Journal Of Harmonized Research (JOHR)

Journal Of Harmonized Research in Pharmacy
7(1), 2018, 34-42

ISSN 2321 – 0958

Original Research Article

OVERVIEW OF CLEANING VALIDATION IN PHARMACEUTICAL INDUSTRY

Pankaj P Chandratreya and Dr. Deenanath Jhade

Sri Satya Sai University of Technology & Medical Sciences, Sehore, (M.P.)

Abstract: An essential part of any pharmaceutical manufacturing facility which operates under cGMP Guidelines and adheres to Quality Systems Regulations (QSR), is the availability of well-developed and validated cleaning procedures for all installed equipment. This will ensure that the cleaned equipment is free from residues of active ingredient from the previous product manufactured on that equipment and also from traces of detergent, if used in cleaning process. Additionally, the equipment will also be free from microbial contamination which can be carried forward into the next batch.Documented evidence that demonstrates effectiveness of the cleaning methods employed within the facility to consistently reduce potential carryover of product (including intermediates and impurities), cleaning agents and extraneous material into subsequent product to levels which are below predetermined limits is the key to produce quality products.

Keywords: Cleaning, Chemical, Decomposition Residues

Introduction: Cleaning validation is necessary to establish consistency and uniformity in equipment cleaning procedures by implementing practices that have been found acceptable. It must be accepted that in case of cleaning validation process, as with validation of other processes, there are several ways of validating the process. Ultimately, the assessment of any validation process depends on availability of scientific data that demonstrates that the process is able to consistently perform as expected and produces an outcome that meets predetermined specifications. In addition, the levels must be acceptable to the regulatory authorities responsible for ensuring the safety and quality of the pharmaceutical products.[1]

For Correspondence:
pankaj.chandra12@gmail.com.
Received on: February 2018
Accepted after revision: March 2018

Objective: The objective of cleaning validation is to demonstrate with adequate documented evidence that the equipment / utensil cleaning procedures can consistently remove residues of

the manufactured product to levels below the calculated acceptance limits. "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"[2].

Cleaning Philosophy: Multi-product facilities present the greatest difficulty in introducing a cleaning procedure which is practical and easy to implement [3]. The underlying philosophy for cleaning validation of API is that carry-over residue into the next product should not exceed $1/1000^{th}$of the therapeutic dose of the previous product manufactured using a train of equipment [4,5]. For routine operations, the train of equipment or utensils is cleaned separately and the total residues on equipment surface are estimated. This is done to determine the amount of residue that may be potentially being carried over to the next product. A cleaning procedure generally covers thorough cleaning using detergents / neutralizing agents / solvents. These may be used either alone or in appropriate combination to assist in removal of residues from equipment surface, followed by final rinsing with purified water or water for injection. The final rinse water is then tested for residues of the previous product and/or pH / TOC / conductivity and the results are compared with pre-defined acceptance criteria. At the core, requirements for cleaning validation of the cleaning process are almost similar for manufacturing of drug substances and drug products. Nonetheless, the cleaning process of equipment and facility for drug substances is considered to be more complex as compared to the cleaning procedure for formulated drug products like tablets, capsules or topicals. This is attributed to following reasons:

i. Drug substance manufacturing processes depend on the combination of several reactants which are subject to extreme conditions of temperature, heat, pH and the reaction vessel's surface.

ii. The manufacturing process of drug substances involves multiple stages with chemical / physical / biological transformation. These reaction steps increase also the possibility of generation of impurities that may carried over to the final API.

iii. The equipment / ancillary systems used for manufacturing of drug substances more complex. Subsequently, cleaning of internal surfaces / components / pipelines present greater difficulties.

In comparison, the manufacture of a finished product is different from API, as it involves materials that are is stable under normal conditions and can be stored for prolonged periods without losing their physical and chemical characteristics.

Considering the differences between manufacturing processes of drug substances and drug products, following scenarios are considered important in validating a cleaning procedure during manufacturing.

