Review Article

Overview of Cleaning Validation in Pharmaceutical Industry

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Abstract:

Manufacturing of Pharmaceutical drug products and drug substances shall demonstrate a control to reproduce consistently the desired quality of product, wherein the control of cross-contamination plays an important roll. Residual materials 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 impurity profile of the subjected product. An effective cleaning shall be in place to provide 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.

Key words:

Contamination, cleaning validation, residue, levels of cleaning.

Introduction

The cleaning validation is necessary to establish the consistency and uniformity by discussing practices that have been found acceptable. One should recognize that with cleaning validation, as with validation of other processes, there can be more than one way to validate a process. At the end, the test of any validation process is whether scientific data shows that the system consistently does as expected and produces a result that consistently meets predetermined specifications.

Objective

"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".[1]

The main objective of cleaning validation of equipment / utensils / components is to demonstrate sufficient documented evidence to ensure that the cleaning process can consistently remove residue of the subjected product below the established Acceptance Criteria.

Cleaning Philosophy

Patients shall not be exposed to more than 1/1000 of the therapeutic dose of another API (as carry over residue).

Usually equipment train / individual equipment / utensil and / or components are cleaned separately and are clubbed with a pre-wash and/or inspection program. Any cleaning procedure generally comprises of thorough cleaning with detergents / neutralizing agents / chelants / solvents alone / in suitable combination followed with

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final rinsing with Purified Water or Water for Injection. The final rinse water is then tested for the pH &/or TOC &/or conductivity in conformance with pre-defined acceptance criteria.

Fundamentally, the requirements for cleaning validation & the cleaning process are almost similar for manufacturing of drug substances and drug products. Nevertheless, the cleaning process of equipment & facility for drug substances are considered to be more complex as compared to the cleaning procedure for Drug Product. The reason behind this can be as follows:

i. Normally, the process involved in the manufacturing of drug substances & equipment used therein are more complex as compared to the manufacturing process of drug products.

ii. Generally the manufacturing process of drug substances comprises of multiple stages which involves chemical / physical transformation. This in-turn increases the probability of generation of more residues.

iii. The equipment / ancillary systems used for the manufacturing of drug substances are many a times complex, where cleaning of internal parts / surfaces / pipes may be difficult.

Considering the above mentioned differences between manufacturing of drug substances & drug product, following points shall be taken into considerations while framing a cleaning process / procedure.[2]

a. It is very important to identification each of the potential contaminant and their clinical and toxicological effects.

b. Carry over of residue from the early steps may subsequently be removed in the latter stages (e.g. purification steps); hence in the early stages the cleaning requirement shall not be very stringent; the

cleaning requirement shall become more stringent as it approaches to the final stages of manufacturing.

Potential Residues[3]

Manufacturing of drug substances involves, in general, chemical &/or physical transformation through a series of processing steps. Equipment train / equipment &/or ancillary system may be used for either multi product manufacturing or for dedicated individual products. The inadequate cleaning process/methods may lead to the fact that following residues may carry forward as contaminant in the next batch to be manufactured in the same equipment:

a. Precursors of the drug substance.
b. By-products and/or degradation products of the drug substance
c. Product from previous batch.
d. Solvents and other excipients employed during manufacturing process.
e. Microorganisms
f. Cleaning agents and lubricants.

Cleaning Validation Policy

It is advisable for the manufacturing facilities of drug substances to have an Cleaning Validation Policy. Responsibilities of specific department should be outlined in this and it should be approved. This policy should serve as a general guideline and direction to the company as how to deal with areas associated with Cleaning Validation.

The policy should incorporate at least, but not limited to, the following types of statements:

i. Definition &/or abbreviation of terms used during validation (i.e. rinse, flush, wash).
ii. Specifying the company policy on validation of cleaning procedures related to equipment, including ancillary.
iii. Company policy on dedication of equipment product wise (e.g highly active / highly potent products to be manufactured on multi-product equipment).
iv. Policy for analytical validation.
v. Rationale for fix acceptance criteria.
vi. Policy on revalidation.

