

Module 2

Justification for Elemental Impurity Levels Higher than an Established PDE

ICH Q3D Elemental Impurities

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Section 3.3 Justification for Elemental Impurity Levels Higher than an Established PDE

- **Levels of elemental impurities higher than an established PDE (see Table A.2.1) 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).
- **Examples of justifying an increased level of an elemental impurity using a subfactor approach of a modifying factor (Ref. 2,3) are provided below. Other approaches may also be used to justify an increased level. Any proposed level higher than an established PDE should be justified on a case-by-case basis.**

Wording in guideline

Guideline Example 1

- **Element X is present in an oral drug product. From the element X monograph in Appendix 3, a No-Observed-Adverse-Effect Level (NOAEL) of 1.1 mg/kg/day was identified. Modifying factors F1-F5 have been established as 5, 10, 5, 1 and 1, respectively. Using the standard approach for modifying factors as described in Appendix 1, the PDE is calculated as follows:**
- **$PDE = 1.1 \text{ mg/kg/d} \times 50 \text{ kg} / 5 \times 10 \times 5 \times 1 \times 1 = 220 \text{ } \mu\text{g/day}$**
- **Modifying factor F2 (default = 10) can be subdivided into two subfactors, one for toxicokinetics (TK) and one for toxicodynamics, each with a range from 1 to 3.16. Using the plasma half-life of 5 days, the TK adjustment factor could be decreased to 1.58 for once weekly administration (~1 half-life), and to 1 for administration once a month (~5 half-lives). Using the subfactor approach for F2, the proposed level for element X administered once weekly can be calculated as follows:**
- **$\text{Proposed level} = 1.1 \text{ mg/kg/d} \times 50 \text{ kg} / 5 \times (1.6 \times 3.16) \times 5 \times 1 \times 1 = 440 \text{ } \mu\text{g/day}$**
- **For practical purposes, this value is rounded to 400 $\mu\text{g/day}$.**

Wording in guideline

Guideline Example 2

- The TK adjustment factor approach may also be appropriate for elemental impurities that were not developed using the modifying factor approach
- For element Z, a Minimal Risk Level (MRL) of 0.02 mg/kg/day was used to derive the oral PDE. From literature sources, the plasma half-life was reported to be 4 days. This element is an impurity in an oral drug product administered once every 3 weeks (~ 5 half-lives). Using first-order kinetics, the established PDE of 1000 µg/day is modified as follows:
- Proposed level = $0.02 \text{ mg/kg/d} \times 50 \text{ kg} / 1/3.16 = 3.16 \text{ mg/day}$
- For practical purposes, this value is rounded to 3000 µg/day.

Wording in guideline

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:
$$\text{PDE} = \text{SP} \times \text{Mass Adjustment} / [\text{F1} \times \text{F2} \times \text{F3} \times \text{F4} \times \text{F5}]$$

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 $F2 = F2.1 \times F2.2$
 - 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 ($10^{1/2}$)
 - 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 calculate 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
 - $\text{PDE (Oral)} = 1.1 \text{ mg/kg/d} \times 50 \text{ kg} / 5 \times 10 \times 5 \times 1 \times 1 = 220 \text{ µg/day}$
- 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
 - $F2 \text{ (modified)} = F2.1 \times F2.2 = 1.58 \times 3.16 = 4.99 \sim 5$
 - $AL = 1.1 \text{ mg/kg/d} \times 50 \text{ kg} / 5 \times 5 \times 5 \times 1 \times 1 = 440 \text{ } \mu\text{g/day}$
 - For practical purposes, this value is rounded to $\sim 400 \text{ } \mu\text{g/day}$.
- For once monthly dosing
 - $F2 \text{ (modified)} = F2.1 \times F2.2 = 1 \times 3.16 = 3.16$
 - $AL = 1.1 \text{ mg/kg/d} \times 50 \text{ kg} / 5 \times 3.16 \times 5 \times 1 \times 1 = 611 \text{ } \mu\text{g/day} \sim 600 \text{ } \mu\text{g/day}$

