Regulatory Basis

FDA CFR Sec. 211.67 Equipment cleaning and maintenance.

Reference: CFR - Code of Federal Regulations Title 21

Purpose

The manual describes recommended approaches to develop and validate sampling and test methods for cleaning verification using rinse and swab samples.

Training Colleagues that perform sampling and testing activities (e.g. development or routine testing activities) in support of validation need to be qualified to perform those tasks.

Scope and Applicability

This guideline is applicable to all plants and equipment used to manufacture medicinal products and APIs and/or their intermediates (excluding biotechnology processing) within Operations and R & D.

Microbiological aspects of cleaning are not considered in detail in this guideline. The risk of microbiological contamination and the associated actions to mitigate this risk should be assessed on a case-by-case basis, eg generally equipment is not left water wet. Such risk assessments should consider manufacturing and cleaning operations; materials used in production and cleaning; facility design and controls; API susceptibility to microbial growth and the use of the API.

Note: R&D do not carry out formal cleaning validation during development(owing to the limited number of batches and changing processes/equipment), but cleaning verification must be carried out.

Definitions

Cleaning Validation

Cleaning validation is a validation program to verify that the processes and procedures used to clean product residue from process equipment and components, will consistently and significantly reduce the amount of active and/or excipient(s) and cleaning agent(s) to a concentration within calculated acceptance limits

Drug Substance (DS) or Active Pharmaceutical Ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product that when used in the production of a drug becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body. Note: Also known as Bulk drug or Drug Substance.

Acceptable Carryover Quantity (ACQ)

The maximum quantity of guiding substance that can be carried over into subsequent manufacture.

contaminants (e.g. lactose).

Visibly Clean

A state of cleanliness characterized by the absence of any residues visible to the naked eye assessed following a written procedure. This can be quantified (e.g. as part of analytical method validation) where a quantitative result (based on the worst case level for visibly clean) is required for carry over calculation.

Responsibilities

All Operations and R&D sites are responsible for developing an approach to cleaning of plant and equipment used to manufacture APIs that is justified and consistent with the requirements of this guideline and current GMP.

Each site shall put cleaning procedures in place. Each site shall ensure that analytical methods used for the determination of residual contaminants are appropriately validated.

Each site shall generate sufficient supporting data to support cleaning verification, establishment or validation as appropriate.

Operations Sites

Each Operations site shall implement validated cleaning procedures as required in this Guideline.

General Discussion

A description of the laboratory method selected and the rationale for its selection should be included in the method validation report. Analytical techniques such as HPLC, UV, TLC (thin layer chromatography), TOC (total organic carbon) and GC are commonly used at GMP sites for this analysis.

Protocol Contents

Contents of Equipment Cleaning Analytical Method Validation Protocols should include or reference the following:

- Approval signatures and dates of approvals
- Sampling Method
- Analytical Method
- Experiments to be executed; and
- Acceptance criteria including the Residue Acceptance Limit (RAL)

Method Validation

Method validation should encompass the residual limits for each product and/or equipment item. Method validation shall be performed in accordance with guidelines “Analytical methods for Equipment Cleaning”.

There are several swab types and sizes to choose from in the marketplace, and while there is no standard swab type that is required, the following short list of swabs has been recommended for use by site subject matter experts:

- Texwipe Alpha Swabs TX761
- Texwipe, Large Alpha Swab. #TWTX714A
- Alphawipes
- Non Woven Swabs NT2300

Swab Pre-treatment

If it is determined that special pre-treatment is required for the swabs, the Standard Test Procedure should define what is required. It should include the type of pre-treatment to be performed prior to use of the swabs, storage conditions and/or shelf life of treated or untreated swabs. Special requirements related to the swab or product may also be included.

Area Swabbed

The area to be swabbed must be defined, typical areas range from 5cm x 5cm to 4" x 4". It shall include special requirements and/or calculations for specific areas or equipment. It should be constant and well defined at each site to ensure consistency. This may be a standard area, as defined by site procedure (and executed using a template), or may be a specific area for that piece of equipment. The actual area to be swabbed may be defined in the validation protocol.

Swabbing the defined area called for by the test procedure can sometimes be difficult on the shop floor. For example a mill screen or sieve might have been identified for swabbing; however, the irregular surface might make it difficult to accurately swab an accurate surface area. The following is guidance on this problem:

- Choose solid, flat or semi-flat surfaces when selecting swab locations, if possible. Swab locations should be chosen based upon their difficulty to clean not the difficulty to swab sample.

- If a porous or irregular surface must be swabbed some consideration should be given regarding how much the swab surface area should be adjusted to correct for the change in availability of surface area when sampling a mesh or irregular surface. The typical swabbing instruction of "swab a "25cm X 25cm" area can be modified to fit the specific case. In any event, if the surface area to be swabbed is changed in the geometric plane of primary interest to accommodate an irregular shape, the rationale should be documented.

- A template of a non-porous material can be fabricated and used as a guide to ensure the individual performing the swab sample swabs the specified area. A flexible material would be preferred to allow for the template swabbing of curved surfaces.

- Individuals who perform swab sampling can demonstrate their proficiency at swabbing an accurate area without templates by comparison of their "free hand" recovered values to a recovery value obtained using a measured area.

Swab Standard Test Procedure Content

The intent of this section is to provide guidance on the development and content of Standard Test Procedures (STP) with the possibility of transfer of the STP to another gmp site with limited or no

