1. **Definition.**  
Documented evidence that provides a high degree of assurance that a cleaning procedure will consistently remove chemical and microbiological residues to predetermined levels of acceptability.

2. **When cleaning validation performed.**  
   2.1 Initial qualification of process/equipment.  
   2.2 Critical change in a cleaning procedure.  
   2.3 Critical change in formulation.  
   2.4 Significant change in formulation.  
   2.5 Change in a cleaning process.  
   2.6 Change in cleaning agent.

3. **Worst case product.**  
Worst case product is selected based on risk level marking. This risk matrix is predominantly focused on permitted daily exposure value with the highest scale than other risk factor.

4. **Calculation of maximum allowable carry over Limit (MACO)**  
Four approaches followed for calculation of MACO  
   1. Dose based criteria  
   2. Toxicity based criteria (LD50)  
   3. PDE/ADE base criteria  
   4. 10 ppm Criteria  

4.1 **Dose based criteria**  
Not more than 1/1000 of minimum daily therapeutic dose of the previous product in the maximum daily dose of the next product.

4.1.1 **MACO Calculation for Swab**  
\[
\text{MACO (mg/swab)} = \frac{\text{SF} \times \text{SRDD(A) in mg} \times \text{MBS (B) in mg} \times \text{Swab area cm}^2}{\text{LRDD(B) in mg} \times \text{Shared equipment surface area (cm}^2\text{)}}
\]

4.1.2 **MACO Calculation for Rinse**  
\[
\text{MACO (Total equipment’s in mg)} = \frac{\text{SF} \times \text{SRDD(A) in mg} \times \text{MBS (B) in mg}}{\text{LRDD (B) in mg}} \times \text{mg}
\]
MACO (one equipment in mg X mg X [equipment surface area cm²] = Y
mg= Total equipment product contact shared surface area cm² mg

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

4.2 Toxicity based criteria (LD50)

NOEL = \frac{LD50 (mg/kg) X adult average weight (kg)}{2000}

4.2.1 MACO Calculation for Swab

MACO (mg/swab) = \frac{SF X [NOEL (A) in mg] X [MBS (B) mg] X [Swab area cm²]}{[LRDD(B) in mg] X Shared equipment surface area (cm²)}

4.2.2 MACO Calculation for Rinse

MACO (Total equipment’s in mg) = \frac{SF X [NOEL (A) in mg] X [MBS (B) in mg]}{LRDD (B) in mg} = X

MACO (one equipment in mg) = \frac{X mg X [equipment surface area cm²]}{Total equipment product contact shared surface area cm² mg} = Y

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

4.3 ADE/PDE Based criteria

PDE = NOEL X adult average weight (kg) X F₁ X F₂ X F₃ X F₄ X F₅

MACO = \frac{PDE X BS (mg)}{LRDD (mg)}
Cleaning Validation Notes

4.3.1 MACO Calculation for Swab

\[ \text{MACO mg/swab} = \frac{\text{MACO (mg) \times \text{[Surface area of swab (cm}^2\text{)]}}}{\text{shared equipment surface area cm}^2}\]

4.3.2 MACO Calculation for rinse sample

\[ \text{MACO (one equipment in mg)} = \frac{\text{MACO (mg) \times \text{[Surface area of equipment (cm}^2\text{)]}}}{\text{shared equipment contact surface area (cm}^2\text{)}}\]

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

4.4 10 ppm Based criteria

Not more than 10ppm of active pharmaceutical ingredient of previous product is permitted in next product.

\[ \text{Mac10} = 10 \text{ ppm} \times \text{Minimum Batch Size of Product ‘B’ in kg.}\]

\[ \text{MACO} = \frac{\text{[Mac10] \times \text{[Swab Area]}}}{\text{[Shared equipment surface area between products]}}\]

4.4.1 MACO Calculation for Swab

\[ \text{MACO mg/swab} = \frac{\text{10ppm Previous product A (mg) \times \text{[Surface area of swab (cm}^2\text{)]}}}{\text{shared equipment surface area cm}^2}\]

4.4.2 MACO Calculation for rinse sample

\[ \text{MACO (one equipment in mg)} = \frac{\text{10ppm Previous product (mg) \times \text{[Surface area of one equipment (cm}^2\text{)]}}}{\text{shared equipment contact surface area (cm}^2\text{)}}\]

\[ \text{MACO} = \frac{\text{X}}{\text{Total rinse volume used for one equipment in ml}}\]

Thank you

Dnyaneshwar Chakane