Section A-Research paper

CLEANING VALIDATION: REGULATORY EXPECTATIONS AND METHODOLOGICAL CHALLENGES.

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Abstract

Quality, safety, and efficacy of finished formulation must be controlled throughout the product life cycle. Cross-contamination by drugs from previous batches, cleaning or sanitizing agents may lead to adulterated product. Cleaning validation protocol follows the Quality risk management process (ICH Q9) with estimation of the criteria for Acceptable Daily Exposure (ADE), Permitted Daily Exposure (PDE), Maximum Acceptable Carry Over (MACO) and No Observed Adverse Effect Level (NOAEL) determination for API in multipurpose equipments. The development and validation of analytical cleaning method follows ICH Q2 (R2) guidelines. Optimization of swab or rinse sampling protocols, bracketing and worst-case ratings, cleaning process qualification and verification on equipment surfaces are some of the challenges that requires careful consideration as per various available regulatory guidelines. The article provides an elaborated overview on various challenges, regulatory and technical requirements for cleaning method validation suggested by various regulatory agencies.

Keywords Cleaning validation, cross-contamination, sampling techniques, acceptance criteria.

Introduction

Validation can also be defined as documented evidence which provide a high degree of assurance that a particular process will constantly produce a product which will meet its predefined specifications and quality attributes.[1]

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Cleaning validation is an established procedure that demonstrates the efficacy and reliability of cleaning pharmaceutical production equipment.[2,3]

The major objective of validation is to ensure that a cleaning technique complies with federal and other standard regulations. The use of a method like this is essential for locating and correcting major problems that were previously foreseen and could compromise the safety, efficacy, or quality of succeeding batches of pharmaceutical products produced using the same equipment.[4,5]

Objective

(i) To make sure the product is pure and safe.[2]

(ii) Cleaning validation aims to verify that the cleaning procedure is successful in removing product contaminants, degradation substances, preservation ingredients, excipients, and/or agents for cleaning, as well as in controlling any microbiological contamination. In addition, it is also necessary to make sure that there are no chances of active component contamination.[2]

(iii) The cleaning validation's objective is to offer cleaning techniques for pharmaceutical equipment that are not only in line with cGMP and current regulatory criteria, but that are also practical, economical, and supported by reliable scientific data.[6]

(iv) To prevent cross-contamination.[2]

(v) To prevent product mix-ups.[2]

As per the FDA response, validation should be conducted and confirmed by triplicate study such as if it happens right once, it’s an accident, twice, it’s coincidental, and three times, its validation.[6]

For the purpose of the cleaning validation protocol, the following specific duties and responsibilities are assigned:[7]

Table 1. Specific Duties and Responsibilities:

Area	Responsibility
Production	To make the facility/equipment available for validation.
Quality Control	To perform testing of samples.
Validation Team	To define protocols, assess risk, execute, document, review, and approve validation activities.
Quality Assurance	To analyze the samples collected during execution. To execute the protocol. To prepare, review and approve protocol.

Regulatory Expectations as per various regulatory agencies

An essential part of any successful GMP compliance strategy at an authorized drug manufacturing plant is cleaning validation. As the pharmaceutical industry abandons the outdated V model in favor of Health Based Exposure Limits (HBEL) derived from conventional methods, cleaning validation has really been one of the most modifying and contentious issues of the year 2018–19.[8]

U.S. Food and Drug Administration (USFDA)

The USFDA updated its recommendations for cleaning equipment under Section 211.67 of the 21CFR in 2018. FDA recommends that the utensils and other tools must be regularly disinfected, organized, and, according to the type of medicine, sanitized to avoid flaws or dirt that could negatively impact the efficacy, safety, identity, strength, quality, or purity of a medicine. This goes beyond what is mandated by law or any established standards.[9]

In addition to the 211.67, the FDA has released a number of other publications that serve as industry guidelines. Some related terminologies are as follows:

Acceptable Residue: Equipment contaminants that can be easily prevented and removed is not accepted. In order to remove a predetermined "accepted" level of residues, cleaning methods must be established on the basis of scientific understanding of the chemical and its interactions with other substances in the processing plant. Therefore, it is not advisable to design analytical methods simply with the intention of obtaining an acceptable residue.[10,11]

Total Organic Carbon (TOC): The FDA has approved the use of TOC as a suitable method for regular residue assessment and for cleaning validation due to the fact that under TOC studies, the contaminated substance(s) is expected to be organic containing carbon which will probably be easily oxidized.[10,11]

Rinse sampling: The rinse sample approach has the benefit that the solvent will reach every part of the apparatus, even hard-to-reach places that cannot be disassembled. This method will therefore provide the most accurate indicator of the amount of residue still present in the equipment if it is done correctly.

