POST-DISCOVERY DEVELOPMENT VALIDATION

# PFQ

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# How to Improve Cleaning Processes

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# How to Improve Cleaning Processes

## Some key methods for a more efficient cleaning validation process

***Editor's Note:*** *This article is the first in a two-part series about cleaning validation methodology. Part two, which will focus on validation challenges and practices, will appear in our July/August issue.*

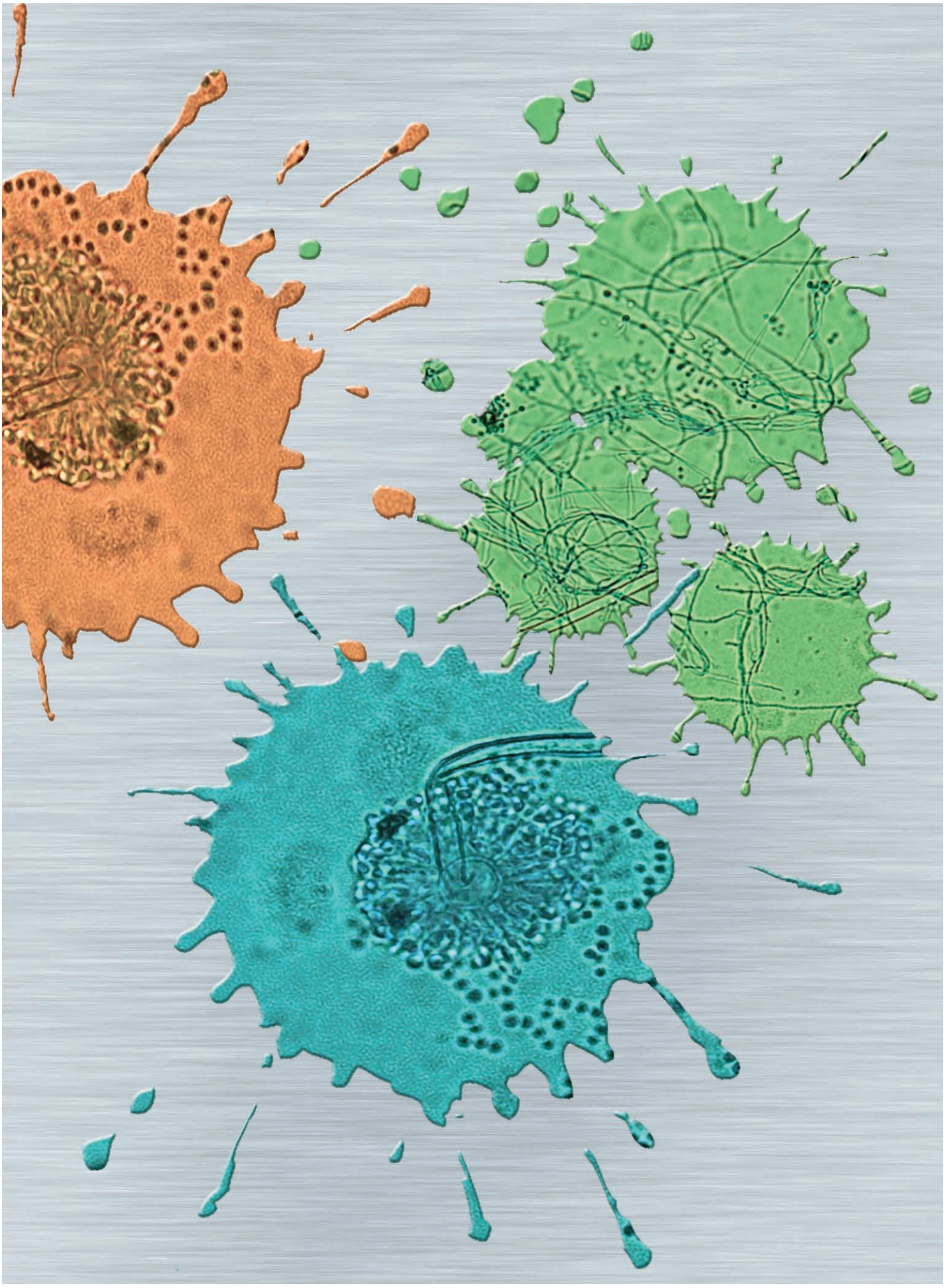
Pharmaceutical manufacturing equipment must be properly cleaned to ensure the removal of product residue, cleaning chemical residue, and microbes prior to manufacturing. Because cleaning methods are developed and validated to prevent the risk of producing contaminated products by confirming that the cleaning process is sufficient, it's important to establish method limits and select the proper cleaning techniques and detection methods.

