



REGULATORY ASPECTS OF CLEANING AND CLEANING VALIDATION IN ACTIVE PHARMACEUTICAL INGREDIENTS

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ABSTRACT

Pharmaceutical product and active pharmaceutical ingredients (APIs) can be contaminated by other pharmaceutical products or APIs, by cleaning agents, by microorganisms or by other materials e.g. air borne particles, dust, lubricants, raw materials, intermediates, etc. In the manufacturing of the pharmaceutical products, it is a must to reproduce consistently the desired quality of product. Residual material from the previous batch of the same product or from different product may be carried to the next batch of the product, which in turn may alter the quality of the subjected product. An effective cleaning shall be in place to provide documented evidence that the cleaning method 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 level. The purpose of this review is to provide information about importance of cleaning validation of API in pharmaceutical industry and this information is in accordance with the regulatory guidelines.

Keyword: cleaning procedure, validation procedure, Guideline on cleaning procedure.



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INTRODUCTION

Cleaning validation is established documented evidence providing a high degree of assurance that a specific cleaning process will produce consistent and reproducible cleaning results that meet a predetermined level. It is applicable to the cleaning of process manufacturing of active pharmaceutical ingredient in the pharmaceutical industry. The importance of cleaning validation is not only required to company with law but also to meet customer's needs. It ensure that the safety identity strength and purity of the product which are the basic requirements of 'current good manufacturing practice. It provides the manufacturer with enough confidence that internal control is properly formed.¹ Cleaning validation in a manufacturing process has to be designed and carried out in a way that prevents the cross-contamination as much as possible. These processes important in pharmaceutical operation have achieved an increasing emphasis in the past decade both by the regulatory agency and industry itself.²

The important benefit of such authentication work is that identification and correction of potential problems previously suspicious, which could compromise the 'efficacy, safety or quality' of 'subsequent batches of drug product' produced within the equipment.³ The cleaning procedure will be certified to prove that it is consistent with the 'expected system and will produced the result that consistently complete the default specification. The basic reason 'behind' the 'process' of good, effective, consistent 'cleanliness' is to avoid contaminated substance of product made 'in the same 'equipment'. The purpose is to provide 'high quality pharmaceutical products' to our patients. The basic process of 'removing the residue and contaminants from the equipment are mechanical' action, 'dissolution, detergency' and 'chemical reaction'.⁴ The 'procedure' for cleaning will generally be standardized. Cleanliness certification' should be directed to the action in which the pollution of the substance will create the highest risk for active pharmaceutical ingredients. Cleaning validation is documented 'evidence to establish 'hat 'cleaning procedures' are removing 'residue to

predetermined levels' of acceptance such as 'batch size, dosing, "toxicology, and 'equipment' size. Cleaning recognition reflects pharmaceutical, biological and radiographic manufacturing area in which 'both the inspectorate' and pharmaceutical industry is important.⁵

Principle⁶

Cleaning validation' is to verify the 'effectiveness of the cleaning' 'procedure for removal' of product residues, degradation products, 'preservatives, excipients, and/or cleaning agents' as well as the 'control of potential' 'microbial contaminants. 'In addition one needs to ensure there is no risk associated with cross-contamination of active ingredients. Cleaning procedures must strictly follow carefully established and validated methods.

Advantages of Cleaning Validation:¹

Safety is important in validation because it can also results in increased operator safety. Properly calibrated validated instruments and gauge used to reduce accident and results in safety. Better customer quality through proper validation, market recall is avoided which results in better customer care and quality of the product.

Cleaning Validation in Active pharmaceutical Ingredient manufacturing' plants²

Cleaning Validation in the context of Active Pharmaceutical Ingredient manufacturer may be defined as, The 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'.

Different types of 'cleaning validation' for API:

Different mechanisms are used to remove residue such as, mechanical action dissolution,' detergency, specification, and chemical reaction.'

Mechanical action: This method is eliminated from the physical' action such as scrubbing, brushing and pressurized water.

Dissolution: Dissolution use 'solvent to dissolve' residues. Water is generally chosen to be non toxic, economical, environmentally friendly and does not leave any residue. Some residues are removed only by alkaline or acidic solvent.

