Regulatory Aspects of Cleaning and Cleaning Validation

Larry Greenstein

Quality Operations, Quality Unit, Bio-Technology General, Ltd.

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Why clean?

Pharmaceutical production equipment is cleaned in order to reduce the level of residuals to acceptable levels so that the equipment is suitable for the manufacture of the same or other product.

Residuals include:

organic contamination: (product, by-products, process-related contaminants),

microbiological contamination: (bacteria, viruses, mycoplasms, endotoxins), and

cleaning agents: (acids, bases, detergents, organic solvents)

Why validate?

To demonstrate that the cleaning procedure as designed and performed, **consistently** reduces residual organic and microbiological contamination and cleaning agent to acceptable levels.

Topics

- FDA Regulations
- European Regulations
- Lifecycle Approach to Cleaning Validation

FDA Expectations

- Firms to have ***written procedures*** detailing the cleaning processes used for various pieces of equipment.
- Firms to have ***written general procedures*** on how cleaning processes will be ***validated***.
- The ***general validation procedures*** address ***who is responsible*** for performing and approving the validation study, the ***acceptance criteria*** and when revalidation is required.
- Firms to prepare ***written validation protocols*** **prospectively**, including ***sampling procedures*** and ***analytical test methods***, to carry out the studies as prescribed in the protocols and document the results.
- Writing a ***final validation report***, approved by management and states whether the cleaning process is valid. The data should support that the residues have been reduced to an acceptable level.

Evaluation of Cleaning Validation

Define:

- When the equipment or system is *clean* in order to determine effectiveness of the cleaning procedure.
- If relevant, what kind of *manual cleaning procedure* is required, i.e., scrubbing by hand, solvent wash.
- *Variability* of the manual procedures from batch to batch, product to product.
- *Number of cleaning processes* for each piece of equipment depending on the products being produced and whether cleaning is between batches of the same product or between batches of a different product.

Note: When cleaning between batches of the same product, need only meet criteria of “visibly clean” for the equipment. Between batch cleaning does not require validation.

Equipment Design

Overall design:

Equipment used in the manufacture, process, packing or holding of a drug product shall be of the ***appropriate design***, ***adequate size***, and ***suitably located*** to facilitate operations for its ***intended use*** and for its ***cleaning*** and ***maintenance***.

Construction:

Equipment shall be constructed so that ***surfaces*** that contact components, in-process materials or drug products shall ***not*** be ***reactive***, ***additive*** or ***absorptive*** so as to ***alter*** the ***safety***, ***identity***, ***strength***, ***quality*** or ***purity*** of the drug product beyond the established requirements.

Any substances required for operation, such as lubricants or coolants, shall not come in contact with components, drug product containers, closures, in-process material or drug products do as to alter the safety, identity, strength, quality or purity of the drug product beyond the established requirements.

Equipment Design (2)

- In larger systems, such as those employing long transfer lines or piping, check the flow charts and piping diagrams for the identification of valves and written cleaning procedures.
- Ensure that operators have received sufficient ***training*** in cleaning these systems, pipes and valves.
- Identify and control the length of time from the end of use to the start of cleaning ("dirty hold time") so as to prevent drying or caking of residues which will directly affect the efficiency of the cleaning process.
- Regardless of the cleaning method employed, ***microbiological aspects*** of cleaning should be considered.
- ***Preventive measures*** should be employed rather than trying to remove microbial contamination once it has occurred.
- ***Store*** equipment ***dry***, do not allow stagnant water to remain in the equipment.

Documentation:

The amount of documentation required for executing various cleaning steps will vary depending on the ***complexity*** of the system and cleaning process and the ***ability to train*** the operators.

Analytical Methods:

Determine the ***specificity*** and ***sensitivity*** of the analytical method used to detect residuals or contaminants *(specific test or total organic carbon (TOC))*.

Perform a ***recovery study*** to challenge the analytical method and sampling method.

Sampling:

Two types:

1. Direct sampling of the equipment surface *(swabbing)*, and
2. Collection of rinse solution.

Direct surface sampling:

Determine the type of ***sampling material*** *(swab)*, and that it ***does not interfere*** with the test.
Determine that the ***material*** is ***suitable for sampling*** and ***solvent suitable for extraction*** *(carry out recovery studies using stainless steel and glass coupons)*.

