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BfArM

ICH Q3D: How to Deal with Other Routes of Administration in the EU

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Outline

- **Guideline recommendation to determine route specific PDEs**

- **Examples how PDEs for “other routes” may be established**




ICH Q3D approach to other routes of administration

- **Route specific PDEs**
  - Established in Q3D for oral, parenteral, inhalation
  - No PDEs established for other routes
  - PDEs for other routes of administration need to be derived on a case by case approach




Other Routes of Administration in Q3D
Derive route specific PDEs

deriving PDEs for these other routes should follow the principles established for deriving PDEs for

- **oral, parenteral and inhalation**
  - use oral PDE as starting point to derive PDE
  - based on scientific evaluation parenteral or inhalation PDE may be more appropriate




Approaches recommended in ICH Q3D to derive route specific PDEs

factors for modification of established PDE

- **local effects to be expected?**
  - yes - assess if modification of PDE is necessary
  - consider doses/exposures at which local effects are expected vs. doses/exposure of AE used to set established PDE
  - no – no modification of established PDE necessary
- **bioavailability data of the element via the intended route available**
  - compare with bioavailability by route with established PDE
    - significant difference observed and no local effects expected
      - application of correction factor to established PDE possible
      - e.g. bioavailability for route with established PDE 50% and for intended route 10% - modification factor of 5 may be applied
- **before the PDE for the new route is increased compared to established PDE quality aspects may need to be considered**

EMA Guideline on the specification limits for residues of metal catalysts or metal reagents (EMEA/CHMP/SWP/4446/2000)

Approaches for other routes of administration

- **without proper justification, parenteral limits/PDEs should be used for pharmaceutical substances**
- **oral limits/PDEs may be applied if the absorption by other routes of administration is not likely to exceed the absorption following oral administration**
  - for example, for cutaneous administration, oral concentration limits/PDEs are considered acceptable.

Guidance of other areas may provide relevant information for other routes of administration

e.g. for dermal applications

European Scientific Committee on Consumer Safety (SCCS)

- **Note of Guidance for Testing of Cosmetic Ingredients for Their Safety Evaluation (SCCNFP/0321/00)**
  - Retention factor – a factor to estimate the amount of the product available for absorption through the skin
    - considers differences of use between rinse-off and non rinse-off products e.g.
      - Shampoos - rinse-off
      - Deodorants – non-rinse-off

Some retention factors and calculated daily exposure

product	estimated amount applied	Retention factor	Calculated daily exposure g/d
Shower gel	18.67 g	0.01	0.19
Face cream	1.54 g	1	1.54
Lip stick	0.057 g	1	0.057
Deodorant non-spray	1.5 g	1	1.5
Toothpaste	2.75 g	0.05	0.138

from SCCS Note for Guidance for Testing of Cosmetic Ingredients for Their Safety Evaluation (SCCS/1501/12)

Examples for deriving route specific PDEs

Example 1: Suppository for rectal application

Scientific advice procedure (before ICH Q3A sign off)

- **developed for treatment of chronic colorectal disease**
- **daily treatment**
- **daily dose 1000 mg**
- **requested spec. limits for metal catalyst residues**

elem		conc		daily intake
Pt	≤	10 ppm	≡	10 µg/d
Mn	≤	20 ppm	≡	20 µg/d
Ni	≤	30 ppm	≡	30 µg/d
Mo	≤	25 ppm	≡	25 µg/d

Example 1: Suppository for rectal application (cont)

- **PDEs according to "EMA metal catalysts" and ICH Q3A**

elem	PDE µg/d oral		PDE µg/d parenteral	
	EMA	ICH	EMA	ICH
Pt ≤	100	100	10	10
Mn ≤	2500	nd	250	nd
Ni ≤	250	200	25	20
Mo ≤	250	3000	25	1500

Example 1: Suppository for rectal application (cont)

- **local toxic effects are not expected at these level of elemental impurities**
- **no additional data on the rectal absorption of elements were provided**
- **according to the EMA guidance on metal catalysts parenteral PDEs may be used as starting point**
- **BfArM advice:**
  - the product is for rectal application and absorption may be expected not to be higher than by oral application
  - however without further data the recommendation would be to use the parenteral PDEs – to have a safe side approach
  - all limits except for Ni are acceptable – for Ni the limit should be set to 25 ppm




Example 1: Suppository for rectal application (cont)

would the advice be different now?

