Guidance Number: 008

Contents: Product A to Product B Cleaning Limits Calculations Equations and Examples

APPENDIX A – Equation for Calculating RAL_T for Therapeutic Products

First, determine Maximum Allowable Residue as mg of A (activity) per kg of B (drug product):

$$MAR_T = \frac{T_A \text{ (mg of A)} \bullet \text{conversion } (10^0 \text{ mg of B/kg of B}) \bullet (SF)}{B_B \text{ (units)} \bullet C_B \text{ (mg of B/unit)}}$$

Note: If calculated MAR_T > default MAR_T (10 ppm), then use default MAR_T for all RAL_T calculations.

To determine RAL_T for Swabs as (mcg of A) per Swab:

$$^*RAL_T = \frac{MAR_T \text{ (mg of A/kg of B)} \bullet L_B \text{ (kg of B)} \bullet A_S \text{ (sq cm/swab or sq. inches/swab)} \bullet \text{conversion } (10^3 \text{ mcg A})/(\text{mg A})}{E_W \text{ (Equipment Surface Area in sq cm or sq inches/swab)}}$$

To determine RAL_T for Rinsate (mg of A) per kg of Rinse:

$$^*RAL_T = \frac{MAR_T \text{ (mg of A)/(kg of B)} \bullet L_B \text{ (kg of B)}}{W_R \text{ (kg of Rinse Used)}}$$

APPENDIX B – Equation for Calculating RAL_N for Non-Therapeutic Products

To determine Maximum Allowable Residue as mg of N (activity) per kg of B (drug product or formulation weight):

$$MAR_N = \frac{NOEL \text{ (mg of N/day)} \bullet \text{conversion } (10^6 \text{ mg of B/kg of B}) \bullet (SF = 0.01)}{B_B \text{ (units)} \bullet C_B \text{ (mg of B/unit)}}$$

Note: If calculated MAR_N > default MAR_N (100 ppm), then use default MAR_N for all RAL_N calculations.

To determine RAL_N for Swabs as (mcg of B) per Swab:

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

To determine RAL_N for Rinsate as (mg of N) per kg of Rinse:

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

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.

$\mathbf{T_A}$ = Minimum therapeutic dose of A, expressed in milligrams (mg) activity.

$\mathbf{B_B}$ = 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

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

$\mathbf{L_B}$ = Smallest Lot Size of B (kg drug product or formulation B), not activity.

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

$\mathbf{W_R}$ = 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.*

Legend for Variables in Calculations

Acceptable Daily Intake (ADI) – an amount of a substance administered or consumed on a daily basis that will not produce a pharmacological or toxic response.

ADI = Acceptable Daily Intake of Material **N** for a Person weighing 70 kg.

$$\text{ADI} = \text{NOEL} \times [\text{SF of } 0.01], \text{ expressed as mg of } \mathbf{N}/\text{day}.$$

OR

$$\text{ADI (mg/day)} = \frac{[\text{NOAEL (mg/kg/day)} \times \text{BW (kg)}]}{\text{UFC} \times \text{MF} \times \text{PK})}$$

Where:
NOAEL = No-Observed-Adverse-Effect Level
BW = Body Weight
UFC = Composite Uncertainty Factor
MF = Modifying Factor
PK = Pharmacokinetic Adjustment(s)

(*) - If the swab or rinse recovery study for the compound of interest has a recovery of less than seventy (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 [e.g., for sixty-eight (68) percent recovery, multiply the limit by 0.68].

APPENDIX C – Example Cleaning of Therapeutic Drug Product Limit Calculations

Case 1: Dose and Toxicity Example Calculation for Single product combination (Tablet)

A lot of Curitor 10 mg tablets (Product A) was produced using the equipment train in a manufacturing area, composed of weighing, milling, mixer, press and coating equipment. The next product to be manufactured using the same equipment train is Remitor 30 mg tablets (Product B). Curitor is an oral product. Determine the MAR_T and RAL_T for swab and rinse samples.

