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Editor

SAMPLING FOR CLEANING VALIDATION — ANALYTICAL CONSIDERATIONS

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INTRODUCTION — WHY VALIDATE CLEANING?

Greater emphasis has been placed on the development of validated and robust cleaning protocols in recent years due to concerns over the safety of the drug supply. Growth in outsourcing and off-shoring of pharmaceutical manufacturing has only heightened US Food and Drug Administration (FDA) concern over cleaning processes. Inadequate documentation, training, and validation of cleaning processes rank high among the most often cited problems in FDA Form 483 observations and warning letters (McCormick, 2005).

FDA issued the *Guide to Inspections — Validation of Cleaning Process* in 1993. Since that time, the protocols surrounding cleaning processes in pharmaceutical manufacturing environments and sampling and filling suites have received increased attention (Carlson, 2010; Pluta and Sharnez, 2010). The primary regulatory concern driving the need for cleaning validation is contamination of the desired drug substance or drug product. Contamination may be either the same or other Active Pharmaceutical Ingredients (API) from previous batch runs or residual cleaning agent.

Cross-contamination with extraneous residues of any kind presents a safety risk to patients consuming the drug product. It threatens to alter the strength, chemical identity, purity, and integrity of the drug substance or product. Contaminants may elicit their own pharmacologic effect. The equipment and work environments involved in drug manufacturing processes must

be cleaned according to defined and proven procedures at regular intervals to prevent the possibility of cross-contamination. These cleaning processes must be validated in order to provide assurance that they do in fact serve their purpose — to clean the surfaces to a level that avoids the possibility of cross-contamination. This activity also has the beneficial effect of prolonging the useful life of the equipment.

The importance of sampling

Proving that equipment surfaces are sufficiently clean cannot be accomplished without acceptable sampling and testing. Correct sampling with attention to detail is critical in cleaning validation. Testing to determine accurate levels of product and process residues will be meaningless without correct sampling. The importance of sampling methods and techniques are often overlooked — both in their technical aspects as well as actual performance by personnel. This chapter will address the following aspects of sampling with emphasis on swab sampling:

- sampling methods — a general overview of swab sampling and rinse sampling
- swab sampling — including components and properties of the swab and proper swabbing technique
- training for swab sampling — personnel who perform swab sampling must be knowledgeable as well as having manual dexterity to assure accurate results
- sampling and analytical methods, including Total Organic Carbon (TOC) and High Performance Liquid Chromatography (HPLC)

Case studies describing several problem situations with swab sampling are also discussed.

SAMPLING METHODS

Cleaning is performed by a variety of methods to remove residues from the previous manufactured batch in a typical pharmaceutical manufacturing environment. For example, cleaning may utilize water alone, water with commodity chemicals (e.g., sodium hydroxide), water with proprietary cleaning agents, solvents including ethanol, hydroalcoholic solutions (70% isopropyl alcohol (IPA)) or organic solvents, and/or other chemicals, detergents, and disinfectants. After cleaning, the areas thus cleaned must be sampled adequately and appropriately in order to confirm that the equipment is suitably clean. Cleanliness means that the remaining product and process residues are below acceptable levels and the equipment is visually clean. The level of residual cleaning agent must also be less than calculated acceptable levels.

Swab and rinse sampling

Swabbing and rinsing are the two most common techniques used for sampling of cleaned surfaces (FDA, 1993). Swabbing is a direct surface sampling method, while rinsing is an indirect method. In practice, physical access to surfaces and parts of equipment to be cleaned tends to drive the choice of sampling method. For example, swabbing would work particularly

well in more restricted work areas such as isolators, biological safety cabinets (BSC), restricted access barrier systems (RABS), large work surfaces, and accessible corners of equipment — all places that are within three feet of an opening for sampling accessibility. Rinsing is more suitable for pipes, longer tubes and large tanks with connecting valves — places that are not easily reached. The use of swabs is critical in determining the contamination level found around imperfections in production equipment, such as rough surfaces, weld points, possible pinholes, or in places that general rinsing will not easily contact. In general, a combination of both swab and rinse sampling is most desirable in order to accomplish a most comprehensive evaluation of surfaces that were cleaned.

While the FDA guidance indicates a preference for the more direct swabbing method, more recent communication from the International Conference on Harmonization (ICH) ICH Q7A (ICH, 2001) states that sampling methods need to be comprehensive enough to quantify both soluble and insoluble residues that are left behind on the surfaces after cleaning. The exact protocols prescribed will necessarily vary depending on the nature of the products, residues and surfaces. These protocols must be tailored to the needs of each environment.

