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Overview of comments received on ICH guideline Q3D (R1) 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	David Alkewitz, mibe GmbH Arzneimittel
2	David J Snodin, Xiphora Biopharma Consulting
3	Gianni Alampi, Productlife AG
4	German Pharmaceutical Industry Association (BPI e.V.)
5	Susana Almeida (salmeida@medicinesforeurope.com), Medicines for Europe's
6	AESGP
7	SANOFI

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

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)
1	Thank you for providing this document for consultation. During the assessment of this document, I found two discrepancies and one format mistake: 1. The calculated inhalative PDE of Cadmium is 3.43 µg/day. The table A.2.1 of line 850 was not updated (Inhalative PDE of Cd = 2 µg/day, it must be 3 µg/day). Furthermore, line 865 must be Table A.2.2 (not A.2.1) and the calculated inhalative Cd values was not updated (it must be 0.3 µg/g). 2. There is a format mistake in line 1177: 1177 For continuous dosing = $\frac{5\ \mu g/\ m^3 \times 8\ hr/d \times 5\ d/wk}{24\ hr/d \times 7\ d/wk} = \frac{1.19\ \mu g/m^3}{1000\ L/m3} = 0.00119\ \mu g/L$ 1178
2	The creation of ICH Q3D represents a major change on elemental impurities – from a "for-cause" approach to a routine assessment of exposure to potentially toxic elements. No justification for this change in approach has been elaborated in the guidance or elsewhere. Where is the evidence that the previous approach was putting patients at risk? Is there evidence showing that this new approach is identifying potentially harmful levels of elemental impurities? These questions should be answered before firming up on the more onerous aspects of ICH Q3D. A review of the fitness for purpose of the guidance should be performed in 5 years' time based on data gathered by regulatory agencies and industry during that period.
3	Thank you for the information on the draft of ICH guideline Q3D (R1) on elemental impurities. I was really happy to receive the information that the revision of the ICH Q3D concept paper was approved to include PDEs for the cutaneous and transdermal route of administration right now, because I just have to establish 4 risk analysis for dermatological products. Unfortunately in the new draft of ICH guideline Q3D(R1) which you published for comments I cannot find anything about PDEs for the cutaneous and transdermal route of administration (see attached). Is it possible that I did not get the right version? I would therefore be grateful, if you can let me know where I can find these PDEs.
4	The monograph for Cadmium (Cd) on page 39 includes the adapted value for the inhalative PDE of 3,4 µg/day, but in table A 2.1. the old PDE value of 2 µg/day is still included. From our point of view, the table A 2.1 has to be adjusted as the new PDE for inhalative dosage forms is 3,4 µg/day

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5	As noted in the guideline, Q3D is applicable to drug products, with some minor exceptions such as radiopharmaceuticals, vaccines, etc. For industry harmonisation purposes and enhanced quality control, it would be helpful if there were a companion guideline or annex to the current guideline applicable to drug substances and/or excipients. Guidance recommending the testing and evaluation of such drug product components for elemental impurities would permit greater eventual control and reduced variability of elemental impurities within marketed drug products. Though the Q3D guideline outlines both default exposure limits (PDEs) and default control thresholds/limits (30% PDE), how situations that fall outside these default parameters are communicated to the Agency are not discussed. For example: • What type of variation is recommended for existing marketed products if the elemental impurity level is above the default control limit (i.e., > 30% PDE) and the risk assessments revealed that additional control/testing strategy and a change in the API/finished product specification is needed? • What type of variation, if any, would be recommended for existing marketed products if the elemental impurity level is above the default control limit (i.e., > 30% PDE) but below the PDE limit and the conclusion from the risk assessment is that no additional controls/testing is required? • What type of variation, if any, would be recommended if a level of elemental impurities higher than an established PDE was justified (i.e., due to intermittent dosing, short term dosing, etc.)? It is not clear in which section of Module 3 elemental impurity information should be included for new marketing authorizations (3.2.P.2.3, 3.2.P.5.5 or 3.2.P.5.6)? Most sections of the guideline could be greatly enhanced via the use of specific examples – i.e., scenarios that include implementation of the guideline recommendation. Alternatively, or in addition, an annex/appendix could be included that provides multiple scenarios implementing the entirety of the guideline. Such enhancement of the guideline would provide greater clarity with respect to the expected implementation procedures.
7	Sanofi welcomes the opportunity to comment on ICH guidelines Q3D(R1) on elemental impurities