Continuous Process Verification is a concept that many companies have not yet adopted. A continuous verification program is required for residual monitoring after cleaning validation, according to the FDA.[10,11]

European Medicines Agency (EMA)

Health-Based Exposure Limits based on “Permitted Daily Exposure” values as described in “Appendix 3 of ICH Q3C (R4)” are a requirement set out by EMA in guidelines for all pharmaceutical products as of June 1, 2015.[12]

All pharmaceutical items should have HBELs (Health Based Exposure Limits) established. It is necessary to routinely examine the toxicity or pharmacological information utilized in the HBEL calculation over the course of the lifespan of a product.[12,13]

How to use HBELs: The first step is to set up HBELs. These attributes provide a starting point for figuring out what extra controls might need to be implemented through a "Quality Risk Management approach." [8]

Acceptance vs. Alert Limits: Industries must also establish safety limits based on the prior common cleaning standards (that is, depending upon dose) and making sure the cleaning procedures are effective, even though HBELs function as "Residue Acceptance Limits." This indicates that if the initial dose range limit is the most serious, that results in CpK < 1.33, the alert limit should be established based on statistical analysis rather than dose limit.[12,13]

Analytical Testing During Product Changeover: Unless it is determined that the risk is low, this is now necessary. Risk assessment is done based on the level of risk (Toxicity Scale), frequency of the risk (Cleaning Process Capacity), and visual threshold (which determines whether the risk can be seen).[12,13]

Applying LD50: LD50 is no longer a sufficient starting point for determining HBELs for pharmaceutical products.[12,13]

World Health Organization (WHO)

The FDA and WHO cleaning validation guidelines are extremely identical. The fundamental parameters are outlined in "Sections 5.2 and 12.7 of the WHO Good Manufacturing Procedures" for active pharmaceutical components (Annex 2).[8]

WHO clearly accepts the worst-case scenario when as a sample APIs are used to confirm cleaning methods. The computation of residual limitations is based on strength, toxic effects, and stability which should be used to make the choices in addition to considering solubility and cleaning difficulty. However, it is not clear how to include stability in residue limits.[14]

Continuous Process Verification: The WHO advises employing techniques like analytical testing and visual inspection for continuous monitoring. It provides a suggestion about the risk-based process; however, the lack of any additional information is unsatisfactory.[14]

Pharmaceutical Inspection Co-operation Scheme (PIC/S)

In response to the EMA, PIC/S quickly released the revised cleaning validation guideline to control the cross-contamination (PI 046-1 Guideline) for setting HBELs in sharing facilities.[8]

Cross-contamination risk management should be addressed during an inspection, but the time allotted will vary depending on the molecular hazards, the types and number of pharmaceutical products handled, and the level of separation and dedication of the facilities.[15]

Therapeutic Goods Administration (TGA)

TGA mostly adapted the PIC/S cleaning validation guideline for good manufacturing practices (PE009-13). Additionally, it is an initial indication that other nations might also eventually join the new cleaning validation procedure that is based on science and risk.[16]

Health Canada

Health Canada has outlined several requirements in its cleaning validation recommendations (Guide-0028), which are missing from many other guidelines while being widely known in the industry.[17]

Additionally, principle 3.5, states that both the real risk and the worst-case risk must be considered acceptable. It indicates encouragement towards the practice of automatically choosing the worst-case scenario over making an effort to discover the real risk.[17]

Cleaning techniques for remarkably similar things and processes don't need to be independently evaluated. This may depend on what is normal, such as the equipment and surface area, or on a setting with all equipment that comes into touch with the product.[17,18]

In a facility that produces a range of pharmaceutical products, it's critical to balance the expense of dedicating equipment to a particular product against the work required to confirm the cleanliness of a certain exposed component of the equipment.[17,18]

Health Canada has provided the most detailed description of the revalidation standards. To evaluate the influence of relevant modifications on the facility's cleaning condition, a real-time system is required. These adjustments could be made to the cleaning process, raw material sources, product formulation and/or manufacturing processes, new products, detergent formulation, and manufacturing processes, and equipments.[17,18]