Developing a cleaning validation standard operating procedure (SOP) or master cleaning procedure requires that the actual cleaning protocol is defined in conjunction with the cleaning validation protocol. The cleaning process describes how to remove the most difficult to remove substances from the equipment, i.e., the process of cleaning. The cleaning validation protocol describes how to best sample and measure their presence and levels on the equipment surfaces, and to the level (acceptance criteria) required for equipment to be considered clean.

SWAB SAMPLING

Swab sampling directly measures surface residues and is a favored method of sampling. Critical aspects of swab sampling are the selection of the swab and the technique employed in the use of the swab. Personnel training regarding technical aspects of swabs and actual sampling performance are important aspects of swab training.

Selection of the swab

The swab used must offer high absorbency of residues, ultra-low particulates and fibers, and minimal extractable interferences. Polyester swabs that are specially processed to meet the stringent requirements associated with cleaning validation protocols are often the best choice (Miscioscio, 1997). The intrinsic nature of polyester material in combination with the special processing and cleaning methods for cleaning validation can provide the right balance of desirable functional and analytical characteristics that other materials such as cotton, nylon, rayon or blends thereof cannot meet. The swab material cannot be so sorptive that it may not release the analyte for sufficient recovery, nor can it be so minimally sorptive that it does not pick up sufficient residue off the surface. Other factors that should be considered are the non-volatile residue (NVR) and ionic burden of the swab. Such contaminants can become a problematic source of interference in the recovery assay especially in HPLC methods of analysis. The manufacturing process involved in making the swabs and their raw materials should be under automated statistical process control (SPC) to ensure the highest level of consistency in the key

functional attributes such as sorption capacity and particulate contamination levels. The quality of a cleanroom swab should be critically evaluated in the consistency of its testing results over a period of time (Kalelkar and Postlewaite, 2011).

Proper swabbing procedure

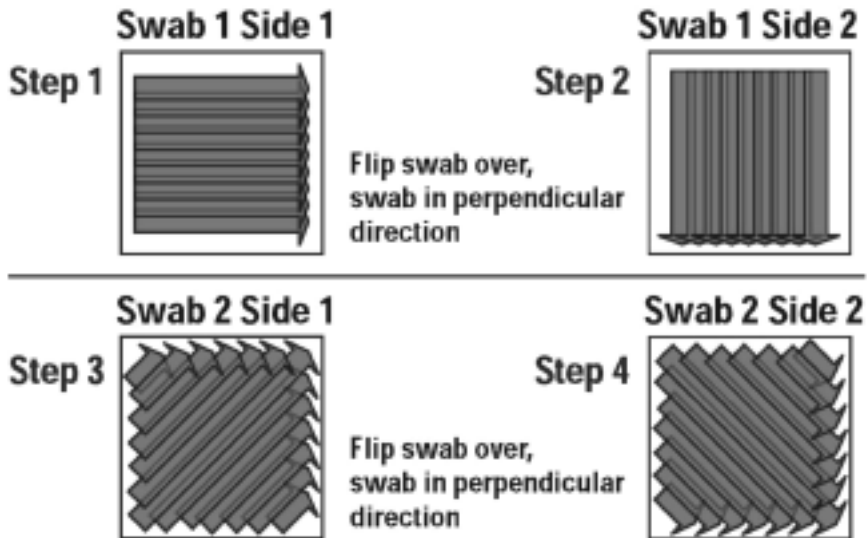
The swab to be used for sampling is typically pre-wetted with water or another appropriate solvent in order to remove residues from the surface to be sampled. Squeezing the sides of the swab against the inside of the vial upon pre-wetting prior to sampling removes excess solvent. This is important because excess solvent can itself serve as a source of residues leading to variable results. Excess solvents may leave extractable substances of interest on the surface which either reduces the percent recovery or indicates a false positive for a successful cleaning process. There is a direct physical interaction between the swab, the solvent, the surface, and the residues to be removed; therefore, the choice of swab is critical to the effectiveness of the sampling process. The chemical nature of the residues to be removed has a major impact on the procedure and analytical method of choice, since the residue can vary from the active therapeutic molecule (small molecules or biotechnology agents) to preservatives, impurities, degradants, reaction intermediates, and biotech growth medium components.