Advantages:

- Areas that are reasonably accessible can be evaluated.
- "Dried out" or insoluble residues can be sampled by physical removal.

Rinse samples:

Advantages:

- A larger surface area can be sampled.
- Inaccessible systems that cannot be easily dissembled can be sampled and evaluated.

Disadvantage:

- Residue or contaminant may be insoluble or occluded in the equipment.

Use a direct measurement of the residue or contaminant for validating the cleaning process.
(specific test where possible or TOC)

Establishing Limits

FDA *does not intend to establish acceptance specifications* for determining whether a cleaning process is validated.

Rationale for residue limits establishes should be *logical* based on the manufacturer's *knowledge* of the materials involved and *practical, achievable and verifyable* and *scientifically justifyable*.

It may be necessary to *set limits* not only for the actives but also for *partial reactants* and *partial by-products (e.g., multimers, cleavage products)* or for *chemical variants* that may be more difficult to clean.

Eudralex Volume 4, Annex 15: Qualification and Validation

Cleaning validation should be performed in order to confirm the ***effectiveness*** of any ***cleaning procedure*** for all product contact equipment.

Simulating agents may be used with appropriate scientific justification.

When similar types of equipment are ***grouped*** together *(bracketing)*, a ***justification*** of the specific equipment selected for cleaning validation is expected.

Although ***visual inspection*** is an important part of the acceptance criteria, it is ***not*** generally acceptable as a ***sole criteria***.

Repeated cleaning and retesting until acceptable residue results are obtained is not an acceptable approach.

It is recognised that cleaning validation may take a long time to complete. Therefore cleaning validation after every batch may be required for some products. Sufficient data should be presented to support that the equipment is clean and available for further use.

Where an automated process is used, specific operating ranges of utilities and equipment should be used *(e.g., flow rate, pressure, temperature)*.

For all cleaning processes, an assessment should be performed for to *determine* the *variable factors* which influence cleaning effectiveness and performance (e.g., operators, rinsing times, etc.). If variable factors are identified, use *worse case situations* as the basis for the cleaning validation studies.

Limits for carryover of *product residues* should be based on a *toxicological evaluation*. *Justification* for the limits should be documented in a *risk assessment* which includes supporting evidence.

Limits should be established *for cleaning agents*.

Where the product is known to degrade at extremes of pH and/or heat and may become inactive, toxicological evaluation may not be necessary.

If it is not feasible to test for specific residues, other representative parameters may be use; e.g., TOC and conductivity.

Risk present by microbial and endotoxin contamination should be considered during the development of cleaning validation protocols.

Influence of the time from the end of use until cleaning *(DHT)* and the end of cleaning until use *(CHT)* should be taken into account in order to ***define DHTs and CHTs*** for the cleaning process.

Where campaign manufacture is carried out, the impact of the ease of cleaning at the end of the campaign should be considered and the maximum length of the campaign (in time and number of batches) should be the basis for the cleaning validation exercises.

Where a ***worst case product approach*** is used as a cleaning validation model, a ***scientific rationale*** should be provided for the selection of the ***worst case product*** and the impact of new products to the site.

Worst case criteria may include ***solubility***, ***cleanability***, ***toxicity*** and ***potency***.

Cleaning validation protocols should specify or reference the ***sampling locations***, the ***rationale*** for these locations and define ***acceptance criteria***.

Sampling should be carried out by ***swabbing*** and/or ***rinsing*** or any other means depending on the equipment.

Sampling materials should not affect the results. ***Recovery*** should be shown to be possible ***from all product contact materials*** ***(e.g., stainless steel, glass)*** sampled in the equipment with all the sampling methods used.