Steps in the calculations:

1. Obtain equation inputs
2. Determine the SF to be used
3. Determine the Dose MAR_T (maximum allowable residue) using both Product A and B dose data
4. Determine the Toxicity MAR (as mg of product A per kg of product B) using Product A toxicity data.
5. Compare the calculated Dose MAR_T and Toxicity MAR to the default limit of 10 ppm, and select the lowest
6. Determine the Residue Acceptability Limit (RAL) using the lowest MAR_T

Step 1. Obtain MAR_T and RAL_T equation inputs

Curitor tablets [Product A]

Minimum Therapeutic Dose (T_A) of Product A = 10mg
(Available from the normal prescribing information, e.g. PDR)
In this example, the T_A is all that is needed for the product being cleaned.

Remitor 30 mg tablets (next product in equipment) [Product B]

B_B = Maximum daily dose of B, expressed in units of dosage = number of dosage units per day
= **5 tablets**

C_B = Dosage unit weight of B, expressed as mg of drug product = Tablet Weight of B
= **273 mg/ tablet** (weight of one tablet of Remitor 30 mg)

B_B (units) x C_B (mg of B/unit) = 5 tablets x 273 mg/tablets
= **1,365 mg** (Maximum Daily Dose of Remitor tablets)

Batch Size = 500kg

Information for Toxicity MAR calculations:
Acute Oral LD50 (rat) = 393 mg/kg
No Observable Effects Limit (NOEL) = (Acute Oral LD50) x SF (0.0005/day) x (70 kg)
= 393 mg/kg x 0.005/day x 70 kg
= 13.755 mg Curitor/day

ADI = Acceptable Daily Intake (ADI) of Curitor for a person weighing 70 kg
= NOEL x [SF of 0.01], expressed as mg of Curitor /day
= 13.755 mg Curitor/day x 0.01
= 0.13755 mg Curitor /day

Other inputs
Equipment train (shared) surface area - 320,000 cm^2
Swab area = 10 cm x 10 cm = 100 cm^2
Rinse check weight – 400 kg (or 400 L water)

Step 2. Determine the SF to be used
A SF of 1/100 (0.01) will be used.

Step 3. Determine the Dose Maximum Allowable Residue (MAR_T)

$$MAR_T = \frac{T_A \text{ (mg of Curitor)} \bullet \text{conversion } (10^6 \text{ mg of Remitor tablet/kg of Remitor tablet}) \bullet (SF = 0.01)}{B_B \text{ (units)} \bullet C_B \text{ (mg of Remitor formulation per tablet)}}$$

$$= \frac{10\text{mg} \times 10^6\text{mg/kg} \times 0.01}{(5 \text{ tablets} \times 273 \text{ mg/tab})}$$

= 73.3mg Curitor/kg Remitor tablets
= 73.3 ppm or 73.3 mg/kg in the total equipment train

Thus, maximum residue limit 73.3 mg of active ingredient in Curitor per kg of Remitor formulated drug product.

Step 4. Determine the Toxicity Maximum Allowable Residue (Tox MAR)

$$\text{Tox MAR} = \frac{\text{ADI (mg of Curitor/day)} \bullet \text{conversion } (10^6\text{mg of Remitor/kg of Remitor})}{B_B \text{ (units)} \bullet C_B \text{ (mg of Remitor per tablet)}}$$

$$= \frac{0.13755 \text{ mg} \times 10^6\text{mg/kg}}{(5 \text{ tablets} \times 273 \text{ mg/tab})}$$

= 100.8 mg Curitor/kg Remitor
= 100.8 ppm or 100.8 mg/kg in the total equipment train

Thus based on Toxicity data, a maximum residue limit of 100.8 mg of Curitor (Product A) is allowed to be carried over into Remitor (Product B).

Note: Another approach to calculate the Tox MAR can be found in the Draft ISPE Baseline guide on Risk-MAPP[5].

Step 5. Compare the calculated MAR_T and Tox MAR to the default limit of 10 ppm, and select the lowest

Use 10 ppm in the **RAL_T equation** as this is lower than the calculated limit for MAR_T (73.3 ppm) and Tox MAR (100.8 ppm).