- Carry-over to the next batch in a campaign
- Carry-over to downstream processes if common equipment is used
- Carry-over to the product when product change-over occurs

In case of drug substances, carryover of residue from the early stages may be removed in the final stages (eg. purification stage); hence, requirements for cleaning are not in very rigorous in the early stages of manufacturing, whereas adequate cleaning controls are required at all stages of manufacturing for a drug product formulation.

In both cases, it is very important to identify potential contaminants and their clinical and toxicological effects.

Potential contaminants

Pharmaceuticals produced in a multi-product manufacturing facility can be contaminated by potentially harmful and toxic substances. In such facilities, the equipment is commonly used for manufacturing several different products of

varying potencies. Improper equipment cleaning procedures can lead to possible contamination of the products with different types of residues, which include,

- Product residues and decomposition residues
- Cleaning agent residues
- Microbial contamination with bacteria, mould and pyrogens
- Lubricants used in preventive maintenance activities

Cleaning Validation Policy: All manufacturers must have a cleaning validation policy in place. This policy serves as a general guideline and training document for the company regarding the approach to various aspects of cleaning and cleaning validation. These include the following at the minimum:

Responsibilities of specific departments for execution of the cleaning validation and testing of residues from samples

Approach for Analytical method validation

Cleaning frequency, which specifies the number of batches of the same product that can be manufactured at a stretch

Cleaning interval, wherein the equipment hold time before cleaning is specified. An accepted practice in the industry is a hold time of not more than three days. This policy should serve associated with Cleaning Validation.

The level of cleaning specified between batches of the same product and that specified during product change-over.

Procedures on bracketing wherein equipment of similar design or functionality may be bracketed based on cleaning procedures used.

Procedures for worst-case determination and selection of reference products for cleaning based on the ingredient's water solubility as well as practical experience in cleaning that product.

Requirements or frequency for revalidation of cleaning procedures.

Level / degree of Cleaning : *Three* types of scenarios are normally expected during manufacturing and are considered important in validating a cleaning procedure and require different levels of cleaning in case of drug products.

- Carry-over to the next batch in a campaign
- Carry-over to downstream processes if common equipment is used
- Carry-over to the product when product change-over occurs

Carry-over to the next batch in a campaign

For economic as well as practical reasons, a pharmaceutical facility which manufactures products for the commercial market normally manufactures in campaigns, wherein a number of batches of the same product are manufactured at a stretch. During the campaign, the equipment can be considered as dedicated for the specific product. Hence, the level of cleaning specified between batches is different from that specified during product change-over.

Accordingly, carry-over of residues to the next batch in the campaign does not have the same criticality as carry-over to the next product. The only point of concern is that cleaning should ensure that the batch receives acceptable limits of:

- Residues from the cleaning agent[6]
- Degradation products

Residues from the cleaning agent can be estimated using analytical techniques. However, determining the level of degradation products which may be produced when large number of batches are manufactured, presents several difficulties.

One way avoid this difficulty is to ensure that the standard operating procedures include a requirement for complete or thorough cleaning after a specified number of batches have been manufactured. As a thumb rule, thorough cleaning is specified after manufacturing five batches of the product.

Degradation products may also be generated when equipment is left un-cleaned for prolonged periods after being used for manufacturing. Hence, an equipment hold time

of not more than three days is the accepted industry practice.

Carry-over to downstream processes

A batch can be contaminated with carry-over from an upstream process when two or more steps in a production process are performed in the same equipment. This scenario is illustrated in below in Figure 1.