Detergency: This 'process is carried' out by four ways such as 'wetting agent, solubilizer, 'emulsifier, and dispersant in removing' the residue and 'contaminants from' equipment. Wetting agent is used because it 'decrease the surface tension' of 'cleaning solution, thus' they can easily 'penetrate into the residue.'

Specification: This method depends on 'the breakage of ester bond' in 'fat residue to form fatty acid' and 'glycerol which are soluble' in water. 'For this purpose, 'some alkalis' can be used' such as NaOH, KOH.

Chemical reaction: oxidation' and 'hydrolysis reaction chemically' breaks the 'organic residues.'

Cleaning agents:⁵

Selection criteria

It is the 'ability to remove' the product residue. Its 'compatibility with' the equipment.

This method is very easy and sensitive' of assay method. This method's very easy for removal and verification 'of removal.

His toxicity should be low.

Typical cleaning agents' are commonly used

Alkaline Chemical – NaOH'
Acidic Chemical – Phosphoric acid'
Oxidizer chemical - NaOCl > pH 7'
Detergent formulation
Water

Sampling techniques:¹

Sampling is required according to the cleanliness certification protocol. There are 'two main sampling techniques' are used in 'pharmaceutical industry' such as swab method and Rinse method. Choosing suitable extraction solution' is one of the important steps to establish a swab or rinse method. To choose a useful extraction solution, solubility of 'target residue' should be 'checked' in the selected solution. Various alcohols, water, 'buffers', or the combination of them are' the very 'common extraction solutions used' to clear the cleaning validation procedure. Factors that 'need to be considered to' choose the suitable sampling method: design of equipment, solubility of the residue, useful and available analytical methods.

Swab Sampling:

Generally, there is a need for content that is 'absorptivity' and to 'physically wipe the surface' and 'recover the 'analyte, 'there is a need to clear the surface material was the preferred method available with human hand or arm. It can be used as the 'basic information for' the 'preparation of a method' of 'analysis and detection' limit.

Advantages of Swab Sampling:'

- It can be dissolve and physically remove' the sample.
- Variation surface compatibility.
- It is economically and widely available.'
- Can allow a sample of a defined area.
- It is 'applicable to active, microbial' and cleaning agent residue.'

Disadvantages

- Variation in results,
- Sampling errors may be frequent,
- Sampling technique difficult to standardized,
- Rubbing force varies from person to person,
- If solvent evaporate, it may influence the result,
- Swab can leave significant' portion of fibers.

Limitation

- An Invasive technique' that 'may introduce fibers.'
- Results may be 'technique dependent.'
- Swab material and design' may 'inhibit recovery' and 'specificity of the method.'
- Evaluation of large, complex' and 'hard to reach areas difficult.'

Rinse Sampling:

Rinse sampling does not employ mechanical action on the surface and the sample is collected as a final rinse or rinse applied specifically for collecting a validation sample. The maximum allowable carry over (MACO) is usually calculated on each individual product change over scenario according to the procedures outlined above and individual acceptance criteria are established using the following equation:

$$\text{Target value (mg/L)} = \text{MACO (mg)} / \text{Volume of rinse or boil (L)}$$

Advantages

- Adaptable to on-line monitoring
- Easy to sample
- Non-intrusive
- Less technique dependent than swabs
- Applicable for actives, cleaning agents and excipients
- Allows sampling of a large surface area
- Allows sampling of unique (e.g., porous) surfaces

Limitation:

- Limited information about actual surface cleanliness in some cases.
- May lower test sensitivity.
- Residues may not be homogeneously distributed.
- Inability to detect location of residues.
- Rinse volume is critical to ensure accurate interpretation of results.
- May be difficult to accurately define and control the areas sampled, therefore usually used for rinsing an entire piece of equipment, such as vessel.

Level of Cleaning:⁴

The manufacturing processes of an active pharmaceutical ingredient are typically different chemical reaction and purification steps that are made to make physical changes. In general, early steps undergo further process and purification and so

Table no 2: level of cleaning

LEVEL 2	LEVEL 1	LEVEL 0
1. Product changeover of Equipment used in final step 2. Intermediates of one Batch to final step of another 3. It is essential Acceptance Criteria: Based on TTD/Toxicity, 10 ppm whichever is lower.	1. Intermediates or final Step of one product to Intermediate of another 2. Early Step to intermediates in a product sequence 3. Progression between level 0 and 2 depending on process and nature of contaminant based on scientific rational. Acceptance Criteria: General limit 500 ppm.	1. In-campaign batch to batch change over 2. No validation required. Acceptance Criteria: Visual observation.

