

Regulations for cleaning validation

(October 2007)

Below you find a compilation of the most important guidelines worldwide concerning cleaning validation. All guidelines are component of the GMP Manual, part GMP regulations, covering more than 30 international guidelines.

1. PIC/S PI 006: Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation, 2004 (excerpt)
2. FDA: Guide to Inspections Validation of Cleaning Processes (1993)
3. EU-GMP-Guideline, Annex 15 Qualification and validation, 2001 (excerpt)

For further information:

Cleaning Validation: Practical Compliance Solutions for Pharmaceutical Manufacturing
By **Destin A. LeBlanc (2006)**, Hardcover 238 pages

Cleaning and Cleaning Validation: A Biotechnology Perspective (Misc.), 1995, Hardcover 190 pages

1. PIC/S PI 006: Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation (excerpt)

7 Cleaning validation

7.1 Principle

7.1.1 Pharmaceutical products and active pharmaceutical ingredients (APIs) can be contaminated by other pharmaceutical products or APIs, by cleaning agents, by micro-organisms or by other material (e.g. air-borne particles, dust, lubricants, raw materials, intermediates, auxiliaries). In many cases, the same equipment may be used for processing different products. To avoid contamination of the following pharmaceutical product, adequate cleaning procedures are essential.

7.1.2 Cleaning procedures must strictly follow carefully established and validated methods of execution. This applies equally to the manufacture of pharmaceutical products and active pharmaceutical ingredients (APIs). In any case, manufacturing processes have to be designed and carried out in a way that contamination is reduced to an acceptable level.

7.1.3 Cleaning Validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing of pharmaceutical products or active pharmaceutical ingredients (APIs).

7.1.4 Objective of the Cleaning Validation is the confirmation of a reliable cleaning procedure so that the analytical monitoring may be omitted or reduced to a minimum in the routine phase.

7.2 Purpose and scope

7.2.1 These Recommendations describe the validation of cleaning procedures for the removal of contaminants associated with the previous products, residues of cleaning agents as well as the control of potential microbial contaminants.

7.2.2 These Recommendations apply to the manufacture of pharmaceutical products (final dosage forms) and of active pharmaceutical ingredients (APIs).

7.3 General

- At what point does a piece of equipment or system become clean?
- What does visually clean mean?
- Does the equipment need to be scrubbed by hand?
- What is accomplished by hand scrubbing rather than just a solvent wash?
- How variable are manual cleaning processes from batch to batch and product to product?
- What is the most appropriate solvent or detergent?
- Are different cleaning processes required for different products in contact with a piece of equipment?
- How many times need a cleaning process be applied to ensure adequate cleaning of each piece of equipment?

7.3.5 Cleaning procedures for **products** and processes which are very similar, do not need to be individually validated. It is considered acceptable to select a representative range of similar products and processes concerned and to justify a validation programme which addresses the critical issues relating to the selected products and processes. A single validation study under consideration of the "worst case" can then be carried out which takes account of the relevant criteria. This practice is termed "Bracketing".

7.3.6 At least three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.

7.3.7 Raw materials sourced from different suppliers may have different physical properties and impurity profiles. Such differences should be considered when designing cleaning procedures, as the materials may behave differently.

7.3.8 Control of change to validated cleaning procedures is required. **Re-validation** should be considered under the following circumstances:

(a) Re-validation in cases of changes to equipment, products or processes,

(b) Periodic Re-validation at defined intervals.

7.3.9 Manual methods should be reassessed at more frequent intervals than clean-in-place (CIP) systems.

7.3.10 It is usually not considered acceptable to "**test until clean**". This concept involves cleaning, sampling and testing, with repetition of this sequence until an acceptable residue limit is attained. For the system or equipment with a validated cleaning process, this practice of "test until clean" should not be required. The practice of "test until clean" is not considered to replace the need to validate cleaning procedures.

7.3.11 Products which simulate the physicochemical properties of the substance to be removed may be used instead of the substances themselves, where such substances are either toxic or hazardous.

7.3.1 Normally only cleaning procedures for **product contact surfaces** of the equipment need to be validated. Consideration should be given to non-contact parts into which product may migrate. For example, seals, flanges, mixing shaft, fans of ovens, heating elements etc.