Level / degree of Cleaning

The level or degree of cleaning and validation required for the manufacturing process of drug substances mainly depends on:

i. Usage of equipment (dedicated equipment or not)
ii. Manufacturing stages (early, intermediate or final step)
iii. The nature of the potential contaminants (solubility toxicity etc.)

In case of Drug Products

Different cleaning situation may arise during the manufacturing of drug products, such as;

a. Batch to batch changeover cleaning.
b. Product to product changeover cleaning

In case of non-dedicated drug product manufacturing facility, different cleaning procedures may exist depending on the manufacturing step and nature of the next manufacturing step to be followed in the same equipment. This results in two different levels of cleaning as explained below.

Level 1 Cleaning

This is used between manufacturing of different 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.

The above two degree or level of cleaning differs from each other in terms of the degree of risk associated with it, acceptance limit, degree of cleaning & method of verifying the cleaning process, Table 1.

Table 1: Comparison between levels

	Level 1	Level 2
Risk	Lowest	Highest
Acceptance Limit	Highest	Lowest
Degree of Cleaning	Less Extensive	More Extensive
Verification of Cleaning	Visual Inspection	Analytical Testing

In case of Drug Substance

Different cleaning situation may arise during the manufacturing of drug products, such as;

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

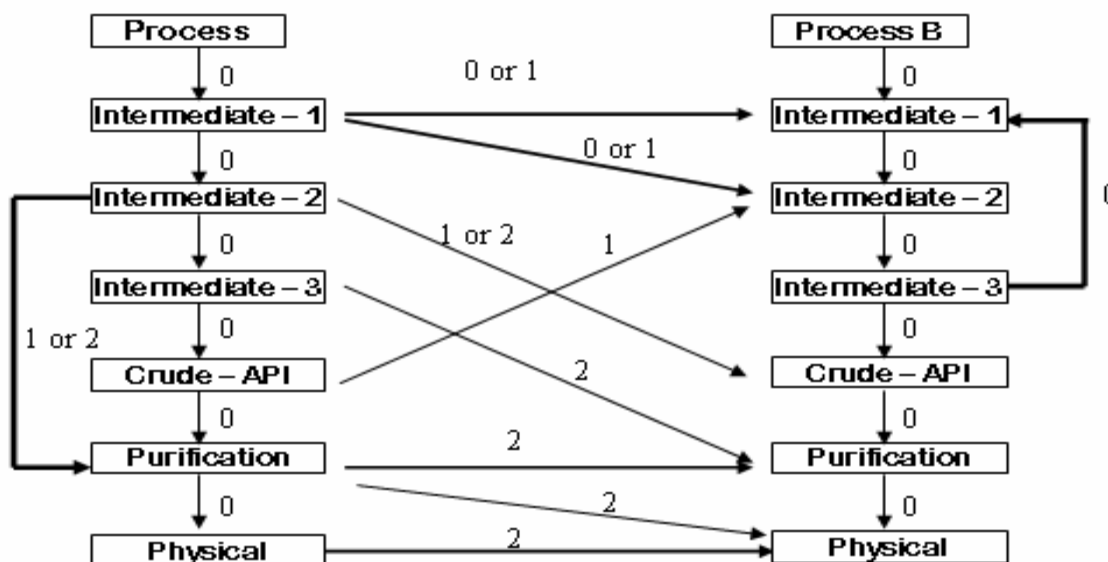In case of non-dedicated drug substance manufacturing facility, different cleaning procedures may exist

Table 2: The CEFIC-APIC Guide to cleaning Validation

Level	Level of cleaning	Cleaning validation
2	Residue carry over of the previous product is crucial. Cleaning required till pre-defined carry over limit is met	Essential
1	Residue carry over of the previous product is less crucial. Cleaning process should reduce the potential carry over to a less stringent limit as required for level 2.	Increase from not required to necessary (lower acceptable carry over limits)
0	If carry over of the previous product is not crucial, only gross cleaning	Not required.

Figure 1: Typical Product Changeover Scenarios[4]

depending on the manufacturing step and nature of the next manufacturing step to be followed in the same equipment. This results in two different levels of cleaning as explained below.