Potential residues⁶

The Active Pharmaceutical Ingredient Industry involves the manufacture of API by both chemical and physical means through a series of multiple steps processes. Plants or individual pieces of equipment including ancillary equipment, may be used in multi-product manufacture or dedicated to individual products. The result of inadequate cleaning procedures is that any of a

potential carryover of the previous product would be removed. This is necessary to ensure that the active pharmaceutical ingredient is free from unacceptable levels of contamination by previous substances, and it varies depending on the step being cleaned and next substance being manufactured in the same piece of equipment train. APIs and related intermediate are multipurpose equipment with frequent product changes which results in a high amount of cleaning¹⁰.

The degree or level of cleaning and validation required for process in API manufacturing depends largely on: The equipment usage (i.e. dedicated equipment or not), the stage of manufacture (early, intermediate or final step), the nature of the potential contaminants.

Level 1 Cleaning

It is used during the creation of various batches of the same product. Example, In a manufacturing Campaign for product A, there are 3 Batches to be manufactured as shown below. Batch 1 Batch 2 Batch 3 For a given equipment &/or equipment train, if batch 1 in the campaign is to be followed by Batch 2 in the campaign, then a level 1 cleaning is required.

Level 2 Cleaning

This is used between manufacturing of different Batches of different Product and / or at the end of manufacturing campaign even if same product is planned for the next campaign.

Table 1: Comparison between levels⁵

Parameter	Level 2	Level 1	Level 0
Risk	Highest	Lowest	Lowest
Acceptance	Lowest	Highest	Highest
Degree of	More	Less	Less
Verification	Analytical	Visual	Visual

number of contaminants may be present in the next batch manufactured on the equipment such as:

- It is a precursors to the Active Pharmaceutical Ingredient.
- By-products and/or degradation products of the Active Pharmaceutical Ingredient.
- The previous product.
- Solvents and other materials employed during the manufacturing process.

- Micro-organisms-This is particularly the case where microbial growth may be 'sustained by the product.'
- Cleaning agents themselves and lubricants.

Cleaning procedures⁹

In chemical production a 100 % carry-over' of 'residue from the equipment' surface to the 'next product to be manufactured' is very unlikely 'based on the way the process' is 'run and on technical' considerations. 'The residue remaining' on the equipment surface can, during' the 'next production cycle, be carried' over into the reaction mixture consisting' of 'solvent and raw materials'. In most cases, however, any residue in solution' will be 'eliminated from the process' together with the solvent, and' 'insoluble residue by physical' 'separation processes' (e.g. filtration), so likely carry over into the end-product will be low. The final step in a multi-step 'chemical synthesis is selective' purification of the API' (e.g. by crystallization), during which contaminants' are 'removed from the process' and/or insoluble 'residues are removed' by 'physical separation'. From the original reaction' 'mixture of edict, agent' and 'solvent there remains' only a 'fraction of the original' mass as API at the' end of the 'chemical process.' It is also to be' 'noted that, during' subsequent 'pharmaceutical production, the API' is further 'diluted through the' excipients that are added.'

Equipment parameters' to be evaluated⁸

- Identification of the' equipment to be cleaned'.
- Difficult to clean areas.
- Property of materials.
- Ease of disassembly.
- Fixed or not.

Residues to be cleaned

- Cleaning limits.
- Solubility of the residues.
- Length of campaigns.

Cleaning agent parameters to be evaluated

- Preferably 'materials that are normally' used in the process.
- Detergents available.
- Solubility properties.
- 'Environmental considerations.'
- Health and 'safety considerations.'

Cleaning techniques to be evaluated

- Manual cleaning.
- CIP (Clean-in place).
- COP (clean-out-of-place).
- Semi automatic.
- Automatic.
- Time considerations.'
- Number of cleaning cycles.'

For new product: In case there are more than one API for' the 'new product, each API shall' be evaluated for the below detailed 'parameters and based on the

evaluation' one API shall be 'selected as worst case' product.