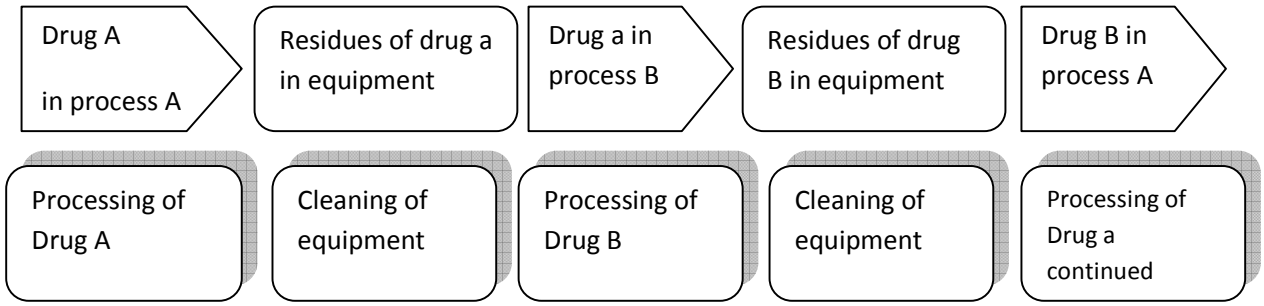

Figure 1: Carry-over for Common Equipment

The situation described above usually does not have any adverse impact on the final formulation, unless the two processes are designed to be free from residues of either drug in each of the processes. An example of the above would be extended release formulations with components A and B formulated to release in vivo at different times.

Carry-over to product during product change-over

Contamination of next product, illustrated in Figure 2 below, can come from three sources:

- Residues from the previous production process
- Residues from the degradation of previous product and
- Residues from the cleaning agent used

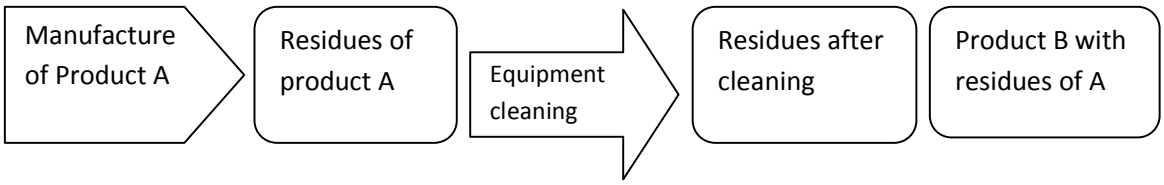

Figure 2: Carry-over for Product Change-over

The situation described above represents a greater risk to the patient as compared to contamination of the formulation during a campaign. There is also a risk of cross contamination of the product during product change-over.

Thus, the above situation requires a much greater effort during documentation of the cleaning status of the equipment.

In case of drug substances**,** different cleaning situations may arise during the manufacturing of drug substances, as given below:

i. Batch to batch changeover cleaning
ii. Changeover from manufacture of early stage product to intermediate of same product.
iii. Changeover from manufacture of intermediate stage of one product to intermediate of next product.
iv. Changeover from manufacture of intermediate stage of one product to final stage of next product.
v. Changeover from product to next product

Different levels or types of cleaning are necessary for the different scenarios mentioned above.

Level 1 (Type A) Cleaning: Level 1 or Type A is used when different batches of same product are manufactured in a campaign.

For example, in a manufacturing campaign for product A, 3 batches are manufactured as shown below.

Batch 1 – level 1 cleaning - Batch 2 – level 1 cleaning - Batch 3

If products are manufactured on a common equipment or set of equipment, if first batch in the campaign is followed by the second batch of the same product, then level 1 cleaning is required is adequate.

Level 2 (Type B) Cleaning: Level 2 or Type B cleaning is used when batches of different product are manufactured one after another or at the end of the manufacturing campaign even if the same product is planned for manufacture in the next campaign.

There is difference in the two levels of cleanings when considered in terms of the degree of risk accompanying the cleaning, the acceptance limits, the extent of cleaning and the method used to verify the cleaning process.

The two types or levels of cleaning differ from each other in terms of the level of risk associated with them, the acceptance limits for carry-over, extent of cleaning and method of applied to verify the cleaning process. The differences are compared in Table 1.