The CEFIC-APIC Guide to cleaning Validation recommends three levels of cleaning, which is outlined in Table 2, can be implemented,. Nevertheless additional levels of cleaning might be necessary depending upon the nature of the process & requirements of individual company

The above levels of cleaning differ from each other in terms of the degree of risk associated with it, acceptance limit, and degree of cleaning & method of verifying the cleaning process.

Table 3: CEFIC-APIC Levels of Cleaning

	Level 0	Level 1	Level 2
Risk	Lowest	Moderate	Highest
Acceptance Limit	Highest	Moderate	Lowest
Degree of Cleaning	Less Extensive	More Extensive	Much extensive
Verification of Cleaning	Visual Inspection	Not required	Analytical Testing required

Conceptually two different product changeover scenarios exists which have a big impact on the degree / level of cleaning required:

i. Previous & the following product do belong to the same synthetic chain (product change over within process 'A' or within process 'B')[4]. Previous & next product is identical (in campaign cleaning). In this case level 0 can be applied; no cleaning validation required. Nevertheless, left over residue due to side products, degradants & microbiological proliferation shall be considered.

ii. Cleaning between different steps of the same synthetic chain. The following product is the next step in the synthetic chain. There is a very low risk to impact the quality of the final drug substance, because the previous product serves as the starting material of the following process; further the analytical methods applied for the following product are generally suitable to detect the previous product also. For this level 0 cleaning is applicable. The following product is not the next step of the synthetic chain. Normally there is a high risk of contamination of the drug substance if the product in the sequence is is close to the final step of the manufacturing process. If it is specified or harmless level 1 cleaning may be acceptable. Previous and following products do not belong to the same synthetic chain (change over from one step of process 'A' to another step of process 'B'). The level of cleaning required depends on the stage of manufacture. If the following product is an early stage of the drug substance manufacturing process, lower level of cleaning is acceptable. Similarly in case of intermediate or final stage higher levels of cleaning is required.

Approaches to Cleaning Validation

In order take lean approach to minimise validation requirements, following points are taken into consideration:

i.   By adopting Bracketing procedure the substances are grouped.
ii. A worst case scenario rating is used to select the worst case in each group.
iii. Validation of worst case.

Bracketing Procedure

The total manufacturing processes are grouped such as early steps, critical steps and API.

Each group of processes is further grouped as per equipment usage similarities. All the processes are then divided as per the solubility and worst case scenario rating is made. If two or more equipment trains are used for a given manufacturing process, a choice of the trains made for the same purpose. The combination of substances in a train can be chosen based upon one or more the following strategies, or combinations of them.

i.   Substances with the same cleaning procedure produce in the same train.

Table 4: Comparison over Levels of cleaning

Level	Attributes	Acceptance Criteria	Cleaning Validation
LEVEL 0	Batch to Batch cleaning in an Identical Process (Same intermediate & same API) Change in the early steps of another product The following process is the next step in the same chemical chain	Visual Observation	Not required
LEVEL 1	Changeover between intermediate of one product to final intermediate of another product Change in early steps to intermediate of another product Changeover from early steps to final step of same product API to intermediates	General limit 500 ppm	Increases from not required to necessary
LEVEL 2	Changeover of one API to another API Changeover of any intermediate to any API Changeover from early steps to final step of same product Change over from physical operation of one product to physical operation of neither product.	Based on TTD / Toxicity, 10 ppm which ever is lower	Essential

ii. Substances with low TDD/ low batch size (and the opposite), produce in the same train.

iii. Non toxic substances, produce in the same train

iv. Substances with high solubility, produce in the same train

Worst Case Rating :

i. Solubility in subjected solvent

ii. Maximum Toxicity

iii. Minimum Therapeutic Dose

iv. Difficult to Clean

v. Lowest Limit based on therapeutic dose / toxic data, batch sizes, surface areas, etc

Elements of Cleaning Validation

This is followed by a more detailed view of the individual elements in this section.

i. Establishment of acceptance criteria

ii. Cleaning procedure
   a. Identification of the equipment
   b. Characterization of the products (Previous: activity/toxicity, solubility, subsequent: dosage, lot size)
   c. Determination and characterization of the cleaning agents

iii. Analytical method and its validation

iv. Sampling Procedure and necessary validation of same

v. Validation protocol

vi. Validation report

Establishment of Acceptance Criteria

The Cleaning Validation should demonstrate that the procedure consistently removes residues of the substance previously manufactured down 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 Active Pharmaceutical Ingredient manufacture there may be partial reactants and unwanted by-products which may not have been chemically identified.

