Non-Sterile Products Workshop

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Topics and Questions

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Cross-contamination in Non-Sterile Manufacturing

This workshop is primarily focused on solid dose manufacturing, but similar considerations apply to semi-solids and other non-sterile dosage forms

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Strategies to consider

- Cleaning validation
  - MACO (Maximum Allowable CarryOver) calculation
  - Swab and rinse water recovery, and possibly stability studies
  - Analytical method issues
- Zoning and Airflows

MACO (Maximum Allowable CarryOver) calculation

- Three methods are commonly used
  - Health Based Exposure Limits (HBEL). Calculate the maximum amount of Product A that might be allowed in Product B based on the toxicity and/or exposure limits for Product A.
  - Calculate the maximum amount of Product A that might be allowed in Product B based on1/100 or 1/1000 of the minimum therapeutic dose of Product A in a single dose of Product B.
  - Calculate the maximum amount of Product A that might be allowed in Product B based on 10ppm of Product A in a single dose of Product B.

How do you decide which calculation to apply?

- My recommendation is to do all three calculations, and then apply the one that has the lowest calculated MACO.
- In my experience, this is most often the 10ppm approach, but all three calculations should be done and written clearly, so that the scientific rationale is clear.

Swab studies

- The first thing to do is to identify the swab to be used, and to document it in procedures:
  - Supplier/manufacturer name
  - Catalogue number
  - Material of construction
- If anything changes, should this be managed under change control?

Recovery studies using swabs

- What surfaces will be included in the recovery studies?
- You will need a «coupon» of each surface type.
- How much material will you apply to the surface?
- How many replicates of each application?
- What is the minimum acceptable percentage recovery?
- How much variation in recovery would be acceptable?
- Are there surfaces where swab recovery studies are inappropriate or not valid?

Rinse water recovery studies

- What concentration of spiking to use?
- How many replicates to test?
- What is the minimum acceptable percentage recovery?
- How much variation in recovery would be acceptable?

Factoring

- If you get less than 100% recovery, how do you factor that into the experimental determination of residues?
  - Example: if you have 80% average recovery, do you factor your experimental determination of residues by dividing the result by 0.8?
- Do you apply a factor based on the average observed recovery, or the minimum observed recovery?
  - Example: if you have 80% average recovery, and a minimum recovery of 70%, which one do you apply in the experimental determination of residues?

Swab stability studies

- Do you need to do swab stability studies to validate the hold time between the experimental swabbing after cleaning and the analysis of the swab?
  - Example 1: The swab recovery studies were done in a laboratory (your own QC or maybe a contract lab) where the swabs were tested immediately after the swabbing.
  - Example 2: In the experimental determination of residues. The swabs might be tested 24 hours after the swabbing. How do you establish the validity of the swab result after 24 hours?

Analytical methods

- Determine the linearity range of the method in the area of the MACO concentration value.
- Determine the Limit of Detection (LOD) and Limit of Quantitation (LOQ) for the analytical method.
- How much difference should there be between the LOD or LOQ and the MACO?
  - Example: If the calculated MACO gives a swab limit of 10ppm and the LOQ is 9ppm, with LOD of 3ppm is that acceptable?

After the validation

- Can you really treat a manual cleaning process as validated, or do you need additional controls?
- Is visual inspection of cleaned equipment enough to show that you are routinely achieving carryover less than the MACO?
- Do you need to do some form of analytical verification after routine cleaning?
- If so, what do you test? Swabs? Rinse water?

Zoning and Airflows

- WHO and ISPE guidance is that the working rooms (granulation and tablet compression) should be at the lowest point in the pressure gradient in solid dose manufacturing.
  - What is an acceptable pressure difference between these rooms and the adjacent corridor?
  - Does your BMS measure that pressure difference, and is there alarm functionality in the system?
  - Do you need to demonstrate containment within these rooms through smoke studies?

Other Topics and Questions

Use of AI

- Reference Draft EU Annex 22
- Where you use AI is entirely up to you, provided that you have justification for ist benefits over a human system.
- Set-up: right people, good documentation, risk management principles
- Measure performance
  - Test the system
  - Confidence Scoring
  - Human review

Direct Compression

- This is very much a product filing isssue
  - Formulation development
  - MA filing and compliance with the MA.
  - Stability considerations, including potential generation of genotoxic impurities over the shelf life.