7.3.2 Cleaning procedures for product changeover in the case of marketed products should be fully validated.

7.3.3 Generally in case of batch-to-batch production it is not necessary to clean after each batch. However, cleaning intervals and methods should be determined.

7.3.4 Several questions should be addressed when evaluating the cleaning process. For example:

7.4 Documentation

7.4.1 A **Cleaning Validation Protocol** is required laying down the procedure on how the cleaning process will be validated. It should include the following:

- The objective of the validation process,
- **Responsibilities** for performing and approving the validation study,
- Description of the equipment to be used,
- The interval between the end of production and the beginning of the cleaning procedures,
- Cleaning procedures to be used for each product, each manufacturing system or each piece of equipment,
- The number of cleaning cycles to be performed consecutively,
- Any routine monitoring requirement,
- Sampling procedures, including the rationale for why a certain sampling method is used,
- Clearly defined sampling locations,
- Data on recovery studies where appropriate,
- Analytical methods including the limit of detection and the limit of quantitation of those methods,
- The acceptance criteria, including the rationale for setting the specific limits,
- Other products, processes, and equipment for which the planned validation is valid according to a "bracketing" concept,
- When Re-validation will be required.

7.4.2 The **Cleaning Validation Protocol** should be formally approved by the Plant Management, to ensure that aspects relating to the work defined in the protocol, for example personnel resources, are known and accepted by the management. Quality Assurance should be involved in the approval of protocols and reports.

7.4.3 A **Final Validation Report** should be prepared. The conclusions of this report should state if the cleaning process has been validated successfully. Limitations that apply to the use of the validated method should be defined (for example, the analytical limit at which cleanliness can be determined). The report should be approved by the Plant Management.

7.4.4 The cleaning process should be documented in an SOP.

7.4.5 Records should be kept of cleaning performed in such a way that the following information is readily available:

- the area or piece of equipment cleaned,
- the person who carried out the cleaning,
- when the cleaning was carried out,
- the SOP defining the cleaning process,
- the product which was previously processed on the equipment being cleaned.

7.4.6 The cleaning record should be signed by the operator who performed the cleaning and by the person responsible for Production and should be reviewed by Quality Assurance.

7.5 Personnel

7.5.1 Operators who perform cleaning routinely should be trained in the application of validated cleaning procedures. Training records should be available for all training carried out.

7.5.2 It is difficult to validate a manual, i.e. an inherently/variable cleaning procedure. Therefore, operators carrying out manual cleaning procedures should be supervised at regular intervals.

7.6 Equipment

7.6.1 The design of the equipment should be carefully examined. Critical areas (those hardest to clean) should be identified, particularly in large systems that employ semi-automatic or fully automatic clean-in-place (CIP) systems.

7.6.2 Dedicated equipment should be used for products which are difficult to remove (e.g. tarry or gummy residues in the bulk manufacturing), for equipment which is difficult to clean (e.g. bags for fluid bed dryers), or for products with a high safety risk (e.g. biologicals or products of high potency which may be difficult to detect below an acceptable limit).

7.7 Microbiological aspects

7.7.1 The existence of conditions favourable to reproduction of **micro organisms** (e.g. moisture, temperature, crevices and rough surfaces) and the time of storage should be considered. The aim should be to prevent excessive microbial contamination.

7.7.2 The period and when appropriate, conditions of storage of equipment before cleaning and the time between cleaning and equipment reuse, should form part of the validation of cleaning procedures. This is to provide confidence that routine cleaning and storage of equipment does not allow microbial proliferation.

7.7.3 In general, equipment should be stored dry, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations.

7.8 Sampling

7.8.1 Samples should be drawn according to the Cleaning Validation Protocol.

7.8.2 There are two methods of sampling that are considered to be acceptable, direct surface sampling (**swab method**) and **indirect sampling** (use of **rinse solutions**). A combination of the two methods is generally the most desirable, particularly in circumstances where accessibility of equipment parts can mitigate against direct surface sampling.

A Direct Surface Sampling

(i) The suitability of the material to be used for sampling and of the sampling medium should be determined. The ability to recover samples accurately may be affected by the choice of sampling material. It is important to ensure that the sampling medium and solvent are satisfactory and can be readily used.

