Applying Q3D to Other Routes of Administration

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Guiding principles in initiating the route dependent safety assessment

• Consider the oral PDEs in Appendix 3 as a starting point
  – Based on a scientific evaluation, the parenteral and inhalation PDEs may be a more appropriate starting point.
• Assess if local effects are expected when administered by the intended route of administration.
  – If local effects are expected, a modification to an established PDE may be necessary.
  – Consider the doses/exposures at which these effects can be expected relative to the adverse effect that was used to set an established PDE.
• If local effects are not expected, no adjustment to an established PDE is necessary.
Guiding principles in initiating the route dependent safety assessment (cont)

• If available, evaluate the bioavailability of the element via the intended route of administration and compare this to the bioavailability of the element by the route with an established PDE.

• When a difference is observed, a correction factor may be applied to an established PDE. For example, when no local effects are expected, if the oral bioavailability of an element is 50% and the bioavailability of an element by the intended route is 10%, a correction factor of 5 may be applied.

• If a PDE proposed for the new route is increased relative to an established PDE, quality attributes may need to be considered.
Examples

- Example 1: whole body lotion
  - Example 1a: whole body lotion with elemental impurities having a range of reported bioavailabilities
- Example 2: topical face cream
- Example 3: ear drops
- Example 4: elemental impurity with local toxicity
  - Example 4a: elemental impurity with no information available on local toxicity
- Example 5: ophthalmic product with systemic exposure
Retention factors

• The retention factor was introduced by the SCCNFP to take into account rinsing off and dilution of finished products by application on wet skin or hair (e.g. shower gels, shampoos, …) [SCCNFP/0321/00; http://ec.europa.eu/food/fs/sc/sccp/out130_en.pdf]
• Range from 0.01 (1%, e.g., shampoo) to 1 (100%, e.g., face cream)
• Other similar terms: exposure time, duration of contact
• Available from the public literature and from government sources
  – SCCS/1501/12
  – Api, Basketter, Cadby et al, 2008
  – SCCNFP/0690/03
• Retention factor is not bioavailability!
Example 1: Whole body lotion

- Whole body lotion; 30 g/d
- Scenario:
  - No skin breaks
  - No penetration enhancers
  - No systemic absorption of the API
  - For external use
  - Application 3-4 times per day
  - Product is designed to sit on skin surface (retention factor = 1)
  - No local elemental impurity toxicity
- This example uses an estimate of daily application obtained from regulatory/literature sources.
Example 1 (cont)

- Investigate scientific literature/regulatory sources for estimates of daily exposure (e.g., SCCS1501/12, http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/scs_s_006.pdf)
- Oral PDE = 100 µg/d; oral absorption is 100% oral, 5% dermal

- Calculate Systemic Exposure = Oral PDE / Dermal absorption
- Proposed Acceptable Intake EI X = 100 µg/d / 0.05 = 2000 µg/d
- Concentration: 2000 µg/d / 30 g/d = 67 µg/g
- Note that the number of times applied per day is factored into the equation of total amount administered per day (30 g)
Example provided during Step 3

**UV protection face cream (female)**

**Exposure**

Daily exposure determined by habits and practices data (from US EPA Exposure Handbook and 90\textsuperscript{th} percentile usage data from Colipa as reported in Api et al., 2008) \textsuperscript{7}.

- Retention factor = 1.0 (i.e., leave-on product)
- Product exposure = 1,500 mg/day or 2.70 mg/cm\textsuperscript{2}/day
- Default body weight = 60 kg
- Product exposure is 25 mg/kg/day = A in calculations
- Surface area of application = 555 cm\textsuperscript{2}
- Percutaneous absorption of lead = 0.3\% (Moore et al., 1980)\textsuperscript{5} which is DA\textsubscript{p} after dividing by 100 in calculations.
**Example continued**

*Lead limits in a leave-on face cream OTC drug*

**SED** = Systemic Exposure Dose = ICH Parenteral PDE for Pb = 5 μg/day (ICH Q3D Step 2b, 2013) divided by body weight (e.g., 60 kg for an adult female) = 83 x 10⁻⁶ mg/kg/day.