Batch size of the product: The product which has minimum' batch size 'should be considered as worst' case product, which makes the acceptance criteria' more stringent.

Based on Label Claim of API: The Product with highest' strength can be considered' as worst case product.

Dose for the product: The product having maximum' daily dose can be considered' as worst case product.'

Solubility of the API: Product' having least solubility in water' and 'higher strength can be considered' as 'worst case product on basis of' solubility.

Based on Therapeutic Potency: The most Potent product' 'can be considered' as the 'worst case' product on the basis of therapeutic potency.'

For new equipment: When' new product is 'identified as worst case, the' total surface area for' the equipment shall be arrived' by 'identifying the equipment' used for manufacturing.'

Validation protocols⁴

A Validation Protocol is necessary' to define the 'specific items and activities' that will 'constitute a cleaning validation study.' It is 'advisable for companies' 'to have drawn up' a 'Master Validation plan' indicating the 'overall Cleaning Validation strategy' for 'either the product range' / 'equipment type' / entire site. The 'protocol must be prepared' prior to the 'initiation of the' study and must' either includes or 'reference the documentation' required to 'provide the following' information:

- Background
- Purpose of the validation study'
- Scope of the' validation study'
- Responsibilities for performing' the validation' study
- Sampling procedures to be used'
- Testing methods to be used'
- Acceptance criteria
- Change control
- Approval of protocol' before the study'
- Deviations

Validation Reports^{8,}

A 'validation report is necessary' to present the 'results, conclusions and secure' approval of the study'. The report should' include the following:'

- Summary of or reference' to the procedures used' to clean, sample and test.
- 'Physical and analytical test results or references for same, as well as any pertinent observations.'
- Conclusions 'regarding the acceptability of the results, and the status of the procedure(s) being validated

- Any 'recommendations based on the results' or 'relevant information obtained' during 'the study including revalidation practices if applicable.'
- Review of 'any deviations from the' protocol.

Life Cycle approach' to the 'cleaning validation.¹⁰

'As explained in' the "Guidance for 'industry Process' validation: General principles' and industries", FDA is 'proposing three stage validation' approach, Stage1: Process design, stage 2: Process qualification and' stage3: Continues process verification'. This approach is 'applicable' to not only 'for the manufacturing process' for a 'product but also applicable' to the 'other processes which are following' and validating. 'Equipment cleaning process' is 'one of them, following to clean' the 'equipment for good quality' of product, 'the process which is following for' cleaning of equipments were validating' 'to provide the documented' 'evidence and to prove' that the procedures' are 'producing consistently good results' as per 'the set acceptance criteria.'

STAGE – 1:

Identification of the equipment' to be cleaned'

- Material of construction 'of the equipment'
- Identification of hard to clean' areas
- Physical and chemical properties' of the residue.
- Previous Product solubility.
- Selection of cleaning agents' based on the solubility of the residue.
- Determining the cleaning' procedure.
- Cleaning process parameters.
- Lab testing methods.
- Establishing Acceptable limits.

STAGE – 2:

Design of a facility' and 'qualification of utilities and equipments'

- Process Performance Qualification.
- PPQ Protocol.'
- PPQ protocol execution 'and Report.'
- Execution of cleaning.
- Cleaning documentation.
- Validation conformance.

STAGE – 3:

Continued process verification,

- Trending of the collective data.'
- Maintaining validations.
- Preventive Maintenance.
- Periodic review of the' process.
- Change controls, deviations' & 'Implementation' of CAPAs.
- Revalidation.

Guidelines on cleaning validation' according to WHO: ²

Good manufacturing practice in' API manufacturing' proceeds from initial process steps to final process steps. Similarly, cleaning the equipment proceeds from the initial cleaning step to the final cleaning step, and which are reflected in the quality' of 'the API and

subsequently' in the 'drug product based' on 'effective cleaning and validation.

- Product-contact surfaces' (Consideration should be given' to 'non-contact parts into' 'which product may migrate for example, seals, fans of ovens, heating' elements etc.)
- Cleaning after product changeover' (when one pharmaceutical formulation' is being 'changed to another, completely' different formulation).
- Between batches in campaigns' (when the same formula is being manufactured' over a period of time, and on different days). It seems acceptable that' a campaign can last' a 'working week, but anything' longer becomes 'difficult to control' and define.'

