Administration by other routes and other safety aspects

Anja Slikkerveer, MD, PhD, ERT

EFPIA PDEG Expert for Q3D

Scientific Director Translational Science, Astellas Pharma Europe B.V.

5 April 2016

EMA London

Waiver

The content of this presentation has been taken from training modules 1 and 2, as posted on the ICH website. Where differences exist, it is recommended to refer to the ICH materials.

This presentation reflects my personal considerations based upon experience in the Q3D EWG and IWG, and does not reflect the opinion of Astellas Pharma BV.

Topics

- Acceptable limits for other routes of administration
- Exceeding PDE- is it safe?

Gold Waterfall,
Jinguashi, Keelung, Taiwan

Module 1

Developing an Acceptable Level for Other Routes of Administration

ICH Q3D Elemental Impurities

Disclaimer:
This presentation includes the authors' views on Elemental Impurities theory and practice.
The presentation does not represent official guidance or policy of authorities or industry.

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

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

- It is preferred to use Acceptable Level (AL) for any permitted daily exposure which is not in the stated in the Q3D guideline
- Training material is available (module 1)
- Methodology will be illustrated for the dermal route
  - Can be applied to other routes
- Very little data are available which are suitable to set route specific PDE
  - Common pitfalls are
    - Form of EI is not well-described or not relevant
    - Dose/exposure is not stated
  - Most commonly, the route specific AL will be a conversion from an existing PDE