Table 1: Comparison between cleaning types

Description	**Type A (Level A)**	**Type B (Level B)**
Risk level	Low	High
Acceptance limit for carry-over	High	Low
Extent of cleaning	Less extensive	Thorough cleaning
Verification of cleaning	Visual inspection / use of non-specific methods	Analytical testing using specific validated methods

Approaches to Cleaning Validation: It is theoretically possible to clean equipment until it is completely free from residues of the active ingredient. However, this would involve extensive and prolonged periods of cleaning process which is not economically feasible.

Accordingly, for all practical purposes, published literature and regulations permit the widely prevalent practice to clean equipment to levels where they may contain measurable amounts of residues of the active ingredient and contaminants. A "contaminant" is an "unacceptable" residue such as drug product degradant or end toxins.

The residues of the active ingredient and contaminants must be medically safe, not affect product quality and be unavoidable by practical means [7].

Grouping Procedure: To rationalize the cleaning validation study which would otherwise involve performing a study for every product to product change-over (product A to product B) and minimize validation requirements, grouping may be used to prioritize cleaning validation studies or may be used to eliminate some of the numerous possible combinations of product and equipment studies that otherwise must be performed.

Grouping is a method by which a group of products or equipment is considered to be similar or equivalent for the purpose of cleaning validation. When considering similar products, a worst-case member of the family is selected for demonstrating cleaning validation. When considering equivalent, any member of the family may be selected as representative of any other member.

When grouping equipment, following are the considerations:

i. All products manufactured on the equipment group.

ii. All the equipment in the group cleaned with the same cleaning agent.

iii. All equipment cleaned with the same cleaning procedure.

Other equipment grouping considerations include:
i. Equivalent in terms of position or role in the manufacturing process.
ii. Similar functionality.
iii. Similar design.
Whatever equipment grouping approach is followed, cleaning validation must always be carried out to meet lowest limit of the entire product group manufactured in the group of equipment.

Worst case matrix: Validation may be simplified using Worst Case Matrix [8]. In this procedure to simplify validations, a matrix of worst case equipment to clean and worst-case residues to remove are created. This is initiated by first assembling an equipment matrix and residue matrix that defines all shared and dedicated equipment with what residues they are exposed to. By conducting an evaluation of the products and equipment, it is possible to identify and document a "worst case", for the most difficult to clean residues and equipment. A complete validation can then be performed on these worst-case equipment and residues, which in turn will eliminate the need to validate the process for easier-to-clean equipment and easier-to-clean residues. Typically, groups of worst case situations are established with one piece of equipment representing a group of similar or easier-to-clean equipment. Similarly, product residues are grouped and one residue is chosen to represent a group of similar or easier-to clean residues. The chosen product is termed "Reference Product".

Reference Product: Product selected from the group which is most difficult to clean based on the ingredient's water solubility as well as practical experience in cleaning that product.

Worst case values include, lowest dose of the product, the smallest batch size that can be manufactured using the equipment (or smallest number of dosages that can be made from the batch); the maximum daily dosage of the product (or highest number of doses) and equipment surface area.

Here, the assumption is made that the reference product will simulate the most potent product of the group that will be taken in as a potential residue, in the highest formulated daily dosage of the next product having the smallest batch size.

A single validation study or "Bracketing" study under consideration of the "worst case" can then be carried out which takes account of the relevant criteria. It also mentions that at least three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.[9]

Establishment of Acceptance Criteria

Cleaning Validation should demonstrate that the cleaning procedure consistently removes residues of the substance previously manufactured on the equipment to levels that are acceptable and that the cleaning procedure itself does not contribute unacceptable levels of residual materials to the equipment. The limits set should be practical, achievable and justifiable.

In the manufacture of drug substances there may be incomplete reactants and other unwanted by-products which may not have been chemically identified.

Therefore, there must be greater focus on by-products as well as the main reactants of the chemical process followed for manufacturing the drug substances. Manufacturers should use sound scientific rationale to decide the residue(s) to quantify, to achieve final product quality and prevent cross-contamination.