There is a mechanism in place to ensure any changes that might have an impact on the method of cleaning are assessed and recorded. Substantial changes have to occur when a change control procedure-approved documented change proposal has been satisfactorily reviewed. Few changes that don't directly affect the final product's quality or the product being produced should be managed through the documentation system. The revalidation of the cleaning method should be taken into account during the review.[17,18]

Parenteral Drug Association (PDA)

PDA has released two different documents with regards to cleaning validation. “PDA Technical Report 49” for biotechnology products and “PDA Technical Report 29” for actives.[19,20,21]

International Society for Pharmaceutical Engineering (ISPE)

ISPE updated their “Baseline Guide on Risk-MaPP” (Risk-Based Manufacture of Pharmaceutical Products), which was then released in its second edition in 2017. The changes

primarily follow the 2015 EMA guidance on establishing HBELs. The high-level ideas and specific implementation instructions for creating a validation for the cleaning, this advice appropriately reflects SOP that is based on risk and research.[22,23]

Active Pharmaceutical Ingredients Committee (APIC)

Many companies, particularly, especially those that only generate raw API products, employ the APIC cleaning validation guidelines. In order to include the EMA recommendation on applying HBELs, details of cleaning validation in "Active Pharmaceutical Ingredient Plants," a guideline issued by APIC in 2014, was amended in 2016 as well. "Chapter 4, Acceptance Criteria," introduced the most significant improvements. In order to be consistent following the EMA's guidelines for building the HBEL (health-based exposure limits), the APIC guidance was modified in 2016. "The Chapter 4 Acceptance Criteria" contained the main modifications. In 2021, new guidance was released on the use of health-based exposure limits that is more in line with the EMA Q&A and resolves a number of industry-related concerns (HBELs).[24,25]

American Society for Testing and Materials (ASTM)

The most recent publication in the cleaning validation standards is the "Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation," ASTM E3106 - 18e1. A number of concepts and methods outlined in the "FDA's Guidance for Industrial Process Validation" are based on science, risk, and statistics that are combined in these standards, which makes them distinctive. This manual complies to and supports ICH Q8, Q9, Q10, and Q11 standards.[8]

Methodological Challenges

The following are the issues that were encountered during the cleaning validation programme:

The residue's physical and chemical attributes as a cleaning principle: This technique is influenced by numerous factors. The development of novel cleaning techniques, new cleaning agents, potential supplier qualification, further training, and validation are all time- and money-consuming tasks. So far, in fact, it takes a lot more time and money to fix issues when established procedures are insufficient.[26]

Factors to consider when choosing the most challenging residue to remove: The solubility and toxicity of the target molecule are two factors that many practitioners use to estimate worst-case residues. This strategy might work when all the products produced at a facility are relatively simple to clean, like aqueous parenteral solutions with soluble components, but it differs when dealing with more complicated dosage forms. Inactive excipients may have a substantial impact on the cleanability of products containing polymers, such as controlled release tablet products. It is advised to consult with manufacturing staff members who carry out actual cleaning.[27,28]

Worst-case compounds are determined by residue solubility: These evaluations require solubility information from the cleaning solution. Any program that enables the cleaning of multiproduct equipment must include a vital component that involves choosing a worst-case compound for cleaning validation. The physical and chemical characteristics of the residues under actual cleaning conditions, as well as bench and pilot-scale data, must be carefully considered when developing these evaluations.[29,30]

The stability of the residue in developing analytical techniques: In most cleaning validation processes, the target analyte must be quantitatively measured, and the analytical result must be compared to predefined acceptance criteria. Small molecule API residues are frequently quantitated using a particular HPLC technique. Analytical techniques are approved to quantify the active ingredient at concentrations suitable for carryover into the next batch of the product. Prior to starting a cleaning process, wet residues may stay in the equipment for a long time. The

recovered residue is then examined after swab sampling. Degradants should be detected by analytical procedures.[31,32]

Many validation factors, including specificity, linearity, precision, the limit of detection (LOD), and the limit of quantitation (LOQ), were established in order to validate the method.[33]

Specificity: The capacity to assess an analyte clearly in the presence of components that could be expected to be present is known as specificity.[34]

Accuracy: Accuracy is the degree to which test results obtained through a procedure are within its actual value. Accuracy is frequently expressed as a percentage recovery by the presence of known, additional analyte concentrations. The degree of exactness in an analytical process is measured by accuracy.[35]

Linearity: The capacity of an analytical method to produce test results that are directly proportional to the concentration (quantity) of analyte in the sample is known as linearity.[36]

Precision: The degree of variance between a set of measurements obtained from repetitive sampling of the same homogenous sample under the specified conditions represents the precision of an analytical method. There are three levels of precision: repeatability, intermediate precision, and reproducibility.[37]

Analytical method validation requirements as shown below in table 2.[24,25]

Table 2. Analytical Method Validation requirements.

