

Why The Swab Matters in Cleaning Validation

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WHAT IS CLEANING VALIDATION?

The U.S. Food and Drug Administration (FDA) issued its *Guide to Inspections—Validation of Cleaning Process*¹ in 1993. Since that time, the protocols surrounding cleaning processes in pharmaceutical manufacturing environments and sampling and filling suites have received increased attention.^{2,3} The primary regulatory concern driving the need for cleaning validation is cross-contamination of the desired drug substance either by other active pharmaceutical ingredients (API) from previous batch runs or by residues from the cleaning agents used.

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, and integrity of the drug substance and formulation. Therefore, the equipment and work environments involved in drug manufacturing processes must be cleaned at regular, prescribed intervals to prevent the possibility of such cross-contamination. These cleaning protocols 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.

In recent years, increased emphasis has been placed on the development of validated and robust cleaning protocols given the concerns over the safety of our drug supply. Growth in the levels of outsourcing and off-shoring of pharmaceutical manufacturing has heightened the FDA's concern over cleaning processes. Inadequate documentation, training, and validation of cleaning processes rank high among the four most often cited problems in Form 483 and warning letters that have been issued by the U.S. FDA.⁴

WHY SWABBING?

In a typical pharmaceutical manufacturing environment, cleaning might be performed by using 70% isopropyl alcohol (IPA) and/or other chemicals, detergents, and sanitizing agents in order to remove residues from the previous batch run. The areas thus cleaned must now be sampled adequately and appropriately in order to validate the cleaning protocol.

Swabbing and rinsing are the two most common techniques used for sampling of such cleaned surfaces. 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, hoods, and accessible corners of equipment, while rinsing would work best in pipes and longer tubes. In general, a combination of both is most desirable in order to accomplish the most comprehensive coverage of surfaces to be cleaned.

While the FDA guidance indicates a preference for the more direct swabbing method, more recent communication from the International Conference on Harmonisation (ICH) ICH Q7A⁵ 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.

THE SWABBING PROCEDURE – CONSIDERATIONS

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. 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. There is a direct, physical interaction between

the swab, the solvent, and the residues to be removed; therefore, the choice of swab is critical to the effectiveness of the sampling process. The swab used must offer ultra-low particulates and fibers, high absorbency, and minimal extractable interferences. Polyester swabs are specially processed to meet the stringent requirements associated with cleaning validation protocols. The physical nature of the swabbing process 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 to such sampling activity. The recommended directions and motions used in actual swabbing of an area as shown in Figure 1 should be detailed in the training to ensure the highest levels of consistency. Alternate swab sampling patterns may certainly be used if they would help maximize percent recovery.

A suitable extractable 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. These sample prep procedures place a heavy premium on the intrinsic quality of the materials used in the swab head and the filters. The use of anything less than the highest quality of suitably pre-treated polyester swabs can prove to be a source of extraneous contamination in the subsequent assay.

The method development and validation steps are often conducted on test coupons to serve as examples of the equipment or surfaces to be cleaned. 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.* have reported a systematic study of a variety of solvent conditions and pH and their impact on the percent recovery and efficiency of filtration.⁶ 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.