After sampling the surface, the swab is snapped at the pre-scored notches on the handle so that the head of the swab can be subsequently prepared for analysis. To break the handle cleanly, the notch should be aligned with the top edge of the vial. This minimizes the use of scissors in critically clean environments, such as aseptic suites, wherein the action itself could result in more particulate residues or contaminants. A suitable extraction solvent is used to release the residues from the swab head. Depending on the particular SOP in each area, this swab sample may need to be filtered and/or sonicated to extract the residues as completely as possible. Such otherwise innocuous steps in the sample preparation procedure can measurably impact the results of the detection assay used if they result in leaching from the various materials involved. Sample preparation procedures place a heavy premium on the intrinsic quality of the materials used in the swab head, filters, and other analytical consumables. The use of the highest quality of suitably engineered and pre-treated polyester swabs can provide assurance that any extraneous contamination observed in the subsequent assay does not originate from the swab. Under extreme sample preparation conditions, such as use of acids, temperature and sonication, certain monomers or oligomers of polyester have been observed in HPLC. Conditioning or pretreating the swabs using the solvent system, and other physical process steps such as sonication can serve to reduce the background contribution from the swab.

TRAINING FOR SWAB SAMPLING

Swab sampling is a critical activity. The physical and chemical nature of the swabbing method implies that significant levels of operator training be conducted prior to implementation of cleaning validation protocols. This training should serve to minimize the subjectivity that is inherent in such a manual sampling activity. The recommended directions and motions used in actual swabbing of an area as shown in Figure 19.1 should be detailed in the training to ensure the highest levels of consistency. This training must be documented. Training also must be

Figure 19.1 Recommended swab sampling procedure ensures complete residue pick-up from the defined surface area. An additional step of swabbing the perimeter of the sampling area may be included if necessary



Proper swabbing procedure

- Define region to be tested.
- Dampen swab with diluents.
- Swab with overlapping pattern. Flip swab and repeat, passing swab in perpendicular direction. Repeat procedure with second swab at 45° angles.
- Swab with entire head flat against surface.
- Snap swab head at the notch along narrow edge of swab handle. Allow swab head to fall into vial.
- Transfer for TOC or HPLC analysis.

conducted as often as needed so that the sampling procedure maintains its repeatability and reproducibility. Alternate swab sampling patterns may certainly be used if they help maximize percent recovery.

Training for swab sampling should include actual sampling of coupons of the surfaces to be sampled. These surfaces are more ideal in accessibility and physical characteristics (e.g., smoothness). Coupon materials must be as comparable as possible to actual manufacturing equipment. Training should also occur at the sites to be sampled. This training stage of training focuses on the location and the necessary techniques for each location (see chapter 23 in this volume for further discussion of this topic).

CASE STUDIES

Case studies 1 and 2 demonstrate the importance of knowledge and understanding the criticality of swab sampling technique in cleaning validation.

In case study #1, solvent evaporation during the swabbing process by a new sampling person resulted in false negative data, i.e., residue present was not recovered causing a low analytical value. When a different sampling person performed the same sampling procedure, residue levels for all samples significantly exceeded acceptance criteria, indicating inadequate cleaning.

In case study #2, an increased batch size for a liquid product required cleaning validation for a large volume manufacturing tank. Sampling was required from multiple locations on the tank. One sample location required use of an extension pole for sampling in the tank. Samples taken with the extension pole were the only acceptable samples in the tank. Sampling technique with the extension pole had never been practiced or evaluated. Personnel had never used the extension pole and were not experienced with swabbing technique using the extension pole. False negative data again resulted.

Case study #1: False negative cleaning data

Introduction

This case study describes cleaning validation for cleaning of residue from a small molecule tablet dosage form. The active ingredient in the tablet was a potent drug. The calculated acceptance criteria for residual active drug was approximately 0.5 µg/cm², or below the level that is able to be visually observed. Three lots were required for cleaning validation. The following are discussed:

- Background — a description of the cleaning validation event
- Investigation — interviews and actions conducted to investigate the event
- Discussion — key information, activities, and analysis
- Corrective and Preventative Actions (CAPA) — actions and improvements implemented in the cleaning process, sampling process for cleaning validation, and training of sampling personnel
- Cleaning validation of modified cleaning process — implementation of the new process

Background

A small molecule pharmaceutical manufacturing site was performing process validation and cleaning validation for a new tablet product. The new product was an extended release formulation of a currently marketed immediate release product. It contained a polymeric matrix. The matrix provided prolonged dissolution for extended release performance.

The first new product lot was manufactured and cleaning was completed. Equipment was visually clean. Swab sampling was done. Cleaning validation analytical test data indicated that no active drug was present in all swab samples. A second lot was manufactured. Cleaning was completed. Swab sampling was done. Cleaning validation analytical test data again indicated that no active drug was present in all swab samples. A third lot was manufactured. Cleaning was completed. Swab sampling was done. To everyone's surprise, cleaning validation analytical test data indicated high residue levels significantly above the required acceptance criteria — a clear failure of the cleaning process.

