Summary - Guidance on Selection Criteria of Dose and Toxicity Data for Use in Cleaning Limits Calculations

For consistency, use of Acute Oral LD50 values obtained using rats as the study population is recommended to be used. The justification for utilising rat acute oral LD50 values is based on a commonly referenced article on this subject. Layton et al suggests that a safety factor to be used in calculating the Acceptable Daily Intake (ADI) be in the range of $1x10^{-3}$ to $5 x10^{-6}$. This factor is based on small mammal and oral rat data. The MAR formula, therefore, require the overall safety factor of $5 x 10^{-6}$ {$5 x 10^{-4}$ in the No Observable Effect Level (NOEL) calculation and another $1 x 10^{-2}$ in the ADI calculation, which incorporates the NOEL}. The ADI is used in the Toxicity Maximum Allowable Residue (MAR) calculation. The safety factor of $5 x10^{-4}$ has been reported in other literature articles for NOEL and appears to generally be accepted in the industry.

The following points can be considered when selecting Dose data to be used in the calculations of Maximum Allowable Residue for Therapeutics (MAR_T) or Dose MAR:

- In cases where multiple formulations of an API are being produced in Drug Product (DP) manufacturing, or if the specific dosage form and/or dose to be used is unknown (e.g. APIs for external sales), then the most conservative published minimum therapeutic dose (T_A) of the API for all DP formulation uses should be utilised in the MAR_T calculations.

- In the DP manufacturing plant where more than one dosage form or delivery system (e.g. oral tablet, injectable liquid, topical cream/ointment) of the same API are produced on a given equipment item, the minimum therapeutic dose [T_A] (used in the numerator of the equation) is specific to the drug product dosage form/delivery system.

Site A produces a 300 mg and 400 mg oral capsule and at site B the 100 mg oral capsule is produced; published minimum therapeutic dose is 100 mg. Thus site A producing the 300 mg and 400 mg capsule would use 100 mg as the minimum therapeutic dose for the product. Published minimum therapeutic doses of an API usually reflect the pharmacological activity for a specific route of administration such as injectable, oral or topical.

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