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CLEANING VALIDATION FOR ESTIMATION OF OXYTOCIN RESIDUE ON THE SURFACE OF THE INSTRUMENTS USED IN MANUFACTURING & FILLING LINES OF PARENTERAL PREPARATION IN THE PHARMACEUTICAL INDUSTRY USING SWAB/RINSE SAMPLING AND BY HPLC & TOC TECHNIQUE.

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ABSTRACT:

Cleaning validation refers to the cleaning-specific processes and outcomes that have been demonstrated to yield permissible results even in the worst-case situation. It is possible for cleaning agents, extraneous material, microorganisms, or other active pharmaceutical ingredients (API) to contaminate pharmaceutical products to a level that is above predetermined levels.

To prevent cross-contamination, manufacturing and cleaning equipment must be designed for efficient and reliable cleaning, and the cleaning procedures must be approved as efficient. The residual residues on the equipment must be regulated based on the findings of confirmed analytical data since human safety depends on them.

Keywords: Acceptance Criteria, Cleaning Validation, HPLC (High-Performance Liquid Chromatography), Methods of cleaning, MACO (Maximum Allowable Carry Over), Recovery Study, Sampling Method, Selection of Worst Case, TOC (Total Organic Carbon).

FDA REQUIREMENTS:

- The FDA advises drug manufacturers to have documented SOPs with information on how to clean certain equipment parts in place.
- The removal of both soluble and insoluble residue should be done according to prescribed protocols.
- Cleaning validation should be performed by the authorized methodology created under the direction of regulatory rules, and observations should be recorded.

- The FDA mandates that all people participating in cleaning validation be qualified in terms of cleaning, sampling, analysis, the analytical technique to be utilized, and method sensitivity.

WHEN CLEANING VALIDATION IS REQUIRED?

- Initial certification of cleaning technique and machinery
- Significant adjustments to the chosen cleaning technique
- Significant Master Formula adjustments
- A different cleaning substance

TYPE OF CLEANING:

❖ **Type A Cleaning:**

It involves cleaning contact parts of equipment to a level of visual cleanliness. This cleaning procedure doesn't need to be validated as there is no chance of cross-contamination. It involves:

- Change over from one batch to the next batch of the same product with the same potency.
- Change over from one batch to the next batch of the same product with higher potency.

❖ **Type B Cleaning:**

It involves a thorough cleaning of the contact and non-contact parts of equipment as per the respective cleaning procedure. Finally, the cleaned equipment shall be rinsed with a defined volume of water for injection and then taken with a swab/wash water to assure a level of chemical cleanness.

- Changeover of one batch to the next batch of the same product with descending potency.
- After any maintenance of contact parts.
- Product-to-product changeover.
- In case of color change (any strength).

MINIMUM CLEANING VALIDATION REQUIREMENT:

If it is not possible to verify every piece of equipment for every product, then as a minimum requirement the Validation Policy must include scenarios that depict the worst-case obstacles to the method. For instance:

• Elimination of goods that include substances with high biological activity.

• Removing goods that include the least soluble byproducts, intermediates, or products.

Worst Case Selection:

Based on the following, the criteria for defining the worst scenario for MAR (Maximum Allowable Residue) evaluation are defined:

• The lowest recommended daily API dose for adults.

• potent API class.

• The least amount of active is soluble in water.

• Minimum MAR value for API.

• The study will require the highest strength.

Matrixing:

• If there is a "Multi Product" production line, product matrix/grouping must be used in cleaning validation planning.

• The product must first be categorized by formulation and dosage form, taking into account factors including potency, toxicity, and solubility.

• The types of equipment employed in the manufacturing of these product groups should be further segregated.

According to the cleaning technique and chemicals, more distinctions must be established. Each product in a group must have the same composition, use the same equipment, and follow the same cleaning instructions.

SAMPLING PLAN:

Sampling is intended to find any residue that could remain on freshly cleaned equipment surfaces and be passed to the following production batch.

As a result, the sampling strategy must be such that the data it gathers about the residue is accurate and representative.

According to the following factors, sampling must be done:

Location with the most cleaning challenges:

• If cleaning is insufficient, it is more probable that residues will build up in difficult-to-clean areas of the production equipment, from which sampling is to be scheduled.

• The decision must be supported by sound scientific reasoning and should take into account the equipment's setup.

• One factor that may be exploited is production-related knowledge of how difficult it is to remove material. It is advised that the study tak

e the form of operator and supervisor interviewing.

❖ **Locations that are likely to produce non-uniform contamination of the next batch:**

- There are locations in the manufacturing equipment wherefrom the residue may preferentially be transferred to only a limited portion of the next batch.

❖ **Representative functional locations:**

- At least one sample from each representative functional area, such as an equipment sidewall or blade, must be taken into consideration.

SAMPLING TECHNIQUE:

Sampling may either be performed by swabbing or by rinsing.

❖ **Rinse sampling:**

Following the specific procedure, rinse water samples must be taken after the equipment has been washed with purified water of a certain quality or water for injection.

Rinse water samples need to be sent to QC with a notification slip.