### Step One: Set Limits

One of the first steps in the development of an effective cleaning validation method is the determination of the necessary, non-regulated limits. Often, this can be the most daunting step for pharmaceutical manufacturing facilities throughout the cleaning validation process simply because of how specific each limit must be for every product produced. Pharmaceutical companies have several details to consider when setting their limits.

The regulation agencies approach cleaning validation limits with the idea that because of the vast variety of materials and equipment used to manufacture products throughout the industry, it would be impractical to try to set general limits.[1] Most of them give examples of where limits should be set based on general criteria, however.

The Food and Drug Administration (FDA) Guide to Inspections Validation of Cleaning Processes, for example, states, "The firm's rationale for the residue limits established should be logi-



cal based on the manufacturer's knowledge of the materials involved and be practical, achievable, and verifiable." The FDA gives examples of analytical detection levels such as 10 parts per million (ppm), biological activity levels such as 1/1000 (0.1%) of the normal therapeutic dose, and organoleptic levels such as no visible residue.[2] One can easily apply these examples to determine the amount of allowable carryover of product residues:

- No more than 10 ppm of any product should appear in another product;
- No more than 0.1% of the normal therapeutic dose of any product will appear in the maximum daily dose of the following product; and
- No amount of product residue should be visible on the surface of the equipment after the cleaning procedure has been performed.

## Step Two: Inspect Visually

The FDA states, "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." One way to enhance visual detection is to set up spiking studies, in which coupons of the same type of surface that is going through the cleaning procedure are spiked with known amounts of residue. The coupons are then observed by trained personnel to determine at which level they appear clean. The coupon with the highest level of residue that appears to be clean by the personnel is considered the acceptance limit for that particular residue.[3]

The problem with visual inspection is that there are too many variables that can influence the results. The coupons must be observed in the exact same viewing conditions as the equipment in the field. Not all equipment can be inspected under conditions similar to a coupon sitting on a lab bench. The lighting, viewing angle, and even the distance of the observer from the surface should all be the same. If any of these circumstances is altered, the results may be skewed.

Issues may also arise when trying to simulate end-point residues on surfaces after the cleaning process. The question most commonly asked when viewing a spiked surface is, "Is the viewer seeing the actual residue stain, or are they just seeing the edge of the stain?"[1] Most visual spiking studies include spiking a solution of dissolved product onto the surface and allowing it to dry. Sometimes a stream of nitrogen is used to speed up the drying process and to discourage product degradation. It is much easier to see the edge of a stain at low levels than it is to see the body of the stain itself. Under visual inspection, a stain of uniform thickness that covers the entire surface of a piece of equipment may be falsely mistaken for a clean surface. In this situation, a more sensitive means of detection would greatly improve recognition of a dirty surface.

Even though visual cleanliness is widely accepted as a means of evaluating product carryover, manufacturers should take their detection abilities one step further and develop a validated and quantitative method. This type of method is required when there is a change in the type of product being manufactured. The forms of detection generally use sample-based cleaning procedures involving collection of either swab or rinse samples. A quantitative method provides greater specificity, accuracy, and sensitivity than the visual approach.


The stainless steel coupon below left shows a 10 µg Liquinox stain (edge) while the coupon on the right shows a 200 µg Liquinox stain (body).

## Step 3: Swabbing Versus Rinsing

The selection of an appropriate extraction solution is an important step in establishing a swab or rinse procedure. Your decision should be based on the solubility of the cleaning detergent residue or pharmaceutical product residue in the selected solution. Various alcohols, water, buffers, or combinations of the three are common extraction solutions used for cleaning procedures. Once an extraction solution is chosen, equipment surfaces may be extracted using a swabbing or rinse method.