Experiments	**Possible Acceptance Criteria**
Accuracy: Carry out nine analyses at a minimum of three concentration levels.	
It should be given as percent recovery Difference between the mean and the true value	90-110.00% ≤10.00%

Linearity: The linearity experiment should include a minimum of five concentration levels, five replicates each.	
Visually Correlation coefficient	Linear ≥0.99000
Precision: Carry out a minimum of 9 measurements (For example, three concentrations with three replicates each) that span the range specified by the process.	
Repeatability (intra-assay precision):	
Overall relative standard deviation over the whole range of the method. Relative standard deviation within one concentration level.	≤ 10.00 % ≤ 20.00 %
Intermediate Precision (may include robustness, ruggedness): Establish precision after changing the method parameters (= robustness, such as solution stability, pH, mobile phase composition, flow rate, temperature, columns, etc.). This may be done on different days, for different analysts, on different equipment.	
Specificity: Test samples containing the analyte and other contaminants. Test samples without the analyte.	Specify acceptable deviation Negative results
LOD/LOQ: A common method for establishing LOD and LOQ is the same as that used for establishing the lower limit for the range of the method.	LOD = 3σ/S LOQ = 10σ/S

R^2= coefficient of determination, LOD= limit of detection, LOQ= limit of quantitation,

σ = The residual SD of the regression line, S= slope of the calibration curve.

Uneven equipment surface contamination: The goal of contamination control in cleaning validation is to reduce carryover between subsequent products made on the same machines and equipment (i.e., the amount of a contaminant from one product that can be transferred into a different product made on the same machinery must be less than a predetermined acceptable limit). According to Mullen and Foreman's method, which uses the shared surface area of production equipment to calculate the maximum permitted carryover, the maximum residue level that is acceptable for transfer is based on their findings (MAC). This method makes the assumption that

all surfaces will be equally contaminated and that residue from one product will completely and uniformly transfer to the next product.[38]

Acceptance criteria calculation as per regulatory expectations are summarized below:[39,40,41,42]

Calculation of Acceptance Criteria:

Acceptance criteria using health-based data

Calculating the HBEL as an Acceptable Daily Exposure (ADE) or Allowed Daily Exposure is recommended (PDE). They are practically equivalent and provide an estimation of a daily exposure that, if continuously absorbed over the course of a lifetime by any method at or below this dose, is unlikely to have any detrimental effects. In order to safeguard patients, they are computed using following equations in mg/day:

$$ADE = NOAEL \times BW / Ufc \times MF \times PK$$

$$MACO = ADE_{previous} \times MBS_{next} / TDD_{next}$$

The Maximum Allowable Carryover (MACO) must be built upon the Acceptable Daily Exposure (ADE) or Permitted Daily Exposure (PDE), which can be estimated when the necessary data are available.

MACO- Maximum Allowable Carryover: Quantity from one product to another (mg)

ADE- Acceptable Daily Exposure (mg/day)

NOAEL -No Observed Adverse Effect Level (mg/kg/day)

BW - What is the average weight of an adult? (e.g.,60 kg)

MF- Modifying Factor: factor - unpredictability not covered by the other considerations.

PK- Modifications for Pharmacokinetics

UFc- Composite Uncertainty Factor: Factors that represent variation between individuals, between species, and from the sub-chronic to the chronic.

TDD_{next} - Standard Therapeutic next product's daily dosage (mg/day).

MBS_{next} - Minimum batch size for the next product(s).

Acceptance criteria as per general limit

If the outcomes of MACO calculations are quantitatively less or any toxicological data is unavailable for intermediates, the method of a broader limit might be applicable. A MACO upper limit may be decided for the product as an internal policy. It is generally accepted to use the general limit to define the maximum concentration (MAXCONC) of a contaminated component in a subsequent batch as an upper limit.

MACO = MAXCONC x MBS

MBS Minimum batch size of the next product(s)

$MACO_{ppm}$ Maximum Allowable Carryover.

MAXCONC maximum allowed concentration (kg/kg or ppm) of the prior batch in the following batch.

Acceptance criteria for therapeutic macromolecules and peptides:

1/1000th of the therapeutic dose frequently combined with the use of a 10 ppm general maximum limit.

