Guidance Number: 018

Table 1 – For Changeover Cleaning From the Specified Compound Type[1]

Compound Type	Compound Type Definition	Cleaning Validation required?[6]	Verification Method to be used During Routine cleaning (after validation, if required)[2]	Additional Verification During Validation	Limits	Material Examples
Therapeutic compounds	Final APIs and intermediates that do or may have pharmacologic activity	Yes, for equipment producing one or more final APIs or intermediates - post introduction of API starting material	Major equipment - visual and rinsate or swabbing Minor equipment and Major equipment that can be completely disassembled and 100 percent visually inspected - visual inspection	Swabbing	RAL calculated based on lowest MAR of tox, dose, and 25 ppm Wt%.	Final APIs, crude APIs (unfinished)
API intermediates	Intermediates - post introduction of API starting material					Later stage intermediates that are included in process validation scope
API starting materials	Raw materials incorporated as a significant structural fragment into the structure of the API					Later stage materials included in process validation scope

Table 1 (continued from previous page):

Compound Type	Compound Type Definition	Cleaning Validation required?[6]	Verification Method to be used During Routine cleaning (after validation, if required)[2]	Additional Verification During Validation	Limits	Material Examples
Clinical materials API	Pre-commercial API production	No	Major equipment - visual and rinsate or swabbing Minor equipment and Major equipment that can be completely disassembled and 100 percent visually inspected - visual inspection	Not Applicable (N/A)	RAL calculated based on lowest MAR of tox, dose, and 25 ppm Wt%[3]	APIs for clinical use only
Early intermediates	Intermediates produced prior to introduction of API starting materials or used to form the API starting material	No	Major equipment - visual and rinsate or swabbing, Minor equipment and Major equipment that can be completely disassembled and 100 percent visually inspected - visual inspection	N/A	RAL calculated based on lowest of tox MAR, and 50 ppm Wt%[4]	Early intermediates, before introduction of API starting materials

Table 1 (continued from previous page):

Compound Type	Compound Type Definition	Cleaning Validation required?[6]	Verification Method to be used During Routine cleaning (after validation, if required)[2]	Additional Verification During Validation	Limits	Material Examples
'Other' residues	Generally Recognized as Safe (GRAS) compounds	No	At least visual inspection	N/A	Visually Clean	e.g., NaCl, buffers, some raw materials, reagents
	Organic Solvents		Major equipment - visual and rinsate, if required Minor equipment and Major equipment that can be completely disassembled and 100 percent visually inspected - visual inspection.		Visually Clean and analytical limit if dictated by toxicity	Organic Solvents
	All Other		Major equipment - visual and rinsate or swabbing, Minor equipment and Major equipment that can be completely disassembled and 100 percent visually inspected - visual inspection.		RAL calculated based on lower of tox MAR and 100 ppm Wt%	Some raw materials, reagents

Table 1 (continued from previous page):

Compound Type	Compound Type Definition	Cleaning Validation required?[6]	Verification Method to be used During Routine cleaning (after validation, if required)[2]	Additional Verification During Validation	Limits	Material Examples
Cleaning Agents	Commercial Cleaning Agents	Yes[5]	Major equipment - visual and rinsate or swabbing Minor equipment and Major equipment that can be completely disassembled and 100 percent visually inspected - visual inspection	None	RAL calculated based on lower of tox MAR, and 100 ppm Wt% of largest component (non-water)	Commercial detergents such as CIP 100, CIP 200
Dedicated Equipment	Any	No	Visual inspection	N/A	Visually Clean	Any in dedicated equipment

Table 1 (continued from previous page):

Compound Type	Compound Type Definition	Cleaning Validation required?[6]	Verification Method to be used During Routine cleaning (after validation, if required)[2]	Additional Verification During Validation	Limits	Material Examples
Cleaning Agents	Commercial Cleaning Agents	Yes[5]	Major equipment - visual and rinsate or swabbing Minor equipment and Major equipment that can be completely disassembled and 100 percent visually inspected - visual inspection	None	RAL calculated based on lower of tox MAR, and 100 ppm Wt% of largest component (non-water)	Commercial detergents such as CIP 100, CIP 200
Dedicated Equipment	Any	No	Visual inspection	N/A	Visually Clean	Any in dedicated equipment

1. Table 1 is not intended to identify which compounds or materials are required to be tested for, only what sampling is to be performed and limits applied once the selection is made via the Cleaning Evaluation Report.
2. Swabbing shall be used only for routine verification where rinsate is not feasible and 100 percent visual inspection is not possible, unless a rationale is provided.
3. Dose MAR to be considered only if dose is known.
4. For equipment producing multiple compound types (e.g., final APIs and early intermediates), the most conservative limit for all compound types produced in the equipment must be selected.
5. Separate validation of removal of cleaning agents is not required if the removal of the cleaning agent is included in the validation of the equipment cleaning from process compounds. Validation of removal of cleaning agents is not required for equipment producing only early intermediates or other residues of chemically synthesized APIs.

