| Cleaning Validation Matrix for…. | |
|---|---|
| **Document No.:** GB/CVM/D-RR | **Effective Date:** |

## 1. General Information:

The product matrix has been made with an objective of selecting worst case, calculation of Maximum Acceptable Carry Over and the final acceptance criteria. The matrix contains, the details of the product as batch size, Smallest recommended daily dose and largest recommended Daily Dose and that of active as solubility and LD50.

The Product Matrix contains:

1. Strength (in mg): Different strengths of the product.
2. Smallest Recommended Daily Dose SRDD): This is smallest Dose.
3. Largest Recommended Daily Dose ( LRDD): This is largest Dose
4. Minimum Batch Size in Kg Units
5. Solubility: Mainly Pharmacopoeial references, if not in Pharmacopoeia, it is taken from Merck index or Drug profile.

   Approximate volume of solvent in milliliters per gram of solute

| | |
|---|---|
| Very soluble | less than 1 |
| Freely soluble | from 1 to 10 |
| Soluble | from 10 to 30 |
| Sparingly soluble | from 30 to 100 |
| Slightly soluble | from 100 to 1000 |
| Very slightly soluble | from 1000 to 10 000 |
| Practically insoluble or Insoluble | more than 10 000 |

## 2. Product Matrix:

**3. Equipment Matrix:**

| Sr. No. | Equipment Name | I. D. No. | Area | Capacity | Equipment Contact Surface Area ($cm^2$) |
|---|---|---|---|---|---|
| | | | | | |

**4. Equipment Train:**

| Sr. No. | Product Name | Active | Therapeutic category | TD (mg) | $LD_{50}$ | MDD (mg) | B. Size (Kg) | Solubility (in Water) | Preferred Swab Medium | Equipment train |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |

| Sr. No. | Equipment Train A | Equipment Train B | Equipment Train C | Equipment Train D | Equipment Train E |
|---|---|---|---|---|---|
| 1. | | | | | |
| 2. | | | | | |

**5. Selection of worst Case Product:**

OSD Bock of Galpha Laboratories Limited, Baddi is designed as multi-product facility to manufacture and pack Oral Dosage Form, which include Solid dosage forms (Tablets & Capsules).

Due to complexity of manufacturing and packing of multiple products using same equipment a Bracketing approach is considered to prioritize Cleaning Validation Program based on scientific rational.

The approach evaluates overall cleaning requirement of the product range and concentrates the validation effort to develop 'Worst Case' situation, where common cleaning procedures are followed for similar type (Operating Principle and Capacity) of equipment.

The 'Worst Case' is considered on the basis of following factors:

**5.1 Selection Criteria:**

**A. Evaluation and selection of worst case previous product:**

- Lowest value of SRDD of previous product should give the lowest MACO value.

**B. Minimum value of Batch size:**

- Lowest value of batch size of next product should give the lowest MACO value.

**C. Largest Recommended Daily Dose (LRDD):**

- Highest value of LRDD of next product should give the minimum MACO value.

**D. Common Product Contact Surface Area (Longest Equipment Train)**

- The highest value of product contact surface area should give minimum MACO value.
- The highest value of product contact surface area in the equipment train is **671269 sq.cm,**this value is considered in calculation of MACO

**5.2 Calculations of maximum allowable carry over (MACO) limit:**

Four approaches are followed for the calculation of Maximum Allowable Carry over (MACO) Limit:

**5.2.1 Dose Based Criteria:**

It defines 1/1000 (Safety factor for orals) of the normal therapeutic active dose of any product, which should not appear in largest recommended daily dose of the next product. Calculate MACO of the Active Residue for cleaning validation study.

**5.2.1.1 MACO calculation for swab sample:**

S.F X [SRDD (A) in mg] X [MBS (B) mg] X [Swab Area $cm^2$]

$$\text{MACO (mg/swab)} = \frac{\text{S.F X [NOEL (A)] in mg X [MBS (B) mg] X [Swab Area in cm}^2\text{]}}{\text{[LRDD (B) in mg] X [shared equipment surface area between products (cm}^2\text{)]}} =$$

**5.2.1.2 MACO calculation for rinse sample:**

$$\text{MACO (Total equipments in mg)} = \frac{\text{S.F x [SRDD (A) in mg] x [MBS (B) in mg]}}{\text{[LRDD (B)] in mg}} = \text{X mg}$$

$$\text{MACO (one equipment in mg)} = \frac{\text{X mg x [Equipment surface area cm}^2\text{]}}{\text{Total equipment product contact shared surface area cm}^2} = Y$$

$$\text{MACO (mg/ml)} = \frac{Y}{\text{Rinse volume used for final rinse of equipment in ml}} = Z$$

**5.2.2 Toxicity Based criteria(LD50):**

It defines that 1/1000 of a toxic dose for oral products of an amount which is not known to show any harmful biological effect in the most sensitive animal system known, e.g., no effect that should not appear in largest recommended daily dose of the next product.

