Module 1

Developing an Acceptable Level for Other Routes of Administration

ICH Q3D Elemental Impurities

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

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Outline

- **General guiding principles**
- **Considerations for some topical products**
  - Examples to illustrate principles
    - Topical dermal
    - Ear drops
- **Considerations for ophthalmologic drug products**
  - Example: Eye drop

General approach to developing a Route-Specific Acceptable Level (AL)

Guiding principles in initiating the route-dependent safety assessment

- Consider the oral Permitted Daily Exposures (PDEs) in Appendix 3 as a starting point
  - Consider the intended effect of the product – local (anti-itch cream) or systemic (nicotine patch)
  - The parenteral PDE may be the appropriate starting point if high bioavailability of the DP is intended
- Assess if local effects are expected when administered by the intended route of administration.
  - If local effects are expected, a modification of established an oral 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 oral PDE.
- If local effects are not expected, adjustment to an oral PDE may not be necessary.

Guiding principles in initiating the route-dependent safety assessment (cont)

- Evaluate the bioavailability of the EI (if available) via the intended route of administration and compare this with the bioavailability of the EI of the oral PDE.
- When a difference is observed, a Correction Factor (CF) may be applied to an established oral 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.
- Evaluate the duration of exposure as an important contributor to exposure (see discussion around Retention Factors (RF), slide 8)
- If an acceptable level (AL) for the new route is increased relative to an established PDE, the impact on quality attributes may need to be considered.

Considerations for some topical dermal products

- Oral bioavailability overestimates dermal bioavailability
  - The gastrointestinal tract is designed to solubilize and absorb material
  - The dermal system is a barrier to absorption, leading to lower bioavailability, and thus may justify a higher AL than the PDE determined for the oral route
- In some cases (e.g., Ni), a lower starting point than the oral PDE may be needed to account for sensitisation and potential toxicity to the skin
- Use of penetration enhancers (e.g., some transdermal patches) may necessitate a lower starting point than the oral PDE
- Quality attributes may play a role in the final concentration in any topical drug Product (DP)!

Local and systemic considerations for topical dermal products

- Note: the following information was extracted from the scientific literature and/or Q3D monographs and may be useful under some situations, but should be tailored to any particular topical dermal DP
- Class 1 Elements: oral PDE (dose or concentration) may be sufficient for topical dermal DP
  - As: bioavailability estimates of 3% has been used in risk assessment
  - Cd: a default of 1% bioavailability is acceptable
  - Hg: up to 30% may be retained in the skin; systemic availability is unknown
  - Pb (inorganic): dermal absorption is negligible and a default of 1% may be acceptable
- Class 2/3 Elements: bioavailability and/or local toxicity concerns. Parenteral or inhalation PDE (dose or concentration) may need to be considered for some dermal DP
  - Tl: percutaneous absorption may occur through rubber gloves; the skin is a target organ after oral exposure
  - Platinoids (Pd, Pt, Rh, Ru, Ir), Ni, Ag, Sb have animal and/or human data suggesting local toxicity

References for slide 8

- Class 1 EI
  - National Environmental Policy Institute; Assessing the Bioavailability of Metals in Soil
  - for Use in Human Health Risk Assessments, 2000. (http://geoweb.tamu.edu/Faculty/Herbert/geol641/docs/MetalsBioavailability.pdf)
- Thallium
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  - Q3D monograph
- Platinoids
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  - Cristaudo, A., Sera, F., Severino, V., De Rocco, M., Di Lella, E., and Picardo, M. (2005). Occupational Hypersensitivity to Metal Salts, Including Platinum, in the Secondary Industry. Allergy. 60: 159–164.
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- Nickel
  - Hindsen M, Bruze M, Christensen OB. Flare-up reactions after oral challenge with nickel in relation to challenge doses and intensity and time of previous patch test reactions. J Am Acad Dermatol. 2001; 44(4):616-23.
  - Jensen CS, Menne T, Lisby S, et al. Experimental systemic contact dermatitis from nickel: A dose-response study. Contact Dermatitis. 2003; 49(3):124-32.
- Gold
  - Russell, M.A., Langley, M., Truett, A.P., King, L.E., and Boyd, A.S. (1997). Lichenoid Dermatitis after Consumption of Gold-Containing Liquor. J. Amer. Acad. Derm. 36(5): 841-844.
- Antimony
  - Agency for Toxic Substances and Disease Registry (1992). Toxicological Profile for Antimony and Compounds. Accessed through Expub at http://www.expub.com/ in February, 2015.