$MACO = NOEL_{previous} \times MBS_{next} / SF_{next} \times TDD_{next}$

$NOEL_{previous}$ No Observed Effect Level (mg/day).

TDD_{next} Standard Therapeutic Daily Dose of the next product (mg/day).

MBS_{next} Minimum batch size of the next product(s).

SF_{next} Safety factor.

Most challenging areas of the equipment to clean:

The following factors are suggested as part of a systematic method to identify the sampling places in manufacturing equipment that are difficult to clean:

Analysis of technological equipment: The equipment's problematic hard-to-clean sections, type of processing (wet or dry), materials of construction (MOC), geometrical configurations, and processing method are all noted. For example, cleaning stainless steel is typically more difficult than cleaning glass or Teflon. The smoothness of the surface can also have a considerable impact on a particular MOC's capacity to be cleaned.[43,44,45]

Equipment observation following processing: After processing typical pharmaceutical items, the equipment is inspected. There are some areas with large accumulations of process residues.[46,47]

Analyzing the disassembly of equipment: After disassembly, the apparatus is examined. Equipment parts that are removed apart for cleaning and subsequent evaluation have a far lesser risk than those that are fixed to the equipment assembly and cleaned within. It is observed that the fixed equipment assembly's components are easily accessible.[48]

Analyzing the cleaning process: The equipment cleaning process is examined. After equipment disassembly, parts and equipment locations that were previously recognized as being difficult to clean might not still be tough to clean.[49,50]

Operator consultations: Based on their actual experience, cleaning techniques for difficult-to-reach regions of the equipment may be improved.[51,52]

Bracketing and worst-case rating

Equipment in the facilities that is used to clean a variety of products is subject to cleaning validation requirements. The validation process could require a significant amount of work. A worst case strategy for the validation may be used to minimise the amount of validation required.

- The substances are grouped using a bracketing process.
- To choose the worst case in each group, a worst case rating procedure is applied.

Bracketing Procedure:

The first step is to create groups and subgroups, a process that will be referred to as "bracketing," from which the worst cases can later be selected based on the results of the rating. A company policy, SOP, or other document on cleaning validation should include the bracketing technique.

There are several ways for applying the bracketing procedure:

Based on Equipment Train: The initial requirement for grouping is that the products/substances in a group are produced in the same equipment trains and cleaned out using the same cleaning method/SOP.

Based on Substances/Products: A choice regarding the goods to be produced in each of the trains employed for the same purpose is made.[24,25]

Cleaning Procedures:

Numerous cleaning techniques are frequently used for a single train that produces a variety of contaminants. The second requirement is that the same cleaning procedure (method) must be

applied for the substances/products within a group in order to justify bracketing into groups. Where the products/substances in the same class are cleaned similarly, with the same solvents, and tend to have some chemical similarity with each other (such as salts, chemical structure, etc.).

As an example, the following four categories of cleaning procedures are mentioned:

Class I: Water-soluble compounds.

Class II: Substances soluble in methanol.

Class III: Acetone-soluble compounds.

Class IV: A distinct classification for unique compounds with predetermined solubility.[24,25]

Investigations and Worst Case Rating (WCR):

In a cleaning validation programme, existing drugs will be prioritised according to a worst-case rating study/Risk assessment that takes into account the company's preferred specific criteria. The following parameters can be chosen by a company that are relevant to the developing molecules in their facility (companies should assess individual situations):

a) Hardest to clean: experience from production (Category 1 = Easy; Category 2 = Medium; Category 3 = Difficult);

b) Solubility in used solvent (Category 1: Very soluble, freely soluble; Category 2: Soluble, sparingly soluble; Category 3: Slightly soluble, very slightly soluble, practically insoluble, insoluble);

c) Lowest Acceptable Daily Exposure or Permitted Daily Exposure (Category 1: >500 µg; Category 2: 100 – 500 µg; Category 3: 10 – 99 µg; Category 4: 1 – 9 µg; Category 5: <1 µg) [If

ADE / PDE data are not available, other data such as pharmacological dose, OEL or toxicity data (LD50) may be used];

d) Lowest therapeutic dose or toxicity data (Category 1: >1000 mg; Category 2: 100 – 1000 mg; Category 3: 10 – 99 mg; Category 4: 1 – 9 mg; Category 5: <1 mg).[24,25]

Worst Case Rating:

The chemicals or products must be scientifically categorised by cleaning class (method) and equipment class (train/equipment). Each existing pairing of classes is considered as a separate group. After this bracketing is complete, the "Worst Case Rating (WCR)" is permitted. There must be cleaning validation studies for at least one worst case in each group.