Step 6. Determine the Residue Acceptability Limit (RAL_T) (for swabbing)

$$\mathbf{RAL_T\ (swab)} = \frac{\mathbf{MAR_T}\ (\text{mg of } \mathbf{A}) \bullet \mathbf{L_B} \bullet \mathbf{A_S}\ (\text{sq cm/swab}) \bullet \text{conversion}\ (10^3\ \text{mcg } \mathbf{A})/(\text{mg } \mathbf{A})}{\mathbf{E_W}\ (\text{Equipment Surface Area in sq cm})}$$

$$= \frac{MAR_T\ (\text{mg/kg})\ (\text{Batch size, Remitor tablets})\ (\text{swab surface area})(\text{conversion})}{\text{Equipment Surface area } (\text{cm}^2)}$$

$$= \frac{10\ \text{mg Curitor/kg } (500\ \text{Kg})\ (100\ \text{cm}^2/\text{swab})\ (10^3\ \text{mcg Curitor}/(\text{mg Curitor})}{320{,}000\ \text{cm}^2}$$

= 1,562.5 mcg Curitor/swab
{RAL_T is 15.63 mcg Curitor per cm^2 equipment surface area}

Residue Acceptability Limit (RAL_T) (for rinse)

$$\mathbf{RAL_T\ for\ rinse} = \frac{MAR\ (\text{mg/kg})\ (\text{Batch size, Remitor tablets})}{\text{Weight of Rinsate (kg)}}$$

$$= \frac{10\ \text{mg/kg } (500\ \text{Kg})}{400\ \text{kg}}$$

= 12.5 mg /kg of rinsate or 12.5 ppm (w/v)

APPENDIX C – Example Cleaning of Therapeutic Drug Product Calculations (Cont.)

Case 2: Example Dose Calculation for worst case limit for Multiple Products (Tablet)

For the second case, five products (A, B, C, D, and E) are manufactured in the same equipment train. Determine the worst case limit. A summary table on the following page has the inputs and results. For this case use a SF of 1/1000.

Products A, B, C, D, and E → Products A, B, C, D, and E

SETTING WORST CASE LIMITS

I. Calculate the worst case next product ratio, $L_B/ (B_B \times C_B)$

1. Select the product with the smallest batch size, L_B for all products in the group
   Define: _____ kg as the smallest batch size. Batch size is material in equipment such as formulated product, (Answer: 200 Kg – product C).

2. Select the product with the highest maximum daily dose of products in the group,
   a. C_B, dosage unit weight in mg _____ (Answer: 800 mg tablet)
   b. B_B, number of dosage units per day_____ (Answer: 4 tablets/day)
   c. $B_B \times C_B$ is maximum daily dose _____ (Answer:3,200 mg, product E)

3. Calculate the ratio: $L_B/ (B_B \times C_B)$ for the two products in 1 and 2c
   a. Product C (smallest batch size) Ratio is _____
      (Answer: Product C - 0.152)
   b. Product E (highest max daily dose) Ratio is _____
      (Answer: Product E - 0.219)
   The product with the lowest ratio is the worst case next product (Product C - 0.152)

II. Identify the product with the lowest, T_A

4. Select the product with the lowest minimum therapeutic dose, T_A (Answer: 2.5 mg of product A)

III. Calculate the MAR_T for the product sequence providing the lowest RAL (worst case product being cleaned and worst case next product)

5. Calculate MAR_T, using T_A from product A, and maximum daily of dose product C for the worse case next product from I. MAR_T _____(Answer: 1.89 ppm; Product A to C, refer to page 7 for formula and calculations)

6. If worst case MAR_T is greater than 10 ppm, use 10 ppm in the RAL equation. If not, use the calculated MAR_T (Answer: 1.89 ppm).

IV. Calculate the RAL_T for the worst case in section III

7. Calculate RAL_T, using A_S for product being cleaned and E_W of equipment train (Answer: 378 mcg/swab, refer to page 7 for formula and calculations).

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.

Product A to C: Determine MAR_T

$$MAR_T = \frac{T_A \text{ (mg of Product A)} \bullet \text{conversion } (10^6 \text{ mg of Product C/kg of Product C}) \bullet (SF = 0.001)}{B_B \text{ (units)} \bullet C_B \text{ (mg of Product C formulation per tablet)}}$$

$$MAR_T = \frac{2.5\text{mg} \times 10^6\text{mg/kg} \times 0.001}{(3 \text{ tablets} \times 440 \text{ mg/tab})}$$

$$= 1.89 \text{ mg A / kg C tablets}$$

$$= 1.89 \text{ ppm or } 1.89 \text{ mg/kg in the equipment train}$$

Thus, maximum residues limit 1.89 mg of active ingredient in A per kg of C drug product.

Compare the calculated MAR_T to the default limit of 10 ppm, and select the lowest
Use 1.89 ppm in the **RAL_T equation** as this is lower than 10 ppm default limit.