Examples

- Examples for some topical products
  - Example 1: whole body cream
  - Example 2: whole body cream
  - Example 3: topical face cream
  - Example 4: ear drops
  - Example 5: EI with local toxicity
  - Example 6: anti-itch cream
  - Example 7: eye drop

Retention factors

- The time a product remains at the location it is administered (retention time) needs to be considered.
  - For skin, the retention factor (RF) is related to dose/exposure as discussed in section 3.2 of Q3D
  - Retention factors ≠ bioavailability!
  - Other similar terms to retention factor: exposure time, duration of contact
- The retention factor was introduced by the Scientific Committee on Cosmetic Products and Non-Food Products (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)
- Sources:
  - SCCS/1501/12
  - Api, Basketter, Cadby et al, 2008
  - SCCNFP/0690/03

Example 1: Whole body cream

- Whole body lotion applied at 3-4 times per day (based on surveys) for a total of 30 gm/day
- Scenario for this example:
  - Intact skin only
  - Product is designed to sit on skin surface (RF = 1)
  - No penetration enhancers
  - No systemic absorption of the API
  - No local elemental impurity toxicity reported
- This example uses an estimate of daily application (30 gm/day, 3-4 times/day) obtained from regulatory/literature sources and not a labeled dose (e.g., apply as needed).

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/sccs_s_006.pdf)
- Oral PDE of Element X = 100 µg/day; oral absorption is 100%, 5% dermal absorption
- Calculate Systemic Exposure = Oral PDE x CF (correction factor; see section 3.2 of Q3D and slide 6)
- AL for EI X = 100 µg/day x (1 / 0.05) = 2000 µg/day
- Concentration: 2000 µg/day / 30 g/day = 67 µg/gm
- Note that the number of times applied per day and surface area are factored into the equation of total amount administered per day (30 gm).

Example 2: whole body cream

- Instead of a fixed bioavailability of 5%, a range for bioavailability of 40-65% is reported in the literature.
- Preferred options
  - Use the high end of 65%
  - Other approaches may be acceptable if scientifically justified

Example 3: Topical face cream

- Facial cream in a 28 gm (1 oz) 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, 4 gm/day)
  - Application 3-4 times per day
  - Product is designed to stay on skin (RF = 1)
  - Oral bioavailability 100%; dermal 5%
  - No local elemental impurity toxicity
- This example uses a label recommendation to determine the concentration of elemental impurity in the product.

Example 3 (cont)

- To set an AL, use the oral PDE and adjust for bioavailability of 5% (0.05) and Retention Factor = 1
- AL = PDE x CF x RF
- AL EI X = 100 µg/day x (1 / 0.05) x 1 = 2000 µg/day
- According to the label, the tube of 28 gm is to be used 3-4 times per day over 7 days, or 4 gm/day
- Concentration 2000 µg/day / 4 gm/day = 500 µg/gm

Example 4: ear drops

- Risk assessment indicates 2 elemental impurities may be present
- A search of the scientific literature indicates no route specific toxicity is expected
- Determination of starting PDEs for derivation of ALs may be different for different EIs
  - EI X:
    - High bioavailability by this route; parenteral PDE proposed as the starting point
  - EI Y:
    - Low systemic bioavailability by this route (<1%); oral PDE proposed as the starting point

Example 5: elemental impurity with local toxicity

- Drug product delivered via subcutaneous (SC) route
  - Sarcomas at the site of injection when EI X administered in a 90 day toxicology study in rats by the SC route
    - No observed effect level (NOEL) for sarcomas is 1 mg/kg/day when administered 3 x/wk by the SC route
  - No tumors were observed other than at the injection site
  - Suspected mechanism for sarcoma development is local irritation
  - To derive an AL, 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
    - A factor of 10 for F4 was used since sarcomas are seen at the site of injection
  - AL = 1 mg/kg/day x 50 kg x (3 day/7 day) / 5 x 10 x 5 x 10 x 1 = 9 µg/day