Therefore, it may be necessary to focus on by-products as well as the principle reactant. Companies should decide on which residue(s) to quantify based on sound scientific rational.

Chemical Determination

It is generally the residual Active Pharmaceutical Ingredient or intermediate, which is of greatest concern rather than reaction side products or residual impurities.

There are a number of options available when determining acceptance criteria. Where either toxicological or therapeutic data is available then calculation A or B is preferable. If data is not available for either of these calculations or if the result is more stringent calculation C should be used.

Limiting the level based on toxicity data.

MACO (maximum allowable carry over) is calculated with suitable safety factors applied and this is converted to the maximum allowable carryover to the API.

Pharmacological Dose Method

The philosophy is to reduce the levels of residual product in each piece of equipment, such that no greater than 1/1000 of the normal therapeutic dose will be present per typical dose of the next product to be run in the equipment. The validation protocol should include a calculation, which ties this philosophy to the acceptance criteria for the samples to be tested.

Limiting the level of product which could appear in the following product. Limits from 10ppm up to 0.1% (based on the ICH impurity document which indicates that up to 0.1% of an individual unknown or 0.5% total unknowns material may be present in the product being tested)

FDA Statement on 0.1% impurities[2]

P. Alcock, in Human Drug cGMP Notes, P. Motise, June 98: „...we have found that some firms have 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. ...") may be

used depending on the stage of the process. It is also 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.

Physical Determination

There should be provision during routine cleaning for a visual examination of the equipment, verifying that it is free of visible residues. The validation protocol should include this requirement as acceptance criteria. During validation, special attention should be given to areas that are 'hard to clean' (e.g. agitator shafts, thermowells, discharge valves etc.) and areas that would be difficult to verify on a routine basis.

Microbiological Determination

Appropriate studies shall be performed (e.g. swab sampling, rinse sampling) wherein the possibility of microbial contamination of subsequent product is reckoned possible and presents a product quality risk.

It is not possible to have a standard fixed limit for determining the effectiveness of a cleaning procedure, because of the variety of equipment and products are used throughout the drug substance manufacturing industries.[6] There must be a sound, scientific rationale, based on the product knowledge, to fix residue limit. As per the Guide to inspections of Validation of Cleaning Processes the limits should be *"practical, achievable and verifiable"*[5]. Some of the limits that are rampant in the industry are analytical detection level such as 10 *ppm*, biological activity level such as 1/1000 of the normal therapeutic dose and visibility criteria residue. But one should remember that these limits may not be applicable to each and every product. [7]

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.   Use &/o Application of the product.
vi. Nature of all the products manufactured in the same equipment.
vii. Batch size of al the products manufactured in the same equipment.

The limit is often based on allowing not more than a fraction of a therapeutic dose to be present in a subsequent product. The fraction in this case is called as a "Safety factor". For example quantitative limit for a contaminant in an opthalmic product is 1/5000th fraction of smallest therapeutic dose. 1/5000 in this case is a "Safety factor".

The Safety Factor is a measure of degree of risk for a particular situation. The degree of risk may be different for BPC / API's and drug product manufacturing, but again it will be different for different dosage forms such as tablets and parenteral preparations. Normally accepted Safety Factor for different dosage forms are given in table 5.

Table 5 : Safety factor for different dosage forms[3]

Dosage Form	Safety Factor
Parenteral Products	1000 – 10000
Oral Dosage Forms (tablets, Capsules etc.)	100 – 1000
Topical Products	10 – 100

Conclusion:

At the end of Part-I article it can be concluded that to control the carry over of left over residue from previous batch to the next batch an effective, validated cleaning mechanism shall be in place. This shall contain a defined cleaning validation policy, different levels of cleaning depending on the criticality/ risk associated, approaches of cleaning validation and elements of cleaning validation. In Part-II of this article the other elements of cleaning validation (i.e. calculation of limits, cleaning procedure, analytical methods & its validation, sampling procedure & necessary validation, validation protocol & validation report) will be discussed.

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