ICH Q3D(R2) Elemental Impurities

Step 4

Step 4 document – to be implemented

27 May 2022

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Legal Notice

2

Background

- **This document was developed based on a Concept Paper (15 September 2016) and an updated Work Plan (4 February 2022).**
- **After the public consultation and the EWG discussion, the document including Limits for Elemental Impurities by the Cutaneous and Transcutaneous Route and some corrected permitted daily exposures (PDEs) has been signed off as *Step 4* document (26 April 2022) to be implemented by the ICH Regulatory Members.**

Key Principles

- This presentation will provide a summary of the new Appendix for “Limits for Elemental Impurities by the Cutaneous and Transcutaneous Route”
- This presentation will concomitantly provide summaries of the error corrections to the PDEs of 3 elemental impurities in ICH Q3D(R1).

Guideline Objectives

- The objectives and scope remain the same as indicated in the ICH Q3D Guideline finalized in December 2014.
- The Guideline revision (R2) is focused on establishment of limits for elemental impurities by the dermal route of exposure.
- The Guideline revision (R2) also includes error corrections of the PDEs for silver (oral), gold (oral, parenteral and inhalation) and nickel (inhalation).

Table of Contents

- Summary of limits for elemental impurities (EI) by the cutaneous and transcutaneous route
- Error correction of silver (Ag) PDE by oral route exposure
- Error corrections of the gold (Au) PDEs by oral, parenteral and inhalation routes exposure
- Error correction of nickel (Ni) by inhalation route exposure

Summary of cutaneous PDEs

- The new appendix document of cutaneous PDEs of elemental impurities were developed by the EWG. The table of contents of the appendix is as follows.

1. Background
2. Scope
3. Principles of Safety Assessment for Cutaneous Products
4. Establishing The Cutaneous Permitted Daily Exposure (PDE)
5. Cutaneous Concentration Limits for Ni And Co
6. Product Risk Assessment
7. Cutaneous PDE Values
8. References

Summary of cutaneous PDEs (1)

- Background
  - Dermal absorption is dependent upon the properties of the skin, the anatomical site, the nature of the chemical applied and the characteristics of the application. But quantitative data are generally lacking for most EI and its ions
  - A generic approach was adopted to establish limits as opposed to an element-by-element basis
- Scope
  - This Appendix does not apply to drug products intended for mucosal administration, topical ophthalmic, rectal, or subcutaneous and subdermal routes of administration

Summary of cutaneous PDEs (2)

- Principles of Safety Assessment
  - In general, there is no indication for local toxicity on the skin, with the exception of sensitization
  - A generic approach for deriving a cutaneous PDE has been developed based on a systematic adjustment of the parenteral PDE, which assumes 100% bioavailability
  - The available data indicate that EIs are generally poorly absorbed through intact skin even in the presence of enhancers.
  - For drug products intended to treat skin with substantial disruption of the basal cell layer of the epidermis, the parenteral PDE is generally an appropriate starting point

Summary of cutaneous PDEs (3)

- Establishing The Cutaneous PDE (for systemic toxicity)

➢ The limited available data suggest that transcutaneous absorption of most EI is less than 1% for intact skin

➢ The Cutaneous Modifying Factor (CMF) was developed for deriving protective PDE due to lack of reliable quantitative data

1. **For EIs other than arsenic (As) and thallium (Tl), a maximum Cutaneous Bioavailability (CBA) of 1% is used.**
2. **To account for the various factors that can enhance CBA, a factor of 10 is applied to increase the CBA (adjusted CBA).**
3. **To calculate the CMF, the parenteral BA (100%) is divided by the adjusted CBA.**

Summary of cutaneous PDEs (4)

- Establishing The Cutaneous PDE (for systemic toxicity)

Cutaneous PDE = Parenteral PDE x CMF

- PDE for EIs (other than TI and As) (CMF=10)

  (Adjusted CBA = 1%(absorption) X10 =10%; ∴CMF = 100% / 10% = 10)

  - Cutaneous PDE = Parenteral PDE x 10

- PDE for As (CMF = 2, absorption is approximately 5%)

  (Adjusted CBA = 5%(absorption) X10 =50%; ∴CMF = 100% / 50% = 2)

  - Cutaneous PDE = 15 µg/day x 2 = 30 µg/day

- PDE for TI (CMF = 1, absorption is high, but no quantitative data)

  (Adjusted CBA = 100% (absorption); ∴CMF = 100% / 100% = 1)

  - Cutaneous PDE = 8 µg/day x 1 = 8 µg/day

Summary of cutaneous PDEs (5)

- Cutaneous and Transcutaneous Concentration Limits (CTCL) for Ni and Co
  - The CTCL in addition to the PDE is warranted for Ni and Co to reduce the likelihood of eliciting skin reactions in already sensitized individuals.
  - The dermal concentration limit of 0.5 µg/cm^2/week (EU directive) is applied to set a CTCL of Ni.
    - The CTCL calculation is based on that cutaneous products application of 1 FTU (fingertip unit) corresponding to 0.5 g dose is normally applied to a 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

  - Recent report suggested the same CTCL is applied to Co.