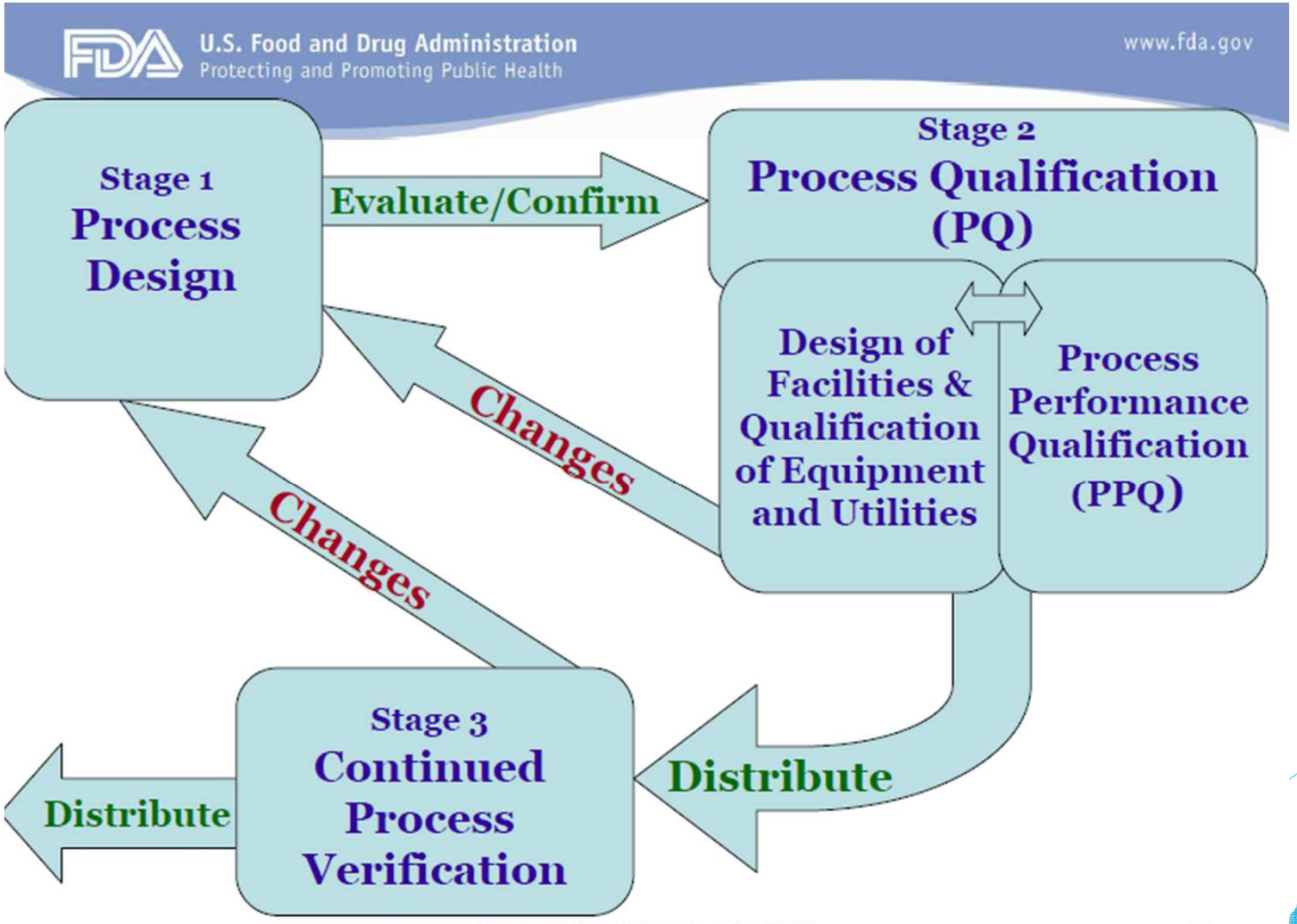
The ***cleaning procedure*** should be performed an ***appropriate number of times*** based on a ***risk assessment*** and ***meet*** the ***acceptance criteria*** in order to prove the cleaning method is validated.

(Three times may be sufficient; more may be required depending on the complexity of the system)

Where a ***cleaning process*** is ***ineffective*** or is not appropriate for some equipment, dedicated or other appropriate measures should be used for each product.

Where ***manual cleaning*** of equipment is performed, the ***effectiveness*** of the cleaning procedure should be ***confirmed*** at a justified frequency.

