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APPROACHES AND ADVANCES IN CLEANING VALIDATION

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ABSTRACT:

As it is well known that contamination is major concern in pharmaceutical industry. There are various factors which possibly cause contamination in pharma industry, and one of such factor is improper cleaning, improper cleaning of processing area, equipment, and apparatus which can leads to severe hazards. Hence, it's a major concerned to have proper cleaning procedure. Pharmaceutical products can be contaminated by other pharmaceutical product or API, or by other cleaning agent, dust particles, and previous batches. Because of this, pharma industries always ensure that cleaning procedures are strictly followed and validated. In cleaning validation different parameters, material, process controls are monitored and validated so that a consistent cleaning procedure can be develop and documented. Apart from commercial procedures like matrix there are various advancements comes in existence in cleaning validation procedure like safety factor API acceptance limit.

Key Words:
CV: Cleaning Validation
MAC: Maximum Allowable Carryover

1. Introduction:

Cleaning validation is documented evidence that gives high degree of assurance that one can consistently clean a system or piece of equipment to predetermined and acceptable limits. Cleaning validation program should be effective and applicable to the cleaning of process equipment in pharmaceutical industry. This ultimately results in product free from contamination. So it is quite essential to verify and frequently validate the cleaning procedures to make assured safety, effectiveness, to verify the quality of the subsequent batches of drug substances and regulatory requirements.

2. Scope and approaches of cleaning validation:

Cleaning validation approach contains an approach called PDCA approach plan, do check and act. The approach includes effective cleaning and sanitizes the used equipments an areas with adequate intensity to remove chemicals, microorganisms, as well as allergens. A graphical and detail description is required list of used equipments, qualification of equipments, evaluation of hazards, sampling process, analytical techniques, Cleaning validation protocol, cleaning validation report and its procedures.

3. Purpose of Cleaning Validation

Cleaning validation is required because pharmaceutical product can be cross-contaminated with chemical residues and microbes that can compromise patient safety. Ineffective cleaning processes not only lead to more contamination and batch failures.

Cleaning validation program shall ensure that all residues are removed to predetermined levels to ensure the quality of the next product manufactured is not compromised

by waste from the previous product.

4. Cleaning Validation sampling technique:

Sampling sites shall be selected based on the inaccessibility of cleaning of the equipment and these locations are inaccessible i.e. Their inaccessibility makes them difficult to

clean therefore, before choosing for sampling sites one must be conscious in selecting the desired sampling location. Equipments generally have two types of sites of cleaning one is hot spot, this location is likely to be

more dirty during manufacturing and difficult in cleaning. And second one is critical sites, those location which are difficult to clean and if remain dirty shows more contamination in next batch. These sites shall be listed and properly studied while approaching cleaning validation. Beside sampling site sampling site also chosen on basis of -

a. Material of construction
b. Ease of disassembly
c. Mobility

There are various sampling methods used in cleaning validation, but swab and rinse sampling method is most commonly used. Different techniques are –

4.1 Swab Sampling

After cleaning the equipment, product contact surfaces could be swabbed to assess surface cleanliness. Swabs used should be compatible with the active ingredients and should not interfere with the assays and results. They should not cause or result in any degradation of the compound.

4.2 Rinse Sampling

Rinse sampling does not employ mechanical action on the surface and the sample is collected as a final rinse or rinse applied specifically for collecting a validation sample.

4.3 Placebo Sampling:

Placebo is recognized as both potential cleaning techniques and potential sampling techniques. Placebo material comprises of all typical excipients but not the active ingredient. And the placebo batches were passed through a same line so that it will have possibility to scrub of the clean system. The principle involved in placebo is that it is passed through the same pathway as the product therefore; it will have the possibility to scrub off residual product along those pathways. And it usually employed for measuring system cleanliness. It majorly depends on excipients solubility in placebo and appropriate contact time of the placebo for collecting representative sample.

4.4 Direct Sampling:

It is done by using FTIR or photoelectron emission techniques. By employing these techniques, specific spectra obtained from residue remaining on the surface will directly measure the quality of the surface. The advantage of using these techniques is that sampling and analysis will be taking place in one step and there will be no real loss of sampling system where as in swab sampling direct analysis of the surface is limited to the area that are accessible for inspection.

There are several merits and demerits of all four technique, all these points cover in below table , Table-I.