The samples must be examined for the presence of residual active ingredients to prove that the amount of residue following Type "B" cleaning is below the established Acceptance requirements.

❖ **Swab sampling:**

Pre-treatment of swabs: All swabs to be used for method validation must first be treated in the manner described below.

The strongly recommended approach, as some residue may need a mechanical or physical action to remove from the surface; Take 10ml of diluents in a test tube, dip one fresh swab stick, and sonicate for five minutes.

Depending on the size, accessibility, and compliance of the equipment, at least 1–5 sites must be swabbed.

Swab samples from the places indicated in the sampling sites must be taken for chemical/microbiological analysis to validate the cleaning.

The part of the equipment that is hard to clean should be taken into consideration when choosing the sample position.

An expert in microbiology must collect the sample for the microbiological examination.

To ensure that the equipment is clean before collecting the swab samples, it must be visually inspected and its odor verified (if any substance has an odor).

Please take note that the surface area should only be taken into account once when determining the total surface area if the same equipment is used again in a chain.

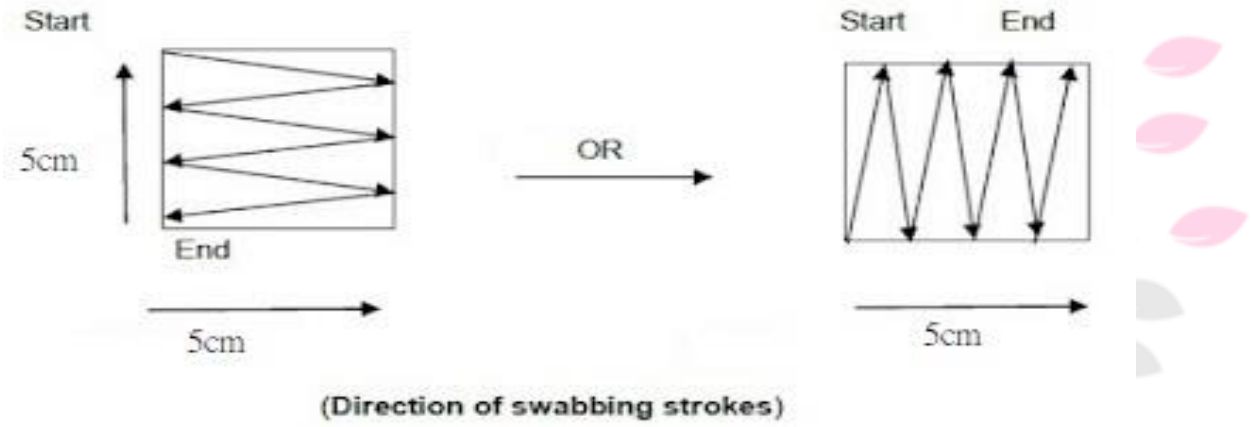
- **Swab sampling for chemical analysis:**

After the equipment has been thoroughly cleaned and has passed the visual inspection test, swab samples must be obtained. According to the analytical technique validation, the swab must be dipped in a swabbing medium, or solvent for the API, in a 10 ml test tube. Swab samples from various equipment regions must be gathered. The area to be swabbed must be measured.

Sampling errors: attention should be exercised during the swab sample; the sampling area (should not be less than 25cm2). To prevent any sampling mistakes, use the necessary force while collecting samples from the equipment's sampling area, which is 5 cm by 5 cm.

- **Sampling Patterns.**

Wipe the defined area in zigzag directions as shown in the figure. Apply only one time at a surface for one time only. Collected the swab by application of normal force.



(Direction of swabbing strokes)

Note: Avoid lifting the swab stick from the contact surface during the collection of swabs. Refer to the diagram above to collect the sample-using swab.

- **Handling of Swab sampler:**

Use of a sterile swab, preparation of swabbing medium, aluminum foil covering of the test tubes, and due care should be given when handling the swab are all required. Each sample must be swabbed, put into a test tube with proper labeling, and covered with aluminum foil before being delivered to the QC lab for analysis.

➢ **Swab Sampling for Microbial Analysis:**

- Before taking the swab, sterile hand gloves must be worn.
- Sterile normal saline solution should be used to wet sterile swabs.
- The swab should now be passed over the product contact surface or a comparable surface.
- The strokes should be used as shown in the following figure.
- The sample must be processed for microbiological testing as away.

RECOVERY FACTOR:

• The result in the examined sample falls within the permitted range. The swab recovery factor needs to be used to alter it. By adding the swab recovery factor in the actual analytical calculation, for example, if the RF is 0.80 (80%) and the analytical technique measures it at 1.3 ppm, the value is corrected by dividing the analytical data by the RF, 1.3 ppm / 0.80 = 1.6 ppm.

• • The recovery factor may also be included in the analyzed sample's numerator as an alternative. When comparing the analytical findings to the calculated limit, the overall logical conclusion must be the same, even if different numbers must be utilized and the RF 0.80 must be included in the numerator.

SELECTION OF ANALYTICAL METHOD:

• Appropriate analytical techniques must be chosen to design and validate analytical procedures for the identification of product residue in cleaning validation samples.

