1. Purpose

The Purpose of this guideline is to define the minimum requirements for cleaning and validation of cleaning processes for formulated product. It also covers post validation monitoring of the effectiveness of cleaning processes.

This guideline provides equations and examples for calculating the Maximum Allowable Residue (MAR), and Residue Acceptability Limits (RAL) for Drug Products and Non-Therapeutics.

Examples are provided for determining the acceptable equipment cleaning residue limits for therapeutic drug products (MAR_T and RAL_T) and for non-therapeutic ingredients (MAR_N and RAL_N). For the therapeutic drug products both single product combination (Product A to B) and multiple products combination examples are given.

2 Scope and Applicability

This document is applicable to all commercial and investigational formulated products manufactured within a R&D and Operations facilities. It sets standards for cleaning and cleaning validation that suppliers of formulated products should be assessed against. Cleaning for primary packaging operations is also included.

This guideline applies to the validation of cleaning procedures for equipment used in manufacture of pharmaceutical products, but excludes Active Pharmaceutical Ingredients (API) and their intermediates.

Microbiological aspects of cleaning and determination of effectiveness are not considered in this document. Such activities should be treated on a case-by-case basis with due consideration given to manufacturing operations, area classifications, dosage forms etc.

The attached Appendices give equations and example calculations for therapeutic drug product cleaning limits for a solid oral dosage form (tablet), creams/ointment and ophthalmic product. In Case-1 therapeutic example it is included the calculation of Maximum Allowable Residue (MAR) limits using two formulas; dose MAR_T and toxicity MAR. It also includes an example for determining the worst case limit for shared equipment using multiple products. Example for residue limits calculation of CIP® 100 detergent, a non-therapeutic ingredient is also given.

3 Definitions

3.1 Hot Spot

A surface which is judged to be difficult to clean, or where microbiological growth may be foreseen, such as bends, valves, feed controls, sleeve couplings, bushing and hidden surfaces.

3.2 Limit of Detection

The lowest amount of a given substance in a sample that can be detected but not quantified with the selected analysis procedure.

3.3 Limit of Quantification

Legend for Appendices A & B

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

RAL = Residue Acceptability Limit based on MAR, as (mcg A or **N**)/swab or (mg A or **N**)/(kg rinsate).

A = The last product (therapeutic compound) in the equipment prior to cleaning.
N = The last material (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 = Dosage unit weight of B, expressed as mg drug product or formulation of B per dosage unit, not activity.

SF = Safety Factors:
- Refer to PQS V7105

A_S = Area swabbed to remove all Product A or Material N residue in a specified area (sq cm/swab or sq inches/swab).

L_B = Smallest Lot Size of B (kg drug product or formulation B), not activity.

E_W = Sum of product contact surface area of all common equipment items/units between product A and B (sq cm or sq inches).

W_R = Weight of rinse used to produce aliquot sample for evaluation (kg).

Acute Oral LD_{50} = The dose of material N at which fifty (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 seventy (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.*

Note: Alternatively the lowest RAL can be determined by performing the MAR and RAL calculation for the following two A/B sequences: 1) Next product B with smallest batch size, 2) Next product B with the Highest Max Daily Dose. The lower of the two is the product sequence with the lowest RAL.

Summary Table for Case 2: SETTING WORSE CASE LIMITS for Therapeutic Compounds

	Input	Input	Input		Result	Input	Input	Result	Input	Input	
Product	T_A	B_B	C_B (mg dosage unit) (note 1)	mg active per dosage (info only)	Max Daily Dosage (mg dosage unit/day) (note 2)	L_B (kg)	$L_B / B_B * C_B$ (kg B/mg B)	MAR_T (mg A/Kg next drug product) (A to C)	A_S (cm^2)	E_W (cm^2)	RAL_T A to C mcg or mcg/swab worst case
A	2.5	1	150	2.5	150	650	4.33	1.89	100	100,000	378
B	5	2	250	5	500	1000	2.00	--	100		---
C	10	3	440	20	1,320	200	0.152	--	100		---
D	50	5	250	50	1,250	750	0.600	--	100		---
E	100	4	800	100	3,200	700	0.219	--	100		---
Worst case comment	A is lowest		Highest weight		E Next product is highest	C is smallest batch	C is lowest ratio	A to C is lowest and less than 10 ppm		100,000	A to C is lowest