Table: I – Merits and demerits of various sampling technique

S.No	Sampling Method	Merits	Demerits
1.	Swab Sampling	1.Dissolve and substantially remove the sample. 2. Adaptability to widespread Variation of surfaces. 3 Cost effective	1.An Invasive method that may introduce fibers. 2.technique dependent 3. Swab material and design may inhibit recovery and specificity of the method.
2.	Rinse Sampling	1.Adjustable to on-line Monitoring 2.Easy for illustration 3.Non-intrusive and Less technique dependent than swabs 4.Appropriate for actives, cleaning agents and excipients 5.Allows sampling of a large surface area	1. May lower test Sensitivity 2. Residues may not be homogenously distributed 3. Inability to detect location of residues. 4. Rinse volume is critical to ensure accurate elucidation of Results.
3.	Placebo Sampling	1.Placebo contacts the same surfaces as the product 2.Applicable for hard-to-reach surfaces 3. Requires no additional sampling steps	1. Lowers analytical specificity and inhibits detect ability 2. Takes longer and adds expense since equipment must be cleaned after the placebo run.
4.	Direct Sampling	The gain of using these techniques is that sampling and investigation will be taking place in one step and there will be no real forfeiture of sampling system	The contaminant might not be soluble or may be materially occluded in the equipment. It is completed by using FTIR or photoelectron emission methods. By employing these techniques, specific spectra obtained from residue

5. Mechanism of Cleaning Validation:

There are several mechanisms involves in cleaning validation:

Mechanical Action –

- brushing
- scrubbing
- pressurized water to remove particulates.

Dissolution-

It involves dissolving residues with a suitable solvent. The most common and practical solvent is water because of its advantages as water is non-toxic, cheap, does not leave residues, and is environment friendly. However, in some cases it may be preferable to use a non-aqueous solvent or a combination of both aqueous and non-aqueous solvents due to the solubility characteristics of the materials. Alkaline or acidic solvents, for example, can enhance dissolution of the materials and could be advantageous.

Detergency requires the use of surfactant, usually in an aqueous system. Detergents act in four different ways:

- wetting agents
- solubilizers
- emulsifiers, and
- dispersants.

Usually detergents posses all these properties which broaden their action

6. Current and future prospective of cleaning validation:

In current scenario industries are using MAC (maximum allowable carryover) assessment of an APIs which is logical and innovative approach.

6.1 Product and Equipment Grouping:

This is grouping method used for bracketing of product and equipment which are considered as similar or equivalent for purpose of cleaning validation. This grouping helps to segregate the worst case products. Grouping or matrixing helps to banish some of the combinations of product and equipment study that might otherwise need to perform.

Grouping or matrixing done on basis of-

1. Manufacture on same equipment group
2. Cleaned with same cleaning agent
3. Cleaned with same cleaning procedure

Grouping products and equipment for cleaning validation is probably the most important strategic decision affecting the overall success of a program that can be validated and maintained over time using continued process verification. Grouping by therapeutic or product family might somewhat limit the validation effort, but still will most likely result in too many cleaning validation.

Grouping by dosage form (e.g., tablets, liquids, capsule, injections etc.) seems reasonable and sometimes necessary based on different equipment and cleaning process conditions.

The most efficient way to group products is using a worst case approach to determine the product that presents the greatest challenge for cleaning validation.

Equipment grouping -

similar types of equipment are grouped together, a justification of the specific equipment selected for cleaning validation is expected. Equipment grouping needs to be done strategically in parallel with the product grouping. The objective should be that equipment grouping does not significantly add to the cleaning validation effort. For example, a large and a small piece of the same unit operation (e.g., V-blender) might be considered as sufficiently different for cleaning as to warrant separate validation. Or grouping could decide to bracket each group of equipment and validate the largest and smallest equipment in the group

6.2 Worst case products:

A worst-case product approach has been accepted by regulatory agencies European Commission (EC)

Annex 15 (1) states, "Where a worst-case product approach is used as a cleaning validation model, a scientific rationale should be provided for the selection of the worst-case product." But there is no such defined set down procedure to select worst case; there are different parameters for selection of worst case. First and most effective approach is **Water solubility of API**, this approach depends on the fact that poorly soluble drugs are hard to clean.

But this approach truly avoiding the excipient interruptions in activity, hence we can say that in future there shall be approach of API and excipient chemistry. Cleaning assessment can be more practical if other physical characteristics like hydrophobicity as well as operator experience, who is very well known that which material is hard to clean.