Chemical Determination: For drug substance manufacture, it is usually the Active Pharmaceutical Ingredient or intermediate residues which are of utmost concern rather than reaction by-products or degradation impurities, which are present in extremely minute quantities.

There are a number of options available when determining acceptance criteria. Where either toxicological or therapeutic data is available, then calculation limit based on the dose

criterion is set at 100th dose in the next product. The minimum daily dose of the previous product and the maximum daily dose of the following product shall be used for the calculation. This type of calculation can be applied when a final API stage follows on directly from the final stage of another API. Where not all the dose data are available for all of the products, but toxicological data for the previous product are, the limit value is calculated according to the usual formula (ADI value, NOEL value).

In the same way, as with the dose criterion (reduction from 1/1000th to 100th), the safety factor may also be reduced from 100 to 10.

When neither dose nor toxicological data are available for the previous product, the limit is set at 100 ppm. In other words, 100 ppm (relative to the batch size of the following product) of a defined previous product may remain as residue on the surface of the equipment.

Toxicity data: According to "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" processing of pharmaceuticals using shared equipment must be assessed by determination of Health Based Exposure Limits (HBEL) if highly hazardous substances are manufactured.

The EU Guideline mandates that limits for the carryover of product residues of hazardous substances should be based on a toxicological evaluation to determine the product specific permitted daily exposure (PDE) value. It is also required that risk assessment be performed to justify selection of PDE value.[10]. If the value for 1/1000th of the minimum therapeutic dose is lower than PDE calculated for oral route, the manufacturer is permitted to use it to calculate the maximum allowable carry-over.

For non-hazardous substances, the guideline permits the use of $1/1000^{th}$ of dose criteria.

Pharmacological Dose Method: The principle is to reduce the levels of residues of the product in individual equipment, such that no more than 1/1000th of the normal therapeutic dose will be present in the normal dose of the next product manufactured using the equipment. The cleaning validation program should include a calculation which is based on this principle to arrive at the acceptance criteria for the samples to be tested.

The calculation is based on allowing not more than a fraction of a therapeutic dose to be present in the subsequent product. The fraction in this case is called "Safety factor". For example, the acceptance limit calculation for carry-over in an ophthalmic product uses $1/5000^{th}$ fraction of lowest therapeutic dose. 1/5000 in this case is a "Safety factor". The Safety Factor is a measure of degree of risk for a particular type of formulation. The degree of risk may be different for drug products and drug substances. For different dosage forms such as tablets and parenteral preparations, normally accepted Safety Factors are given in table 2.

Table 2: Safety factors for different dosage forms [1]

Dosage form	Safety factor
Parenteral products	1000 - 10000
Oral solid dosage forms	100 - 1000
Topical preparations	10 - 100

10ppm criteria or 0.1% carry-over limit

For substances where the therapeutic dose is not readily available or applicable, eg., cleaning agents or detergents, limiting the level of product which could appear in the following product is based on the 10ppm criteria or 0.1% carry-over limit (based on the ICH impurity guideline which indicates that up to 0.1% of an individual unknown or 0.5% total unknown material may be present in the product being tested)

It cannot be used for substances where the therapeutic dose is known. P. Alcock and P. Motise, specify in Human Drug cGMP Notes, June 1998 that some firms incorrectly applied as their acceptance limit the 0.1% impurity identification threshold as discussed in both the ICH impurity guideline and the U.S.P. General Notices. This application of the 0.1% impurity

threshold is inappropriate because the limit is intended for qualifying impurities that are associated with the manufacturing process of related compound and not extraneous impurities caused by cross contamination.

It is necessary to evaluate the ability of the cleaning procedure to remove any cleaning agents introduced. The acceptance criteria for the residual-cleaning agents should reflect the absence of these materials, within the range of the capabilities of the assay and sampling methods. The individual company must decide on the Acceptance Criteria which are justifiable for their particular situation.