Guideline Example A2: subfactor approach: oral MRLs

- This example illustrates that the 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.
- Case: oral DP dosed once every three weeks contains EI Z
- Established PDE in Q3D: Oral PDE of 1000 µg/day
 - $\text{PDE (Oral)} = 0.02 \text{ mg/kg/d (MRL)} \times 50 \text{ kg} = 1000 \text{ µg/day}$
- Based on the dosing interval relative to the plasma elimination half-life (4 days), F2.1 can be modified from 3.16 to 1 (~5 half lives, defaults to a minimum of 1). F2.2 remains 3.16.
 - $\text{F2 (modified)} = \text{F2.1} \times \text{F2.2} = 1 \times 3.16 = 3.16$
 - $\text{AL} = \text{oral PDE} \times (\text{modified F2} / \text{original F2})$
 - $\text{AL for Z} = (0.02 \text{ mg/kg/d} \times 50 \text{ kg}) \times (3.16/10) = 1000 \text{ µg/day} \times 0.316 = 316 \text{ µg/day} \sim 300 \text{ µg/day}$

Example A3: subfactor approach: intermittent dosing

- This example illustrates that the subfactor approach can be applied to indirectly calculated PDEs like IV PDEs derived by division by 10.
 - The factor 10 is the default factor to correct for bioavailability differences between oral and IV route (section 3.1 of Q3D).
- Case: once weekly intravenous administration
- Established PDE in Q3D:
 - Oral PDE = $0.12 \text{ mg/kg/d} \times 50 \text{ kg} / 1 \times 10 \times 5 \times 1 \times 1 = 120 \text{ } \mu\text{g/day}$
 - IV PDE = $120/10 = 12 \text{ } \mu\text{g/day}$
- F2.1 can be modified based on the dosing interval relative to the plasma elimination half-life of 10 days to 2.33 (ratio dosing interval/ half-life = $7/10 = 0.7$ see Module 2 Annex for values). F2.2 remains 3.16.
 - F2 (modified) = $F2.1 \times F2.2 = 2.33 \times 3.16 = 7.36$
- Oral AL = $0.12 \text{ mg/kg/d} \times 50 \text{ kg} / 1 \times \mathbf{7.36} \times 5 \times 1 \times 1 = 163 \text{ } \mu\text{g/day}$
- IV AL = $163 \text{ } \mu\text{g/day} / 10 = \sim 16 \text{ } \mu\text{g/day}$

B] Modification of modifying factors

- PDEs were developed for lifetime exposure
- Modifying factors can be adjusted to consider non-chronic use:
 - The duration of the study used to set the PDE relative to the intended clinical use (Factor F3)
 - The nature and severity of the toxicity observed, and whether the toxicity was reversible (Factor F4)
- Examples:
 - B4: Intermittent dosing
 - B5: Single dose treatment

Example B4: Intermittent dosing modifying F3

- Case: treatment for osteoporosis which needs to be administered IV every 3 months.
- Drug Product preparation: reconstituted dry powder in sterile water at 1 mg/ml is shown to contain 23 µg of EI X.
- Established PDE in Q3D: parenteral PDE of 12 µg/day
 - $\text{PDE (Oral)} = 0.12 \text{ mg/kg/d} \times 50 \text{ kg} / 1 \times 10 \times 5 \times 1 \times 1 = 0.12 \text{ mg/d} = 120 \text{ µg/day}$
 - $\text{PDE (parenteral)} = \text{PDE (Oral)} / 10 = 12 \text{ µg/day}$

Example B4: Intermittent dosing modifying F3 (cont)

- Justification to change F3 from 5 to 2:
 - The established PDE was based on a 3 month study in rats which extrapolated to long term dosing with a F3 = 5.
 - Low dosing frequency compared to daily dosing
 - No evidence that EI X, shows acute toxicity or local effects
- Modified calculation:
 - Oral AL = $0.12 \text{ mg/kg/d} \times 50 \text{ kg} / 1 \times 10 \times 2 \times 1 \times 1 = 300 \text{ } \mu\text{g/day}$
 - Parenteral AL = PDE (Oral)/ 10 = 30 $\mu\text{g/day}$
- Therefore it can be concluded that the observed level of 23 μg of EI X can be justified for this DP from a safety perspective
- Quality attributes may need to be checked.