NOEL shall be calculated by following equation:

$$\text{NOEL} = \frac{LD_{50}\text{ (mg / kg) x 50 (kg a person)}}{2000}$$

**5.2.2.1 MACO calculation for swab sample**

$$\text{MACO (mg/swab)} = \frac{\text{S.F X [NOEL (A)] in mg X [MBS (B) mg] X [Swab Area in cm}^2\text{]}}{\text{[LRDD (B) in mg] X [shared equipment surface area between products cm}^2\text{]}} = \ldots\text{mg/swab}$$

**5.2.2.2 MACO calculation for rinse sample:**

$$\text{MACO (For total equipments in mg)} = \frac{\text{S.F X [NOEL (A) in mg] X [MBS (B) in mg]}}{\text{[LRDD (B) in mg]}} = X$$

$$\text{MACO (one equipment in mg)} = \frac{\text{X x [Equipment surface area in cm}^2\text{]}}{\text{Total equipment product contact shared surface area}} = Y$$

$$\text{MACO (mg/ml)} = \frac{\text{Y}}{\text{Rinse volume used for final rinse of equipment in ml}} = Z$$

**5.2.3 <u>Toxicity Based criteria(ADE/PDE value) :</u>**

$$\text{MACO} = \frac{\text{PDE x BS (mg)}}{\text{LRDD (mg)}}$$

**5.2.3.1 MACO calculation for swab sample**

$$\text{MACO (mg /swab)} = \frac{\text{MACO (mg) x Surface area of swab (cm}^2\text{)}}{\text{Shared equipment contact surface area (cm}^2\text{)}}$$

**5.2.3.2 MACO calculation for rinse sample**

$$\text{MACO (one equipment in mg)} = \frac{\text{MACO (mg) x surface area of equipment (cm}^2\text{)}}{\text{Shared equipment contact surface area (cm}^2\text{)}}$$

$$\text{MACO (mg / ml)} = \frac{\text{MACO value of one equipment}}{\text{Total rinse volume used for one equipment in ml}} =$$

**5.2.4 10ppm Based criteria:**

NMT 10 ppm of previous product shall appear in next product

**10ppm of previous product** = MBS (B) (in kg) x 10ppm (0.00001 mg/mg)

$$= \frac{\quad}{\quad} =$$

A= Previous product selected as worst case

B= minimum batch size of next product

**5.2.4.1 MACO calculation for swab sample:**

$$\text{MACO (mg /swab)} = \frac{\text{10 ppm of previous product A (mg) x Surface area of swab (cm}^2\text{)}}{\text{Shared equipment contact surface area (cm}^2\text{)}} = \ldots \text{ mg/swab}$$

**5.2.4.2 MACO calculation for rinse sample:**

$$\text{MACO (One equipment in mg)} = \frac{\text{10 ppm of previous product (mg) x surface area of one equipment (cm}^2\text{)}}{\text{Shared equipment contact surface area (cm}^2\text{)}} = X$$

$$\text{MACO (mg / ml)} = \frac{X}{\text{Total rinse volume used for final rinse of equipment in ml}} = \ldots$$

**5.3 Comparison of MACO values calculated for Swab sample & rinse sample:**

**5.3.1 For swab sample calculated:**

| Criteria For MACO Calculation | mg / swab | mcg / swab | mcg / sq. cm |
|---|---|---|---|
| Dose Based Criteria | | | |
| 10 ppm Based Criteria | | | |
| Toxicity Based Criteria($LD_{50}$) | | | |
| ADE/PDE based criteria | | | |
| **Minimum MACO** | | | |

**Remark:**

**5.3.2 For Rinse sample:**

| Criteria For MACO Calculation | mg / ml | mcg / ml |
|---|---|---|
| Dose Based Criteria | | |
| 10 ppm Based Criteria | | |
| Toxicity Based Criteria($LD_{50}$) | | |
| ADE/PDE based criteria | | |
| **Minimum MACO** | | |

**Remark:**

6. **Summary :**

Summary report prepared from all the above criteria in table

a. **Least Soluble Drug:**
b. **High Potent Drug:**
c. **High Toxic Drug:**
d. **Longest Equipment Train:**

| Sr. No. | Product / Active Ingredient | Potency | Solubility | Maximum Daily Dose | Equipment Train |
|---|---|---|---|---|---|
| 1. | | | | | |

7. **Conclusion:**

Based on the criteria mentioned above following products are identified for cleaning validation.

8. As per above summary and conclusion it is recommended that cleaning validation shall performed on following product.

| Functional Area | Name | Designation | Signature & Date |
|---|---|---|---|
| **Prepared By (Quality Assurance)** | | | |
| **Reviewed By** | | | |

| | | | |
|---|---|---|---|
| **(Head Production)** | | | |
| **Reviewed By**<br>**(Head Quality Control)** | | | |
| **Reviewed By**<br>**(Head Engineering)** | | | |
| **Approved By**<br>**(Head Operation)** | | | |
| **Approved By**<br>**(Head Quality Assurance )** | | | |