B Rinse Samples

(i) Rinse samples allow sampling of a large surface area. In addition, inaccessible areas of equipment that cannot be routinely disassembled can be evaluated. However, consideration should be given to the solubility of the contaminant.

(ii) A direct measurement of the product residue or contaminant in the relevant solvent should be made when rinse samples are used to validate the cleaning process.

7.9 Detergents

7.9.1 The efficiency of cleaning procedures for the removal of **detergent residues** should be evaluated. Acceptable limits should be defined for levels of **detergent after cleaning**. Ideally, there should be no residues detected. The possibility of detergent breakdown should be considered when validating cleaning procedures.

7.9.2 The composition of **detergents** should be known to the manufacturer. If such information is not available, alternative detergents should be selected whose composition can be defined. As a guide, food regulations may be consulted. The manufacturer should ensure that he is notified by the detergent supplier of any critical changes in the formulation of the detergent.

7.10 Analytical Methods

7.10.1 The analytical methods should be validated before the Cleaning Validation Study is carried out.

7.10.2 The analytical methods used to detect residuals or contaminants should be specific for the substance to be assayed and provide a sensitivity that reflects the level of cleanliness determined to be acceptable by the company.

7.10.3 The analytical methods should be challenged in combination with the sampling methods used, to show that the contaminants can be recovered from the equipment surface and to show the level of recovery as well as the consistency of recovery. This is necessary before any conclusions can be made based on the sample results. A negative result may also be the result of poor sampling techniques.

7.11 Establishment of Limits

7.11.1 The pharmaceutical company's rationale for **selecting limits** for product residues should be logically based on a consideration of the materials involved and their therapeutic dose. The limits should be practical, achievable and verifiable.

7.11.2 The approach for setting limits can be:

- product specific Cleaning Validation for all products,
- grouping into product families and choosing a "worst case" product,
- grouping into groups of risk (e.g. very soluble products, similar potency, highly toxic products, difficult to detect).

7.11.3 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% 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. Spiking studies should determine the concentration at which most active ingredients are visible,

(d) For certain allergenic ingredients, penicillins, cephalosporins or potent steroids and cytotoxics, the limit should be below the limit of detection by best available analytical methods. In practice this may mean that dedicated plants are used for these products.

7.11.4 One cannot ensure that the contaminate will be uniformly distributed throughout the system. It is also an invalid conclusion to make the assumption that a residual contaminant would be worn off the equipment surface uniformly or that the contamination might only occur at the beginning of the batch.

7.11.5 In establishing residual limits, it may not be adequate to focus only on the principal reactant since chemical variations (active decomposition materials) may be more difficult to remove.

1. FDA: GUIDE TO INSPECTIONS VALIDATION OF CLEANING PROCESSES

Note: This document is reference material for investigators and other FDA personnel. The document does not bind FDA, and does not confer any rights, privileges, benefits, or immunities for or on any person(s).

I. INTRODUCTION

Validation of cleaning procedures has generated considerable discussion since agency documents, including the Inspection Guide for Bulk Pharmaceutical Chemicals and the Biotechnology Inspection Guide, have briefly addressed this issue. These Agency documents clearly establish the expectation that cleaning procedures (processes) be validated.

This guide is designed to establish inspection consistency and uniformity by discussing practices that have been found acceptable (or unacceptable). Simultaneously, one must recognize that for cleaning validation, as with validation of other processes, there may be more than one way to validate a process. In 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.

This guide is intended to cover equipment cleaning for chemical residues only.

II. BACKGROUND

For FDA to require that equipment be clean prior to use is nothing new, the 1963 GMP Regulations (Part 133.4) stated as follows "Equipment *** shall be maintained in a clean and orderly manner ***." A very similar section on equipment cleaning (211.67) was included in the 1978 CGMP regulations. Of course, the main rationale for requiring clean equipment is to prevent contamination or adulteration of drug products. Historically, FDA investigators have looked for gross insanitation due to inadequate cleaning and maintenance of equipment and/or poor dust control systems. Also, historically speaking, FDA was more concerned about the contamination of nonpenicillin drug products with penicillins or the cross-contamination of drug products with potent steroids or hormones. A number of products have been recalled over the past decade due to actual or potential penicillin cross-contamination.