C = (% Pb concentration/100) in calculations that results in an equivalent parenteral Pb exposure to parenteral PDE.

\[
C = \frac{SED}{(A)(DA_p)} = \frac{(83 \times 10^{-6} \text{ mg/kg/day})}{(25 \text{ mg/kg/day})(0.003)} = 0.0011 \text{ or } 0.11\%.
\]

Thus, a topical face cream with UV protectant can have up to 1,100 ppm Pb to equal the parenteral PDE limit for lead. This is explained by the limited dermal penetration rate of 0.3% versus 100% availability when administered parenterally.
FDA approach

- Parenteral PDE for lead 5 ug/d (should use the oral PDE but it is the same # for lead)
- Retention factor = 1 for a leave-on product
- Bioavailability 0.3%
- Dermal Exposure = 1500 mg/d (from EU cosmetics guideline)

- AI dermal = 5 ug/d x 1 / 0.003 = 1667 ug/d

- Concentration = 1667 ug/d / 1500 mg/d = 1.1 ug/mg = 1100 ug/g
  = 1100 ppm
Example 1a

• Instead of a fixed bioavailability, a range for bioavailability of 40-65% is reported in the literature.
• Preferred options
  – Use the low end of 40%
  – Other approaches may be acceptable if scientifically justified
Example 2: Topical face cream

- Facial cream in a 1 oz (28 g) tube
- Scenario:
  - No skin breaks
  - No penetration enhancers
  - No systemic absorption of the API is detected
  - For external use only for up to 7 days (1 tube)
  - Application 3-4 times per day
  - Product is designed to be stay on skin (retention factor 1)
  - Oral bioavailability 100%; dermal 50%
  - No local elemental impurity toxicity
- This example uses a label recommendations to determine the concentration of elemental impurity in the product.
Example 2 (cont)

- To set an Acceptable Intake use the oral PDE and adjust for bioavailability of 50% (0.5) and a retention factor of 1
- Dermal PDE elemental impurity $X = 100 \mu g/d \times 0.5 \times 1 = 200 \mu g/d$
- $28 \text{ g} / 7 \text{ d} = 4 \text{ g/d}$
- Concentration $200 \mu g/d / 4 \text{ g/d} = 50 \mu g/g$
Example 3: ear drops

- Risk assessment indicates 2 elemental impurities may be present
- A search of the scientific literature indicates no route specific toxicity is expected
- Elemental impurity X:
  - High bioavailability by this route; parenteral PDE proposed
- Elemental impurity Y:
  - Low systemic bioavailability by this route (<1%); oral PDE proposed
Example 4: Elemental Impurity with local toxicity

- DP via SC route
  - Sarcomas at the site of injection when EI-X administered in a 90 day toxicology study in rats by the SC route
    - NOEL for sarcomas is 1 mg/kg/d when administered 3 x/wk
    - No tumors other than injection site noted
    - Suspected mechanism is local irritation
  - To derive an acceptable intake, apply the modifying factors as outlined in Appendix 1.
    - F1 = 5; F2 = 10; F3 = 5; F4 = 10; F5 = 1
    - Adjust for 7 days of dosing
    - AI = 9 ug/d
Example 4a – elemental impurity with no information on local toxicity

- Dermal product with a retention factor of 0.5
- No information about bioavailability
- Consider the formulation
  - Penetration enhancers used (product intended to have systemic effects) – start with parenteral PDE
  - No penetration enhancers (product intended for local use) – start with oral PDE
- Use the retention factor to adjust the proposed acceptable intake
Example 5: An ophthalmic with systemic exposure

- Intravitreal injection
- No local ocular toxicity
- Systemic toxicity was renal tubular necrosis when administered IV
- DS is detected systemically
- Apply the parenteral PDE
Thank You!