This comparison can also include a comparison to a Toxicity MAR as shown in Case 1, Steps 4 and 5. A table for toxicity data can be created similar to the table for the dose data above in Case 2 if a worst case limit evaluation for toxicity data is performed.

Determine the Residue Acceptability Limit (RAL_T) (for swabbing)

$$RAL_T \text{ (swab)} = \frac{MAR_T \text{ (mg of A)} \bullet L_B \bullet A_S \text{ (sq cm/swab)} \bullet \text{conversion } (10^3 \text{ mcg A})/(\text{mg A})}{E_W \text{ (Equipment Surface Area in sq cm)}}$$

$$= \frac{MAR_T \text{ (mg/kg) (Batch size, Product C) (swab surface area)(conversion)}}{\text{Equipment Surface area } (cm^2)}$$

$$= \frac{1.89 \text{ mg Product A/kg (200 Kg)(100 } cm^2\text{/swab) (}10^3 \text{ mcg Curitor/(mg Curitor)}}{100{,}000 \text{ } cm^2}$$

$$= 378 \text{ mcg Product A/swab}$$

Product A to C: Determine MAR_T

$$MAR_T = \frac{T_A \text{ (mg of Product A)} \bullet \text{conversion } (10^6 \text{ mg of Product C/kg of Product C}) \bullet (SF = 0.001)}{B_B \text{ (units)} \bullet C_B \text{ (mg of Product C formulation per tablet)}}$$

$$MAR_T = \frac{2.5\text{mg} \times 10^6\text{mg/kg} \times 0.001}{(3 \text{ tablets} \times 440 \text{ mg/tab})}$$

$$= 1.89 \text{ mg A / kg C tablets}$$

$$= 1.89 \text{ ppm or } 1.89 \text{ mg/kg in the equipment train}$$

Thus, maximum residues limit 1.89 mg of active ingredient in A per kg of C drug product.

Compare the calculated MAR_T to the default limit of 10 ppm, and select the lowest
Use 1.89 ppm in the **RAL_T equation** as this is lower than 10 ppm default limit.

This comparison can also include a comparison to a Toxicity MAR as shown in Case 1, Steps 4 and 5. A table for toxicity data can be created similar to the table for the dose data above in Case 2 if a worst case limit evaluation for toxicity data is performed.

Determine the Residue Acceptability Limit (RAL_T) (for swabbing)

$$RAL_T \text{ (swab)} = \frac{MAR_T \text{ (mg of A)} \bullet L_B \bullet A_S \text{ (sq cm/swab)} \bullet \text{conversion } (10^3 \text{ mcg A})/(\text{mg A})}{E_W \text{ (Equipment Surface Area in sq cm)}}$$

$$= \frac{MAR_T \text{ (mg/kg) (Batch size, Product C) (swab surface area)(conversion)}}{\text{Equipment Surface area } (cm^2)}$$

$$= \frac{1.89 \text{ mg Product A/kg (200 Kg)(100 } cm^2\text{/swab) } (10^3 \text{ mcg Curitor/(mg Curitor)}}{100{,}000 \text{ } cm^2}$$

$$= 378 \text{ mcg Product A/swab}$$

APPENDIX C – Example Cleaning of Therapeutic Drug Product Calculations (Cont.)

Case 3: Example Dose Calculation for Single product combination (Creams/Ointment)

Terracort ointment and Trosyn cream topical products are filled in the same filling machine. Calculate the Maximum Allowable Residue (MAR_T) and Residue Acceptability Limit (RAL_T) when the last product filled in the machine was Terracort ointment and the next product to be filled is Trosyn cream.

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

Terracort ointment [Product A] – This product contains 2 active ingredients: Oxytetracycline and Hydrocortisone.

Minimum Therapeutic Dose (T_A) of Product A = 15 mg of Oxytetracycline and **10 mg of Hydrocortisone** (Available from the normal prescribing information, e.g. PDR)

- Calculations will be performed using hydrocortisone because this is considered the worst case between oxytetracycline and hydrocortisone for cleaning based on solubility. Therefore, in the calculation whenever Terracort is mentioned it is referring to hydrocortisone.

