Document on Selection Criteria of Dose and Toxicity Data for Use in Cleaning Limits Calculations

Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion
This document provides points to consider when selecting Dosage and Toxicity data for use in the Cleaning Limits calculations.

This document is intended to standardise the approaches currently taken in selecting source data to be used in the cleaning limits calculations.

Toxicity Data considerations
When selecting data for use in the Toxicity Maximum Allowable Residue (MAR) calculations, the following points should be considered:

- For consistency, use of Acute Oral LD_{50} values obtained using rats as the study population is recommended to be used. The justification for utilising rat acute oral LD_{50} 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.

- In cases where rat acute oral LD_{50} values are not available, but other species' toxicity data are available, the acute oral LD_{50} value of the next largest mammal can be used. Likewise, if oral LD_{50} data are not available, LD_{50}data from other administration routes may be used.

- For API intermediates without available toxicity data, the toxicity of the subsequent API could be used in the limits calculations if the intermediate is the same molecule as the API (e.g. crude API) or a base form of an API salt, for example. Alternatively (and more commonly), in cases where intermediate toxicity data are not available, the calculation may be conducted for the Wt% MAR only, omitting the Toxicity MAR calculation altogether.

- Include a reference of the source of the compound toxicity data used in the toxicity MAR calculations in site documentation.

- Another approach to calculate the toxicity MAR can be found in the Draft ISPE Baseline guide on Risk-MAPP .

drug product) for each changeover. For example, if it is a pediatric drug product A to pediatric drug product B changeover, then use the pediatric dose for Product A in the MART calculation.

- Option 2: Normalize the dose whenever a pediatric product is involved in the calculation. Document the average body weight factor for the adult (usually a 70 kg adult) and for the pediatric patient used for MART calculations. Refer to the following example.

Option 2: Normalization Examples

- For ophthalmic products, use the published TA or daily dose as TA (if TA is not specified in the reference or if it is not possible to estimate the TA) for MART calculations. If the TA is reported in drops, determine the equivalency of one drop in ml. For example 1 drop/day is equal to 0.03 ml and each drop contains 50 mcg of active X; therefore the maximum daily dose is 1.5 mcg of X/drop.

- The maximum daily dose is calculated over a 24-hour period (e.g. Take one 500 mg tablet per 8 hour period = 500 mg x 3 times/day = max daily dose of 1,500 mg/day. For a liquid the maximum daily dose = maximum number of doses in a day x µl in one dose or mg in one dose.

- The minimum therapeutic dose is the minimum amount of drug that may be administered, usually express as weight (e.g. mg).

- Include a reference of the source of the dose data used in the dose MAR calculations in the site documentation.