One event which increased FDA awareness of the potential for cross contamination due to inadequate procedures was the 1988 recall of a finished drug product, Cholestyramine Resin USP. The bulk pharmaceutical chemical used to produce the product had become contaminated with low levels of intermediates and degradants from the production of agricultural pesticides. The cross-contamination in that case is believed to have been due to the reuse of recovered solvents. The recovered solvents had been contaminated because of a lack of control over the reuse of solvent drums. Drums that had been used to store recovered solvents from a pesticide production process were later used to store recovered solvents used for the resin manufacturing process. The firm did not have adequate controls over these solvent drums, did not do adequate testing of drummed solvents, and did not have validated cleaning procedures for the drums.

Some shipments of this pesticide contaminated bulk pharmaceutical were supplied to a second facility at a different location for finishing. This resulted in the contamination of the bags used in that facility's fluid bed dryers with pesticide contamination. This in turn led to cross contamination of lots produced at that site, a site where no pesticides were normally produced.

FDA instituted an import alert in 1992 on a foreign bulk pharmaceutical manufacturer which manufactured potent steroid products as well as non-steroidal products using common equipment. This firm was a multi-use bulk pharmaceutical facility. FDA considered the potential for cross-contamination to be significant and to pose a serious health risk to the public. The firm had only recently started a cleaning validation program at the time of the inspection and it was considered inadequate by FDA. One of the reasons it was considered inadequate was that the firm was only looking for evidence of the absence of the previous compound. The firm had evidence, from TLC tests on the rinse water, of the presence of residues of reaction byproducts and degradants from the previous process.

III. GENERAL REQUIREMENTS

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.

FDA expects firms to have written general procedures on how cleaning processes will be validated.

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.

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.

FDA expects firms to conduct the validation studies in accordance with the protocols and to document the results of studies.

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."

IV. EVALUATION OF CLEANING VALIDATION

The first step is to focus on the objective of the validation process, and we have seen that some companies have failed to develop such objectives. It is not unusual to see manufacturers use extensive sampling and testing programs following the cleaning process without ever really evaluating the effectiveness of the steps used to clean the equipment. Several questions need to be addressed when evaluating the cleaning process. For example, at what point does a piece of equipment or system become clean? Does it have to be scrubbed by hand? What is accomplished by hand scrubbing rather than just a solvent wash? How variable are manual cleaning processes from batch to batch and product to product? The answers to these questions are obviously important to the inspection and evaluation of the cleaning process since one must determine the overall effectiveness of the process. Answers to these questions may also identify steps that can be eliminated for more effective measures and result in resource savings for the company.

Determine the number of cleaning processes for each piece of equipment. Ideally, a piece of equipment or system will have one process for cleaning, however this will depend on the products being produced and whether the cleanup occurs between batches of the same product (as in a large campaign) or between batches of different products. When the cleaning process is used only between batches of the same product (or different lots of the same intermediate in a bulk process) the firm need only meet a criteria of, "visibly clean" for the equipment. Such between batch cleaning processes do not require validation.

1. Equipment Design

Examine the design of equipment, particularly in those large systems that may employ semi-automatic or fully automatic clean-in-place (CIP) systems since they represent significant concern. For example, sanitary type piping without ball valves should be used. When such nonsanitary ball valves are used, as is common in the bulk drug industry, the cleaning process is more difficult.

When such systems are identified, it is important that operators performing cleaning operations be aware of problems and have special training in cleaning these systems and valves. Determine whether the cleaning operators have knowledge of these systems and the level of training and experience in cleaning these systems. Also check the written and validated cleaning process to determine if these systems have been properly identified and validated.

In larger systems, such as those employing long transfer lines or piping, check the flow charts and piping diagrams for the identification of valves and written cleaning procedures. Piping and valves should be tagged and easily identifiable by the operator performing the cleaning function. Sometimes, inadequately identified valves, both on prints and physically, have led to incorrect cleaning practices.

Always check for the presence of an often critical element in the documentation of the cleaning processes; identifying and controlling the length of time between the end of processing and each cleaning step. This is especially important for topicals, suspensions, and bulk drug operations. In such operations, the drying of residues will directly affect the efficiency of a cleaning process.