Rinsing is suitable for small surface areas where traditional

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A variety of swabs can be used in cleaning. One key in selecting a swab is to ensure that the swab does not contribute excessive interference or background during analysis.

swabbing procedures may be difficult. The specified area should be rinsed long enough to ensure complete coverage of the entire surface and sufficient removal of the target residue. Rinsing methods provide a more simplistic sampling approach because they avoid possible swab interference in the detection method or extraction issues in removing the residue from the swab surface.

Swabbing is ideal for hard-to-clean areas and can physically remove insoluble residues. Swabs are selected for their ability to recover the monitored residue from a given surface and their ability to release the residue to an extraction solution for analysis. The selected swab should not contribute excessive interference or background during analysis. Another consideration in swab selection is whether the area being swabbed is easily accessible or hard to reach. Swabs that are long with small heads are excellent for general purposes and hard-to-reach areas. Other swabs with larger heads are better suited for cleaning broad, flat areas.

Swabbing patterns can vary and are dependent on the surface or equipment being swabbed. Surface areas are defined and swabbed with the chosen solvent, which is usually the same as the extraction solution. Prior to swabbing, swabs are soaked for a few minutes in a vial of the extraction solution. Excess solution is removed from the swab head by gently pressing the head on the inside of the vial.

The prepared swabs are used to swab the appropriate area, which can be accomplished using various swabbing patterns. Common patterns use partially overlapping parallel strokes in one direction or back-and-forth strokes. Whichever you choose, it is important that you flip the swab head to the other side and repeat the same pattern at right angles to the first pattern (see Figure 1.A). Another variation involves overlapping zigzag strokes in opposite directions, making sure that the swab head never leaves the surface being evaluated. An easy way to look at this is first, horizontally, and second, vertically (see Figure 1.B).

The swab head is placed back into the vial after clipping the handle above the head with a clean cutting tool. One swab may be sufficient to remove residue, but a second or even a third swab can be used to repeat the swabbing pattern, increasing residue recovery.

Depending on the extraction solution, using a dry swab after the wet swab may be advantageous, helping to ensure that any remaining solution on the coupon is collected. Other swabbing patterns can be adapted for special surfaces or pieces of equipment.

## Step 4: Choose Your Detection Methods

There are multiple detection options available for cleaning validation.

**Ion Mobility Spectrometry (IMS)**

IMS characterizes chemical substances based on their gas-phase ion mobilities, provides detection and quantitation of trace analytes, and offers atmospheric pressure chemical ionization (APCI), a soft ionization technique that produces molecular weight information.

**Benefits:**

• Offers ultra-fast quantitative analysis (~30 seconds per sample);

- Has sub-nanogram sensitivity;
- Has the ability to analyze a broad range of compounds with no chromophore needed;
- Does not require mobile phases, columns, or vacuum for operation; and
- Designed for different ways of sample introduction, either by thermal desorption off a membrane (solid residue on swab giving a qualitative analysis or solution deposited on the membrane, which allows quantitative analysis) or by high performance injection, which allows for a gas chromotography-style temperature programmable split/splitless injection.

**Drawbacks:**

- Compounds must be vaporizable and ionizable for IMS detection to be used;[4]
- Samples must be relatively clean;
- Ultra pure extraction solutions should be used; and
- Technique is not suitable for multiple component matrices.