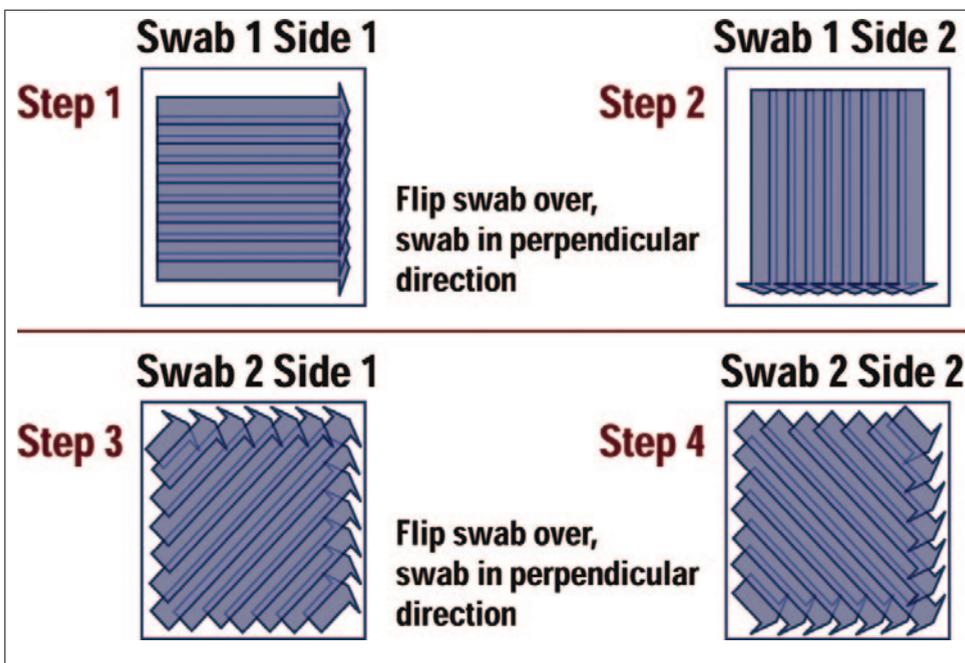


Figure 1: Recommended directions and motions of swabbing.

ANALYSIS OF RESIDUES—ANALYTICAL CONSIDERATIONS

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. That purpose (cleaning the surfaces to avoid any cross-contamination) is best measured in the validation step as a percent recovery of seeded residue. Such a measurement provides an estimate of Residue Acceptable Limit (RAL). The measurement of percent recovery is accomplished through an analytical test, typically either HPLC (High Performance Liquid Chromatography) or TOC (Total Organic Carbon).

HPLC-UV systems commonly carry additional detectors such as 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 particular assay detector with each of the variables involved in the protocol. It is best to conduct a pre-study of the influence of the various factors involved in the cleaning in order to ensure that their effect on the final percent recovery measurement is well understood. It is typically very cumbersome to deconvolute an aberrant percent recovery result 'after-the-fact' for a method that may have been in use over a long period of time. Cleaning Validation is a complex activity requiring a careful choice of sampling procedure and analytical method. It is therefore highly recommended to always use only the highest quality materials for swabs, filters, and solvents in cleaning validation protocols in order to assure that they cannot serve as sources of aberrant results, if and when those results do occur.

Both HPLC and TOC are highly sensitive methods that serve as assays for cleaning validation protocols. HPLC by its very nature is a specific assay in that it can identify peaks and assign them to specific residues, while TOC is a classically 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 quantitation limits must be evaluated as part of method development.

While HPLC is a very commonly used tool 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 spectrum, or the detector of choice. In the event that such interference in the assay is unavoidable, understanding and perhaps even quantitating the interference so that the cleaning validation protocol is appropriately "science-based" would pass muster under an investigation. 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.

TOC (Total Organic Carbon) is a conductometric assay that correlates with carbon concentration, which provides an overall, non-specific estimate of residue burden left behind on the surface from a previous batch run. TOC measurements are highly sensitive and typically reported at the part per billion (ppb, or µg/L) level. As such, great care must be taken during the swab sampling and sample preparation to minimize external sources of organic carbon contamination.

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 and do not contribute even trace levels of impurities that can interfere with the results.

References

1. Guide to Inspections of Validation of Cleaning Processes, FDA Office of Regulatory Affairs, Rockville, MD, 1993.
2. Carlson, J. "Is swabbing a regulatory requirement?" *Journal of GXP Compliance*, (14):1, 2010.
3. Pluta, P. and Sharnez, R., "Avoiding Pitfalls of Cleaning Validation." *Journal of GXP Compliance*, (14):3, 2010.
4. McCormick, D. "Poor OOS Review Leads Causes of FDA Citations." *Pharma Technol.* Oct 2005
5. ICH Guidance for Industry, Q7A; Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Aug 2001.
6. Yang, P, Burson, K., Feder, D. and Macdonald, F. "Method Development of Swab Sampling for Cleaning Validation." *Pharmaceutical Technology*, Jan 2005.

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