Rating Procedure:

- Selection of a common, general residual limit reasonable enough to include the lowest calculated limit to all the substances. If so, this limit may be valid for the particular equipment as a common general limit. The next lowest limit is assessed if it turns out that the lowest limit is too low to serve as a general limit for all substances.
- Criteria for the validation of a cleaning procedures

  1. It is required that the substance with the lowest solubility (in the cleaning solvent/solution) must be tested for each cleaning procedure for the substances with common, general limit. If more than one substance satisfies this requirement, the substance that is most challenging to clean shall be selected.

  2. Any substance that cannot be placed within this "bracket" needs to be separately validated.[24,25]

Section A-Research paper

Sampling procedures

Swab Sampling: The approach is usually referred to as direct surface sampling. Swabbing is a subjective manual technique that involves physical contact between the swab and the surface; as a result, it might differ from operator to operator. This method relies on physically eliminating any residue that endures after cleaning and drying an item of equipment.[53]

If there are any leftovers, they are extracted into a specified volume of a solvent that has enough solubility to dissolve any residual contaminants from the active substance. Then, a highly sensitive analytical approach is used to determine how much contamination is present in each swab.[54,55,56]

Method of swab sampling as shown in figure no.1.[1]

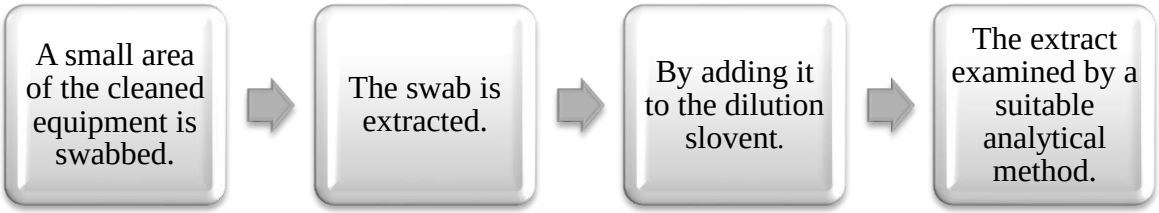

Figure.1 Method of swab sampling.

Swab Limits: The total area of the direct contact surface may be used to determine the contamination target value per square meter. It is useful for estimation of detection limit.[57,58]

Target value [µg/dm^2] = MACO [µg] / Total surface [dm^2]

Rinse Sampling: Large vessels, hoses, etc. are sampled using the rinse method (reactors, pumps, big equipment etc.). The cleaning agent was rinsed across the whole surface area of the apparatus. The sample is collected from the equipment and placed in the clean and dried sample bottle.[57,58]

Rinse Limits: Based on repeatability and comparability, rinse samples may also be used to estimate the quantity of residue left in the equipment after cleaning (Cycle durations, external temperature, volume, etc.). The selection of the rinse agent during cleaning validation supposed to be chosen while keeping in mind the analyte solubility and the rinse solvent's reactivity with the contaminants such as hydrolysis.[59,60]

Target value (mg/L) = MACO (mg) / Volume of rinse or boil (L)

Reliability and Training: Despite the fact that swab sampling is a crucial part of most cleaning validation procedures, some organizations view it as a routine task that can be completed without special training.[61-85]

The cleaning personnel must have the ability to consistently recover residue from equipment surfaces if the analytical results of the swab samples are to be accepted. Therefore, it's crucial that personnel who handle swab samples for cleaning validation receive thorough training. The training method should replicate the worst-case scenarios relevant to the product residues that are sampled at the site. The training should incorporate suitable quantitative acceptance criteria to show the trainee's competency. The manual dexterity and abilities necessary for swab sampling should be reinforced and maintained through periodic recertification of personnel. If an auxiliary tool, like an extension pole, is utilized for sampling, the training should confirm that the residue can be adequately recovered when the tool is used. Test results from swab samples are questionable, if personnel performing swab sampling is not qualified through appropriate training.[62]

Conclusion

Cleaning validation provides a means of proving that the contamination levels have been reduced below preapproved contamination acceptance limits. It may be concluded that to control the carryover of left-over residue from previous batch to the next batch an effective, validated cleaning mechanism should be developed considering various prescribed fundamentals described by various regulatory agencies.

Declarations

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