VIEW POINT

CLEANING VALIDATION AND REGULATORY ASPECTS

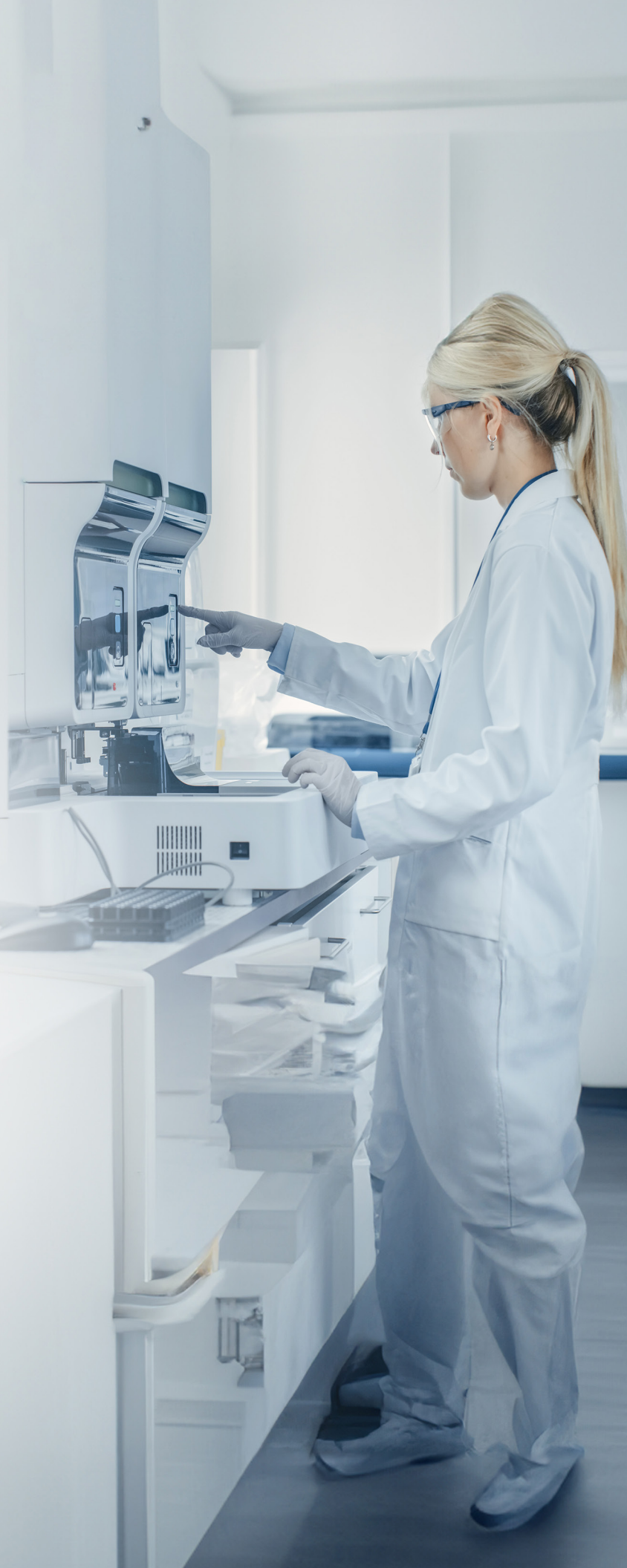
Infosys®
Navigate your next

Introduction

The process of providing documented evidence that cleaning methods employ within a current Good Manufacturing Practice (cGMP) facility for equipment cleaning consistently controls potential carryover of product (including intermediates and impurities), cleaning agents, and extraneous material into a subsequent product to a level which is below predetermined levels. Cross contamination of APIs with chemical residues and microbes can compromise patient safety. Inadequate cleaning not only leads to batch failures and downtime, but also results in rejection by FDA and related fines due to drug adulteration. As per CFR 211.67(a) contamination that would alter safety, identity, strength, quality, or purity of the drug product should be prevented.

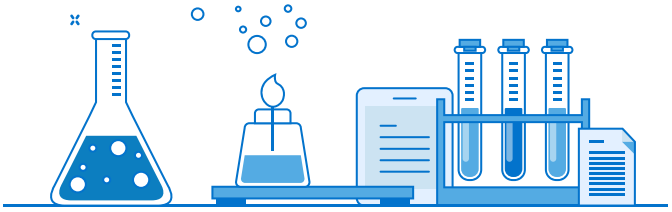
This PoV will focus on the following:

- The cleaning process and the various steps of cleaning process validation
- Factors impacting the level of cleaning
- Sampling techniques
- Regulatory guidelines governing cleaning process validations
- Expectations of regulatory agencies



The Cleaning Process

Any equipment in a GMP facility will have to be cleaned for the next use. Cleaning is minor when the equipment is used for the same project from lower to higher strength product manufacturing, however cleaning is major when the equipment is used for various products of variable strengths.



