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International Journal of Pharmaceutical and Phytopharmacological Research

Int.J.Pharm.Phytopharmacol.Res. 2011, 1(1): 8-16

Current Perspectives on Cleaning Validation in Pharmaceutical Industry: A Scientific and Risk Based Approach

Harshal A. Pawar*, Nandini D.Banerjee[1], Sandip Pawar[2], Prashant Pawar[3]

[, 1] Dr.L.H.Hiranandani College of Pharmacy, Ulhasnagar*
[2] Executive –Technology Transfer, Sandoz Pvt.Ltd, Kalve, Thane
[3]Manufacturing Chemist, Wardex Pharmaceutical Pvt.Ltd. Mahalaxmi, Mumbai

Received on: *01/07/2011* ***Accepted on:*** *08/08/2011*

ABSTRACT

In the manufacturing of the pharmaceutical products it is a must to reproduce consistently the desired quality of product. The current Good Manufacturing Practice (cGMP) regulations recognize that cleaning is a critical issue to ensure product quality. The control of cross contamination plays a very important role in maintaining the quality of the product. The manufacturing of API and pharmaceutical products involves series of processing steps and use of various equipments. In many cases, the same equipment may be used for processing different products. 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 quality 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 level. The documented evidence of the consistent performance of the cleaning process is given by the validation process. It ensures safety, efficacy, and quality of the subsequent batches of drug product. In this article the various aspects of the cleaning validation such as different types of contaminants, sampling procedures, analytical techniques and regulatory requirements are discussed in detail.

Key Words: Contaminants, Cleaning validation, TOC, HPLC, FDA

INTRODUCTION

Medicinal products may be contaminated by other medicinal products, by cleaning agents, by microorganisms or by other material (e.g. Air borne particles, dust, lubricants, raw materials, intermediates etc.). In many cases, the same equipment may be used for processing different products. To avoid contamination of medicinal products, adequate and validated cleaning procedures are essential. The cleaning of equipment is an area of increasing regulatory importance within the pharmaceutical industry. 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). Cleaning validation is a documented process that proves the effectiveness and consistency in cleaning pharmaceutical production equipments. Validations of equipment cleaning procedures are mainly used in pharmaceutical industries to prevent cross contamination and adulteration of drug products hence is critically important. The most important benefit of conducting such a validation work is the identification and correction of potential problems previously unsuspected, which could compromise the safety, efficacy

or quality of subsequent batches of drug product produced within the equipment. The present article summarizes the updated information on various aspects of cleaning validation.

OBJECTIVE

The main 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.It demonstrates that the cleaning process can consistently remove residue of the subjected product below the established acceptance criteria[1].

The equipment cleaning validation in an Active Pharmaceutical Ingredient (API) manufacturing and pharmaceutical production is necessary to prevent contamination of a future batch with the previous batch material. The cleaning of 'difficult to reach' surface is one of the most important consideration in equipment cleaning validation. Equipment cleaning validation in an API facility is extremely important as cross contamination in one of the pharmaceutical dosage forms, will multiply the problem. Therefore, it is important to do a step-by-step evaluation of API process to determine the most practical and efficient way to monitor the effectiveness of the cleaning process[2].

REASONS FOR CLEANING VALIDATION [3-6]

Effective cleaning is a key to product quality assurance. Cleaning is performed to remove product and non-product containing materials. It is necessary to Validate cleaning procedures for the following reasons:

a. It is a customer requirement - it ensures the safety and purity of the product.
b. It is a regulatory requirement in Active Pharmaceutical Ingredient product manufacture.
c. It also assures from an internal control and compliance point of view the quality of the process.

DIFFERENT TYPES OF CONTAMINANTS [7]

The manufacturing of API and pharmaceutical products involves series of processing steps and use of various equipments. Equipments or ancillary systems may be used for manufacturing multiple product or single dedicated product. The inadequate cleaning process may leads to the fact that following residue may carry forward as contaminant in the next batch to be manufactured in the same equipment.

1. Precursors to the Active Pharmaceutical Ingredient
2. By-products and/or degradation products of the Active Pharmaceutical Ingredient
3. Contamination of one batch of product with significant levels of residual active ingredients from a previous batch
4. Microbiological contamination: Maintenance, cleaning and storage conditions may provide adventitious microorganisms with the opportunity to proliferate within the processing equipment.
5. Contamination with unintended materials or compounds such as Cleaning agents, lubricants etc.