Solubility is the first and major approach used in most of the pharma industries. Hardest to clean products in combination with lowest ARL (Acceptable residual limits) should be considered for worst case product.

- The criteria for selection of solubility status shall be as follows:

Group	Included descriptive terms	Appropriate quantities of Solvent by volume for 1 part of solute by weight
01	Very soluble Freely soluble	Less than 1 Part From 1 to 10 Parts
02	Soluble Sparingly soluble	From 10 to 30 parts From 30 to 100 Parts
03	Slightly soluble Very slightly soluble Practically insoluble	From 100 to 1000 parts From 1000 to 10000 parts More than 10000 Parts

ADE concept:

The Acceptable Daily Exposure defines a limit at which a patient may be exposed every day for a lifetime with acceptable risks related to adverse health effects.

Therapeutic doses:

An investigation of therapeutic doses is typically base on oral and/or parenteral data. In the cases where the therapeutic doses are not available, corresponding values based on the toxicity could be used (recalculated according to company procedure). An example or rating numbers, with explanations, are

presented in Table II:

Therapeutic Dose	Rating
>100 mg	**1**
100- 1000 mg	**2**
10-99 mg	**3**
1-9 mg	**4**
<1 mg	**5**

DETERMINATION OF MAXIMUM ALLOWABLE CARRYOVER RESIDUE AND ACCEPTANCE CRITERIA:

- A matrix for determination of MAC shall be prepared for each equipment chain for the selected group of products.

- Maximum Allowable Carryover (MAC) shall be calculated as follows:

  - **Dose Criteria:** Not more than 1/1000th dose of any product, which shall appear in the maximum daily dose of another product manufactured subsequently

$$\text{MAC (mg per 100 cm}^2\text{)} = \frac{\text{SF x Minimum therapeutic dose of product A in mg x Batch Size of product B (in numbers)}}{\text{B x SA}} \text{ x M Maximum daily dose in units of product}$$

Where,

Product A = Product under cleaning validation study

Product B = Product manufactured subsequently in units.

MAC = Maximum Allowable Carryover

SF = Safety Factor: 0.001 (1/1000th of the dose)

SA = Total Equipment Product Contact surface Area common between Product being cleaned and subsequently manufactured product in cm2.

M = 100 cm2 (Swab area)

PPM Criteria: Not more than 10 PPM of any product residue shall appear in another product manufactured subsequently

$$\text{MAC (mg per swab)} = \frac{\text{10 X Batch Size of product B}}{\text{SA}} \text{x M}$$

Where,

Product B = Product manufactured subsequently in Kg.

MAC = Maximum Allowable Carryover.

SA = Total Equipment Product Contact surface Area common between product being cleaned and subsequently manufactured product in cm^2

M = 100 cm^2 (Swab area)

BASED ON TOXICOLOGICAL DATA:

Procedure to calculate MACO by using toxicological data-

Calculate the NOEL number (No Observable Effect Level) according to the following equation and use the result for the establishment of MACO.

$$NOEL = \frac{LD50\ (g/kg) \times 70\ (Kg\ a\ person)}{2000}$$

From the NOEL number a MACO can then be calculated according to:

$$MACO = \frac{NOEL \times MBS}{SF \times TDD_{next}}$$

MACO: Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous").

NOEL: No Observed Effect Level

LD50: Lethal Dose 50 in g/kg animal. The identification of the animal (mouse, rat etc.) and the way of entry (IV, oral etc.) is important.

70 kg: 70 kg is the weight of an average adult.

2000: 2000 is an empirical constant

TDD_{next}: Largest normal daily dose for the next product

MBS: Minimum batch size for the next product(s) (where MACO can end up).

SF: Safety factor.

6.3 Acceptance limits of APIs

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% (1/1000th) 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.

6.4 Safety factors to be considered in cleaning validation

By using several factors mentioned above we are able to achieve a robust cleaning procedure but there are several other factors which needs to cover while doing cleaning validation, one of such factor is safety.

In case of drugs with narrow therapeutic index acceptable limits (mentioned in existing cleaning validation procedures)shall be a question because drugs have different safety profile. If the products have the same dosage they will have same acceptance limits but they have different safety profiles. In case of warfarin, a drug with very narrow therapeutic index and other drugs having tetrogenic effect , is $1/1000^{th}$ limit is safe in such case of drugs.

