

- 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 .
- Toxicity data for residual organic solvents in which the process controls (e.g. drying or flushing etc.) after cleaning with organic solvents are not in place or effective removal of the residual solvent cannot be demonstrated, ICHQ3 guide⁹ limits could be used as a basis for calculating residual organic solvent limits after cleaning. A toxicity MAR could be used as comparative limits in the cleaning limit calculations.

Therapeutic Dose Data considerations

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.
- For the selection of the SF for an oral dosage form the following is recommended:
 - Do the dose calculation using a SF of 1/1000
 - Evaluate if the Residue Acceptable Limit (RAL) is practical and achievable.
 - If the RAL limit obtained is practical and achievable, then a SF of 1/1000 should be used for the dose calculation.
 - If on the contrary, the limit obtained is not practical and achievable then evaluate the risk of contamination and take into consideration the product type. If the product does not have a safety concern (e.g. cytotoxic) then perform the dose limit calculation with a SF of 1/100.
- The minimum therapeutic dose [T_A] (in the numerator of the equation) of a drug product delivery system should be used if the site manufactures a higher strength product by that same delivery system.

Example 1 – Drug product

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.