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes
104 - 105	5	**Comments:** The given timelines are not up-to-date as the ICH Q3D requirements are already valid for legacy products since January 2018. **Proposed change:** The following sentence should be deleted: *"Application of Q3D to existing products is not expected prior to 36 months after publication of the guideline by ICH."*
149	5	**Comments:** For alternative routes of administration (ophthalmic, topical, transdermal, submucosal, vaginal, etc.), minimal guidance is provided to aid relatively harmonised PDE derivations – only consideration of potential local effects and bioavailability differences are provided. **Proposed change:** Ideally, PDE values for all routes of administration would be provided. In lieu of this, enhanced guidance for these alternative routes of administration is requested. For example, how is a lack of bioavailability data by a given route considered and factored into the calculation? Indication of whether these need to be derived on a route basis or if they can be product-specific (without an underlying route PDE) would be beneficial.
162	5	**Comments:** It would be helpful if the adjustment of an established PDE limits to an alternative route based on bioavailability was discussed and described in greater detail. For example, can it be adjusted based upon differences in bioavailability demonstrated in a non-human species? For example, should the minimum, average, or maximum bioavailability for a given route of administration be used and what sources of this information are considered appropriate? **Proposed change:** Greater detail regarding the proposed implementation of such adjustments including example(s) of adjustment(s) for less than ideal situations (i.e., limited data set).
174-176	5	**Comments:** Though situations which may lead to acceptable elemental impurity levels higher than the established PDE limits are noted, the extent to which such situations should or may impact the acceptable limit is not discussed or quantified. For example, if a drug product is dosed once per week (i.e.,

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		once per seven days), does the acceptable limit increase 7-fold (i.e., 7xPDE)? As another example, is the default PDE applicable to any dosing greater than 30 days (i.e., short-term) or could alternative limits be derived for a drug product dosed for 3 months compared to lifetime dosing (i.e., PDE limit)? **Proposed change:** The quantitative impact of such factors (dosing duration and frequency), at a minimum, should be discussed and example derivations provided.
250	5	**Comments:** Greater clarity regarding what other guidelines or regional regulations are applicable is needed. **Proposed change:** Provide examples of applicable guidelines and/or regulations.
258-260	5	**Comments:** The wording here should provide greater clarity. For example, is the information/data generated referring to safety/toxicity information and/or elemental content (ppm) information? Can safety information provided by one supplier/manufacturer support use of an excipient/API from another manufacturer?
395-399	5	**Comments:** The guideline notes the "control threshold is defined as a level that is 30% *of the established PDE* in the drug product". However, it does not indicate the applicable control threshold in cases where the acceptable exposure (due to intermittent dosing, short term dosing, etc.) is different than the "established PDE" (assumption is that it is 30% of the utilized acceptable exposure. **Proposed change:** Guideline should clearly delineate that the control threshold is 30% of the PDE/acceptable exposure limit utilized.
406-415	5	**Comments:** This section of the guideline is vague, noting that the "variability of the level of an elemental impurity should be factored into the application of the control threshold" without stating how or providing examples. **Proposed change:** A much more detailed explanation (preferably with examples) of how component variability (or lack thereof) impacts the application of the control threshold should be provided.
		Comments:

