Appendix 5: Established PDEs for Elemental Impurities by the Cutaneous and Transdermal Route

Working Draft Aug 9, 2019

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1 BACKGROUND

In December 2014, the Steering Committee of ICH approved the ICH Q3D Guideline for Elemental Impurities developed by the Expert Working Group. The Guideline provided Permitted Daily Exposures (PDEs) for 24 elemental impurities (EI) for the oral, parenteral, and inhalation routes. In section 3.2 of the guideline, principles for establishing PDEs for other routes of administration are described. During the course of the development of Q3D, interest was expressed in developing PDEs for the cutaneous and transcutaneous route as these products remain the most significant area where PDEs for EI have not been formally established.

In establishing cutaneous and transcutaneous limits the role of skin is paramount. The skin is an environmental barrier and a complex organ that has many functions, including to limit the penetration of exogenous materials, metabolism, prevention of water loss, temperature regulation, and as an immune organ (Monteiro-Riviere and Filon, 2017). The skin is composed of both an outer epidermis and an inner dermis, each being composed of multiple cellular layers. Dermal (or percutaneous) absorption, i.e., the transport of a chemical from the outer surface of the skin into systemic circulation, is dependent upon the properties of the skin, the anatomical site, the substance attempting to penetrate it, and characteristics of the application. The primary barrier to absorption is the outermost layer of the epidermis (i.e., the stratum corneum) which typically consists of 15-20 layers of non-viable cells. The stratum corneum serves as a highly

effective barrier to hydrophobic compounds and charged molecules such as metal cations. For this reason, transdermal delivery into the systemic circulation of materials including any active pharmaceutical ingredient, API typically requires physical and chemical methods to assist in the percutaneous absorption of the API.

In respect of these "penetration enhancers", it is noteworthy that methods that enhance penetration for an API are usually not applicable for EIs due to fundamental differences in physico-chemical properties.

Limited research has been conducted to evaluate the systemic exposure of elements applied to the skin however concentrations of EIs have been shown to reduce/diminish when applied to the skin within formulated products, without appearing in the systemic circulation. For example for mercury vapor, Hursh et al. (1989) showed that approximated 50% of the mercury vapor taken up by the skin was shed by desquamation of epidermal cells for several weeks after exposure, while the remainder was slowly released in to the general circulation. Hostýnek et al (1993) describes that Ag is preferentially accumulated in the skin and is not liberated. Available data indicates that gold is not readily absorbed through skin due to inertness and lack of ionization by bodily fluids. Gold, in salt form, has been shown to bind readily to sulfhydryl groups of epidermal keratin and remain in the skin (Lansdown, 2012). Metal binding proteins are present in some fetal and adult skin (e.g., basal keratinocytes of epidermis and outer hair root sheath) but not other cell types (e.g., exocrine portion of the eccrine glands), indicating the skin has the potential for binding and metabolism of metals (van den Oord and De Ley, 1994)

Together these represent a significant barrier to systemic exposure as illustrated by quantitative absorption data reviewed by Hostýnek et al (1993) for Ag, Cd, Cr, and Ni and Pb (ATSDR, 2019); this reported < 1% absorption. Percutaneous absorption of EI is discussed in more detail in section 3.

Elements evaluated in this guideline were assessed by reviewing publicly available data contained in scientific journals, government research reports and studies, and regulatory authority research and assessment reports. In general, studies in the scientific literature simply report disappearance of metals from the cutaneous layer rather than percutaneous absorption. Quantitative data are generally lacking for most EIs and the associated counterion (Hostynek, 2003). Furthermore there are no standards for occupational exposure for the dermal route that are suitable for use for risk assessment. As a consequence, it was necessary to adopt a generic approach to establish limits as opposed to on an element by element basis.

2 SCOPE

This Addendum to Q3D applies to cutaneous and transdermal drug products (referred to as "cutaneous products" throughout this Addendum) whether intended for local or systemic effect. This Addendum does not apply to drug products intended for mucosal administration (oral, nasal, vaginal), topical ophthalmologic, rectal, or subcutaneous and subdermal routes of administration.