7. Conclusion :

By this article we have concluded that the cleaning validation program should be effective and consistent to produce product which effective and safe. Cleaning validation program is step wise activity start from cleaning to selection of worst case product, calculation of MACO. After determination of residue type, appropriate methods must be employed to collect samples of the residue. Then these samples will be analyzed by a suitable method and results will be compared with the acceptance limits calculated before commencement of the study. There are various new ideas and technique which are coming in existence from the traditional approach, these include safety parameters of drug. And this article primarily covers all aspects related to cleaning validation like mechanism of cleaning validation, different levels of cleaning, cleaning procedure, sampling procedure, product grouping and equipment characterization, and elements of cleaning validation.

REFRENCES-

1. FDA Guide To Inspections: Validation Of Cleaning Processes..

2. United States vs. Barr Laboratories, Inc. Civil Action No. 92-1744, US District Court for the District of New Jersey

3. Jimenez, F.J., "*Enforcement of the Current Good Manufacturing Practices for Solid Oral Dosage Forms After United States v. Barr Laboratories*" 52 Food Drug L.J. 67, 1997.

4. Bodavula Samba Siva Rao: Cleaning validation of albendazole tablet 400 mg. Pharma Innovations. 2012; 1(4): 76-94.

5. Kumar S: A review on concept of cleaning validation in pharmaceutical Industry. International Research Journal of Pharmaceutical Sciences 2012; 3(7): 17-19.

6. Sanjay Dey, Anindya G: Overview of cleaning validation in pharmaceutical industry. Indian Journal of Pharmaceutical Quality Assurance 2010; 2(2): 26-30.

7. Ovais, M., and Lian, Lai Yeo, "Setting Cleaning Validation Acceptance Limits for Topical Formulations,"*Phamaceutical Technology*, January 2008, www.pharmtech.com

8. Lakshmana P: Cleaning validation and its importance in pharmaceutical Industry. Pharma Times 2010; 42(7): 21--

9. Beg S, Kohli K, Swain S, Hasnain MS. Development and validationof RP-HPLC method for quantitation of amoxicillin trihydrate in bulk and pharmaceutical formulations using box-behnken experimental design. J Liquid Chromatography Relat Technol. 2012;35(3):393–406.

10. Pradhan DP, Annapurna MM. Stability indicating LC-TQ-ESI-MS method for the quantification of Racecadotril in presence of its degradants. *Res J Pharm Technol*. 2019;12(7):3437–4

11. Kumar SV, Rudresha G, Gurav S, Zainuddin M, Dewang P, Kethiri RR. Validated RP-HPLC/UV method for the quantitation of air aterone in rat plasma and its application to a pharmacokinetic study in rats. *Biomed Chromatography*. 2013;27(2):203–7.

12. Pradhan DP, Annapurna MM. Study of forced degradation behavior of fluorometholone by reversed-phase

high performance liquidchromatography. *Int J Green, Pharm*. 2018;12(3):675–9.

13. Rao RN, Talluri MVNK. An overview of recent applicationsof inductively coupled plasma-mass spectrometry (ICP-MS) in determination of inorganic impurities in drugs and pharmaceuticals.*J Pharma Biomed Anal*. 2007;43(1):1–13

14. EC, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 15: Qualification and Validation, Section 39, p. 243 (2015).

15. FDA, "Guide to Inspection of Validation of Cleaning Processes," (Division of Field Investigations, Office of Regional Operations, Office of Regulatory Affairs, Washington, D.C. July 1993).

16. J. Canhoto, et. al., J. Val. Technol. 11 (1) (November 2004).

17. R. Song, A. Canhoto, and A. Walsh, "Cleaning Process Development: Cleanability Testing and 'Hardest-To-Clean' Pharmaceutical Products" Pharm. Online, January 2019.

18. ISPE, Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP), Section 16.2., 2015.

19. R. J. Forsyth, V. Van Nostrand, Pharm. Technol. 29 (10), 152–161 (2005). 7. R. J. Forsyth, Pharm. Technol. 40 (4), 50-57 (2016).

20. A. Walsh, D. Liu, M. Ovais, "Justification and Qualification of Visual Inspection for use in Cleaning Validation for a Low Risk, Multi-Product Facility" Pharm. Online, August 2018.

21. R. J. Forsyth, Pharm. Technol. 38 (1), 42 – 46 (2014). PT