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Overview of cleaning validation in pharmaceutical manufacturing unit

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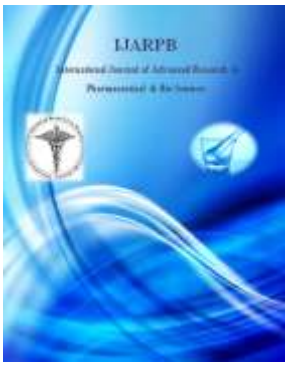

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ABSTRACT

Manufacturing and cleaning equipment must be designed for effective and consistent cleaning to avoid cross-contamination and the cleaning processes must be verified as effective. this article provided background on cleaning validation and the associated regulations, cleaning methods, validation strategy, validation samples, acceptance criteria, clean hold time, training, change control, and revalidation[7].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[8].

KEYWORDS: Contamination, residue, levels of cleaning, cleaning validation, Cleaning Protocol

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INTRODUCTION

It is 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. Cleaning validation is primarily applicable to the cleaning of process manufacturing equipment in the pharmaceutical industry[5]. The focus of cleaning validation is those cleaned surfaces that, if inadequately cleaned, could potentially contaminate the product subsequently manufactured in that same equipment. This primarily covers product contact surfaces in the cleaned equipment. Cleaning validation is not performed only to satisfy regulatory authorities. The safety of patients is the primary objective, and product contamination presents serious liability issues for any pharmaceutical manufacturer or contract organization.

The basic mechanisms involved in removing the residues and contaminants from the equipment are mechanical action, dissolution, detergency and chemical reaction[6].

Mechanical action – It refers to the removal of residues and contaminants through physical actions such as brushing, scrubbing and using pressurized water.

Dissolution – It involves dissolving the residues with a suitable solvent. The most common and practical solvent is water being non-toxic, economical, environment friendly and does not leave any residues. Alkaline and acidic solvents are sometimes preferred as it enhances the dissolution of the material, which are difficult to remove.

3. Detergency-Detergent acts in four ways as wetting agent, solubilizer, emulsifier and dispersant in removing the residues and contaminants from the equipment.

4. Chemical reaction- Oxidation and hydrolysis reaction chemically breaks the organic residues1.

OBJECTIVE

The objective of the 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 need to ensure there is no risk associated with cross-contamination of active ingredients. Cleaning procedures must strictly follow carefully established and validated methods.

It is necessary to Validate Cleaning procedures for the following reasons:

It is a customer requirement - it ensures the safety and purity of the product.

It is a regulatory requirement in Active Pharmaceutical Ingredient product manufacture.

It also assures from an internal control and compliance point of view the quality of the process.

ELEMENTS OF CLEANING VALIDATION

Establishments 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

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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

Cleaning procedure

Cleaning procedures should be sufficiently detailed to remove the possibility of any inconsistencies during the cleaning process.

Equipment parameters to be evaluated

- 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's of the residues
- Length of campaigns

Cleaning agent parameters to be evaluated

- Preferably materials that are normally used in the process
- Detergents available (as a general guide, minimize use of detergents unless absolutely required)
- 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

Other requirements

Sampling Techniques

The selection of either of these techniques must be consistent with sound scientific judgment and must support the objective of the study, which is to demonstrate that the amount of residual material in the equipment has been reduced to acceptable levels[2].

There are three known sampling methods:

Swabbing (Or Direct Surface Sampling) Method[13]

Swab sampling does not cover the entire equipment surface area therefore sites must be chosen with care. It is important that, as a minimum, the swab sites represents worst case locations on the equipment and that the result is then extrapolated to account for the total product contact surface Area.

Advantages

Dissolves and physically removes sample

Adaptable to a wide variety of surfaces

Economical and widely available

May allow sampling of a defined area

Applicable to active, microbial, and cleaning agent residues

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Limitations

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 (e.g., crevices, pipes, valves, large vessels)

Rinse Sampling Method

The solvent rinse occurs after cleaning has been completed
This method is not as direct as swabbing but will cover the entire surface area (and parts inaccessible to swabs)
It is important to ensure chosen solvent has appropriate recovery for residues being quantified
This method allows much greater ease of sampling than swabbing
A reduced no of samples are required to generate a carryover figure.

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., porus) surfaces

Limitations

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
Sampling methodology must be defined since rinse sampling method and location can influence results
May be difficult to accurately define and control the areas sampled, therefore usually used for rinsing an entire piece of equipment, such as a vessel
Reduced physical sampling of the surface

Placebo Sampling Method

Placebo sampling can be used to detect residues on equipment through the processing of a placebo batch subsequent to the cleaning process. It is appropriate for active residue, cleaning agent, particulates and microbial testing. Placebos are used primarily to demonstrate the lack of carryover to the next product. The placebo should mimic product attributes. The equipment characteristics also impact the choice of the placebo batch size.