CLEANING METHODOLOGY [8-10]

Development / Design of cleaning procedure

Cleaning procedures should be sufficiently detailed to remove the possibility of any inconsistencies during the cleaning process. Standard cleaning procedures for each piece of equipment and process should be prepared. Following parameters are to be considered while developing cleaning procedures:

A. Equipment related parameters

1. Identification of the equipment to be cleaned
2. Difficult to clean areas
3. Property of materials
4. Ease of disassembly
5. Fixed or not

B. Residues to be cleaned

1. Cleaning limits

2. Solubility's of the residues
3. Activity and toxicity

C. Cleaning agent parameters

1. Detergents available and their concentration
2. Solubility properties
3. Environmental considerations.
4. Health and safety considerations

D. Cleaning techniques to be used

1. Manual cleaning
2. CIP (Clean-in place)
3. COP (clean-out-of-place)
4. Semi automatic
5. Automatic
6. Time considerations
7. Number of cleaning cycles

E. Cleaning process variables

1. Cleaning agent temperature
2. Wash Rinse Duration & Volume/Flow rates
3. Number of Wash/Rinse cycles
4. Time between use & cleaning
5. Cleaning only after campaigns
6. Operator efficiency

Documentation/ written procedure (SOP)

The documented procedure should include the following points:

1. Detailed definition of levels of cleaning to be performed.
2. Detailed description of cleaning methods.
3. The necessity to inspect and verify equipment cleanliness prior to manufacture of next batch should be stated in the SOP and recorded on the batch record.
4. The SOP should detail where verification of cycle parameters (if automated) and checklists (for complex manual procedures) are necessary.
5. Where microbial contamination may be an issue, consideration should be given to the integrity of the vessel prior to manufacture.
6. Precautions and safety warnings.

Cleaning log should be maintained and cleaned status should be indicated by placing label or card on the equipment.

ESTABLISHMENT OF LIMITS FOR ALLOWABLE RESIDUES/CONTAMINANTS [11]

With regard to the scale of the work involved and to the prospects of a successful cleaning validation outcome, setting an adequate limit for allowable residues on production equipment has an important role to play.

Calculation is normally done based on known daily doses or on toxicological data along with safety factors. An absolute criterion may be applied as an alternative or adjunct to these.

1. For the pharmaceutical production

As per PIC/S PI 006-01 Guidelines Carry-over of product residues should meet defined criteria, for example the most stringent of the following three criteria:

a) No more than 0.1% ($1/1000^{th}$) of the normal therapeutic dose of any product will appear in the maximum daily dose of the following product.

b) No more than 10 ppm of any product will appear in another product.

c) No quantity of residue should be visible on the equipment after cleaning procedures are performed.

In the last 10 years the dose-based calculation (e.g. $1/1000^{th}$ dose) has prevailed In the manufacture of pharmaceutical products. Where dose data are not available, an absolute value (e.g. 10 ppm) is prescribed.

For residues where dose data are not available but toxicological data are (e.g. tensides), it is normal to perform the calculation based on the NOEL/ADI (no effect level/acceptable daily intake) value along with a safety factor (SF).

2. For chemical API production

Based on the various recommendations for pharmaceutical production and after due consideration of the differences between pharmaceutical production and chemical production, the following scientifically founded calculation methods are proposed for APIs.

a) In all cases the production equipment, where it can be inspected, has to be visibly clean.
b)The acceptable residue must never exceed 1000 ppm, even if this were justifiable based on dosage or toxicological data.
c)The limits in chemical production may be 10 times higher than in pharmaceutical production.

SAMPLING

Sampling Locations, Surface area and number [12, 13]

The hard to clean equipment locations (worst-case conditions) are identified based on cleaning experience and the design of equipment. Sample surface areas usually vary from 25 sq cm to 100 sq cm and should be large enough to allow the recovery of contamination quantity sufficient to be detected by the analytical method. The number of samples to be taken for the study depends on various factors such as the equipment surface area, construction material, design, shape and operating principle. Considering the homogeneity of the contaminant on the equipment product contact surface area, several samples, but not less than three samples per piece of equipment, must be taken including the hardest to clean locations.

