

Module 3

Developing an Acceptable Level for a Elemental Impurity not in Q3D

ICH Q3D Elemental Impurities

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Derivation of an Acceptable Level (AL) for element impurity (EI) not in Q3D

- Needs to follow the principles to derive a PDE as outlined in the Guideline (Appendix 1)
- Literature review is needed to find safety information
- Information needs to be judged for quality and applicability
- **Note: example does not represent an ICH Q3D-derived PDE; example is for illustrative purposes only**

Example 1: Safety Qualification of an EI not in Q3D

- Drug Product in a pre-filled syringe (PFS)
- Stopper is a sulfur cured elastomer
 - Elemental sulfur (S) detected from a leachable study of the container closure system and not S from mAb
 - Based on shelf-life of DP, S level determined to be 2.3 µg/dose
- DP is a mAb that has a SC dose regimen (1 dose every 8 weeks)
- Quality attributes
 - Determined that S does not affect the quality of the mAb



Determination of an acceptable level

- **Using Q3D principles an AL for elemental S in a parenteral DP can be developed**
 - Note: not an ICH Q3D-derived PDE; example for illustrative purposes only
- **Limited parenteral data available – use oral study data to calculate an AL**
 - Reported human data suggests that S is relatively nontoxic but an MRL is not available
 - Rabbit iv study; single dose level, limited number of animals, non-GLP, used colloidal sulfur containing polysulfide (Greengard and Woolley, 1940; Studies on colloidal sulfur-polysulfide mixture. Toxicity J.Am.Pharmaceut.Assoc. 29: 289-292)
 - The oral bioavailability of S is unknown
 - A feed study in calves with dietary administration of 2 concentrations of sulfur (as Calcium sulfate) for 85 days showed no effects in health, body weight, Cu and Se levels and activity of Cu and Se dependent enzymes up to a dose of 16 mg/kg/day. Thus the no observed adverse effect level (NOAEL) is 16 mg/kg/day.
 - S intake (oral) = $16 \text{ mg/kg/d} \times 50 \text{ kg} \div (10 \times 10 \times 10 \times 1 \times 1) = 0.8 \text{ mg/day} (800 \text{ } \mu\text{g/day})$
 - This study was considered the most appropriate to determine an AL

Determination of an acceptable level (cont)

- Parenteral AL
- Using the most conservative modifying factor of 100 (section 3.1 of Q3D, oral bioavailability < 1%), a parenteral AL for S is:
$$800 \mu\text{g/day} \div 100 = 8 \mu\text{g/day}$$
- S in PFS DP
 - The calculated AL for S is 8 $\mu\text{g/day}$
 - PFS DP contains worst case level of 2.3 $\mu\text{g/dose}$
 - Patient dosed once every 8 weeks
 - The level of S in the DP is considered acceptable
 - ALs are subject to review and approval by regulatory agencies/authorities
- **Note: This is not an ICH Q3D-derived AL. It is an example for illustrative purposes only.**