Designing the Cleaning Process in Manufacturing Plants

Manufacturing of pharmaceutical 'products involves a series of processing' 'steps and use' of 'various equipment. Equipment and ancillary systems are 'used for manufacturing' of multiple' products or a single dedicated product. Inadequate 'cleaning processes may carry' forward the 'residue as a contaminant' in the next 'batch to be manufactured' in the same' equipment.

Equipment in the Manufacturing Plant

Several aspects should be considered for the 'equipment' in the 'manufacturing' plant.

Equipment Design Considerations

Good design for cleaning should be built into plant/equipment specifications. Equipment cleaning performance and function 'must be considered' during equipment design. Ideally, the equipment 'should be' constructed' of nonreactive, nonadditive, nonadsorptive, and nonporous materials.

Equipment Characteristics

Equipment usage during production is another important aspect to consider 'in establishing a cleaning validation' program. It is important to understand the range of products that are likely to come in contact with the various equipment surfaces; this will help to identify the contamination and 'cross-contamination potential' of the equipment.

Construction Materials

'Equipment should be constructed' such that 'surfaces which contact' components, 'in-process materials, or drug products' will not 'be reactive, additive, or' absorptive, and not alter' 'the safety, identity, strength,' quality, or purity' of the drug product.'

Heating Ventilation and Air Conditioning System

One of the most important areas in pharmaceutical process control is the development of systems to control microorganisms 'during manufacturing' and 'storage of equipment.' Install appropriate 'dedicated and validated' 'heating, ventilation' 'and air conditioning' (HVAC) system in all 'manufacturing areas with' 'suitable air locks' and pressure differentials.

Guidelines on cleaning validation according to FDA:

Cleaning validation in 'the pharmaceutical industry' has been a 'topic of ever-increasing interest' and 'scrutiny in recent Food' 'and Drug Administration' (FDA) inspections. The 'validation of procedures used' to 'clean the equipment employed' during the 'various steps of a manufacturing' process is a clear 'requirement of current' Good Manufacturing Practice' (cGMP). As such, FDA inspectors now expect to see a functioning 'cleaning validation program' with appropriate documentation in place during their inspections.

The 'requirement that equipment be clean' before being used is not a new concept. The 'equally important requirement' that it also be 'sanitary is many times obfuscated' by the word, clean. 'In response to the' often-asked question "what is clean," the 'FDA published a guidance' document: the 2004 FDA' Guide to 'Inspections Validation of Cleaning' Processes." The FDAs guide to inspections, which "intended to cover equipment cleaning' for 'chemical residues' only," includes:

- FDA expects firms to have written procedure (SOPs) detailing the cleaning' processes.
- FDA expects firms to have' written general procedures 'on how cleaning 'processes will be validated and approving the validation study, 'the acceptance' criteria, and when revalidation will be' required.
- FDA expects firms to 'conduct the validation studies' in 'accordance with the protocols' and to 'document the results' of studies."
- Besides 'assuring chemical' cleanliness, "the microbiological 'aspects of equipment cleaning'

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should be considered. This consists largely of preventive' measures..."

- Determine the 'specificity and sensitivity of the analytical method used to detect' residuals or contaminants."
- The firm should 'challenge the analytical' 'method in combination' 'with the sampling' method(s) used to 'show that contaminants can' be 'recovered from the' 'equipment surface' and at what level."
- Direct 'sampling (e.g., with swabs) is most desirable,' although 'rinse sampling may be' satisfactory."

CONCLUSION

Here, we can conclude that cleaning validation is a documented process that proves the effectiveness and consistency in cleaning of API in pharmaceutical industry. It is necessary to have effective cleaning program in place because of the regulatory requirement. However, more fundamental reason that to produce products that as pure and free from contamination. The main purpose of cleaning validation is to establish documented evidence with a high degree of assurance that one can consistently clean a system or a piece of equipment to predetermined and acceptable limits. This article primarily covers the aspects related to cleaning validation guidelines as per WHO and FDA for cleaning validation, types of cleaning, different levels of cleaning, cleaning procedure, sampling procedure, cleaning agent selection, life cycle approach, and validation protocol.

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