Investigation

The above results prompted investigation of several areas associated with the cleaning process. These included operations personnel who cleaned the equipment, Quality Assurance (QA) personnel who inspected the equipment, sampling personnel who swabbed the cleaned equipment, laboratory personnel who analyzed the problem samples, analytical Research and Development (R&D) personnel who developed the analytical method, and engineering personnel responsible for technical aspects of the cleaning procedure. There were many details that needed to be investigated and/or confirmed. Personnel from all groups were interviewed and interacted to address the above issues. Specific questions addressed included the following:

- Cleaning process performance — Did manufacturing personnel correctly perform the cleaning process? Who cleaned the equipment? Were personnel adequately trained?
- Sampling — Did sampling personnel correctly sample the recommended equipment surfaces? Were sampling personnel adequately trained?
- Residue samples — Was the integrity of residue samples adequately protected during transport to the lab? Were samples quickly transferred according to handling, storage, and temperature requirements?
- Analytical laboratory — Was the analytical method correctly performed? Who performed the analysis? Were laboratory personnel adequately trained?
- Analytical R&D — Was the analytical method correctly developed? Was the analytical method validated?
- Cleaning process — What was the basis for the cleaning process? Had the cleaning process been adequately tested by technical people?

Discussion

Interviews and discussion of the above questions did not clearly indicate an obvious cause for the problem. Manufacturing personnel confirmed that they performed cleaning as required by procedure. The mixing tank did not require human involvement in cleaning — all process steps were automated. All associated equipment that was manually cleaned was cleaned according to procedure. The manufacturing supervisor verified that procedures were followed and that

the equipment was visually clean. Quality unit personnel who inspected the equipment also verified that all equipment was visually clean. All inspections were conducted after the equipment was dry. Samples were transported quickly and according to procedure. Samples were also quickly stored in the laboratory upon receipt and under specified conditions. Laboratory personnel confirmed acceptable performance of analytical procedures. Analytical standards over a range of concentrations tested along with the actual cleaning validation samples yielded accurate results. Analytical R&D scientists confirmed acceptable performance of the validated test method.

Two areas with unanswered questions were identified for further investigation. These included the actual swab sampling of equipment surfaces and technical aspects of the cleaning process.

- *Swab sampling*
Swab sampling for the three lots was done by two different sampling technicians. The first two lots were sampled by a newly-trained person. Data for these lots indicated no residual soil. The third lot with failing data was sampled by an experienced technician. The sampling method required wetting of the swab with organic solvent to dissolve residue from the equipment surface. The new technician did all his sampling alone. The experienced technician performed sampling with a colleague to accomplish the sampling procedure in minimum time. She explained the necessity of the rapid sampling technique because evaporation of the sampling solvent must be minimized. The new technician was not aware of the time limitation in sampling. Although not conclusively proven, it was suspected that evaporation of solvent occurred causing residue to not be adequately recovered from the equipment surface. The analytical lab confirmed that if sufficient solvent was not present on the swab, residue recovery would be unsuccessful
- *Cleaning process*
Technical personnel had no previous experience with the cleaning method. The cleaning method had been established many years ago and never required technical evaluation. Manufacturing management decided to use the well-established cleaning method without involvement of technical personnel. Management's rationale was that since the API in the original product had been reliably cleaned for many years, there was no need to evaluate the cleaning process. Technical personnel had not been requested to evaluate the cleaning process used in the failed cleaning validation. In light of the cleaning failure, technical personnel recommended laboratory studies to evaluate available cleaning agents, cleaning process parameters, and related factors in a systematic way

Evaluation of the cleaning process indicated that the process parameters were insufficient to clean the new product. The polymeric matrix in the new product was much more difficult to clean than the original immediate release product. Technical personnel conducted studies to establish new cleaning process parameters suitable for the extended release product

CAPA

Two CAPA activities corrected the problems experienced in the original cleaning validation. These involved new training of swab sampling personnel and a modified cleaning process for the extended release product.

- *Swab sampling training*

Personnel who perform cleaning residue sampling using swabs wetted with volatile solvents were taught the importance of rapidly performing swab sampling. Many of the swab sampling technicians did not have a technical background and did not understand solvent volatility and the consequences for swab sampling. Studies confirmed that the new technician did not perform swab sampling quickly. When sampling was not performed quickly, solvent evaporated and residue was not able to be dissolved. Analytical results on evaporated swab samples indicated extremely low levels of residue which erroneously passed cleaning validation acceptance criteria — a false negative due to solvent evaporation.