Sampling methods/techniques [14-20]

Sampling is the critical step in cleaning method validation. Different sampling methods/techniques have been used for cleaning method validation. 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. The main sampling methods are as follows:

1. Swab sampling method

This method is based on the physical removal of residue left on a piece of equipment after it has been cleaned and dried. A swab wetted with a solvent is rubbed over a previously determined sample surface area to remove any potential residue, and thereafter extracted into a known volume of solvent in which the contaminant active ingredient residue is soluble. The amount of contaminant per swab is then determined by an analytical method of adequate sensitivity.

Swab sampling does not cover the entire equipment surface area therefore sites must be chosen with care. It is important those, as a minimum, the swab sites represent worst case locations on the equipment and that the result is then extrapolated to account for the total product contact surface area. This calculation makes it possible to make a worst case determination of potential carryover into subsequent product.

Due to the nature of this method which employs physical forces as well as chemical forces it may be necessary to perform sampling technique evaluation. A swab recovery study is performed to determine the ability of the swab to quantitatively remove the contaminant from the surface sampled. Generally, companies use special swabs available from suppliers such as: Whatman[R], Texwipe[R], or Coventry[R].

2. Rinse sampling method

This method is based on the analytical determination of a sample of the last rinsing solvent (generally water) used in the cleaning procedure. The volume of solvent used for the last rinse must be known to allow for the quantitative determination of the contamination. Thus, collection of rinse samples should consider location, timing, and volume. It is important to ensure chosen solvent has appropriate recovery for residues being quantified. 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).

3. Coupon sampling method

In this method, coupons of the same materials of construction as the item to be cleaned can be affixed to the equipment, spiked with the product, subjected to the cleaning procedures, and then submitted to the

laboratory for direct analysis and recovery studies.

4. Solvent sampling method

This technique uses a solvent not normally employed in the cleaning process to maximize recovery of expected residues. Known volume of solvent is applied to the surface in question. The method can be used in combination with swabbing.

5. Product sampling method

This method is similar to placebo sampling except that it uses actual product. It requires examination of the next production batch for trace residuals of the previous batch.

6. Placebo sampling method

It can be used to detect residues on equipment through the processing of a placebo batch subsequent to the cleaning process. 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.

7. Direct sampling monitoring

This method is used to evaluate surface cleanliness without surface contact, for example: measurement using spectrophotometric probes.

ANALYTICAL TECHNIQUE [21-46]

The analytical methods used to detect residuals or contaminants should be specific for the substance or the class of substances to be assayed (e.g., product residue, detergent residue, and/or endotoxin) and be validated before the cleaning validation study is carried out. If levels of contamination or residual are not detected, it does not mean that there is no residual contaminant present after cleaning. It only means that the levels of contaminant greater than the sensitivity or detection limit of the analytical method are not present in the sample.

The basic requirements for the analytical method are as mentioned below:

1. The sensitivity of the method shall be appropriate to the calculated contamination limit.
2. The method shall be practical and rapid, and as much as possible, use instrumentation existing in the company.
3. The method shall be validated in accordance with the International Conference on Harmonization (ICH), the United States Pharmacopoeia (USP), and the European Pharmacopoeia (EP) requirements.
4. The analytical development shall include a recovery study to challenge the sampling and testing methods.

Various analytical techniques have been used for testing cleaning validation samples. Commonly used analytical tools for cleaning validation are mentioned in table-1.

Table-1: Commonly used analytical tools for cleaning validation

Traditional Analytical Methods	Modern analytical Techniques
1.Gravimetry 2.pH 3.Conductivity 4.Colourimetry 5.UV-spectroscopy	1. Chromatographic techniques like HPTLC, HPLC and GC etc. 2.Total organic analysis(TOC) 3.Atomic absorption spectroscopy 4.Charged aerosol detection(CAD) 5.Immuno assay: ELISA 6. Capillary electrophoresis. 7.Optically simulated electron emission(OSEE) 8.Portable mass spectrophotometer 9.Bioluminescence

It includes both specific (e.g.HPLC) as well as non-specific methods (e.g.TOC, pH).Selection of suitable analytical method depends on various factors such as nature and type of analytes (Refer table-2)

Table-2: Commonly used methods for some analytes

Analytes	Analytical method
Proteins	ELISA, HPLC, TOC
Organic compounds	TOC, HPLC, UV-VIS, TDS
Inorganic compounds	Conductivity, pH, TDS
Biological system	Vial cell analysis