Summary of cutaneous PDEs (6)

- Product Risk Assessment

- Product assessments for cutaneous drug products should be prepared following the guidance provided in ICH Q3D Section 5
- For Ni and Co, the concentration (µg/g) in the drug product should be assessed relative to the CTCL, in addition to the PDE
- The total Ni and Co level (µg/day) is at or below the PDE, and their respective concentrations do not exceed the CTCL
- "Control threshold" approach is also applied to the CTCL
- Evaluation of the retention during typical conditions of use is important for multiple applications a day. (see Module 1, ICH Q3D training package)

Error correction of Ag PDE by parenteral route

- The parenteral PDE for silver (Ag) is based on a lowest observed adverse effect level (LOAEL) of 0.014 mg/kg using long-term human intravenous exposure data. But, the cited LOAEL (from the reference dose (RfD) of US EPA IRIS document) in the monograph had been already adjusted for oral route exposure
- After further review, the original study cited in the monograph was considered in error. It was considered inadequate to set a parenteral PDE as it involved a low number of patients, and the dosing was not adequately described

Error correction of Ag PDE by parenteral route

- The EWG developed the corrected parenteral PDE as follows
- In a review of the oral toxicity of silver, Hadrup and Lam (2014) report that absorption of a radionuclide of silver (as silver nitrate) was 18% in human.
- the parenteral PDE was calculated by dividing the oral PDE by a modifying factor of 10 (as described in Section 3.1).
  (in the case of oral bioavailability between 1% and 50%)
- The recommended PDE for silver for parenteral exposure is:

  PDE = 167 µg/day / 10 = 16.7 µg/day
- The rounded parenteral PDE in Table A.2.1 is **15 µg/day**

Error correction of Au PDE by all route

- The monograph of Gold (Au) explained that “derivation of the oral PDE of Au is based on a study in mice (Ahmed 2012)”. But, the study was conducted in rats
- F1 of 5 (for rats) in PDE calculation should be used instead of F1 of 12(for mice)
- The oral PDE calculation should be corrected as follows

PDE = 32.2 mg/kg x 50 kg / **12** x 10 x 10 x 1 x 10 = 134 µg/day

PDE = 32.2 mg/kg x 50 kg / **5** x 10 x 10 x 1 x 10 = **322 µg/day**

The parenteral PDE is same as the oral PDE, and the inhalation PDE is 1/100 of the oral PDE

- The PDEs in Table A.2.1 should be also corrected as follows

Monograph

element	Oral	parenteral	inhalation
Au	322	322	3.2

Table A.2.1

element	oral	parenteral	inhalation
Au	300	300	3

Error correction of Ni PDE by inhalation route

Table A.2.1 in STEP2

element	oral	parenteral	inhalation
Ni	200	20	6

- The derivation procedure of Ni PDE by inhalation in the ICH Q3D *Step 4* document in 2014 was not changed from that in the ICH Q3D *Step 2* document in 2013. There was no issue or discussion between the ICH Q3D *Step 2* and ICH Q3D *Step 4*
- The EWG concluded that the current PDE of Ni by inhalation was a transcription error at the ICH Q3D *Step 4* publication in 2014
- The EWG recommend that the PDE of Ni by inhalation in Table A.2.1 should be corrected to "6 µg/day" from "5 µg/day"

(There is no need to change the Ni monograph itself)

Results of Public Consultation

- **No major changes were made in response to the public comments.**
- **In order to address the questions raised in the pub-comments, additional or modified sentences were given in the following parts of the text, footnotes, and table legends.**
  - At the end of Scope and the footnote of Scope
  - At the end of Section 5
  - At the end of the second last paragraph in the Section 6
  - At the legend #4 in the Table A.5.1 and the #2 in the Table A.5.2

Considerations

- **The ICH Q3D Guideline is not intended to provide recommendations for labelling of allergens. Applicants should refer to regional guidance/recommendations or best practice for managing and labeling of allergens.**

(from the footnote of Scope in the Appendix 5)

Guidelines for Implementation

- **The new Appendix 5 to the ICH Q3D Guideline applies to cutaneous and transcutaneous drug products whether intended for local or systemic effect.**
- **The Appendix does not apply to drug products intended for mucosal administration (oral, nasal, vaginal), topical ophthalmic, rectal, or subcutaneous and subdermal routes of administration.**
- **Products not covered by this Appendix should be evaluated in accordance with the approach discussed in section 3.2 of the main text of the ICH Q3D Guideline.**

(from Scope of Appendix 5)

Conclusions (1)

- Develop a new Appendix for “Limits for Elemental Impurities by the Cutaneous and Transcutaneous Route”
- This Appendix does not apply to drug products intended for mucosal administration, topical ophthalmic, rectal, or subcutaneous and subdermal routes of administration
- Establish the cutaneous PDE of all EIs for systemic toxicity (See Table A.5.1)
- Establish the CTCL for Ni and Co for sensitized patients
- The total Ni or Co level is at or below the cutaneous PDE, and their respective concentrations do not exceed the CTCL

Conclusions (2)

- The original PDEs for silver (Ag), for gold (Au), and for nickel (Ni) were incorrect due to calculation or transcription errors.
- The EWG re-evaluated the relevant data and identified the corrected PDE of Ag, and corrected a modifying factor of Au, and corrected a transcription error of Ni.
- The corrected PDE of Ag by the parenteral route is identified as 15 μg/day.
- The corrected PDEs of Au by the oral, parenteral and inhalation routes are identified as 300, 300 and 3 μg/day, respectively.
- The corrected PDE in Table A.2.1of Ni by the inhalation route is identified as 6 μg/day.

Contact

- **For any questions please contact the ICH Secretariat:**

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