Two common cleaning processes are:

Manual Cleaning Sequence
Dismantle the parts of equipment to be cleaned
Pre-wash with tap water
Wash with cleaning solution
Rinse in tap water
Rinse with purified water
Dry using hot air
Visually inspect to check whether the equipment is clean
Reassemble the parts

Clean-in-place Cleaning Sequence
Pre-wash the parts in tap water
Wash with cleaning solution
Blow out using compressed air
Rinse with tap water
Final rinse using purified water
Blow out using compressed air
Dry using hot and compressed air

Steps of Cleaning Process Validation

Determine the most appropriate cleaning procedure for the equipment

Develop and validate the sampling and analytical method (Swab/Rinse)

(determine % recovery, limit of detection, limit of quantitation, accuracy of method, reproducibility, stability over time)

Evaluate equipment surfaces and determine critical parameters

Develop a cleaning validation protocol for the product and the equipment being cleaned

Generate a cleaning validation report detailing the acceptability of the cleaning procedure for the equipment and the product

Process steps:

Determination of most appropriate cleaning process by:

- Generating acceptance criteria
- Identifying the type of equipment, cleaning agents, and available cleaning techniques
- Standard operating procedures (manual/clean-in-place)

Develop and validate the sampling and analytical techniques, where it could be swab or rinse samples.

Equipment to be analyzed for surface area, and difficulty to clean areas for swab samples and volume of rinse for rinse samples.

Cleaning validation protocol to be prepared for each equipment in scope of cleaning individually.

Cleaning validation report to be prepared post cleaning process based on the degree of cleanliness, the protection of the clean equipment from contamination prior to use, and the inspection of equipment for cleanliness immediately before use.

Equipment post cleaning needs maintenance, sanitization, and inspection record-keeping.

Factors Impacting the Level of Cleaning

Level of cleaning is dependent on:

Equipment usage
(dedicated vs. non-dedicated)

Potential contaminants
(toxicity, solubility, stability)

Stage of manufacture
(final steps vs. early steps)

Higher the risk of contamination, greater the requirement to validate the cleaning procedure

The example below demonstrates the required levels and validation requirements:

Level	Description	Validation requirement
Level-2	Product changeover of equipment used in final step	Mandatory
Level-1	Early step to intermediates in a product sequence	Progression level between 0 and 2 depending on process and the nature of contaminant based on scientific rationale
Level-0	In campaign of same product, batch-to-batch changeover	No validation required, however validation is required if there is a break for more than a day

Sampling Techniques

Two types of sampling techniques are generally used in cleaning process validation:

Rinse Sampling

(Sampling and testing of rinse of samples for residual active ingredient)

- Equipment is first cleaned thoroughly, rinse is collected from different parts of equipment (larger surface area, inaccessible systems, cannot be routinely disassembled area, can be sampled)
- A particular volume of rinse is collected
- Rinse is examined by suitable analytical method
- Solvent used should be selected based on the solubility of the active ingredient
- The results are extrapolated to the whole equipment

Swab Sampling

- Swabbing to be done in more restricted work areas, hardest to clean, and accessible corners of equipment leading to an established level of contamination or residue per given surface area
- Small area of the cleaned equipment is swabbed with a pre-defined material and method (swab material, solvent, technique)
- Subsequently the swab is extracted, and the extract is examined by a suitable analytical method
- The quantified residue of the samples is extrapolated to the whole equipment

Regulatory Guidance

- GMP Regulations (Part 133.4) (Year 1963, FDA)
- cGMP Regulations (Part 211.67) (Year 1978)

> “Equipment should be cleaned to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product.”

- 21 CFR 211.180 and 21 CFR 211.182 relates to the records for maintenance, cleaning, sanitation, and inspection of equipment
- Chapter 5 (Production) of the rules governing medicinal products in the European Community says:

> “Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, or documents not required for the current operation.”

- Guide to Inspection for Validation of Cleaning Processes (Year 1993, FDA)
- ICH Q7A, GMP for Pharmaceutical Active Ingredients
- CEFIC: Guidance on aspects of Cleaning Validation in API Manufacturing Plants, 2000
  http://apic.cefic.org/pub/pub-cleaning-validation.pdf

Regulatory Expectations

Expectation of regulatory agencies are:

SOPs for cleaning processes used for various pieces of equipment and validation of cleaning processes to be defined and should be self-explanatory

Creation of the responsibility matrix to perform the validation

Risk assessment to be performed

Validation protocol and report to be up to quality standards

References

- http://apic.cefic.org/pub/pub-cleaning-validation.pdf
- https://www.sciencedirect.com/science/article/abs/pii/B9780323313032000054
- https://www.fda.gov/media/71518/download
- https://www.fda.gov/media/124394/download

Author

Sangita Goyal
Principal Consultant, IC LS

Sangita has around 19 years of professional experience working in the areas of project management, quality management (QC/QA/Regulatory), requirement elicitation, process analysis and testing, R&D consulting to speed innovation, quality, and audit management, and she has worked for leading pharmaceutical companies.

For more information, contact askus@infosys.com

Infosys®
Navigate your next