Whether or not CIP systems are used for cleaning of processing equipment, microbiological aspects of equipment cleaning should be considered. This consists largely of preventive measures rather than removal of contamination once it has occurred. There should be some evidence that routine cleaning and storage of equipment does not allow microbial proliferation. For example, equipment should be dried before storage, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations.

Subsequent to the cleaning process, equipment may be subjected to sterilization or sanitization procedures where such equipment is used for sterile processing, or for nonsterile processing where the products may support microbial growth. While such sterilization or sanitization procedures are beyond the scope of this guide, it is important to note that control of the bioburden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility. This is also particularly important from the standpoint of the control of pyrogens in sterile processing since equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.

2. Cleaning Process Written

Procedure and Documentation

Examine the detail and specificity of the procedure for the (cleaning) process being validated, and the amount of documentation required. We have seen general SOPs, while others use a batch record or log sheet system that requires some type of specific documentation for performing each step. Depending upon the complexity of the system and cleaning process and the ability and training of operators, the amount of documentation necessary for executing various cleaning steps or procedures will vary.

When more complex cleaning procedures are required, it is important to document the critical cleaning steps (for example certain bulk drug synthesis processes). In this regard, specific documentation on the equipment itself which includes information about who cleaned it and when is valuable. However, for relatively simple cleaning operations, the mere documentation that the overall cleaning process was performed might be sufficient.

Other factors such as history of cleaning, residue levels found after cleaning, and variability of test results may also dictate the amount of documentation required. For example, when variable residue levels are detected following cleaning, particularly for a process that is believed to be acceptable, one must establish the effectiveness of the process and operator performance. Appropriate evaluations must be made and when operator performance is deemed a problem, more extensive documentation (guidance) and training may be required.

3. Analytical Methods

Determine the specificity and sensitivity of the analytical method used to detect residuals or contaminants. With advances in analytical technology, residues from the manufacturing and cleaning processes can be detected at very low levels. 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 levels of contaminant greater than the sensitivity or detection limit of the analytical method are not present in the sample. 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, i.e. 50% recovery, 90%, etc. This is necessary before any conclusions can be made based on the sample results. A negative test may also be the result of poor sampling technique (see below).

4. Sampling

There are two general types of sampling that have been found acceptable. The most desirable is the direct method of sampling the surface of the equipment. Another method is the use of rinse solutions.

a. Direct Surface Sampling - Determine the type of sampling material used and its impact on the test data since the sampling material may interfere with the test. For example, the adhesive used in swabs has been found to interfere with the analysis of samples. Therefore, early in the validation program, it is important to assure that the sampling medium and solvent (used for extraction from the medium) are satisfactory and can be readily used.

Advantages of direct sampling are that areas hardest to clean and which are reasonably accessible can be evaluated, leading to establishing a level of contamination or residue per given surface area. Additionally, residues that are "dried out" or are insoluble can be sampled by physical removal.

b. Rinse Samples - Two advantages of using rinse samples are that a larger surface area may be sampled, and inaccessible systems or ones that cannot be routinely disassembled can be sampled and evaluated.

A disadvantage of rinse samples is that the residue or contaminant may not be soluble or may be physically occluded in the equipment. An analogy that can be used is the "dirty pot." In the evaluation of cleaning of a dirty pot, particularly with dried out residue, one does not look at the rinse water to see that it is clean; one looks at the pot.

Check to see that a direct measurement of the residue or contaminant has been made for the rinse water when it is used to validate the cleaning process. For example, it is not acceptable to simply test rinse water for water quality (does it meet the compendia tests) rather than test it for potential contaminants.

c. Routine Production In-Process Control

Monitoring - Indirect testing, such as conductivity testing, may be of some value for routine monitoring once a cleaning process has been validated. This would be particularly true for the bulk drug substance manufacturer where reactors and centrifuges and piping between such large equipment can be sampled only using rinse solution samples. Any indirect test method must have been shown to correlate with the condition of the equipment. During validation, the firm should document that testing the uncleaned equipment gives a not acceptable result for the indirect test.