- **Mn did not remain in ICH Q3D due to low toxicity**
  - Mn would probably not anymore be part of the advice
- **PDE for Ni is tighter in ICH Q3D: parenteral PDE 20 µg/d**
- **ICH Q3D recommends oral PDE as a starting point for deriving route specific PDEs**

- **my guess would be the acceptance of the 30 ppm limit for Ni for the rectal route of administration**
  - although no additional data on rectal absorption have been presented it is unlikely that it will be higher than by oral administration

Example 1: Suppository for rectal administration – data variations

- **Absorption studies in disease model animals show enhanced absorption for Pt and Ni compared to wt via oral administration**
  - in this case parenteral limits would apply
  - the limits for Ni would have to be reduced to 20 ppm in the drug product

Example 2: Dermal gel intended for treatment of severe burns

- **open damaged skin**
- **short term treatment ≤ 5 single treatments on consecutive days**
- **treatment area ≤ 15 % of total body area**
- **applied amount of gel ≤ 10 gr**
- **metals identified in finished product**

elem	conc	max daily exposure
Pb	3 ppm	30 µg
As	6 ppm	60 µg
Ni	10 ppm	100 µg

Example 2: Dermal gel intended for treatment of severe burns (cont)

limits according to EMA metal catalysts" and ICH Q3A

elem	PDE µg/d oral			PDE µg/d parenteral		
	EMA	ICH	exc by	EMA	ICH	exc by
Pb ≤	na	5	6	na	5	6
As ≤	na	15	4	na	15	4
Ni ≤	250	200	0.5	25	20	5

Example 2: Dermal gel intended for treatment of severe burns (cont)

points to be considered

- **PDEs calculated for daily life long exposure**
- **short term exposure in this case ≤ 5 days**
- **higher PDEs possible for short term exposure**
  - e.g. 30 day or less
- **no local toxicity observed - dose/cm² is low**
- **skin barrier severely damaged**
  - without absorption data the precautionary approach is using parenteral PDEs

Example 2: Dermal gel intended for treatment of severe burns (cont)

- **the higher levels of potential daily intake of elemental impurities were accepted**
  - short term application up to 5 times max – cummulative exposure is very low
  - no local toxicity

Example 3: Creme for local parasite treatment

- **identified elemental impurities: Pb and As**
- **no penetration enhancers present**
- **Remains on the skin**
- **daily dose 1 g**
  - Retention factor = 1
  - dermal absorption of Pb 0.3% (Moore et al. 1980)
  - dermal absorption of arsenic 3 % (US EPA 2005)
  - No local effects expected
- **consider oral PDEs as starting point**
  - oral PDE Pb = 5 µg/d
  - oral PDE As = 15 µg/d

Example 3: shampoo for local parasite treatment

- **acceptable limit for Pb**
  - ADE: 5µg/d / 1 / 0.003 = 1667 µg/d
- **acceptable limit for As**
  - ADE: 15 µg/d / 1 / 0.03 = 500 µg/d
- **concentration limits**
  - Pb: 1667 µg/d / 1000 mg/d = 1.67 µg/mg = 1670 ppm
  - As: 500 µg/d / 1000 mg/d = 0.5 µg/mg = 500 ppm

Example 4: Elemental impurity with local toxicity

- **Drug product for i.m. injection**
  - route specific local toxicity data for the element:
    serious inflammation at site of application in 4 week study in monkeys
  - NOEL 3.5 mg/kg/d when applied once a week
  - Calculation of PDE by applying modifying factors

    F1 = 3, F2 = 10, F3 = 10, F4 = 10, F5 = 1

    adjust for weekly dosing

  acceptable PDE = (3.5 mg/kg/d / 7 * 50) / (3 * 10 * 10 *10 * 1)

    PDE = 7 µg/d

    if parenteral PDE is not lower than parenteral PDE applies

Thank you for your attention!