Future training of swab sampling technicians included new test procedures to demonstrate rapid performance of sampling procedures. The previous qualification test did not utilize a volatile solvent and did not require rapid performance. The new qualification test required technicians to demonstrate rapid sampling in order to become a qualified sampling technician.

- *Modified cleaning process*

Technical personnel evaluated the cleaning process and determined that process parameters were not adequate to reliably clean process residues. The cleaning agent concentration was increased, the temperature was increased, and the cleaning time was increased in the new procedure. These parameters enhanced the cleaning process to more effectively clean the polymeric residue.

Cleaning validation of modified cleaning process

The new cleaning process was implemented. Three product lots were manufactured. Cleaning was performed. Worst-case locations on equipment were swab sampled by two-person teams of sampling personnel. All test results passed the acceptance criteria.

Summary

This case study demonstrated two critical errors in the cleaning program at a manufacturing site. Failure to initiate technical review of the cleaning process for a new product resulted in the use of an inadequate cleaning procedure — a serious error by site management. Thereafter, failure to properly sample equipment in cleaning validation nearly resulted in an erroneous conclusion that the cleaning process was acceptable. A relatively trivial error, i.e., loss of solvent in sampling, had a major effect on cleaning validation. The sampling technician did not understand the importance of working quickly to minimize solvent loss. This lack of understanding resulted in a false negative test result and an erroneous conclusion that the cleaning process was acceptable. Fortunately the error was discovered, the cleaning process

was evaluated, and a new cleaning process was developed. The new cleaning process was ultimately validated. The training program was modified to emphasize the importance of rapid performance especially when volatile solvents are involved.

Three important lessons may be learned from this case study:

- Inactive ingredients may have very significant effects on cleaning processes
- Sampling personnel must have good technical understanding of their work
- Training programs must anticipate problems and address these problems in their training programs

Case study #2: Cleaning validation sampling with an extension pole

This case study describes cleaning validation for cleaning of residue from a liquid suspension product. The batch size of a commercial product was increased requiring manufacturing in a large volume mixing tank. The following are discussed:

- Background — a description of the cleaning validation event including residue data
- Investigation — interviews and actions conducted to investigate the event
- Discussion — key information, activities, analysis, and problem solution

Background

A small molecule pharmaceutical manufacturing site was performing process validation and cleaning validation for an increased batch size of a liquid suspension product. The first increased batch product lot was manufactured. An automated Clean-in-Place (CIP) cleaning process was completed. The equipment was visually clean. Swab sampling was done at multiple locations in the mixing tank. Cleaning validation analytical test data demonstrated high residue levels at multiple locations. One particular location had no residue levels, indicating acceptable cleaning. Results indicated that the cleaning process was not adequate and needed to be modified. The acceptable test data from one location were troubling — why was one location acceptable when all other locations were failures?

The above results prompted investigation of several areas associated with the cleaning process. These included operations people responsible for the CIP cleaning process, QA people who inspected the equipment, sampling personnel who swabbed the cleaned equipment, and the laboratory personnel who analyzed the samples.

The great number of failed cleaning samples indicated that the cleaning process was not acceptable. Engineering personnel responsible for technical aspects of the cleaning procedure began work on modifying the cleaning process.

Analytical people verified the accuracy of test results. Sampling personnel were experienced and were adequately trained. Sampling and testing had been previously performed on smaller equipment without any problem. Why did one sampling location on the large equipment yield acceptable data when all other locations indicated cleaning failure?

Investigation

Sampling personnel who performed all swab and rinse sampling were interviewed. All sampling was conducted according to well-established procedures. One sampling procedure, however, required a new approach. The site safety engineer implemented new procedures in which personnel were not allowed to place their heads within the mixing tanks. This policy change required the use of an extension pole for cleaning validation sampling. The extension pole was a telescoping pole, enabling sampling 6–12 feet from the person holding the pole. Use of the pole eliminated the need for a person's head to be inside the manhole in the cover of the mixing tank. All cleaning samples obtained with the extension pole were acceptable.

Discussion

Cleaning sampling personnel who decided to use the extension pole had never used the pole in the past. There was no training on use of the pole. The site training function had not been informed of the new safety regulation. Their training program for cleaning validation sampling did not address use of the pole. Cleaning sampling personnel extended the pole to its maximum limit, and attempted to swab a 100 cm² area as required in the cleaning validation protocol, without any prior experience that this procedure would yield accurate and reliable results.