**Total Organic Carbon (TOC)**

TOC analysis is specific to organic compounds and theoretically measures all the covalently bonded carbon in water.[5]

**Benefits:**

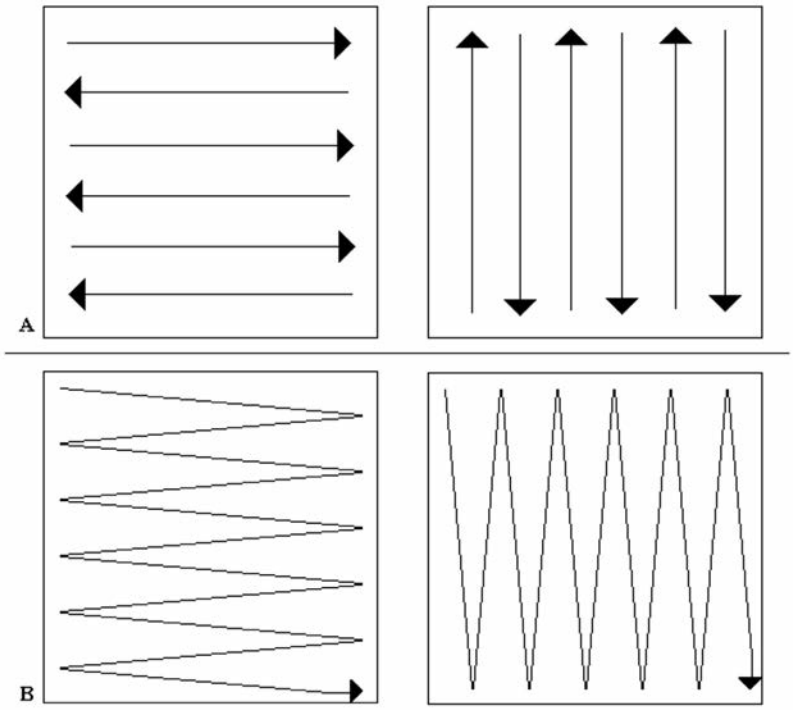
- TOC detection is an acceptable way to detect residues of contaminants.

**Drawbacks:**

- Considered a "worst case" analysis because TOC analysis incorporates all organic molecules in solution and represents surface area depending upon the sampling method (swab or rinse);[5]
- "In order for TOC to be functionally suitable, it should first be established that a substantial amount of the contaminating material(s) is organic and contains carbon that can be oxidized under TOC test conditions"[5];
- Samples must be water soluble;
- Excellent water quality is needed for sensitivity; and
- Certain swab types may also interfere with TOC analysis, so swab selection is critical.

*One way to enhance visual detection is to set up spiking studies, in which coupons of the same type of surface that is going through the cleaning procedure are spiked with known amounts of residue.*

**Figure 1.**




There are a variety of patterns that can be followed when using swabs to clean.

**UV-Visible Spectrophotometry (UV-Vis)**

UV-Vis is commonly used for detection of small molecule active pharmaceutical ingredients or detergent residues for swab and rinse samples.

**Benefits:**

- Not limited to water as the extraction solution;
- Provides quantitative results;
- Does not require a mobile phase or column;
- Offers fast spectral acquisition; and
- Allows for use of a larger swab selection, compared to TOC.

**Drawbacks:**

- Lacks peak separation; and
- Requires chromophore for specificity.

**High Performance Liquid Chromatography (HPLC)**

HPLC can be used for detection of small molecule active pharmaceutical ingredients (APIs) or detergent residues for both swab and rinse samples, allowing for separation of multiple components.

**Benefits:**

- Is not limited to water as the extraction solution;
- Offers peak separation via packed column;
- Provides identification of specific peaks of interest and quantitative results provided a suitable reference standard is used;
- Offers multiple detection options (UV, photodiode array, fluorescence, refractive index, evaporative light scattering, corona charged aerosol detection, etc.);
- Allows for the use of a large variety of swab types due to separation power; and

- HPLC in tandem with mass spectroscopy (MS) offers selectivity while separating the API from its degradates based off mass-to-charge ratio of the compound of interest.[6]

**Drawbacks:**

- May require more development and validation time in comparison to other forms of detection, depending on current information about the API and excipients being used in the formulation; and
- HPLC/MS analysis is more expensive.

### GC and MS

Gas chromatography (GC) and GC/MS are mainly used for detection of detergent residue. These cleaning agents typically contain various solvents or compounds required to effectively clean equipment that may not be cleanable with typical detergents. Most solvent cleaners are volatile and will evaporate from equipment surfaces, but some residue may remain from less volatile compounds.