3 PRINCIPLES OF SAFETY ASSESSMENT FOR CUTANEOUS PRODUCTS

Review of scientific literature indicates a lack of local toxicity other than sensitization. Thallium is the only element that shows systemic toxicity by the dermal route. There is limited information available on percutaneous absorption of the elements addressed in this Addendum to allow calculation of a route specific PDE, or to allow conversion an existing PDE to the dermal route and support an element by element approach. The literature review focused on the forms likely to be present in pharmaceutical products (see main guideline) and therefore the assessment relied on evaluating the available data for inorganic forms of the EI and ranking the relevance of the data in the following order: human in vivo data; animal in vivo data; in vitro data.

As a consequence of the limited data it is not possible to address this on an element by element basis and therefore a generic approach has been developed based on a systematic adjustment of the parenteral PDE to derive a cutaneous PDE by using a Cutaneous Modifying Factor (CMF) (see section 4). The cutaneous PDE has been derived for daily, chronic application to the skin.

3.1 Percutaneous absorption of EI

The extent of absorption into the systemic circulation (systemic absorption) is considered an important component to the safety assessment of the elements. Review of studies of skin penetration, absorption, systemic bioavailability and toxicity of the elements shows a lack of data for many elements. For those elements that have been studied for percutaneous absorption and/or toxicity, the available data are rarely suitable for proper quantitative analysis and the diverse experimental designs preclude inter-study or inter-element comparability (Hostynek, 2003). The data, which are available, indicate EI are generally poorly absorbed through intact skin even in the presence of enhancers. For example, absorption of Pb from lead oxide in an occluded patch in rats was less than 0.005%, as measured by urinary Pb for 12 days following exposure. Penetration of lead oxide was not detectable in an in vitro system with human skin (ATSDR, 2019).

There are numerous factors that may influence percutaneous absorption and systemic bioavailability after cutaneous administration of a substance. These factors may be categorized as:

- subject-related factors (e.g., comparative species differences, location on the body, hydration of the skin/age, temperature),
- compound related factors (e.g., physical state, ionization, binding properties, reactivity and the counterion of the EI), and/or
- application related factors (e.g., concentration and total dose applied, duration of application/exposure, cleaning between applications, surface area, co-applied materials/excipients and occlusion status).

Percutaneous penetration through the skin is element and chemical species-specific and each element would need to be experimentally assessed under different conditions to develop an

effective model. Due to this complexity, it is not feasible to address every possible scenario for each EI in each drug product.

Given the limited amount of data on percutaneous absorption and toxicity by the cutaneous route of administration that has been generated in well-designed studies, the data that was available was used to develop a generic, conservative approach. The cutaneous PDE is derived from previously established element specific parenteral PDE's for which adequate toxicity data are available. To address the low but unquantified percutaneous absorption, and in consideration of all of the potential factors that can influence this absorption, a 10-fold factor (+ 900%) will be applied to the parenteral PDE for most EIs, (i.e. 2-fold reflects a 100% increase). The derivation and application of the factor of 10 is described in more detail in section 4 below.

3.2 PDE for drug products directly applied to the dermis

Based on the above, the PDE for the cutaneous route described in this Addendum should not be applied to drug products intended to treat skin with substantial disruption of the basal cell layer of the epidermis. A compromised basal cell layer could facilitate direct entry of EI into the dermis and its associated blood vessels (potentially increasing systemic absorption). For indications in which drug treatment is intentionally brought into contact with the dermis (e.g. skin ulcers, second- and third-degree burns, pemphigus, epidermolysis bullosa) it is recommended to develop a case-specific justification based on principles outlined in ICH Q3D section 3.3. The parenteral PDE is generally an appropriate starting point for these drug products.

Small cuts, needle pricks, skin abrasions and other quick healing daily skin injuries are not associated with substantial basal cell layer disruption of the epidermis as defined above. The total amount of drug product which can potentially come into contact with the dermis is therefore considered negligible. Cutaneous PDEs therefore will apply to products intended to treat these skin abrasions or other quick healing acute injuries.