• For the detection of product residue, a particular analytical method must be carefully chosen; a non-specific analytical approach may provide incorrect analytical findings.

• The analytical techniques employed during the cleaning procedure's validation must be able to precisely quantify the concentration of every compound of interest that might be present in samples.

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During cleaning validation, specific methods must be used; however, non-specific methods must be used for subsequent cleaning verification or ongoing cleaning monitoring.

❖ **Analytical Method Validation:**

• Any instrumental analytical methods that are used to assess cleaning validation samples must be defined and sensitive enough to detect the normally modest quantities of residue present in samples.

• The equipment must pass validation tests to guarantee that it complies with the following criteria before it may be released for use in the production of another product.

- Specificity
- Limit of detection (LOD)
- Limit of quantification (LOQ)
- Linearity
- Precision
- Recovery of drug from spiked swabs
- Recovery of drug from spiked SS plates and other product contact materials range
- Stability of analytical solution
- Robustness
- Number of cleaning cycle

ELEMENTS OF CLEANING VALIDATION:

❖ **Establishment of acceptance criteria:**

- **Chemical determination:**

➢ Pharmacological dose method (dose criteria):

$$MACO = (I \times K) / (J \times L) \times M$$

MACO: Maximum Allowable Carryover (mg/swab)

I = 0.0001 × smallest strength of product "A" manufactured that will give an acceptable Pharmacological response (in mg).

K= Minimum batch size of the product "B" (in units).

M=Swab area ($25cm^2$)

J= Maximum number of dosage units of product "B" taken daily (in units)

L=Equipment surface area in common between products "A" & "B".

➢ **Physical determination:**

Visual examination of the equipment & verification that it is free of visible residues.

➢ **10 ppm criteria:**

The maximum allowable residue per swab of 10 x 10 cm can be mathematically expressed as:

MAR = R x (S/T) x U

R = 10mg active ingredient in product A/kg of product B

S = Number of Kilograms per batch of the final mixture of product B

T = Equipment surface area in common between products A and B expressed as cm^2.

U = 100 cm^2 swab

Factor R is always 10 mg of the product's active ingredient being cleaned per Kilogram of the final mixture of the recipient product. This is simply 10 ppm stated a different way.

➢ **Microbiological determination:**

Appropriate studies must be performed (swab/rinse sampling) where the possibility of microbial contamination of subsequent products is deemed possible. The procedure for microbial determination of swab analysis is as follows;

a) Prepare the swab in 10 ml of saline solution.

b) Sterilize all prepared swabs at 121.1 degrees centigrade for 15 minutes.

c) Let the swab get cool up to room temperature.

d) Take the desired number of swabs to the location from where the sample is to be collected.

e) Select a 5×5 cm^2 area for an even and easy surface and swab horizontally, vertically cum overlap stroking.

f) After completion of the activity, take all collected swab samples to the microbiology lab for analysis.

g) Perform analysis by membrane filtration method and if pathogen testing requires proceed as per respective SOP.

h) Report the result in CFU/swab.

RE-VERIFICATION/RE-VALIDATION CRITERIA:

- Concurrent validation: Based on the worst-case scenario, three consecutively successful validation investigations for each piece of equipment
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- Three successful validation studies for each piece of equipment for a new product, a new piece of equipment, or modification to the cleaning technique.
- Risk assessment must be carried out if a new product is brought to the facility to evaluate the worst-case product for cleaning validation. Three successful validation studies if the product is determined to be the worst-case scenario.
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- One batch of each worst-case product must undergo revalidation within five years after the last successful run.

- Revalidation must be started if there are any changes to the equipment, product contact parts, or API source and is based on an effective assessment. Cleaning procedures or cleaning aids (such as cleaning agents) must also be validated.

Revalidation must be done if a current cleaning agent's formulation is altered.

VALIDATION REPORT

The results and conclusions must be presented in a validation report to get the study's approval. The following details should be included in the report:

1. A list of all the cleaning techniques used for testing and sample preparation.
2. The outcomes of any relevant physical and analytical tests, or references for those tests.

3. Conclusion on the results' acceptability and the stage of technique validation.
4. Any advice derived from research findings or pertinent data, including, if appropriate, revalidation procedures.
5. Examine any deviations from the plan.
6. In situations when it is doubtful that new batches of the product will be produced for a while. Before then, it is advised to produce reports batch by batch.
7. After validating the data, the report should draw the right conclusion.

CONCLUSION:

This review-based study concludes that cleaning validation is a formalized procedure that establishes the efficiency and regularity of cleaning pharmaceutical equipment. Because of the regulatory requirement, it is essential to have an efficient cleaning program in place. The primary motivation, however, is to create items

that are uncontaminated and clean. And the major goal of cleaning validation is to provide concrete proof that one can reliably clean a system or a piece of equipment to established, acceptable limitations. Additionally, this article focuses on all facets of cleaning validation, including the cross-contamination mechanism, various cleaning levels, cleaning procedures, sample procedures, product grouping and equipment characterization, cleaning agent choice, and cleaning validation elements.

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