**Benefits:**

- Offers improved peak shape over HPLC due to capillary column usage; and
- Provides separation, identification, and quantitation of results when an acceptable reference standard is used.

**Drawbacks:**

- Samples require vaporization.

## Step 5: Microbial Testing

A microbial cleaning validation can also be performed for equipment subsequent to or as part of the chemical cleaning validation. This is sometimes overlooked during the initial planning of the validation program, yet it provides additional data to support the effectiveness of the cleaning process by establishing the post-cleaning bioburden. As with chemical cleaning validations, the suitability and qualification of the recovery method should be considered when selecting methods.

Sample collection must be performed using an aseptic technique. The microorganisms captured on the swab or in the rinse can then be enumerated using direct plating, a pour plate technique, or membrane filtration.

For enumeration of swab samples, the swab is typically extracted in a buffered diluent or neutralizing broth (usually a 10 ml volume) to release organisms. A portion of the diluent can then be aseptically plated using a standard microbiological pour plate method by placing separate 1 ml aliquots into duplicate petri dishes. Tempered nutrient agar is added to these petri dishes, and the plates are swirled to mix.

After the agar solidifies, the plates are inverted and placed into an incubator at the desired temperature for a determined period of time to allow any microorganisms present to grow and become visible on the agar plates. An average count of the plates is obtained to determine the number of colonies (colony forming units or CFU) per milliliter of the original dilution. Plates having no growth are reported as < 1 CFU/ml. The bioburden of the swabbed area is calculated from that result by multiplying the resulting number of CFU recovered by the dilution factor of the swab (i.e., the volume of dilution used).

If more sensitive testing is required due to low bioburden requirements for the equipment or to enhance recovery of bioburden from very clean equipment, a membrane filtration method can be used. In this type of testing, the entire volume of diluent or an equipment rinse sample is filtered through one membrane filter. The filter, usually a 0.45 micron filter, is then aseptically transferred to a prepared, solidified nutrient agar plate and incubated in the same manner as a standard pour plate. Visible colonies are counted at the end of the incubation period, and the CFU per swab or rinsed surface area is obtained. Filter plates having no visible growth are reported in the same manner as above, < 1 CFU, but the sensitivity of the test is increased because the volume sampled (i.e., the entire diluent volume from the swab or an equipment rinse of 100 ml) is greater.

Sample collection must be performed using an aseptic technique. The microorganisms captured on the swab or in the rinse can then be enumerated using direct plating, a pour plate technique, or membrane filtration.

The potential of any remaining chemical residues to inhibit microbial growth must be considered for a valid evaluation of the bioburden. For agents with inhibitory residuals, neutralization methods must be established using the maximum levels anticipated to be recovered in samples submitted for microbial testing.

The determination of appropriate residue limits and selection of appropriate cleaning and analytical techniques described are typically explored during the method development phase. ■