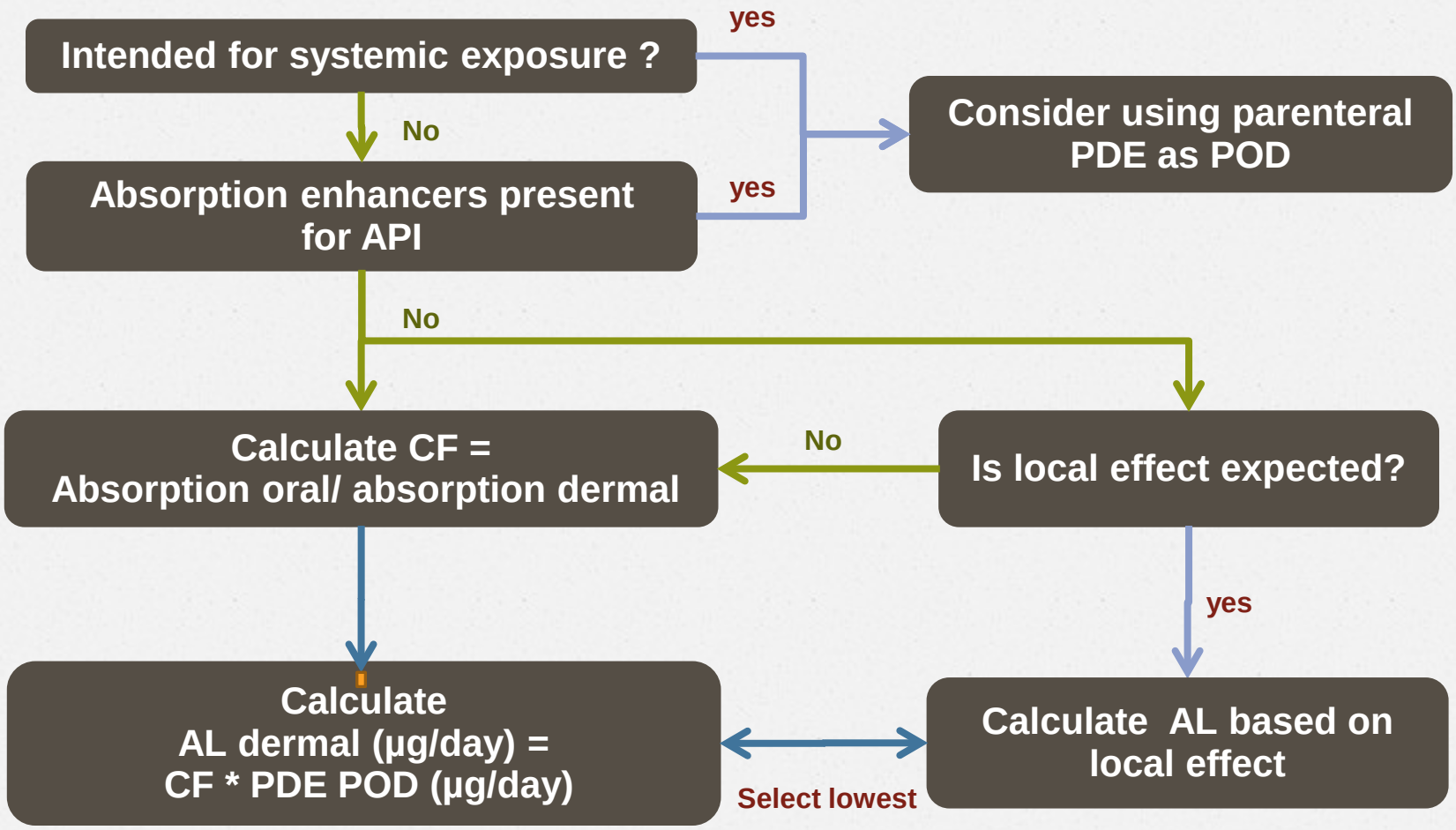
2 step approach for dermal AL

- **Step 1:** Derivation of a dermal AL in µg/day
  - Dependent on local toxicity
    - Compare to endpoint used for setting oral PDE
  - Point of departure is oral PDE
    - Exceptions exist e.g. for products with intended systemic exposure of API
  - Dependent on absorption by the dermal route as compared to the oral route
    - A conversion factor (CF) can be applied to correct
    - Calculate CF = Absorption oral/ absorption dermal
      - Use highest dermal absorption and lowest oral absorption values

- **Step 2**: Derivation of a permitted concentration (PC) in µg/g

Please note that if an dermal AL is increased relative to an established PDE, quality attributes may need to be considered.

Step 1: Dermal AL scheme



Step 2: Derivation of a permitted concentration (PC)

- Dependent on retention factor (RF) of product on the skin
- Dependent on daily dose of drug product
- Above parameters may vary dependent on disease and product leading to a series of permitted concentrations for one EI
  - Use of worst case approach can avoid this

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 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)

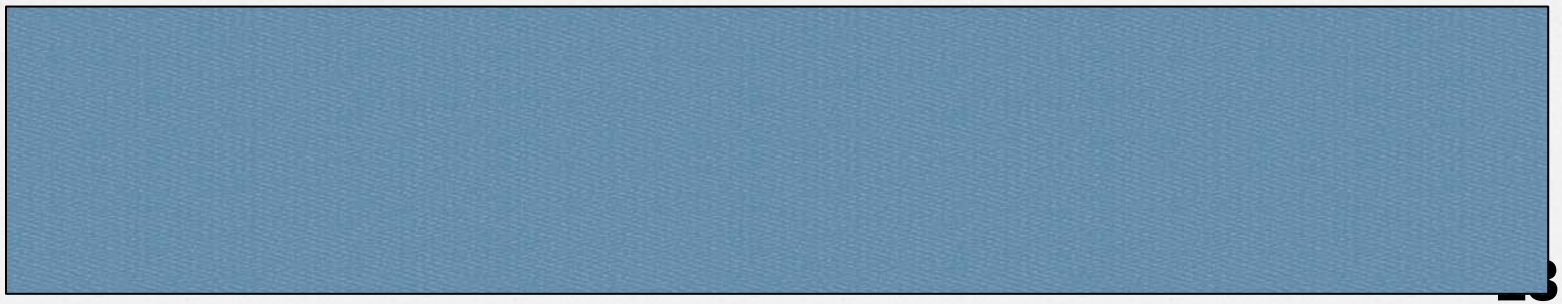
- To set an AL, use the oral PDE and adjust for bioavailability of 5% (0.05) and Retention Factor = 1
- AL = PDE x CF x RF
- AL El X = 100 µg/day x (1 / 0.05) x 1 = 2000 µg/day
- According to the label, the tube of 28 gm is to be used 3-4 times per day over 7 days, or 4 gm/day
- Concentration 2000 µg/day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

Example 1

- Product: Drug X: film-coated tablets
- Strengths: 50 mg
- Maximum daily dose : 100 mg
- Indication: chronic disease

- Risk assessment indicated that EI Z was used during synthesis of the drug substance
- EI Z in the drug substance is 40 µg/g

- Question: Does this result in an acceptable intake of EI Z?



