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Topics Recently Reaching Step 4 of the ICH Process: ICH Q3D(R2)

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ICH Q3D(R2): Guideline for elemental impurities

Purpose of the ICH Q3D guideline

- Provides a framework for the assessment and control of elemental impurities (EIs) in drug products
- Recommends permitted daily exposures (PDEs) for 24 EIs in drug products administered by the oral, parenteral and inhalation routes of administration

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Document history

- ICH Q3D core guideline adopted in December 2014
- Revision to Q3D guideline (R1) adopted in March 2019
  - Cadmium PDE (inhalation route) revised

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Objective of the Appendix

- Develop PDEs for EIs in drug products administered by the cutaneous and transcutaneous routes of administration
- Facilitate harmonization and implementation of EI limits

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Timeline

- Concept paper endorsed in September 2016
- Step 1 draft document endorsed by ICH Assembly (2020)
- Step 3 regulatory consultation, EWG discussion, document revision (2021)
- Step 4 adoption of the Appendix by ICH Assembly (April 2022)
  https://database.ich.org/sites/default/files/Q3D-R2_Guideline_Step4_2022_0308.pdf

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Section 1: Background

- Transcutaneous absorption is dependent upon the properties of the skin, the anatomical site, the nature of the chemical applied, and the characteristics of the application

- Limited research evaluating systemic absorption of EIs applied to skin
  - From the available data, systemic exposure reported to be < 1% absorption for EIs evaluated

- As bioavailability data are lacking for most EIs, a generic approach was adopted to establish limits (as opposed to an element-by-element approach)

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Section 2: Scope

- Applies to cutaneous and transcutaneous drug products intended for either local or systemic effects

- Does not apply to drug products intended for mucosal administration, topical ophthalmic, rectal, or subcutaneous and subdermal routes of administration

- Not intended to provide recommendations for labelling of allergens. Refer to regional guidance, recommendations or best practices.

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Section 3: Principles of safety assessment for cutaneous products

- No indication of local skin toxicity except sensitization (nickel and cobalt)
- No indication of systemic toxicity by the dermal route except for thallium
- Limited information available on transcutaneous absorption of EIs
  - Not possible to determine percent absorption for each element and calculate an element-specific PDE

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Section 3: Principles of safety assessment for cutaneous products

- Generic approach used: Cutaneous PDEs calculated by applying an *upward* adjustment factor (Cutaneous Modifying Factor or CMF) to the parenteral PDE which assumes 100% bioavailability
  - Does not apply to drug products intended to treat skin with substantial disruption of the basal cell layer of the epidermis (e.g., skin ulcers, second and third degree burns)
  - Parenteral PDE an appropriate starting point
- For nickel and cobalt (sensitizers), a concentration limit was also derived to limit skin reactions in sensitized people

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Section 4: Establishing the cutaneous PDE

- Cutaneous PDE = Parenteral PDE x CMF

(A) Determine adjusted cutaneous bioavailability (CBA)

- For EIs except arsenic and thallium, assume max. CBA of 1%
- To account for factors that can enhance CBA, apply adjustment factor of 10: 1% CBA x 10 = 10% (adjusted CBA)

(B) Calculate CMF

- CMF = parenteral bioavailability (100%) ÷ adjusted CBA (10%) = **10**

(C) Calculate cutaneous PDE

- PDE = parenteral PDE (e.g., 2 µg/day for Cd) x 10 = **20 µg/day**

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Section 4: Establishing the cutaneous PDE

- For arsenic, transcutaneous absorption is greater than most other EIs at ~ 5%

(A) Determine adjusted CBA

- 5% x 10 (to account for various factors that can enhance CBA)
  Adjusted CBA = 50%

(B) Calculate CMF

- CMF = parenteral bioavailability (100%) ÷ 50% = **2**

(C) Calculate cutaneous PDE

- PDE = 15 µg/day x 2 = **30 µg/day**

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Section 4: Establishing the cutaneous PDE

- Thallium is highly absorbed through the skin and considered to be equivalent to parenteral levels.

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CMF = 1

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Cutaneous PDE = parenteral PDE (8 µg/day)

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Section 5: Cutaneous concentration limits for Ni and Co

- Application of a cutaneous and transcutaneous concentration limit (CTCL) for nickel and cobalt
- Dermal concentration limit of 0.5 µg/cm^2/week (EU nickel directive) used as point of departure for calculating nickel CTCL
- Assume a 0.5 g dose to skin surface area of 250 cm^2:
  - 0.5 µg/cm^2/week = 0.07 µg/cm^2/day
  - 0.07 µg/cm^2/day x 250 cm^2 = 17.5 µg/day
  - 17.5 µg/day/0.5 g/day = **35 µg/g**
- A similar limit was recently derived for cobalt

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Section 6: Product risk assessment for cutaneous drug products

- Product risk assessments prepared following guidance in Q3D parent guideline (Section 5)
- Both the PDE and CTCL need to be met for sensitizing elemental impurities (nickel and cobalt)
- Estimate worst-case EI exposure based on maximum daily dose
  - May be important to evaluate retention time of drug product considering typical conditions of use
- "Control threshold" can be applied to the PDE and CTCL

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Section 7: Cutaneous PDE values

- Summarizes in tabular format:
  - PDEs for the 24 elemental impurities
  - CTCL for nickel and cobalt
  - Concentration limit for the 24 elemental impurities

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Next steps

- Implementation of the ICH Q3D(R2) guideline across the ICH regions

Acknowledgements

- ICH Q3D expert working group