APPENDIX I – Calculation of MAR

1) Calculate Dose MAR

(For therapeutic compounds and clinical compounds where dose information is available)

Determine Maximum Allowable Residue as mg of A per kg of B (both activity):

$$\text{Dose MAR} = \frac{T_A \text{ (mg of A)} \bullet \text{conversion } (10^6 \text{ mg of B/kg of B}) \bullet \text{(SF)}}{B_B \text{ (units)} \bullet C_B \text{ (mg of B/unit)}}$$

2) Calculate Toxicity (Tox) MAR

(For all compounds, non-therapeutic and therapeutic where toxicity information is available)

Determine Maximum Allowable Residue as mg of N per kg of B (activity):

$$\text{Tox MAR} = \frac{\text{ADI (mg of N/day)} \bullet \text{conversion } (10^6 \text{ mg of B/kg of B})}{B_B \text{ (units)} \bullet C_B \text{ (mg of B/unit)}}$$

3) Compare against Weight % MAR

(Weight% limit in Table 1)

After Dose and Tox MARs are calculated as required, compare against the Weight% limit indicated in Table 1 for the type of compound being cleaned. For equipment producing multiple compound types (e.g., final APIs and early intermediates), the most conservative Weight% limit for all the compound types produced in the equipment must be selected. Select the lowest of the MARs (Dose, Tox, Weight%) to use in the RAL (Limit) calculation in Appendix II.

For example, if the calculated Dose and Tox MARs for a therapeutic compound are both > 25 mg N or A/kg B (ppm), then use the Weight% limit of 25 ppm in the RAL calculation. If either the Dose or Tox MAR are < 25 mg N or A/kg B (ppm) for that therapeutic compound, then use the lowest calculated MAR in the RAL calculation.

APPENDIX II – Calculation of Limit (RAL)

Limit for Swab

To determine Limit (RAL) for Swabs as (mcg of N) per Swab:

$$\text{Swab RAL} = \frac{\text{MAR (mg of N/kg of B)} \bullet L_B \text{ (kg of B)} \bullet A_S \text{ (sq cm/swab)} \bullet \text{conversion } (10^3 \text{ mcg N})/(\text{mg N})}{E_W \text{ (Equipment Surface Area in sq cm)}}$$

Note: If the swab recovery study for the compound of interest has a recovery of less than 70 percent, the recovery must be incorporated into either the limit calculation or reporting of results. To incorporate the recovery into the limit calculation, multiply the limit by the recovery (i.e., for 68 percent recovery, multiply the limit by 0.68).

Limit for Rinsate

To determine Limit (RAL) for Rinsates as (mg of N) per kg of Rinse:

$$\text{Rinsate RAL} = \frac{\text{MAR (mg of N)/(kg of B)} \bullet L_B \text{ (kg of B)}}{W_R \text{ (kg of Rinse Used)}}$$

Note: If the rinsate recovery study for the compound of interest has a recovery of less than 70 percent, the recovery must be incorporated into either the limit calculation or reporting of results. To incorporate the recovery into the limit calculation, multiply the limit by the recovery (i.e., for 68 percent recovery, multiply the limit by 0.68).

Legend for Appendices I & II

MAR = Maximum Allowable Residue, expressed as mg of **A** (activity) for therapeutic or mg **N** for non-therapeutic materials per kg of **B** (activity); may also be expressed as ppm of **A** or **N** permitted in **B**.

Limit (RAL) = Residue Acceptability Limit (RAL) [i.e., MAR, as (mcg **N**)/swab or (mg **N**)/(kg rinsate)]

A = The last product (therapeutic compound) in the equipment prior to cleaning.
N = The last material (therapeutic or non-therapeutic compound) in the equipment prior to cleaning.
B = The product to be produced next in the same equipment after cleaning.

T_A = Minimum therapeutic dose of **A**, expressed in milligrams (mg) activity.
B_B = Maximum daily dose of **B**, expressed in units of dosage (e.g., tablets or capsules).
C_B = Concentration of **B** in each unit, expressed as mg activity of **B** per dosage unit.
SF = Safety Factors:

- Use 0.001 for Dose MAR calculation (dimensionless); or alternatively use 0.01 divided by the lower of either the number of major product-contact pieces of equipment contributed by A, or the number of major product-contact pieces of equipment used to produce B;
- Use 0.01 for ADI calculation for Tox MAR (dimensionless); and
- Use 0.0005/day for NOEL calculation.

A_S = Area swabbed to remove all Product **A** or material **N** residue in a specified area (sq cm/swab).
L_B = Lot Size of **B** (kg activity of **B**).
E_W = Total Equipment Wetted Surface Area (sq cm).
W_R = Weight of rinse used to produce aliquot sample for evaluation (kg).

Acute Oral LD_{50} = The dose of material **N** at which 50 percent of the study population expires, expressed as mg of **N** per kg of body weight.

NOEL = No Observed Effect Level for a Person weighing 70 kg, expressed as mg of **N**/day.
NOEL values are available in Material Safety Data Sheets or calculated as follows:

NOEL = (Acute Oral LD_{50}) x SF (0.0005/day) x (70 kg) expressed as mg **N**/day.

ADI = Acceptable Daily Intake (ADI) of Material **N** for a person weighing 70 kg.

ADI = NOEL x [SF of 0.01], expressed as mg of **N**/day.