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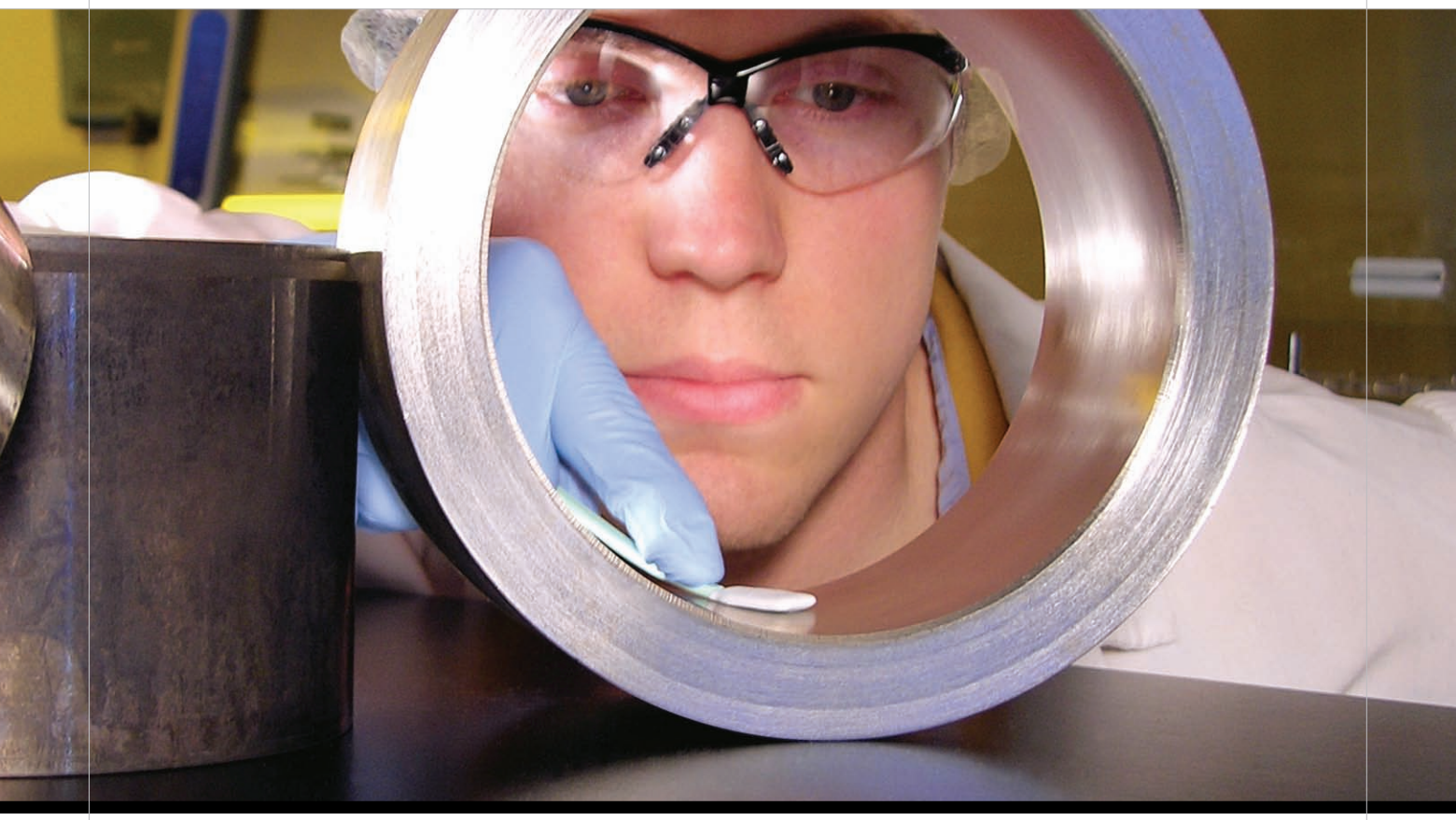

# It's Clean, but Can You Prove It?

## Validation and revalidation are key when establishing cleaning methods

BY **ERIC LINGENFELTER, WES ATKINS,** AND **HENRY EVANS**

***Editor's Note:*** *This article is the second in a two-part series on cleaning validation methodology. Part one, "How to Improve Cleaning Processes," appeared on pages 16-21 of our June issue.*

Method limits, selection of cleaning techniques, and selection of method detection were addressed in the first part of this article. Part two will address method validation, the importance of stability for cleaning validation samples, when revalidation of a cleaning method is necessary, the use of correction factors, and how to handle failing results.

Once the basic cleaning procedure elements have been established (establishment of limits, cleaning procedures, master plan, cleaning protocols, development of analytical method), the method is ready to be validated.[1] This section outlines typical components utilized to validate the analytical method. The validation components presented below are based upon International Conference on Harmonisation (ICH) and United States Pharmacopeia (USP) guidelines.

**Accuracy/Precision:** The accuracy of an analytical procedure expresses the closeness of agreement between the value that is accepted either as a conventional true value or an accepted reference value and the value found. The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.[2]

Accuracy/precision should be assessed using a minimum of three concentration levels, each prepared in triplicate. Accuracy/precision is typically performed with concentrations ranging from 80 to 120% of the final theoretical sample concentration (based upon the maximum contamination limit or MCL), although a wider range may be more appropriate in certain instances.