The use of the sampling pole for cleaning validation sampling did not provide reliable results. The pole could not be adequately controlled by the sampling person to swab in the designated area. Adequate pressure could not be exerted for swab sampling. Use of the sampling pole was not authorized by management or site QA.

The sampling problem was solved by further increasing the batch size of product lot. The new batch size filled the tank to a higher level. This enabled sampling to be accomplished by simply reaching through the manhole cover in the top of the tank. Sampling personnel did not need to use the extension pole to obtain required samples. Sampling personnel did not place their head within the tank manhole cover.

Summary

This case study demonstrated a lack of communication within the manufacturing site. In brief:

- The safety engineer implemented a new policy
- Management and QA were not aware of the policy or its ramifications
- Cleaning validation personnel attempted to comply with the policy, but in doing so implemented an inadequate procedure that yielded inaccurate validation data

The problem was ultimately solved by adjusting the manufacturing batch size so that use of the extension pole was not required.

Sampling personnel were instructed that they should not change their activities without proper training. The use of the extension pole was significantly different from sampling procedures for which they had been trained. Training programs must address worst case situations in their training. Personnel must not do things for which they have not been trained.

ANALYTICAL METHODS

The Residue Acceptable Limit (RAL) level concept was developed through a series of actions starting with the FDA suing Barr Laboratories in 1992 after a series of FDA Form 483s were issued to Barr between 1989 and 1992 (Walsh, 2011). In 1993, FDA won the lawsuit. One outcome of this lawsuit was that cleaning validation was now required. Because of this outcome, the Pharmaceutical Manufacturers Association conducted a survey of its members requesting how they were setting acceptable limits. The responses varied from company to company. Eli Lilly was concurrently undergoing differences of opinion with FDA over cleaning validation and the setting of acceptable carryover limits. In 1993, Fourman and Mullen (1993) proposed using a combination of limits for the carryover of product residues from one batch into another. These limits are:

- no more than 0.001 dose of any product will appear in the maximum daily dose of another product
- no more than 10 ppm of a product will appear in another product
- no quantity of residue will be visible on the equipment after cleaning procedures are performed

The Fourman and Mullen approach allowed pharmaceutical manufacturers to have a set of reasonable limits to reference. Pharmaceutical companies could modify these limits for products having increased toxicity. FDA requires that modifications to these limits are scientifically justifiable.

The purpose of swab sampling as part of a cleaning validation protocol is to be able to prove that the cleaning process served its purpose of minimizing residue cross-contamination. This is best measured in validation as a percent recovery of seeded residue on representative sample surfaces. The range of the developed analytical method must include the RAL level (Shifflet and Shapiro, 2002). The measurement of percent recovery is accomplished through an analytical test such as HPLC or TOC. TOC is often the method of choice for biologics drugs primarily since the development of specific HPLC methods for such molecules can be challenging, given the limitations of commonly-used detectors such as Ultraviolet (UV) and the size of the molecules (Garcia et al., 2010).

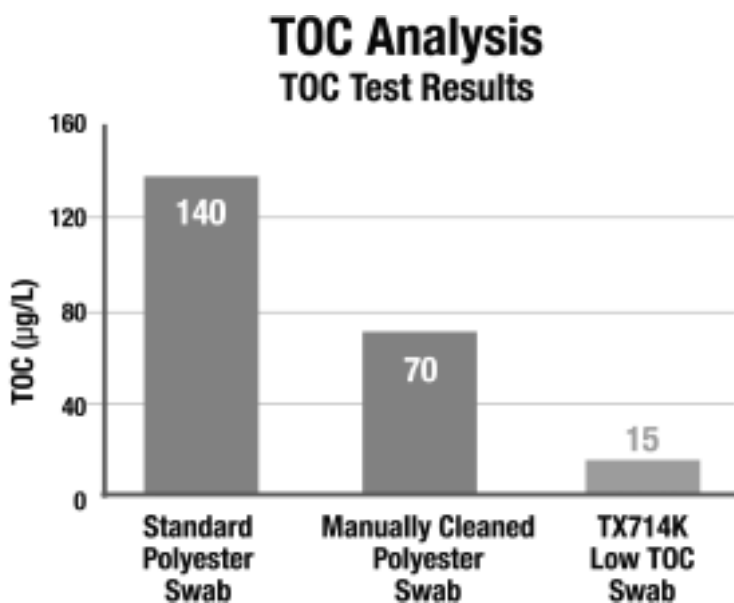
Both HPLC and TOC are highly sensitive methods that serve as assays for cleaning validation protocols. HPLC is a specific assay in that the peaks can be identified and assigned to specific residues, while TOC is a non-specific measure of overall carbon burden in a given

environment. Since these assays are both quantitative, typical analytical parameters such as accuracy, precision, linearity, detection and quantification limits must be evaluated as part of method development.

