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MATERIAL SOLUTIONS. UNCOMPROMISING INTEGRITY.

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Cleaning Validation

FDA guidance and other regulatory documents indicate that cleaning validation is an integral part of verification of the suitability of the manufacturing process in pharmaceutical manufacturing[1-3]. The effectiveness and consistency in cleaning pharmaceutical production equipment is documented in the cleaning validation process, which assures the equipment is suitable for processing of pharmaceutical products or active pharmaceutical ingredients (APIs) and prevents contamination or adulteration of the pharmaceutical products.

Analytical testing of the residue after the cleaning procedure is an essential step in a cleaning validation program as it provides scientific support to the conclusion that the residue has been reduced to an "acceptable level". The general steps for a chemical cleaning validation provided by Jordi Labs are as follows:

1. **Protocol writing and sampling plan**

   A detailed protocol will be provided in accordance with the client needs, including the sampling plan (sampling technique, sampling area), analytical methods to be used and predetermined acceptance criteria.

2. **Method development**

   Develop methods that are suitable for detecting analytes of interest.

3. **Method validation**

   The method will be validated in a controlled GMP environment, typically for recovery, sensitivity, accuracy, and robustness.

The following are some key aspects of Cleaning Validation in the pharmaceutical industry

Definition

- A documented process that assures the effectiveness and consistency of a cleaning procedure in removing contaminants from process equipment.

Purpose

- To remove contaminants from process equipment. Possible contaminants include product residues, degradation products, cleaning agent residues, potential microbial contaminants, etc.
- To ensure product integrity and minimize cross contamination and impurities.
- To ensure compliance with regulatory requirements.

Why is Cleaning Validation Important?

- As stated in the FDA guidance (Validation of Cleaning Processes), "The main rationale for requiring clean equipment is to prevent contamination or adulteration of drug products."

Regulatory requirement and guidance

- Guide to Inspections Validation of Cleaning processes, FDA Inspection note.
  *Note that the FDA guide is intended to cover equipment cleaning for chemical residues only.
- Good Manufacturing Practice (GMP) Guidance for Active Pharmaceutical Ingredients (API), ICH Q7
- Recommendations on Validation Master Plan (VMP), Installation and Operational Qualification (IQ and OQ), Non-sterile Process Validation, and Cleaning Validation, PIC/S PI 006-3.
  *Applies to the manufacture of pharmaceutical products (final dosage forms) and of active pharmaceutical ingredients (APIs)

Sampling Technique

- Direct Surface Sampling (swab method)
- Indirect Sampling (use of rinse solutions)

Testing methods

- Specific method: detects unique compounds in the presence of potential contaminants.
  - Example: High-Performance Liquid Chromatography (HPLC)
- Non-specific method: detects any compound that produces a certain response
  - Example: Total Organic Carbon (TOC), pH and conductivity

Acceptance Criteria

The FDA and ICH Guidance for APIs require that the residue limit has to be practical, achievable, and verifiable based on the minimum known pharmacological, toxicological or physiological activity of the API. Since it is impractical to set universal acceptance specifications due to the wide variation in equipment and products used throughout the industry, defined limits and ways of calculating the limit have deliberately not been prescribed by FDA or ICH Guidance. The following are examples given in the FDA and PIC/S PI 006-01 Guidelines and are common practice in industry,

- Visually clean criteria
  - No quantity of residue should be visible on the equipment after cleaning procedures are performed. Spiking studies should determine the concentration at which most active ingredients are visible. (PIC/S PI 006-03, Section 7.11.3)
  - cGMP requires inspection for visual cleanness before manufacture
- 10 ppm criteria
  - No more than 10 ppm of any product will appear in another product produced with the same system. (PIC/S PI 006-03, Section 7.11.3)

- Therapeutic dose base criteria
    - No more than 0.1% of the normal therapeutic dose of any product will appear in the maximum daily dose of the following product. (PIC/S PI 006-03, Section 7.11.3)

References:

1. Guide to Inspections Validation of Cleaning processes, FDA Inspection note
2. GMP Guidance for API, ICH Q7
3. Recommendations on VMP, IQ and OQ, Non-sterile Process Validation, and Cleaning Validation, PIC/S PI 006-3