Lifecycle Approach to Cleaning Validation



Lifecycle Approach to Cleaning Validation

- **Based on ICH documents:**

Lifecycle Approach to Cleaning Validation

Stage 1 Activities (***process development and understanding***)

- Cleaning method development
- Analytical method development
- Site equipment

Stage 2 Activities (***process qualification***)

- Cleaning documentation
- Validation conformance runs

Stage 3 Activities (***maintaining the validated state***)

- Maintain validation *(periodic testing, re-validation)*
- Change control
- Management review

Stage 1, Process Design/Understanding: Application to Cleaning

FDA process validation guidance topics:

1. *Building and capturing process knowledge and understanding*
2. *Establishing a strategy for process control*

Application to cleaning:

Understand residue chemistry (e.g., solubility, stability)
Determine cleaning agent(s) based on residue chemistry
Determine cleaning process

- Identify sources of variability and establish methods to control variability

Requires:

- Rational analytical method
- Characterisation of equipment to be cleaned
- Training sampling personnel

Stage 2, Process Qualification: Application to Cleaning

FDA process validation guidance topics:

1. *Design of a facility and qualification of utilities and equipment*
2. *Process performance qualification*
3. *PPQ protocol*
4. *PPQ protocol execution and report*

Application to cleaning:

- Qualification of equipment, utilities, facilities
- Process performance qualification (PPQ) – cleaning at commercial scale
- Conclusion that process consistently produces clean equipment
- Conformance runs
  (note: PPQ cleaning runs can be concurrent to conformance runs)

Stage 2, Process Qualification: Application to Cleaning

Requires:

- All support systems, documents, training, personnel, etc., in place.
- Target/nominal operating parameters *(e.g., time, temperature, pressure, flow rate)* within design space
- Testing (swab/rinse)
- Decision to "release cleaning process" for routine commercial use
- Post-validation monitoring plan (risk-based)

Stage 3, Continued Process Verification: (Validation monitoring and Maintenance): Application to Cleaning

Activities to assure process remains in validated state:

Change control - evaluate impact of change and validate (test) as necessary

Trend and assess data; study OOS/OOL and OOT data

Improve process

Improve control to detect variability

Management of non-conformances and deviations

Re-validation – definition

- Is revalidation necessary? When should re-testing be considered?

Periodic Management Review

- Documentation reviewed by management and document the review

References and Related Documents

FDA:

Validation of Cleaning Processes (7/93): Guide to Inspections Validation of Cleaning Processes

eCFR: Title 21 (Food and Drugs), Chapter 1C, Part 211 (cGMP for Finished Pharmaceuticals), Subpart D (Equipment),

- §211.63, “Equipment Design, Size and Location”
- §211.65, “Equipment Construction”
- §211.67: “Equipment Cleaning and Maintenance”

Questions and Answers on cGMP Practices - Equipment

European Commission:

Eudralex Volume 4: EU Guidelines for GMP for Medicinal Products for Humans and Veterinary Use:

- Part 1, Chapter 3: Premises and Equipment
- Part 1, Chapter 5: Production
- Annex 15: Qualification and Validation

Suggested Reading

PDA Technical Report No. 29:"Points to Consider for Cleaning Validation"

PDA Technical Report No. 49: :"Points to Consider for Biotechnology Cleaning Validation"

Active Pharmaceutical Ingredients Committee (APIC): "Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredients Plants"

PIC/S 006-3:"Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation"

"Cleaning Validation In the Pharmaceutical Industry", Mowafak Nassani, Institute of Validation Technology

"Cleaning Validation Procedure and Limit Computation in Pharmaceutical Industry: An Ample Approach", Joymalya Battacharya

"Lifecycle Approach to Cleaning Validation", Paul L. Pluta, Validation Week EU, 2013

Textbooks and Websites

"Cleaning Validation: Practical Compliance Solutions for Pharmaceutical Manufacture",
Destin Le Blanc, Volumes 1-3, PDA

"Cleaning and Cleaning Validation",
Paul L. Pluta (editor), Volumes 1 and 2, PDA

www.cleaningvalidation.com (Destin Le Blanc)

Thank you for your attention!