Total Organic Carbon

TOC is a conductometric assay that correlates with carbon concentration which provides an overall, non-specific estimate of carbon-containing residue burden left behind on the surface from a previous batch run. The sample TOC level is determined by the difference between the total carbonate level after oxidation of the sample and the background carbonate level before oxidation. TOC measurements are highly sensitive and typically reported at the part per billion (ppb) or microgram/L ($\mu\text{g/L}$) level. As such, great care must be taken during the swab sampling and sample preparation to minimize external sources of organic carbon contamination. TOC swabs are specially cleaned and processed in order to ensure extremely low levels (at least <50 ppb) of background in the TOC assay as indicated in Figure 19.2. This ensures minimum background TOC readout and provides greater accuracy to the recovery results. TOC swabs are sometimes offered as part of integrated TOC analysis kits. Even the vials used in TOC testing are specially treated to ensure <10 ppb background.

Figure 19.2 Comparison of background TOC levels of specially engineered low TOC swabs for cleaning validation that minimize background interference in TOC assays



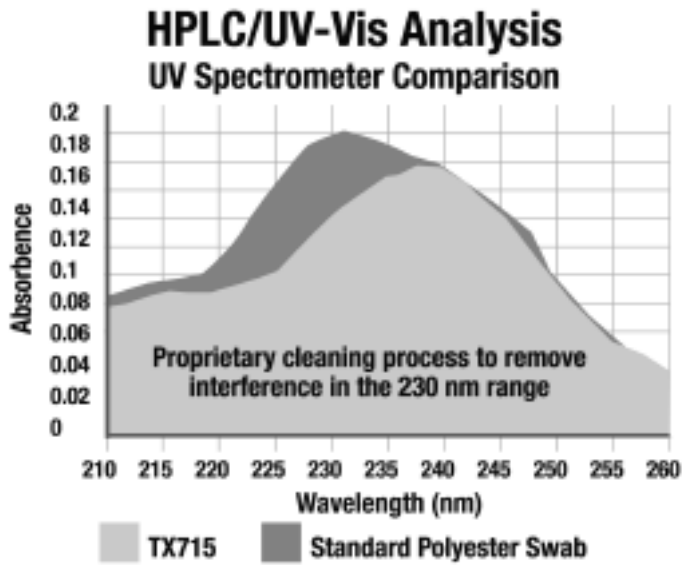
Sometimes the percent recovery of a particular residue is enhanced by changing the pH of the high quality sampling water, e.g., water for injection. Low pH conditions (acidic) formed by the use of a mineral acid, e.g., nitric or phosphoric acid, have little effect on measured TOC values. Organic acids will add to the measured TOC level. However, elevated pH conditions (basic) formed through the use of mineral bases, e.g., sodium or potassium hydroxide, will affect the measured sample TOC level through an elevated background TOC level. This occurs due to the absorption of carbon dioxide from the air, and the formation of the carbonate ion in solution. Organic bases will add to the TOC background. Purging the sample with a carbon dioxide free gas may be warranted to reduce the elevated carbonate ion background. A high background carbonate level can “wash out” a low TOC level due to the difference of large numbers and their associated errors.

High performance liquid chromatography

HPLC systems commonly carry detectors such as UV-Vis or mass spectrometry (MS) for specificity and identification. It is important to realize early in the method development process for cleaning validation that percent recovery will be directly influenced by the interaction of the assay detector with each of the variables involved in the protocol. Conducting a pre-study on the influence of the various factors involved in the cleaning is necessary in order to ensure that their effect on the final percent recovery measurement is well understood. Deconvoluting an aberrant percent recovery result “after-the-fact” for a method that may have been in use over a long period of time is cumbersome. Such investigations of an out-of-spec result, while necessary at the time, can sometimes consume enormous resources, while being little more than looking for a needle in a haystack. Cleaning validation is a complex activity requiring a careful choice of sampling procedure and analytical method. The best approach from a risk management viewpoint is to always use only the highest quality materials for swabs, filters, and solvents in cleaning validation protocols. This practice will minimize their potential as sources of aberrant results.