Advantages

Placebo contacts the same surfaces as the product
Applicable for hard-to-reach surfaces
Requires no additional sampling steps

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Limitations

Difficult to determine recovery (contaminants may not be evenly distributed in the placebo)
Lowers analytical specificity and inhibits detect ability
Takes longer and adds expense since equipment must be cleaned after the placebo run
Placebos must be appropriate for each potential product
Residues may not be homogenously distributed
No direct measurement of residues on product contact surfaces
The preferred sampling method and the one considered as the most acceptable be regulatory authorities is the swabbing method[10]

Analytical Methods

Specific and non-specific are the two analytical methods used widely to detect any compound. The choice of using a specific or non specific method can be difficult. If a drug active is highly toxic, a specific method is always recommended. Chromatographic methods are preferred for cleaning validation studies because of their sensitivity, specificity, and ability to quantify[9].

Specific method

It is a method that detects a unique compound in the presence of potential contaminants.

Some examples of specific methods are high performance liquid chromatography (HPLC), Ion chromatography, Atomic absorption, Capillary electrophoresis, and other chromatographic methods.

Non-specific method

It detects any compound that produces a certain response.
Some examples of non specific methods are Total Organic Carbon (TOC), pH, Titration, and conductivity.
It is always wise to choose the simplest technique that can be used to reach the desired goal.

The basic requirement for the analytical method

The sensitivity of the method shall be appropriate to the calculated contamination limit.
The method shall be practical and rapid, and, as much as possible use instrumentation existing in the company.
The method shall be validated in accordance with ICH, USP, EP requirements.
The analytical development shall include a recovery study to challenge the sampling and testing methods.

Validation Protocols

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 the product range / equipment type / entire site[11, 12].
The protocol must be prepared prior to the initiation of the study and must either include or reference the documentation required to provide the following information:

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The objective of the study:

What cleaning process is to be validated (indicating the product to be removed and the equipment from which it is to be removed)?
If this study is to be employed to demonstrate the acceptability of the cleaning procedure for a group of products the rational for doing so should also be detailed here.
The cleaning procedure(s) to be validated should be identified i.e. cleaning agents, soakage times, equipment parameters, number of cleaning cycles etc.

Scope of the study

The company must evaluate the process and determine which residues are to be tested for and which are not to be based on sound scientific rational.
What residues (including cleaning agents) are to be tested for, why those residues (if more residues may be present than are being tested for all residues should be under control see comments at 8.4). How many times should the study be run before a report is compiled and recommendations made.

Listing of the process parameters to be verified

This is particularly necessary when automated or semi-automated cleaning techniques are to be employed.

Sampling and inspection procedure to be used.

The types of sampling methods to be used, where the samples are to be removed from and how many samples are to be taken. Any particular requirements should also be stated i.e. for sterile sampling / sampling light sensitive products.
An equipment sampling diagram should be referenced.

Personnel responsibilities during the study Test methods to be used

In order for the analytical testing of the cleaning validation samples (swabs or rinses) to yield meaningful results, the analytical methods used should be validated. This should be documented.

The basic requirements are

The ability to detect the target substance(s) at levels consistent with the acceptance criteria
The ability to detect the target substance(s) in the presence of other materials that may also be present in the sample (selectivity)
The analytical method should include a calculation to convert the amount of residue detected in the sample to 100% if the recovery data generated indicates a recovery outside of an allowed range.

Change control

Validated cleaning procedures should be included in the change control program. This will ensure that any proposed changes are evaluated

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fully for their impact on the validated state of the procedure. Where deemed necessary, the proposed revised procedure may need to be validated prior to routine implementation.of. Change control chapter in the CEFIC / EFPIA Guide entitled 'Good Manufacturing Practices for Active Ingredient Manufacturers' In the absence of an intentional change to a procedure, it is reasonable to assume that properly trained operators or a properly qualified automated system will be able to execute the procedure reproducibly and obtain the desired outcome - reduction of residue to acceptable levels[17].

Validation Reports

A validation report is necessary to present the results and conclusions and secure approval of the study. The report should include the following[16].

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.

Approval of conclusions

Review any deviations for the protocol that occurred.

