update Ag PDE-parenteral to 17 and PDE-Oral to 170. Or, clarify rounding rules in Note 1 (Line 4).
13	4	**Proposed change:** Is it possible to add the word "limits" to the header of table A2? Permitted Concentration **limits** of Elemental Impurities for Option 1
17-18 Table A.2.2	4	**Comments:** 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.
45, 48, 60, 110	4	**Proposed change:** intra peritoneal: Proposed change to intraperitoneal (without blank) in whole document
46-69	4	**Comments:** 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	4	**Proposed change:** Can you please add "A factor of 5 for F1 was chosen because rat was species investigated in the most relevant study"
59	4	**Proposed change:** "2/mg/kg": Proposed change to: 2 mg/kg

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65	4	**Comments:** You are mentioning in the absence of parenteral data, but in our opinion intraperitoneal is parenteral. **Proposed change:** We propose the following sentence "In the absence of relevant inhalation data
69, 146, 160	4	"day" is partly abbreviated as "d", mostly not **Proposed change:** consistent use of "day" throughout the whole document, e.g. in Line 69: PDE = 322 µg/**day** / 100 = 3.22 µg/day
131	4	**Comments:** "... the lowest level of silver resulting in argyria was 1 g metallic silver.": Is the cumulative dose meant here? **Proposed change:** If yes, proposed change: "... the lowest **cumulative dose** of silver resulting in argyria was 1 g metallic silver."
261 and 460 ff	4	Line 261: "...the assessment relied on evaluating the available data for inorganic forms of the EI..." **Comments:** Please consider if further clarification is appropriate - also in the main guideline - that all PDEs are applicable only for inorganic forms of the elements.
338-339	3	**Comments:** It would be necessary to give flexibility to use a different CMF value other than 1% in Part 4 - Q3D Appendix 5 section 4.1 **Proposed change:** 1. For EIs other than arsenic (As) and thallium (Tl), a maximum Cutaneous Bioavailability (CBA) of 1% is used. *A different CBA value may be used for a specific element in certain products based on available technical justification or literature data.*
411 and Table 1	1	**Comments:** There is a cutaneous concentration limit (CTCL) for skin sensitizers, specifically cobalt and nickel of 35 ug/g or 35 ppm. When you compare to the skin PDEs for the two (using the assumption of 0.5 g cream), the concentration limit results in 17.5 µg/day cobalt and nickel, compared to the

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		transcutaneous PDEs of 50 and 200 mcg/day. It seems meaningless to have two limits as the concentration-based limit is based on a dose of 17.5 µg/day. Why not just have the cutaneous PDE being based on sensitization similar to some inhalation PDEs. Having two limits applies an unnecessary level of confusion for the pharmaceutical sponsor when 17.5 µg/day will be the PDE that is used since it is the lower of the two values. **Proposed change:** Eliminate the cutaneous concentration limit and just provide a PDE of 17.5 µg/day for both cobalt and nickel.
441	4	**Comments:** 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:** Please change this text to allow for "a justified estimation of a MDD that cover most routine patient use circumstances.
462-463	2	**Comments:** Regarding the exclusion of the Class 2B elements, the cutaneous products should be mentioned in this line as well for better understanding. **Proposed change:** Class 2B elements were excluded from the assessment of oral, parenteral, inhalation and cutaneous product due to the low likelihood that they would be present if not intentionally added (see section 4 of ICH Q3D)
468-469	2	**Comments:** Table 2, Cobalt - Cutaneous conc. for a 10 g daily dose For cobalt, cutaneous concentration for a 10 g daily dose is specified as "5b". Index "b" was not found. We suppose it should be index "2", same as for nickel