Example 1 + answer

- Product: Drug X: film-coated tablets
- Strengths: 50 mg
- Maximum daily dose : 100 mg
- Indication: chronic disease

- Risk assessment indicated that EI Z was used during synthesis of the drug substance
- EI Z in the drug substance is 40 µg/g

- Question: Does this result in an acceptable intake of EI Z?

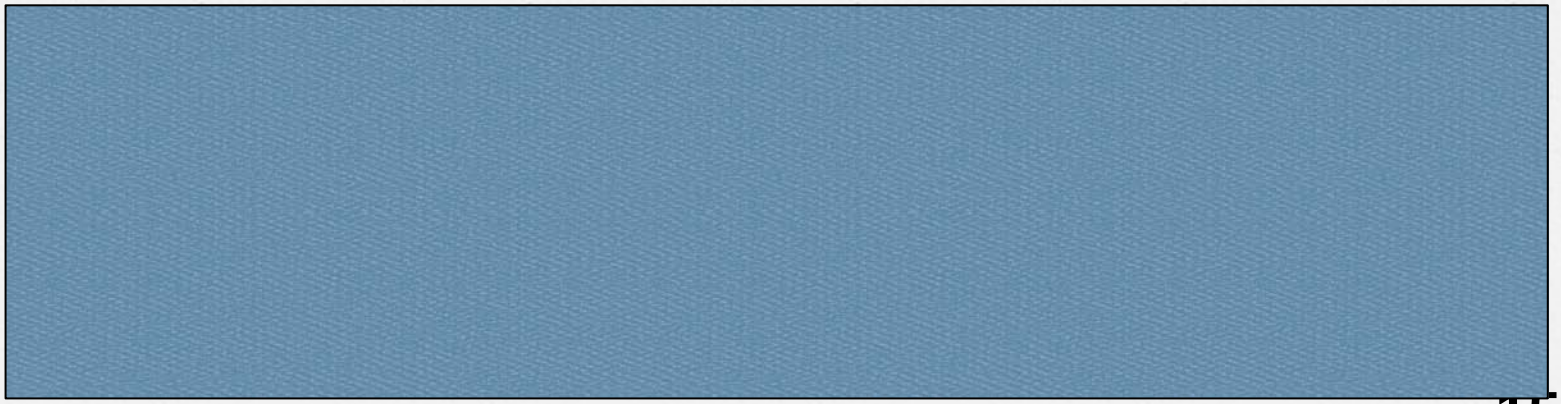
- Answer: Yes
  - Maximum daily dose of 100 mg contains 4 µg EI Z.
  - Oral PD for EI Z = 100 µg day

Example 2

- Product: Drug X: dermal cream
- Strengths: 10%
- Maximum daily dose : 10 g of drug product
- Indication: chronic disease

- EI Z in the drug substance is 40 µg/g

- Question: Does this result in an acceptable exposure to EI Z?



Example 2 + answer

- Product: Drug X: dermal cream
- Strengths: 10%
- Maximum daily dose : 10 g of drug product
- Indication: chronic disease

- EI Z in the drug substance is 40 µg/g

- Question: Does this result in an acceptable exposure to EI Z?