Trosyn cream (next product in equipment) [Product B]

B_B – Is the maximum number of applications per day. According to the dosing information product B is applied daily = **1 application**

C_B – Quantity (in mg) of the topical product in one application (i.e. dosage unit weight)
One application = 2 gm (estimated) = 2000 mg Trosyn
Trosyn Batch Size = 400kg

Other inputs
Equipment train (shared) surface area = 52,000 cm^2
Swab area = 10 cm x 10 cm = 100 cm^2

Step 2. Determine the SF to be used

A SF of 1/100 (0.01) will be used because Terracort and Trosyn are topical products.

Step 3. Determine the MAR_T

(Note appl. = application)

$$MAR_T = \frac{T_A \text{ (mg of Terracort)} \bullet \text{conversion } (10^6 \text{ mg of Trosyn cream/kg of Trosyn appl.}) \bullet (SF = 0.01)}{B_B \text{ (\# of appl.)} \bullet C_B \text{ (mg of Trosyn formulation per appl.)}}$$

$$\text{Maximum Allowable Residue } (MAR_T) = \frac{10\text{mg} \times 10^6\text{mg/kg} \times 0.01}{(1 \text{ appl.} \times 2000 \text{ mg of Trosyn/appl.})}$$

= 50 mg Tearracort / kg Trosyn cream
= 50 ppm or 50 mg/kg in the total equipment train

Thus, maximum residue limit 50 mg of active ingredient in Tearracort per kg of Trosyn formulated drug product.

Step 4. Compare the calculated MAR_T to the default limit of 10 ppm, and select the lowest

Use 10 ppm in the **RAL_T equation** as this is lower than Terracort ppm calculated limit (50 ppm).

This comparison can also include a comparison to a Toxicity MAR as shown in Case 1, Steps 4 and 5.

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

$$RAL_T \text{ (swab)} = \frac{MAR_T \text{ (mg of A)} \bullet L_B \bullet A_S \text{ (sq cm/swab)} \bullet \text{conversion } (10^3 \text{ mcg A})/(\text{mg A})}{E_W \text{ (Equipment Surface Area in sq cm)}}$$

$$= \frac{MAR_T \text{ (mg/kg) (Batch size, Trosyn cream) (swab surface area)(conversion)}}{\text{Equipment Surface area } (cm^2)}$$

$$= \frac{10 \text{ mg Terracort/kg (400 Kg) (100 } cm^2\text{/swab) } (10^3 \text{ mcg Terracort/mg Terracort})}{52{,}000 \text{ } cm^2}$$

= 7,692 mcg Terracort/swab
{RAL_T is 76.92 mcg Terracort per cm^2 equipment surface area}

APPENDIX C – Example Cleaning of Therapeutic Drug Product Calculations (Cont.)

Case 4: Example Dose Calculation for Single product combination (Ophthalmic liquid product)

Two ophthalmic products, Falatan and Dalacom are manufactured using the same equipment train. 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.

This exercise can be calculated using volume or mg for the limits calculation.

A. Limits calculation using volume:

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
Dalacom eye drops: Recommended therapy is one eye drop in the affected eye (s) once daily. Dose should not exceed one drop daily. One ml of solution contains 5 mg of Z (active ingredient of Dalacom). The estimated volume of one drop is equivalent to 0.03 ml.

Product B: Falatan
Falatan eye drops: Recommended therapy is one eye drop in the affected eye (s) once daily. The dosage of Falatan should not exceed one drop daily. One drop contains approximately 1.5 mg of X (active ingredient of Falatan). The estimated volume of one drop is equivalent to 0.03 ml.

Dalacom Ophthalmic Drops [Product A]

Minimum Therapeutic Dose (T_A) of Product A
One drop /day = 0.03 ml (estimated by the site)
1 ml contains 5 mg of Z
T_A (mg) = ml/drop x mg of Z/ml
= 0.03 ml/drop x 5 mg of Z/ml
= **0.15 mg of Z/drop**

Falatan Ophthalmic Drops (next product in equipment) [Product B]

D_B = maximum daily dose of B, expressed as µl (microliters) of formulation
= maximum number of drops per day x volume of one drop (expressed as µl)
According to the dosing information the maximum number of drops per day is **one (1)** and the Quantity (in ml) of one drop expressed in µl (microliters) of formulation is as follows:
D_B = Maximum number of drops per day x ml/drop
= 1 drop x 0.03 ml/drop = 0.03 ml x 1000 µl/1ml = **30 µl**

L_B = Smallest batch size of B (liters of formulation of B)
L_B = Falatan Batch Size = 530.4 Kg (density of 1.00 Kg/L) = 530.4 L

Other inputs
Equipment train (shared) surface area – 108,462 cm^2
Swab area = 25 cm^2

Step 2. Determine the SF to be used (Refer to PQS V7105)
A SF of 1/1000 (0.001) will be used because Dalacom is an ophthalmic product.

