

Guidance 030 Guidance on Selection Criteria of Dose and Toxicity Data

- For Vaccines in which the active ingredient can not be measured or where there is no human dosage information/toxicological data available, for example, for antigens, it is recommended that the dose calculation is not performed at all and that the MAR_T default limit (10 ppm) for RAL_T calculations is used.
- Where there is no human dosage information available, for example, for API intermediates, it is acceptable to calculate the dose limit by using the dosage information from the subsequent API when the intermediate is a closely related form of the active substance. Alternatively (and more commonly), it is recommended that the dose calculation is not performed at all, and that the Wt% MAR default limit is used. This approach is also acceptable for Veterinary Medicines, where no human dose data are available and the veterinary medicine APIs are produced in the same equipment that is used to produce human medicine APIs. For equipment producing only veterinary medicines, the dose data for the relevant animal(s) may be used.
- For DP plants that manufacture both veterinary and human medicines in the same equipment it is recommended to perform both therapeutic and non-therapeutic MAR calculations. Use the lowest calculated limit to compare with the 10 ppm (default limit). Consider the following for MAR_T limit calculation:
 - The sequence of manufacturing (Is the cleanup from Animal Health {AH} to Human Health {HH}, or HH to AH product?)
 - Normalize the dosage of the AH product to a 70 kg human (e.g. if the maximum daily dose of the AH is 15mg/kg/day, if normalized to a human dose (multiply by 70 kg; will result in 1,050 mg/day for an adult of 70 kg).
 - If the equipment is used to produce AH products only:
 - Use MAR_T and RAL_T Equations for actives
 - Minimum and maximum therapeutic dosages
 - Usually on animal weight basis (mg/Kg or mg/lb)
 - May have same (Minimum = Maximum) Dose
 - Safety factors (e.g. 1/1000) and Default MAR_T (10 ppm) are same as with human health.
- Recommendations for MAR_T calculations when a pediatric product and a product for adult use are manufactured in the same equipment:
 - Option 1: Use the lowest published T_A for MAR_T calculation (for pediatric and adult). Evaluate Product A (to be cleaned) and Product B (next product) with respect to their intended uses (e.g. adult or pediatric 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 MAR_T 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 MAR_T calculations. Refer to the following example.