- Answer:
  - Permitted concentration is 300 µg/g: therefore acceptable
    - No dermal effects in literature for inorganic salts; dermal absorption negligible (~1%) ; Oral absorption= 30%
    - CF = oral absorption / dermal absorption = 30/ 1= 30
    - Dermal AL = CF * oral PDE = 30 * 100 = 3000 µg/day
    - Permitted Concentration = RF * dermal AL / Daily dose = 1 * 3000/ 10= 300 µg/g

Sources of reliable assessments

- SCCS = Scientific Committee on Consumer Safety
  http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- EFSA : European Food and Safety Authority
  http://www.efsa.europa.eu/
- IARC = International Agency for Research on Cancer.
  http://www.iarc.fr/
- IRIS = Integrated Risk Information System (US-EPA)
  http://www2.epa.gov/iris
- ATSDR = Agency for Toxic Substances and Disease Registry.
  http://www.atsdr.cdc.gov/
- NTP= national toxicology program

- < note: methodology needs to be reviewed before application to pharmaceutical; however the review are often very useful>

Module 2

Justification for Elemental Impurity Levels Higher than an Established PDE

ICH Q3D Elemental Impurities

Disclaimer:
This presentation includes the authors' views on Elemental Impurities theory and practice.
The presentation does not represent official guidance or policy of authorities or industry.

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

Guiding principles

- The PDEs derived under Q3D have been set to ensure that exposure to an element, which is present as an impurity in a drug product, is safe based on daily exposure over a lifetime.
- The calculations for the PDE were performed using the modifying factor approach (for detail see Guideline appendix 1).
- Typical steps are:
  1. Identify the most relevant study (animal or human)
  2. Identify the most relevant starting point (SP) for the calculation (NOEL, LOAEL etc.)
  3. Select appropriate modifying factors
  4. Calculation:
     PDE = SP x Mass Adjustment / [F1 x F2 x F3 x F4 x F5]

There is only one PDE per route

- Each element has only **one** set of established PDEs for oral, parenteral and inhalation routes of administration, which are specified in the Guideline.
- Although "Levels of elemental impurities higher than the PDE may be acceptable in certain cases", the acceptable level (AL) is not a PDE.

Considerations for acceptance of levels higher than established PDE

- Assessment needs to be prepared on a case-by-case basis, since it depends on the element, the formulation, the clinical use of the drug product, the patient population, etc
- Needs to be justified by a science and risk-based approach
- The higher levels need to have no unfavorable impact on the risk/ benefit/ quality profile of the drug product
- Is subject to regulatory review and approval

Examples for Risk-Based approaches

A. The subfactor approach (WHO, 2009), subdivides F2 into a subfactor for pharmacokinetics and a subfactor for pharmacodynamics

B. Modification of modifying factors used for the established PDE, which improve the alignment with the intended use profile

C. Replacing the study used to define the PDE with a more relevant study (based on exposure duration or route of administration)

Other approaches may be justified.

Note: all approaches will have to be supported by published references and/or proprietary data

A] Subfactor approach

- Described by the World Health Organisation (WHO)
  - WHO. Cobalt and inorganic cobalt compounds. Concise International Chemical Assessment Document. Inter-Organization Programme for the Sound Management of Chemicals (IOMC). WHO, 2006;69.
- This method allows F2 (which corrects for variation) to be written as F2 = F2.1 x F2.2
  - F2.1 represents pharmacokinetics and F2-2 pharmacodynamics
  - When no specific data are available: it is assumed that PK and PD aspects are equally important then the value of both is 3.16 ($10^{½}$)
  - Each F subfactor can range from 1 to 3.16
- The modification of F2.1 can e.g. be based on the elimination half-life relative to the administration duration or frequency
  - After 5 half-lives, a EI is considered to have been completely eliminated

Guideline example A1: subfactor approach: modifying factor

- This example illustrates that the subfactor approach may be used to calculated ALs from oral PDEs which were developed using the modifying factor approach
- Case: oral drug product contains 350 µg of Element X
- Established PDE in Q3D: Oral PDE of 220 µg/day
  - PDE (Oral) = 1.1 mg/kg/d x 50 kg / 5 x 10 x 5 x 1 x 1 = 220 µg/day
- F2.1 can be modified based on the dosing interval relative to the plasma elimination half life (5 days):
  - for a dosing schedule of once per week (~1 half-life) F2.1 could be decreased to 1.58 (50%)
  - for a dosing schedule of once a month (~ 5 half-lives) F2.1 could be decreased to 1
- Refer to Module 2 Annex for method of calculation of F2.1