Step 3. Determine the Maximum Allowable Residue (MAR_T)

$$MAR_T = \frac{T_A \text{ (mg of Dalacom)} \bullet \text{conversion factor } (10^6 \text{ µl /L of Falatan}) \bullet (SF = 0.001)}{D_B}$$

$$MAR_T = \frac{0.15 \text{ mg/drop} \times 10^6 \text{ µl/L} \times 0.001}{(1 \text{ drop} \times 30 \text{ µl of Falatan /drop})}$$

= 5 mg Dalacom /L of Falatan in the total equipment train

Thus, maximum residue limit 5 mg of active ingredient of Dalacom per L of Falatan formulated drug product.

Step 4. Compare the calculated MAR_T to the default limit of 10 ppm, and select the lowest
Use the calculated **MAR_T** in the **RAL_T equation** as this is lower than 10 ppm (10 mg/L) limit.
This comparison can also include a comparison to a Toxicity MAR as shown in Case 1, Steps 4 and 5

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

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

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

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

= 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

Product B: Falatan

Falatan eye drops: Recommended therapy is one eye drop in the affected eye (s) once daily. The dosage of Falatan should not exceed one drop daily. One drop contains approximately 1.5 mg of X. The estimated volume of one drop is equivalent to 0.03 ml

B_B = maximum daily dose of B, expressed as maximum number of drops per day
According to the dosing information the maximum number of drops per day is **one (1).**
C_B = dose unit (mg) **Product density** = 1.00 g/ml
= dose unit in ml x product density
= 0.03 ml x 1.00 g/ml
= 0.03 gm x (1,000 mg/1 gm) = **30 mg**

L_B= 530.4 Kg

Other inputs
Equipment train (shared) surface area – 108,462 cm^2
Swab area = 25 cm^2

Step 2. Determine the SF to be used

A SF of 1/1000 (0.001) will be used because Dalacom is an ophthalmic product.

Step 3. Determine the MAR_T

$$MAR_T = \frac{T_A \text{ (mg of Dalacom)} \bullet \text{conversion } (10^6 \text{ mg Falatan/kg of Falatan}) \bullet (SF = 0.001)}{B_B \text{ (\# of drops)} \bullet C_B \text{ (mg/drop of Falatan)}}$$

Maximum Allowable Residue (MAR_T) = $\frac{0.15 \text{ mg} \times 10^6 \text{mg/kg} \times 0.001}{(1 \text{ drop} \times 30 \text{ mg of Falatan /drop}}$

= 5 mg Dalacom / kg Falatan
= 5 ppm or 5 mg/kg in the total equipment train

Thus, maximum residue limit 5 mg of active ingredient in Dalacom per kg of Falatan formulated drug product.

Step 4. Compare the calculated MAR_T to the default limit of 10 ppm, and select the lowest

Use the calculated **MAR_T in the RAL_T equation** as this is lower than 10 ppm limit.

This comparison can also include a comparison to a Toxicity MAR as shown in Case 1, Steps 4 and 5.

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

$$RAL_T \text{ (swab)} = \frac{MAR_T \text{ (mg of A)} \bullet L_B \bullet A_S \text{ (sq cm/swab)} \bullet \text{conversion } (10^3 \text{ mcg A})/(\text{mg A})}{E_W \text{ (Equipment Surface Area in sq cm)}}$$

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

$$= \frac{5 \text{ mg Dalacom /kg (530.4 kg) (25 } cm^2\text{/swab) } (10^3 \text{ mcg Dalacom /mg Dalacom)}}{108{,}462 \text{ } cm^2}$$

= 611 mcg Dalacom /swab
{RAL_T is 24.4 mcg Dalacom per cm^2 equipment surface area}

APPENDIX D – Example Non-therapeutic Products Limit Calculations

Case 1: Example Toxicity Calculation for non-therapeutic ingredient (detergent) for DP

CIP 100 detergent (A) Followed in the Equipment by Remitor ® 30 mg tablets (Product B)

A cleaning procedure is used for cleaning 5 products in an equipment train. The procedure includes CIP 100 detergent. The next product is Remitor 30 mg (worst case). Use the following to determine the MAR_N and RAL_N.

