Azzur Labs, LLC

CLEANING VALIDATION FAQ

What is Cleaning Validation?

In simple words – Prevention of possible contamination and cross contamination

Process of providing documented evidence that the cleaning methods employed within a facility consistently controls potential carryover of product (including intermediates and impurities), cleaning agents and extraneous material into subsequent product to a level which is below predetermined levels/ acceptance criteria.

What is the objective of cleaning validation?

Prevent possible contamination and cross-contamination

Where is the cleaning validation required?

Not necessarily for non-critical cleaning, e.g. between batches of the same product, or of floors, walls, the outside of vessels etc.

Considering important in multiproduct facilities (Drug, Food) – cleaning validation should be performed. E.g. – equipment, sanitization procedures

Biotech – removal of viral or mycoplasmal (genus of bacteria) contaminants in the biological manufacturing industry.

Solid dosage – between manufacturing two products, contact surfaces

> "Equipment and utensils shall be cleaned, maintained and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug product beyond the official or other established requirements."

What Regulatory expects?

To have written general procedures on how cleaning processes will be validated.

The general validation procedure to address who is responsible for performing and approving the validation study, the acceptance criteria, and when revalidation will be required.

FDA expects firms to prepare scientific base validation protocols for studies to be performed on each manufacturing system or piece of equipment which should address such issues as sampling procedures and analytical methods to be used including sensitivity of these methods.

FDA expects firms to conduct validation studies in accordance with the protocols and to document the results of studies.

FDA expects a final validation report which is approved by QA / Validation compliance and which states whether or not the cleaning process is valid. The data should support a conclusion that residue have been reduced to an 'acceptable level.'

Code of Federal Regulations

The requirements in 21 CFR 211.67(a) states that:

"Equipment and utensils shall be cleaned, maintained and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug product beyond the official or other established requirements."

Similarly, 21 CFR 111.27(d) states:

"You must maintain, clean and sanitize, as necessary, all equipment, utensils and any other contact surfaces used to manufacture, package, label or hold components or dietary supplements. "

Cleaning Validation Protocol

Usually the following topics are mentioned in the cleaning validation protocols:

- Purpose
  - Validate cleaning procedure
- Risk Assessment
  - Risk associated with cleaning procedure / validation activity
- Scope
- Background
  - Background / History of cleaning related to equipment / why validation was initiated etc.
- Responsibilities
- Equipment description
  - Brief description of operation of equipment
- References
  - List SOPs or other related documents
- Worst Case selection

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Validation Strategy / Plan
Time intervals to be validated
- Dirty Idle Time
  - Time between end of use of the equipment and the start of equipment cleaning.
  - Validation of Dirty Idle Time necessary when validating cleaning procedure

- Clean Idle Time
  - Time between completion of equipment cleaning and use of equipment
  - Only Microbiological testing may required as No Chemical was introduced.

- Campaign Length – maximum campaign length of xxx bottles / batches / tablets will be established
- Process Time – maximum process time will be established

Equipment Load Items – parts / equipment to be cleaned
Training – personnel involved in the study must be trained and signed on the training form
Protocol execution instructions – cleaning procedure to be validated
Acceptance Criteria –
- Organoleptic cleanliness – parts and surrounding area must be visually clean
- Active Ingredient
- Cleaning agent / Detergent
- Microbiological

Analytical Methods – methods to analyze samples
Sampling methods – Rodac, Swab, Rinse

Established acceptance criteria

Limits: Practical, achievable and verifiable
Rationale: Logical, based on knowledge of materials
Each situation assessed individually
There should be no residue from:
- Previous product
- Reaction by – products and degradants
- Cleaning process itself (e.g. detergents or solvents)

The acceptance criteria setting approach can:
- Be product specific
- Group products into families and choose a worst case product
- Group products into groups according to risk, e.g. solubility, potency, toxicity, Cleanability

Acceptance criteria may be expressed as :
- ppm
- Mg/in^2

Commonly used acceptance criteria

Visually clean – no residue visible on equipment after cleaning.

No more than 10ppm of the product will appear in another product

No more than 0.1% of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product.

Certain allergenic ingredients and highly potent material may be undetectable by the best available analytical methods

e.g. – penicillin and cephalosporin, potent steroids and cytotoxins

Dedicated manufacturing facilities are needed for these products

Few Terminologies used in cleaning validation

- **Acceptance Criteria** – The amount if residue, above which possible contamination of the subsequent batch processed on the same equipment, may occur.
- **Analytical Methods** – Validated methods used to determine the amount or concentration of chemical residue remaining in the equipment following cleaning.
- **Bioburden** – Level of microorganism present in a system or on the surface
- **Cleaning agent** – Chemical agent or solution used for cleaning

- **Clean in place (CIP)** – An automated system or process of cleaning that involves cleaning equipment without disassembly of the equipment.

  Ex. – Steam Nozzle, cleaning agent in dirty pipes
- **Clean out of place (COP)** – A semi automated system or process of cleaning that involves cleaning equipment with some disassembly or movement of equipment into another location.

  Dissemble the parts and clean in washer (Washer can be Ultrasonic, Jet washer etc.)
- **Contaminant** – Something that may cause contamination of an equipment surface making the subsequent batch unacceptable for use.
- **Dedicated equipment** – Equipment used to manufacture or package a single product.
- **Equipment train** – A series of individual pieces of equipment that are linked together for a given process.
- **Limit of detection (LOD**) – Lowest level of analyte that can be detected
- **Organoleptic** – Involving the use of sense organs. For visual inspection
- **Recovery** – For analytical procedures using swab or rinse sampling, the percent of residue that is recovered from a spiked coupon of known concentration.
- **Maximum allowable carryover (MACO)** = I/J x K/L x M

  Where,
  I = smallest strength of product “A” (previous product manufactured)
  J = Max. no. of dose units of product “B”
  K = number of dose units of product “B” (next product) administered / day
  L = equipment surface area in common between product A and B (cm2)
  M = sampling surface area