V. ESTABLISHMENT OF LIMITS

FDA does not intend to set acceptance specifications or methods for determining whether a cleaning process is validated. It is impractical for FDA to do so due to the wide variation in equipment and products used throughout the bulk and finished dosage form industries. The firm's rationale for the residue limits established should be logical based on the manufacturer's knowledge of the materials involved and be practical, achievable, and verifiable. It is important to define the sensitivity of the analytical methods in order to set reasonable limits. Some limits that have been mentioned by industry representatives in the literature or in presentations include analytical detection levels such as 10 PPM, biological activity levels such as 1/1000 of the normal therapeutic dose, and organoleptic levels such as no visible residue.

Check the manner in which limits are established. Unlike finished pharmaceuticals where the chemical identity of residuals are known (i.e., from actives, inactives, detergents) bulk processes may have partial reactants and unwanted by-products which may never have been chemically identified. In establishing residual limits, it may not be adequate to focus only on the principal reactant since other chemical variations may be more difficult to remove. There are circumstances where TLC screening, in addition to chemical analyses, may be needed. In a bulk process, particularly for very potent chemicals such as some steroids, the issue of by-products needs to be considered if equipment is not dedicated. The objective of the inspection is to ensure that the basis for any limits is scientifically justifiable.

VI. OTHER ISSUES

a. Placebo Product

In order to evaluate and validate cleaning processes some manufacturers have processed a placebo batch in the equipment under essentially the same operating parameters used for processing product. A sample of the placebo batch is then tested for residual contamination. However, we have documented several significant issues that need to be addressed when using placebo product to validate cleaning processes.

One cannot assure that the contaminate will be uniformly distributed throughout the system. For example, if the discharge valve or chute of a blender are contaminated, the contaminant would probably not be uniformly dispersed in the placebo; it would most likely be concentrated in the initial discharge portion of the batch. Additionally, if the contaminant or residue is of a larger particle size, it may not be uniformly dispersed in the placebo.

Some firms have made the assumption that a residual contaminant would be worn off the equipment surface uniformly; this is also an invalid conclusion. Finally, the analytical power may be greatly reduced by dilution of the contaminate. Because of such problems, rinse and/or swab samples should be used in conjunction with the placebo method.

b. Detergent

If a detergent or soap is used for cleaning, determine and consider the difficulty that may arise when attempting to test for residues. A common problem associated with detergent use is its composition. Many detergent suppliers will not provide specific composition, which makes it difficult for the user to evaluate residues. As with product residues, it is important and it is expected that the manufacturer evaluate the efficiency of the cleaning process for the removal of residues. However, unlike product residues, it is expected that no (or for ultra sensitive analytical test methods - very low) detergent levels remain after cleaning. Detergents are not part of the manufacturing process and are only added to facilitate cleaning during the cleaning process. Thus, they should be easily removable. Otherwise, a different detergent should be selected.

c. Test Until Clean

Examine and evaluate the level of testing and the retest results since testing until clean is a concept utilized by some manufacturers. They test, resample, and retest equipment or systems until an "acceptable" residue level is attained. For the system or equipment with a validated cleaning process, this practice of resampling should not be utilized and is acceptable only in rare cases. Constant retesting and resampling can show that the cleaning process is not validated since these retests actually document the presence of unacceptable residue and contaminants from an ineffective cleaning process.

VII. REFERENCES

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- 7) McCormick, P.Y. and Cullen, L.F., in Pharmaceutical Process Validation, 2nd Ed., edited by I.R. Berry and R.A. Nash, 319-349 (1993)

3. EU-GMP-Guideline Annex 15 Qualification and validation (excerpt)

Cleaning Validation

36. Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carry over of product residues, cleaning agents and microbial contamination should be logically based on the materials involved. The limits should be achievable and verifiable.

37. Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant.

38. Normally only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to noncontact parts. The intervals between use and cleaning as well as cleaning and reuse should be validated. Cleaning intervals and methods should be determined.

39. For cleaning procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilising a "worst case" approach can be carried out which takes account of the critical issues.

40. Typically three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.

41. "Test until clean". is not considered an appropriate alternative to cleaning validation.

42. Products which simulate the physicochemical properties of the substances to be removed may exceptionally be used instead of the substances themselves, where such substances are either toxic or hazardous.