In cases where it is unlikely that further batches of the product will be manufactured for a period of time it is advisable to generate interim reports on a batch by batch basis until such time as the cleaning validation study has been completed. (Typically, in Active Pharmaceutical Ingredient Pharmaceutical manufacture, verification is deemed appropriate during development of the cleaning methods. Where products are manufactured infrequently, verification may be applied over a period of time until all measuring data has been collected for the Validation Report.)
The report should conclude an appropriate level of verification subsequent to validation.

Establishment of Limits

The fabricator's rationale for selecting limits for product residues should be logical and based on the materials involved and their therapeutic dose. The limits should be practical, achievable, and verifiable[14].

In establishing product residual limits, it may not be adequate to focus only on the main reactant since by-products/chemical variations (active decomposition material) may be more difficult to remove. In addition to chemical testing, Thin Layer chromatography screening may be needed in certain circumstances.

The approach for setting limits can be

Product specific cleaning validation for all products;

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Grouping into product families and choosing a worst case product;

Grouping by properties (e.g., solubility, potency, toxicity or formulation ingredients known to be difficult to clean);

Setting limits on not allowing more than a certain fraction of carryover;
Different safety factors for different dosage forms.

Carry-over of product residues should meet defined criteria for example the most stringent of the following criteria (i, ii, iii):

i. NMT 0.1% of the normal therapeutic dose of any product to appear in the maximum daily dose of the following product;
ii. NMT 10 ppm of any product to appear in another product;
iii. No quantities of residue to be visible on the equipment after cleaning procedures are performed. Spiking studies should determine the concentration at which most active ingredients are visible.
iv. For certain highly sensitizing or highly potent ingredients (such as penicillins, cephalosporin or potent steroids and cytotoxics), the limits should be below the limit of detection by best available analytical methods. In practice this may mean that dedicated plants are used for these products.

Revalidation

A change control system is in place to ensure that all changes that might impact the cleaning process are assessed and documented. Significant changes should follow satisfactory review and authorization of the documented change proposal through the change control procedure. Minor changes or changes having no direct impact on final or in-process product quality should be handled through the documentation system. The review should include consideration of re-validation of the cleaning procedure[19].

Changes which should require evaluation and likely re-validation include but not limited to:

- Changes in the cleaning procedure;
- Changes in the raw material sources;
- Changes in the formulation and/or process of products;
- New products;
- Changes in the formulation of detergents;
- New detergents;
- Modifications of equipment.

The cleaning process should be reassessed at defined intervals, and re-validated as necessary. Manual methods should be reassessed at more frequent intervals than clean-in-place (CIP) systems.

CONCLUSIONS

A validation policy should be written for a plant including cleaning validation. A cleaning

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validation program should contain the following elements[21]:

Assess equipment and products (previous, following)

Assess impact of this process on routine processes. If covered under bracketing then no further validation is required.

Determine an appropriate cleaning agent and method

Determine acceptance criteria for the residue(s) (including cleaning agents).

Determine degree of evaluation required to validate the procedure.

Decide what residue(s) (including cleaning agents), are to be tested for based on solubilities, toxicities etc. and document rational behind decision.

Develop sampling and analytical methods for recovery and detection of residues (swab/rinse, HPLC/dry residue etc.)

Acceptance Criteria for the Validation

Compile and approve Validation protocol

Perform Validation Studies in accordance with protocol

Compile and approve a Validation report documenting studies, conclusions and recommendations.

Revalidation policy

CLEANING/TESTING RESPONSIBILITIES[4]

Cleaning/ Testing	Done by	Recorded on	Checked by
Equipment cleaning	Machine operator	Equipment usage/ cleaning log book	Production Supervisor
Visual inspection	Cleaning validation officer		
Rinse sample	Machine operator/ cleaning validation officer	Sampling sheets 3,4	Asst. manager QA

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Swab sample	Machine operator/ cleaning validation officer	Sampling sheets 3,4	Asst. manager QA
Ph	Cleaning validation officer/QC analyst	Analytical log book	QA/QC Officer
Conductivity	Cleaning validation officer/QC analyst	Analytical log book	QA/QC Officer
TOC	Cleaning validation officer/QC analyst	Analytical log book	QA/QC Officer
MAC	Cleaning validation officer/QC analyst	Analytical log book	Development manager

EQUIPMENT CLEANING PROCEDURE[4]

VALIDATION REPORT

Equipment name:

Calibrated/validated on:

Location:

Room no.:

Last product:

B. no. of last prod.:

Manufacturing date:

Active ingredient:

Therapeutic group:

Cleaning date:

Cleaning SOP no.: Revision no.:

Sampling technique:

Cleaning sample analysis date: Assay result

Test method reference: Ref. analytical log book:

Limit of detection:

Next product to be manufactured on same equipment:

Safety factor:

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