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		The guideline notes that for a component with inherent variability such as mined excipients, additional data may be needed. However, there is no indication or example(s) of what type or how much additional data would likely be necessary. How this is documented should be defined. For example, use of a form such as that found in [PA/PH/CEP (16)23] (EDQM) could be indicated as appropriate or a similar type of form could be included as an appendix.
555-559	5	**Comments:** This section on "Analytical procedures" is lacking with respect to providing detailed guidance with respect to analytical expectations. Both "appropriate procedures" and "suitable alternative procedures" are noted with minimal indication of what procedures would qualify as such. Additionally, many other aspects of the expected analytical procedures are not discussed. **Proposed change:** ➢ At what point does the level and/or variability of an elemental impurity indicate the need for a final drug product specification limit? ➢ If elemental impurity control is performed via quantification in the drug product, what is considered appropriate regarding the frequency of tests (or skip test possibility)? ➢ Include a more detailed description regarding the expectations of the analytical procedure(s). Taking into consideration that impurity levels often are well below the QL (quantitation limit) or DL (detection limit), can a simplified validation strategy be adopted? ➢ The utility of screening methods should be discussed and defined compared to fully validated methods. When are or aren't screening methods sufficient?
849 and 867	5	**Comments:** Appendix 2 shows rounded PDE values whereas Appendix 3 provides safety assessments/PDE derivations and provides the unrounded PDE values. It is not clear which value(s) should or can be used for the calculation of control limits and/or when evaluating risk potential in the drug product. Does one use the Appendix 2 or Appendix 3 values? Can either be used? Also, the footnote to Table A.2.1 should indicate that the PDE values are applicable to all drug products (new and legacy), not just new drug products. **Proposed change:** "PDEs reported in this table (µg/day) have been established on the basis of safety data described in the monographs in Appendix 3, and apply to ~~new~~ drug products. Either value (rounded or unrounded) is considered appropriate for risk assessment purposes. For practical purposes (e.g.,

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		simplification) in calculations, the PDEs in this table have been rounded to 1 or 2 significant figures."
849 850 1116	7	**Comments:** In the EMA guideline there are two contradictory information about the value of Cadmium PDE for inhalation: According to the appendix 2, that summarize the rounded PDE values for all the impurities, the Cadmium PDE (for inhalation) is 2 µg/day (it corresponds to the previous rounded PDE value which was 1,7 µg/day) -> this information is not up to date: In the part dedicated to the Cadmium, the Cadmium PDE (for inhalation) is 3,4µg/ day (correct value): **Proposed change:** The rounded value in the appendix 2 has to be corrected. This contradictory information is not reported in the FDA guideline as they only published the part dedicated to the Cadmium
850 and 1116	5	**Comments:** There is a rounding error in Appendix 2: - The value for Inhalation PDE of Cadmium is 2 µg/day in Appendix 2. - The value for Inhalation PDE of Cadmium is 3.4 µg/day in Appendix 3. The value in Appendix 2 should be changed to 3 µg/day. **Proposed change:** Change of value in Appendix 2 for Inhalation PDE of Cadmium from 2 µg/day to 3 µg/day.
1286	2	**Comments:** Flawed derivation of the PDE for cobalt – see Snodin DJ, Human and Experimental Toxicology, 2015 (34), 1258-1271. Multiple issues including inappropriate NOAEL, incorrect assessment factors, PDE exceeded by dietary intake in some populations, etc **Proposed change:** Re-evaluation of the PDE for Co using appropriate metrics and methodology.
2340	5	**Comments:** The Appendix 4 of the guideline contains example calculations for drug products with daily dosing of 10 grams or less.

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		Proposed change: Additional example(s) for large volume injectables (100 mL or more) and/or a daily dose more than 10 g would be helpful.
2340 – 2434	5	**Comments:** In Appendix 4 calculation examples are displayed for Option 1, 2a, 2b, and 3. The examples are not always easy to understand as they are not illustrative. **Proposed change:** For example, the composition of the drug product (%) should be included in Table A.4.4.
		Comments: It is not clear how to calculate with results below the limit of detection (BLOD) or quantification (BLOQ). Typically, such values are not generally considered as zero (e.g., demonstration of absence). As it may have a major impact on the evaluation of drug products with multiple components, clarity regarding BLOD/BLOQ values should be provided. In other words, can such results be approximated as zero or does the LOD or LOQ limit need to be considered as the level of elemental impurity? How has the knowledge about the sensitivity of the method been considered and is this relevant to determining what quantitative value is assigned? **Proposed change:** Minimum requirement should be defined for BLOD/BLOQ results. It should be outlined under which circumstances such values can or cannot be considered “0”.
Appendix 2	4	**Comments:** The PDE for Cadmium (inhalation route) has not been adapted in Annex 2 **Comments:** Please adapt it
Appendix 2	6	**Comments:** The PDE for Cadmium (inhalation route) has not been adapted. In Appendix 2, it is specified with 2 µg/day, but in Appendix 3, it is 3.4 µg/day. **Comments:** Please adapt the PDE for Cadmium.