Traditional techniques have the limitation of being time consuming, less sensitive, not reproducible in results etc.Chromatographic methods are the methods of choice, because they separate analytes, are highly specific, highly sensitive, and quantitative; however, the methods are costly and time consuming. For monitoring cleaning procedure, TOC method is used. It offers a moderate cost, and in addition to its rapidity, a detection capability down to the ppb range.
Capillary electrophoresis can be used for many different types of analysis, viz; separation, detection and determination of sodium lauryl sulphate in cationic, anionic and non-ionic surfactants. In some cases the limits of residue are very less that they can't be detected by conventional methods. OSEE is a very sensitive method that can be used for both qualitative and quantitative manner in this regard. Portable mass spectrometer can also be used to detect ultra sensitive measurements and identification of the residue.

ANALYTICAL METHOD VALIDATION:
Once the analytical method or technique of analysis has been finalized, the next step is validation of the method. The method validation includes checking the method for following parameters:

- Precision, linearity, selectivity
- Limit of Detection (LOD)
- Limit of Quantitation (LOQ)
- Recovery, by spiking

REGULATORY REQUIREMENTS [47, 48]
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 FDA's guide to inspections, which "intended to cover equipment cleaning for chemical residues only," includes:
1. FDA expects firms to have written procedures (SOP's) detailing the cleaning processes used for various pieces of equipment. If firms have one cleaning process for cleaning between different batches of the same product and use a different process for cleaning between product changes, we expect the written procedures to address these different scenarios. Similarly, if firms have one process for removing water soluble residues and another process for non-water soluble residues, the written procedure should address both scenarios and make it clear when a given procedure is to be followed. Bulk pharmaceutical firms may decide to dedicate certain equipment for certain chemical manufacturing process steps that produce tarry or gummy residues that are difficult to remove from the equipment. Fluid bed dryer bags are another example of equipment that is difficult to clean and is often dedicated to a specific product. Any residues from the cleaning process itself (detergents, solvents, etc.) also have to be removed from the equipment.
2. FDA expects firms to have written general procedures on how cleaning processes will be validated.
3.FDA expects the general validation procedures to address who is responsible for performing and approving the validation study, the acceptance criteria, and when revalidation will be required.
4. FDA expects firms to prepare specific written validation protocols in advance for the studies to be performed on each manufacturing system or piece of equipment which should address such issues as sampling procedures, and analytical methods to be used including the sensitivity of those methods.
5. FDA expects firms to conduct the validation studies in accordance with the protocols and to document the results of studies.
6. FDA expects a final validation report which is approved by management and which states whether or not the cleaning process is valid. The data should support a conclusion that residues have been reduced to an "acceptable level

7. Besides assuring chemical cleanliness, "the microbiological aspects of equipment cleaning should be considered. This consists largely of preventive measures ..."
8. "Determine the specificity and sensitivity of the analytical method used to detect residuals or contaminants."
9. "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 ..."
10. "Direct sampling (e.g., with swabs) is 'most desirable,' although rinse sampling may be satisfactory
11. If firms have a specific cleaning process for cleaning between different batches of the same product and use a different process for cleaning between product changes, FDA expects the written procedures to address these different scenarios.

CONCLUSION

The growing number of regulation and newer policies regarding the product quality in the pharmaceutical industry has made the cleaning process of utmost importance. It has a pivotal role in the line clearance step for the manufacturing of any new product.

Virtually every aspect of manufacturing involves cleaning, from the initial stages of bulk production to the final dosage form. A wide range of factors influences the potential for cross contamination of materials, and the achievement of robust and effective cleaning operations offers a significant challenge to all product manufacturers. Therefore, 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 level.

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.

ACKNOWLEDGEMENT

Author is very much thankful to Dr. (Mrs.) S.S. Bhalerao, Principal of Hyderabad Sindh National Collegiate Boards (HSNCB's) Dr.L.H.Hiranandani College of Pharmacy, Ulhasnagar for her continuous support & encouragement.

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***Corresponding Author**: Mr.Harshal Ashok Pawar*
Lecturer,
Dr.L.H.Hiranandani College of Pharmacy,
Smt.CHM Campus, Opposite Railway Station,
Ulhasnagar, Dist.Thane, Pin-421003,
Maharashtra (India)
Telephone No. (0251)2561463
Fax No. (0251)2561341
Email ID: hapkmk@rediffmail.com