Guideline example A1: subfactor approach: modifying factor (cont)

ALs for EI X can be calculated as follows:

- For once weekly dosing
  - F2 (modified) = F2.1 x F2.2 = 1.58 x 3.16 = 4.99 ~5

    AL = 1.1 mg/kg/d x 50 kg / 5 x ***5*** x 5 x 1 x 1 = 440 µg/day

    For practical purposes, this value is rounded to ~400 µg/day.

- For once monthly dosing
  - F2 (modified) = F2.1 x F2.2 = 1 x 3.16 = 3.16
  - AL = 1.1 mg/kg/d x 50 kg / 5 x ***3.16*** x 5 x 1 x 1 = 611 µg/day ~ 600 µg/day

Subfactor approach: further applications

- Subfactor approach may be used to calculate ALs where the oral PDEs were developed using human Minimal Risk Levels (MRLs). In the derivation of MRLs modifying factors have already been applied.

- For intermittent dosing: F2.1 can be modified based on the dosing interval relative to the plasma elimination half-life
- Example:
  - Elimination half life = 9.5 days
  - Dosing interval once weekly = 7 days
  - Ratio dosing interval/ half-life =7/10= 0.74
  - F2.1~2.28 and F2 (modified) = F2.1 x F2.2 = 2.33 x 3.16 = 7.20
  - Oral AL = 0.12 mg/kg/d x 50 kg / 1 x 7.20 x 5 x 1 x 1 = 167 µg/day

Ratio (Dosing interval / t1/2)	F2-1	F2@ (F2-1*F2-2)
0.10	3.02	9.54
0.25	2.82	8.91
0.50	2.53	7.99
0.75	2.28	7.20
1.00	2.08	6.57
2.00	1.54	4.87
5.00	1.07	3.38

Other approaches

- Modification of modifying factors (option B)
  - PDEs were developed for lifetime exposure
  - Modifying factors can be adjusted to consider non-chronic use:
  - Changes in F3 (duration) or F4 (severity)
- Change in most relevant study- Point of Departure (POD) (option C)
  - “New” relevant data (internal study or post Q3D published data)
  - Good quality study for a more relevant duration of exposure
    - Changes in dose at NO(A)EL, and all F.

Conclusions

- The intent of Q3D is to develop PDEs and a mechanism to control for EIs
- Development of ALs may be acceptable in certain cases. These cases could include, but are not limited to, the following situations:
  - Intermittent dosing;
  - Short term dosing (i.e., 30 days or less);
  - Specific indications (e.g., life-threatening, unmet medical needs, rare diseases)
- Strong rationale should be provided
  - Rationale should include, but not limited to:
    - Rationale for higher level
    - Statement on impact on DP safety, efficacy and/or quality
- ALs are subject to review and approval by regulatory agencies/authorities

Questions

Backup slides

Annex Module 2

Derivation of F2-1 percentages

- Basis for calculation
  - It can be assumed that the remaining amount is negligible after a period of 5 times the elimination half life (t1/2).
  - The extent of possible accumulation (Rac) can be described by
    Rac = 1 / (1 – 0.5 ^ (dosing interval / t1/2)).
    - Rac reduces to 1 as the dosing interval becomes larger and increases to infinity at a dosing interval close to 0.
  - F2.1 can be calculated from this as
    - F2.1= 1 + 2.16 x (Rac – 1) / Rac,
    - When Rac is infinite then F2.1= 3.16 and when Rac is reduced to 1: F2.1 becomes 1.

Typical values for F2-1

Ratio (Dosing interval / t1/2)	F2-1	F2@ (F2-1*F2-2)
0.10	3.02	9.54
0.25	2.82	8.91
0.50	2.53	7.99
0.75	2.28	7.20
1.00	2.08	6.57
2.00	1.54	4.87
5.00	1.07	3.38

@: F2-2 is 3.16 in all cases