While HPLC is a very commonly used chromatographic technique in the pharmaceutical industry, the complexity, trace level sensitivity, and criticality of the cleaning validation protocol to drug safety merits special attention to the results from HPLC analysis. It is important to avoid using materials that might serve as sources of contamination through interference with the UV or other detector. As indicated in Figure 21.3, swabs engineered for analysis using an HPLC method are specially processed to move the maximum of the UV absorbance from the 190–235 nm range typical of most common residues. In the event that such interference in the assay is unavoidable, understanding and quantifying the interference demonstrates to an FDA or internal investigation that the cleaning validation protocol follows good scientific rationale. Attempts should be made to identify any additional peaks that appear in the chromatograms of swab-extracted samples besides those arising from the expected residues. Such interferences may arise either from out of control changes in the production, cleaning process, or materials, and may also arise from any of the various consumables and fixtures that affect the assay materials.

Figure 21.3 Cleaning validation swabs for HPLC such as the TX715 are specifically engineered to minimize interference in the 190-235 nm UV spectral range



Residue recovery studies

A key activity in the development of the analytical method is the recovery study. In brief, this activity comprises the following:

1. A known amount of residue is applied to a defined area of representative product–contact materials. The product–contact materials should be identical or equivalent to actual equipment materials to be swabbed in cleaning validation
2. The defined area is carefully swabbed using the prescribed solvent and technique described above to transfer residue from the surface to the swab
3. The swab is extracted with designated solvent to transfer residue from the swab for eventual analytical quantitative analysis
4. The percent recovery is calculated as follows:

$$\% \text{ Recovered} = \frac{\text{Amount recovered by swabbing} \times 100\%}{\text{Known amount available for swab}}$$

5. The percent recovered value may be used in future calculations of analytical results

Residue recovery studies in part determine the efficiency of the residue transfer process. This process comprises transfer of residue to swab (above Step 2), followed by transfer of residue from swab to analytical solvent (above Step 3).

Step 2 above is a critical step in which the technique of sampling person quantitatively transfers residue from the surface to the swab. This step is highly dependent on the adsorptive properties of the swab, as well as the manual skills of the sampling person.

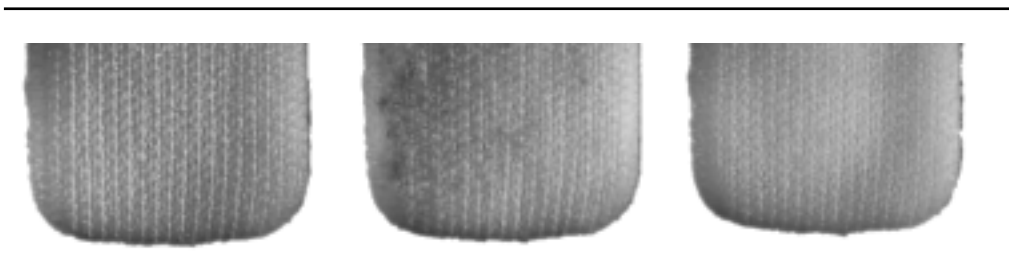
Step 3 above is similarly critical in that residue is transferred from the swab to solvent in the analytical method. This step depends on the desorptive properties of the swab, i.e., release of residue to the solvent.

Residue affinity for product–contact surface

The method development and validation steps are often conducted on test coupons or pre-defined sized templates to serve as examples of the equipment or surfaces to be cleaned. All product–contact materials on equipment are not alike in recovery performance. Stainless steel surfaces differ in degree of polish or surface roughness. Polymeric surfaces may have different porosities. The same residue may be highly recovered (e.g., >90%) from stainless steel but poorly recovered (<20%) from plastic. The choice of filter and solvent used in sample preparation is also critical, since they can have an impact on the recovery, influence extractables, and efficiency of filtration. Yang et al. (2005) have reported a systematic study of a variety of solvent conditions and pH and their impact on the percent recovery and efficiency of filtration. While it may be intuitive to choose the solvent conditions used in the subsequent analysis (e.g., HPLC) as the extractable solvent, this may sometimes compromise the filtering efficiency and the percent recovery.

Figure 21.4 demonstrates the appearance of a typical swab before swabbing, after swabbing, and after extraction.

Figure 21.4 Residue recovery studies — swab appearance



SUMMARY

Cleaning validation is an essential step in the critical cleaning of pharmaceutical manufacturing environments. Swabbing is the preferred method of sampling such surfaces in the process of cleaning validation. The sampling and analysis methods have a direct and measurable impact on the percent recovery results from either HPLC or TOC assays. It is critical to ensure that the swab, filters, and associated materials used during the process are of the highest possible quality, do not contribute even trace levels of impurities that can interfere with the results, and do not affect the percent recovery through absorption.

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