Example B5: single dose modifying F3 / risk-benefit

- Drug product for stroke is acutely administered IV
- Intended use is single administration
- Drug product preparation: reconstituted dry powder in sterile water at 1 mg/ml is shown to contain 17.3 μg of EI X and 50 μg of EI Y.
 - 1 ml is the dose volume needed for the treatment.
 - The levels of the EI X and EI Y cannot be further reduced by process and/or supplier changes.

Example B5: single dose modifying F3 / risk-benefit (cont)

- Established PDE in Q3D
 - EI X: parenteral PDE = 5 µg/day
 - EI Y: parenteral PDE = 20 µg/day
- Origin of PDE
 - EI X: was based on Minimal human Risk Level (MRL); no modifying factors are available for adjustment
 - EI Y: Factor F3 was based on 2-year rodent carcinogenicity study; F3 is already 1
- Changes to Factor F3 cannot be applied in this example; risk-benefit approach can be an alternative

Example B5: single dose modifying F3 / risk-benefit (cont)

- Evaluate risk-benefit
 - Risk
 - No acute toxicity with EI X and Y
 - Benefit
 - Treatment with significant impact on health
 - Potentially life saving
- Risk-benefit conclusion
 - Benefits outweigh risk for the application of the drug product for the intended indication

C] Change of most relevant study

- Could be applicable in case:
 - Other relevant data is presented (internal study or post Q3D published data).
 - Good quality data are available for a more relevant duration of exposure (chronic vs acute).
- Adjustment of
 - NOAEL/NOEL (dose)
 - F1 – Interspecies Extrapolation
 - F3 – Duration of study
 - F5 – NOAEL
- Will need a strong justification

Example C6: new starting point to derive acceptable level

- DP: Oral tablet (once daily) with a 10 day dose regimen for post surgical pain management.
- Established Oral PDE for EI X was based on a 6-month rat study
 - NOAEL was based on renal effects (clinical pathology and pathology)
 - $PDE = 0.06 \text{ mg/kg/d} \times 50 \text{ kg} / 5 \times 10 \times 2 \times 1 \times 1 = 0.03 \text{ mg/d} = 30 \text{ } \mu\text{g/day}$

Example C6: new starting point to derive AL (cont)

- Justification
 - The DP is only approved for short term use
 - The Oral PDE for EI X was based on 6 month rat study
 - Sponsor conducted a 3 month dog study to develop relevant data to justify adaptation of PDE to short term use
 - This allows adjustments to NOAEL (dose), Factors F1, F3 and F4
- AL
 - Available data on EI X from 3 month GLP dog study with a NOAEL of 0.3 mg/kg based on clinical pathology changes (renal)
 - $AL = 0.3 \text{ mg/kg/d} \times 50 \text{ kg} / 2 \times 10 \times 10 \times 1 \times 1 = 75 \text{ } \mu\text{g/day}$
 - F1= 2 for dog, F3 = 10 for short term study (chosen conservatively; a lower value can be argued); F4 = 1 for seriousness of effect

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

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 ($t_{1/2}$).
 - The extent of possible accumulation (Rac) can be described by $Rac = 1 / (1 - 0.5^{(dosing\ interval / t_{1/2})})$.
 - 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
 - $F2.1 = 1 + 2.16 \times (Rac - 1) / Rac$,
 - 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 / t _{1/2})	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