Steps in the calculations:

1. Obtain equation inputs
2. Determine the NOEL (or ADI) and MAR_N (maximum allowable residue; "tox" MAR_N).
3. Compare the MAR_N to the default limit of 100 ppm, and select the lowest.
4. Determine the Residue Acceptability Limit using the lowest MAR_N

Step 1. Obtain MAR_N and RAL_N equation inputs

CIP 100 detergent:
LD50- 860 mg/kg (Available from the MSDS or vendor)
{The LD50 (oral rat) is the only data that is needed for the cleaning agent}.

The following is for the next product in the equipment, Remitor tablets.

B_B – Maximum daily dose of B, expressed in units of dosage = number of dosage units per day = 5 tablets

C_B – Dosage unit weight of B, expressed as mg of drug product = Tablet Weight of B = 273 mg/ tablet (weight of one tablet of Remitor 30 mg)

B_B (units) x C_B (mg of B/unit) = 5 tablets x 273 mg/tablets)
= 1,365 mg (Maximum Daily Dose of Remitor tablets)

Batch Size – 500kg

Other inputs

Equipment train (shared) surface area - 320,000 cm^2
Swab area = 10 cm x 10 cm = 100 cm^2
Rinse check weight – 400 kg (or 400 L water)

Step 2: Determine the NOEL, ADI and MAR_N

NOEL = (Acute Oral LD_{50}) x SF (0.0005/day) x (70 kg); expressed as mg cleaning agent/day
NOEL = LD_{50} x (0.0005/day) x 70 kg
NOEL = 860mg/Kg (0.0005/day) (70 kg) = 30.1 mg/day

ADI = NOEL x 0.01 (SF)
= 30.1 mg/day x 0.01
= 0.301mg/day

{Note: ADI is substituted into MAR_N equation, but shown separately here for clarity.}

Step 3. Determine Maximum Allowable Residue as mg of N per kg of B (drug product or formulation):

$$MAR_N = \frac{\textbf{NOEL}\ (\text{mg of N/day}) \bullet \text{conversion}\ (10^6\ \text{mg of B/kg of B}) \bullet\ (SF = 0.01)}{B_B\ (\text{units}) \bullet C_B\ (\text{mg of B/unit})}$$

$$MAR_N = \frac{30.1\ \text{mg CIP/day}\ (10^6\ \text{mg Remitor drug product /Kg Remitor drug product}) \times 0.01}{(5\ \text{tablets} \times 273\ \text{mg/tablet})}$$

$$MAR_N = \frac{0.301\ \text{mg/day}\ (10^6\ \text{mg/Kg})}{1365\ \text{mg/day}}$$

$$= 221\ \text{mg/Kg}$$

Step 4. Use 100 ppm default limit in the RAL_N as this is lower than the 221 ppm MAR_N ("Tox" MAR)

Step 5. Determine the RAL_N

Residue Acceptability Limit (RAL_N) (for swabbing)

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

$$= \frac{MAR_N\ (\text{mg CIP /kg B})\ (\text{Batch size, Remitor tablets})\ (100\ \text{cm}^2/\text{swab})\ (10^3\ \text{mcg N})/(\text{mg N})}{\text{Equipment Surface area}\ (\text{cm}^2)}$$

$$= \frac{100\ \text{mg/kg}\ (500\ \text{Kg})\ (100\ \text{cm}^2/\text{swab})(1000\ \text{mcg /mg})}{320{,}000\ \text{cm}^2}$$

$$= 15{,}625\ \text{mcg CIP 100 /swab}$$

{RAL_N per surface area is 156.3 mcg CIP /cm^2 equipment swab area}

Residue Acceptability Limit (RAL_N) (for rinse)

$$= \frac{MAR\ (\text{mg/kg})\ (\text{Batch size, Remitor tablets})}{\text{Weight of Rinsate (kg)}}$$

$$= \frac{100\ \text{mg/kg}\ (500\ \text{Kg})}{400\ \text{kg}}$$

$$= 125\ \text{mg /kg of rinsate or 125 ppm}$$

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.