Module 3

Developing an Acceptable Level for a Elemental Impurity not in Q3D

ICH Q3D Elemental Impurities

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

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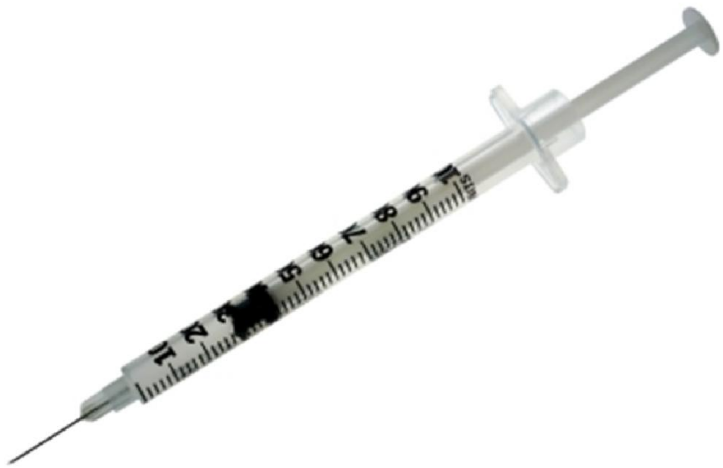
Derivation of an Acceptable Level (AL) for element impurity (EI) not in Q3D

- 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 mg/kg/d x 50 kg ÷ (10 x 10 x 10 x 1 x 1) = 0.8 mg/day (800 µg/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 µg/day ÷ 100 = 8 µg/day

- S in PFS DP
  - The calculated AL for S is 8 µg/day
  - PFS DP contains worst case level of 2.3 µg/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.