Example 6: anti-itch cream for poison ivy

- Scenario
  - No skin penetration of API
  - No absorption enhancers
  - No occlusion; keep away from eyes and mouth
  - Apply as needed (approximate dose is 3 grams/day over 10% body surface area)
  - Retention Factor (RF) = 1
  - Correction Factor (CF) applied (see slide 6)
  - Class 1 EI detected: Hg (1 µg/gm) and Pb (2.5 µg/gm)
  - Class 2 EI detected: Tl (50 µg/gm)

Example 6: anti-itch cream for poison ivy (cont)

- Additional information on bioavailability and toxicity from the scientific literature
  - Hg: up to 30% may be retained in the skin; systemic availability is unknown (NERA, 2000; IPCS, 1996); dermal reactions with liquid elemental Hg are rare (ATSDR Medical Management Guide, 2014; http://www.atsdr.cdc.gov/MMG/MMG.asp?id=106&tid=24)
  - Pb (inorganic): dermal absorption is negligible and a default of 1% may be acceptable (NEPI, 2000); no evidence of local dermal toxicity (ATSDR Environmental Health and Medicine, 2012; http://www.atsdr.cdc.gov/csem/csem.asp?csem=7&po=0)
  - Tl: percutaneous absorption may occur through rubber gloves; high dermal solubility of Tl salts (> 80%); no local effects after skin exposure (IPCS, 1996; Q3D monograph for Tl; http://www.cdc.gov/niosh/ershdb/emergencyresponsecard_29750026.html)

Example 6: anti-itch cream for poison ivy (cont)

- Exposure/day
  - Hg: 3 µg/day; Pb: 7.5 µg/day; Tl: 150 µg/day
- Assessment: calculation of AL for this DP
  - Note: not an ICH Q3D-derived PDE or AL; example for illustrative purposes only
  - Hg: Using the oral PDE of 30 µg/day, a 30% dermal bioavailability and a 10% oral bioavailability, an AL of 10 µg/day may be acceptable
    - CF applied; RF = 1
    - 30 µg/day x (0.1 / 0.3) x 1 = ~ 10 µg/day
    - Conclusion: 3 µg/day is an AL for this DP
  - Pb: Using the oral PDE of 5 µg/day, 100% oral bioavailability and 1% dermal bioavailability, an AL of 500 µg/day may be acceptable
    - 5 µg/day x (1 / 0.01) x 1 = 500 µg/day
    - Conclusion: 7.5 µg/day is an AL for this DP
  - Tl: Using the oral PDE of 8 µg/day, and an oral and dermal bioavailability of 100%, an AL of 8 µg/day is calculated
    - 8 µg/day x (1 / 1) x 1 = 8 µg/day
    - Conclusion: Additional control measures or further safety justification is needed

Considerations for ophthalmologic DPs

- There is very little information available on toxicity of EI by ophthalmological routes of administration. Since the eye is a very sensitive organ, the oral PDE may not be the appropriate starting point.
- Assessment of the acceptability of EI in ophthalmological products needs a route-specific evaluation. Factors to consider include, but not limited to:
  - bioavailability (to the eye and the amount that exits from the eye)
  - retention time in the eye
  - vehicle of the DP (e.g. viscosity)
  - local toxicity to the eye and its adnexa
- EI levels for ophthalmological products may be expressed as concentrations (µg/gm or ppm) and dose (µg/day or µg/dose); both are informative.
- EIs for ophthalmologic products will need to be considered on a case-by-case basis.

Example 7: Eye drops for dry eye

- Aqueous solution with increased viscosity (1.3 cP)
- Retention time in the eye ~ 1 hr
- No absorption, no API detected systemically
- One drop administered as needed (~50 µL), ~ 4 /day
- EI X detected in DP at 0.1 µg/mL (0.1 µg/gm)
  - Total daily exposure to the EI is 0.02 µg/day
  - IV and oral data available with EI X; no ocular toxicity noted in these reports; renal toxicity noted by IV dosing at 10 mg/kg
- Given the available data and the route of exposure, a daily exposure of 0.02 µg/day (0.1 µg/gm) is considered an AL in this DP.