4 ESTABLISHING THE CUTANEOUS PDE

The cutaneous PDE for all relevant EI, is calculated by applying a cutaneous modifying factor (CMF) to the parenteral PDE for each EI.

4.1 Establishing the cutaneous modifying factor (CMF)

The limited available data suggest that percutaneous absorption of most EIs, when studied in intact skin, is less than 1% as described previously (Section 1 and 3). As described in section 3.1, there are multiple factors that can impact this absorption. In lieu of accounting for such factors individually, and in consideration of the relative lack of reliable quantitative metal cation percutaneous absorption data, an approach has been adopted for the derivation of cutaneous PDEs, which is considered protective against potential systemic toxicities. To account for these uncertainties, a CMF is generated using the approach outlined below.

1. For EIs other than As and Th, 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

4. The cutaneous PDE is the parenteral PDE X CMF

4.2 Cutaneous PDE

The Cutaneous PDE can be calculated as

Cutaneous PDE = Parenteral PDE X CMF

4.2.1 Derivation of PDE for EI, other than Th and As

All EIs addressed by ICH Q3D, other than arsenic and thallium, are associated with low CBA (≤ 1%). For these EIs, a CMF of 10 is applied.

For EIs with ≤ 1% CBA, the adjusted CBA is 1% x 10 = 10%
Divide the parenteral BA by the adjusted CBA to derive the CMF
100%/10% = 10
Cutaneous PDE = Parenteral PDE X CMF
Cutaneous PDE = Parenteral PDE X 10

See Table 1 for cutaneous PDEs for individual EIs.

4.2.2 Derivation of PDE for arsenic

For inorganic arsenic, the available data indicate that the percutaneous absorption is greater than that observed for most other EIs (approximately 5%). Based on this, the CMF for arsenic is 2.

Derive the adjusted CBA: 5% x 10 = 50%
Divide parenteral BA by the adjusted CBA to derive the CMF
100%/50% = 2
Cutaneous PDE = Parenteral PDE X CMF
Cutaneous PDE = 15 μg/d x 2 = 30 μg/d

4.2.3 Derivation of PDE for thallium

Thallium is highly absorbed through the skin but quantitative data are not available; it is assumed to be effectively equivalent to parenteral levels. Since the adjusted PDE equals the parenteral PDE, a CMF of 1 is used.

Parenteral PDE = 8 μg/d
Cutaneous PDE = 8 μg/d x 1 = 8 μg/d

Parenteral PDE calculations already include safety factors F1-F5 or are derived from MRLs, (see Appendix 1of ICH Q3D) used to account for variability and extrapolation. Therefore, no further adjustments are necessary for the cutaneous PDE.

The derived cutaneous PDEs are listed in Table 1.

5 CUTANEOUS CONCENTRATION LIMITS FOR NI AND CO

The concentrations of EIs generally present in cutaneous products as impurities are not considered to be sufficient to induce sensitization. However, a concentration limit in addition to the PDE is warranted for Ni and Co to reduce the likelihood of eliciting skin reactions in already sensitized individuals. For other EIs such as Cr, the threshold to elicit a sensitizing response is either approximately equal to the cutaneous PDE (Cr) or much greater than the cutaneous PDE and therefore do not require additional controls (Nethercott et al., 1994).

The dermal concentration limit of 0.5 µg/cm$_2$/wk for Ni was originally established by Menné et al., (1987) as a detection limit in the dimethylglyoxime (DMG) test. The use of nickel in articles intended for direct and prolonged skin contact was regulated by this limit under the EU countries Nickel regulations and under EU Nickel Directive (currently, REACH, Entry 27, Annex XVII). After implementation of the directive, the prevalence of Ni allergy decreased significantly (Thyssen et al., 2011; Ahlström et al., 2019). Although the limit does not completely prevent the elicitation of Ni allergy, the cutaneous concentration of Ni in the drug products should be less than the limit. As the limit is defined as a migration limit from the consumer articles, the cutaneous and transdermal concentration limit (CTCL) of 35 µg/g drug product is calculated based on application of 0.5g and 250 cm$_2$ (Long and Finlay, 1991), as below. A similar limit is applicable to minimize elicitation of allergies to Co (Fischer et al, 2015).