Note 1: In C_B and B_B, B is designated generically as next product B (not Product B in this example).
Note 2: C_B x B_B, is maximum daily dose in dosage unit weight (not activity), e.g.150 mg tablet weight for product A, contains 2.5 mg active.

Summary:

Worst case of A to C is dictated primarily by the small batch size of C in the RAL equation. In this example, batch size has more of an effect than maximum daily dose (in this case - next product E has max daily dose) on the final RAL.

Step 5. Determine the Residue Acceptability Limit (RAL_T) (for swabbing)

$$RAL_T \text{ (swab)} = \frac{MAR_T \text{ (mg of A/Liter of B)} \bullet L_B \text{ (Liter of B)} \bullet A_S \text{ (sq cm/swab)} \bullet}{E_W \text{ (Equipment Surface Area in sq cm)}}$$

$$= \frac{MAR_T \text{ (mg/L) (Batch size, Falatan)(swab surface area)}}{\text{Equipment Surface area } (cm^2)}$$

$$= \frac{5 \text{ mg Dalacom /L of Falatan } (530.4 \text{ L})(25 \text{ } cm^2/\text{swab})}{108{,}462 \text{ } cm^2}$$

= 0.611 mg Dalacom/swab or 611 mcg/swab
{RAL_T is 24.44 mcg Dalacom per cm^2 equipment or surface area}

B. Same example but this time using mg (weight basis) in the limits calculation:

Case information:

Two ophthalmic products Falatan and Dalacom are manufactured using the same equipment train. The cleaning procedures for each one of the equipment are the same for both products. Calculate the Maximum Allowable Residue (MAR_T) and Residue Acceptability Limit (RAL_T) when the last product manufactured in the equipment train was Dalacom and the next product to be filled is Falatan.

Use the same Steps as described in Case 1 under Appendix A to perform the MAR_T and RAL_T calculations:

Step 1. Obtain MAR_T and RAL_T equation inputs

Dosing Information:

Product A: Dalacom – see Appendix C, Case 4, step 1 above

APPENDIX E - Cleaning from the specified compound type

Compound Type	Compound Definition	Cleaning Validation Required?	Routine Verification after Validation	Verification during Validation	Limits	Comments
Therapeutic Compounds	Final DP and active that have therapeutic activity	Yes For changeover cleaning of non-dedicated equipment	Visual Inspection (Rinsate for enclosed systems or periodic monitoring)	Major and minor equipment: Swab for active Refer to notes 2 and 3	Calculate MAR_T and RAL_T Compare calculated MAR_T with 10 ppm May also calculate Toxicity limit and compare to MAR_T and 10 ppm	Refer to note 1
		Yes When required for dedicated equipment (see. PQS V7105)	Visual Inspection	Major and minor equipment: Refer to notes 2 and 3	Refer to notes 1, 2 & 3	Active residues determination is not required
Non-therapeutic compounds	Commercial Cleaning agent	Yes	Visual Inspection (Rinsate for enclosed systems or periodic monitoring)	Major and minor equipment: Swab for cleaning agent residues	Calculate MAR_N and RAL_N Compare calculated MAR_N with 100 ppm	Refer to note 1 Analytical testing is required for validation when the cleaning agent RAL_N cannot be seen.

Notes:

(1) If visual inspection is at or below the calculated RAL, then visual inspection of minor equipment is acceptable for validation purposes.
(2) If detergent is used, then follow cleaning validation requirements for cleaning agents.
(3) Evaluate if microbiological testing is applicable.