Visual examination: Cleaning validation programs should provide for a procedure to visually examine the cleaned equipment to verify that it is free of visible residues. The validation program should include this requirement as acceptance criteria. During validation, particular emphasis should be given to inspection of areas that are 'hard to clean' (e.g. impeller shafts, discharge chutes, chopper blades, etc.) and areas that would be difficult to verify by means of sampling.

Visual inspections can form the sole basis to determine whether equipment cleaning is satisfactory if cleaning is done within a campaign of the same product. This is also adequate for equipment which is dedicated for manufacture of certain products, since there are no quality concerns (except degradation of material) about carryover of some amount of residue from one batch to another.

Fourman and Mullen determined a visible limit of ~100 µg per 2 X 2-in. swab area [11] or ~4 µg/cm2. Jenkins and Vanderwielen observed residues as low as 1.0 µg/cm2 with a light source [12]. Forsyth et al. determined <0.4- to >10-µg/cm2 VRLs for active pharmaceutical ingredients (APIs) and excipients [13].

Microbiological Determination: Appropriate studies shall be performed (e.g. swab sampling, rinse sampling) to determine bioburden on equipment surfaces in cases where the microbial contamination of subsequent product is considered possible and can present a product quality risk. However, limits for microbiological contamination, to determine the effectiveness of a cleaning procedure to reduce microbiological residues, cannot be fixed due to the large variety of equipment and products manufactured by the pharmaceutical industry.

To summarize, a quantitative acceptance limit should be based on one or more of the following:

i. Therapeutic dose.
ii. Toxicity of the material.
iii. Solubility of the potential residue.
iv. Difficulty of cleaning.
v. Dosage form and/or application of the product.
vi. Nature of all the products manufactured in the same equipment.
vii. Batch size of all the products manufactured in the same equipment.

Conclusion: At the end it can be concluded that cleaning validation is a vital aspect in the pharmaceutical industry and having an effective, validated cleaning program to control the carryover of product residues from previous batch to the next batch is critical to ensure product quality. The cleaning program or mechanism shall contain a defined cleaning validation policy, different levels of cleaning depending on the criticality/ risk associated, approaches to cleaning validation and procedure for acceptance criteria determination. Further discussion on cleaning validation elements including calculation of acceptance limits, defined cleaning procedures, sampling techniques to be used, analytical techniques and validation, design of validation protocol contents of validation report, will be included in the concluding part of this article.

References

[1] APIC Document, Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants, May 2014.
http://apic.cefic.org/pub/apic_cleaning_validation_2014.pdf

[2] Alcock, P. and Motise, P. FDA statement: Human Drug cGMP Notes.
[3] PDA Technical Report No. 29, "Points to Consider for Cleaning Validation," PDA J. Pharm. Sci. Technol. 52(6) sup.(1998)
[4] Harder, S., "The Validation of Cleaning Procedures" Pharmaceutical Technology, May 1984
[5] FDA Guide to Inspections: Validation of Cleaning Processes, 1993
[6] D. Rohsner and W. Serve, "The Composition of Cleaning Agents for the Pharmaceutical Industry," Pharm. Eng. 15(2), 20-29 (1995).
[7] FDA's Human Drug. CGMP Note, 2nd Quarter 2001.
[8] J. Agalloco, "Points to Consider in the Validation of Equipment Cleaning Procedures," J. Paren. Sci. Technol. 46 (5), 163–168 (1992). (20)
[9] Validation Master Plan Installation and Operational Qualification, Non-sterile Process Validation, Cleaning Validation, www.picscheme.org/
[10] Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 15
[11] Fourman, G., and Mullin, M., "Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations," Pharmaceutical Technology, April 1993
[12] K.M. Jenkins and A.J. Vanderwielen, "Cleaning Validation: An Overall Perspective," Pharm. Technol. 18 (4), 60–73 (1994).
[13] R.J. Forsyth, V. Van Nostrand, and G. Martin, "Visible-Residue Limit for Cleaning Validation and its Potential Application in a Pharmaceutical Research Facility," Pharm. Technol. 28 (10), 58–72 (2004).