0.5 µg/cm$_2$/wk = 0.07 µg/cm$_2$/d
0.07 µg/cm$_2$/d x 250 cm$_2$ = 17.5 µg/d
17.5µg/d/0.5 g = 35 µg/g

6 PRODUCT RISK ASSESSMENT

Product assessments for cutaneous drug products should be prepared following the guidance provided in ICH Q3D Section 5. Except for Ni and Co, the considerations of potential sources of EI, calculation options and considerations for additional controls are the same for products for the cutaneous route of administration as for products for the oral, parenteral and inhalation routes of administration.

For Ni and Co, in addition to considering the EI levels in the drug product relative to the PDE, the concentration of this EI (µg/g) in the drug product must be assessed relative to the CTCL identified in Table 1. The product risk assessment should therefore confirm that the total Ni and Co level (µg/day) is at or below the PDE and that the respective concentration in the drug product do not exceed the CTCL shown in Table 1.

As described in ICH Q3D Section 5.2, the drug product risk assessment is summarized by reviewing relevant product or component specific data combined with information and knowledge gained across products or processes to identify the significant probable EIs that may be observed in the drug product.

The summary should consider the significance of the observed or predicted level of the EI relative to the PDE of the EI and in the case of Ni and Co, the Ni- and Co-CTCL. As a measure of the significance of the observed EI level, the control threshold, a level that is 30% of the established PDE and CTCL (for Ni and Co) in the drug product provides guidance on when adequate control of EI have been established. The control threshold may be used to determine if additional controls may be required. If the observed or predicted EI level (µg/day) or CTCL (µg/g) is at or below the control threshold limit(s), then additional controls are not required, provided the applicant has appropriately assessed the data and demonstrated adequate controls on EI needed.

Other considerations in developing the product risk assessment for dermal products.

Dermal products are somewhat unique (relative to oral, parenteral or inhalation products) in that in some cases, the drug product can be removed or rinsed from the treated area. In evaluating the potential EIs to which the patient may be exposed, it may be important to evaluate the retention time of the drug product during typical use conditions. For example, certain products e.g. shampoos, have a short retention time and thus the risk assessment can be used to propose an adjustment dependent on a retention factor (see Module 1 of the ICH Q3D training package for more information on retention time; https://www.ich.org/products/guidelines/quality/article/quality-guidelines.html). If the PDE is adjusted in this manner, the new level proposed should be referred to as an Acceptable Level and is subject to consideration by the relevant authorities on a case by case basis.

7 CUTANEOUS PDE VALUES

Table 1 PDE by the cutaneous route

		PDE (µg/day)					CTCL
element	Class	oral	parenteral	inhalation	Cutaneous	Cutaneous conc[1] µg/g	µg/g
Cd	1	5	2	3	20	2	-
Pb	1	5	5	5	50	5	-
As	1	15	15	2	30	3	-
Hg	1	30	3	1	30	3	-
Co	2A	50	5	3	50	5[2]	35
V	2A	100	10	1	100	10	-
Ni	2A	200	20	5	200	20	35
Tl	2B	8	8	8	8	8	-
Au	2B	100	100	1	1000	100	-
Pd	2B	100	10	1	100	10	-
Se	2B	150	80	130	800	80	-
Ag	2B	150	10	7	100	10	-
Pt	2B	100	10	1	100	10	-
Li	3	550	250	25	2500	250	-
Sb	3	1200	90	20	900	90	-
Ba	3	1400	700	300	7000	700	-
Mo	3	3000	1500	10	15000	1500	-
Cu	3	3000	300	30	3000	300	-
Sn	3	6000	600	60	6000	600	-
Cr	3	11000	1100	3	11000	1100	-

[1]PDE expressed in concentration terms, calculated using a 10 g daily dose; [2]The calculated cutaneous concentration of 5 µg/g is based on a 10 g dose; a 1 g dose would permit a daily concentration of 50 µg/g, exceeding the CTCL of 35 µg/g. In this situation, the CTCL limit should be used. Ni should be treated in a similar manner.

8 REFERENCES

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