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Swab accuracy determines a method's ability to recover the compound of interest directly from the swab head.

There are various categories of accuracy/precision that need to be established as part of the method validation.

- Solution accuracy is the measurement of the compound of interest added directly to the extraction solution. Reference standard solution is spiked directly into the diluent to prepare the three levels of concentration. Solution accuracy is performed as a control—usually in triplicate—to prove recovery of the analyte from the extraction solution. This recovery can then be compared to both swab and surface accuracy recoveries. If rinseates are being analyzed, this test is the only one needed to prove accuracy/precision.
- Swab accuracy determines the method's ability to recover the compound of interest directly from the swab head. These studies are performed by directly adding standard material to the swab head and then extracting as per the analytical method. Typically, three replicate-spiked swabs are prepared at the high and low concentrations, while six replicates are prepared at the 100% level.
- Surface accuracy determines the method's ability to recover the compound of interest directly from a defined surface. Coupons of the defined surface material are spiked with reference standard at the three concentration levels mentioned above. The area of the coupon spiked with standard is dependent on the actual cleaning procedure and the surface area typically sampled after manufacturing. Typical surface areas sampled are 25 to 100 $cm^2$.

Acceptance criteria should be evaluated and determined during the development of the analytical methods. Many factors influence the establishment of appropriate criteria, including the surface being swabbed, MCL, type of swab, and instrumentation. Intermediate accuracy/precision should be performed by a second analyst repeating the accuracy/ precision tests listed above. If multiple surfaces are involved in the validation, the second analyst can perform accuracy/precision on select surfaces (worst case) if appropriate.

**Linearity:** The linearity of an analytical procedure is its ability, within a given range, to obtain test results that are directly proportional to the concentration (amount) of analyte in the sample.[2]

A minimum of five concentration levels are typically evaluated, with duplicate injections at each level. Concentrations ranging from the limit of quantitation to 200% of the MCL are typically evaluated during validation. Acceptance criteria are

**Table 1. Summary of Typical Validation Components**

| VALIDATION COMPONENT | DESCRIPTION | TYPICAL ACCEPTANCE CRITERIA |
|---|---|---|
| Accuracy | The accuracy of an analytical procedure expresses the closeness of agreement between the value that is accepted either as a conventional true value or an accepted reference value and the value found.[2] | Swab recovery: mean recovery of 90% - 110% theoretical. %RSD (relative standard deviation) ≤ 10% Surface recovery: mean recovery of 85% - 115% theoretical. %RSD ≤ 15%. |
| Precision | The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.[2] | All system suitability meets method criteria. Intermediate precision data and precision data (combined) must have an RSD of ≤ 15%. |
| Linearity | The linearity of an analytical procedure is its ability (within a given range) to obtain test results that are directly proportional to the concentration (amount) of analyte in the sample.[2] | Correlation coefficient (r) ≥ 0.995 or coefficient of determination (r2) ≥ 0.99. |
| Specificity | Specificity is the ability to assess, unequivocally, the analyte in the presence of components that may be expected to be present.[2] | Detected analyte of interest must not exceed 10% of the mean maximum contamination limit or have an S/N ≥ 10. |
| LOD | The LOD of an individual analytical procedure is the lowest amount of analyte in a sample that can be detected but not necessarily quantitated as an exact value.[2] | Analyte of interest must be detected in all injections and be in the retention time region of the peak of interest (~ S/N of 3). |
| LOQ | The LOQ of an individual analytical procedure is the lowest amount of analyte in a sample that can be quantitatively determined with suitable precision and accuracy.[2] | Analyte of interest must be detected in all injections and be in the retention time region of the peak of interest (~ S/N of 10). |
| Robustness | The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage.[2] | The varied condition must meet the system suitability requirements outlined in the analytical method. |
| Stability | The ability of a standard or sample preparation solution to meet method specifications over time. | Recovery value of 98% - 102% when compared to fresh standard solutions. |

generally based upon either the correlation coefficient or the coefficient of determination of the linear plot. In addition, criteria can be established around both the slope and Y-intercept of the plot.

**Specificity:** Specificity is the ability to assess the analyte unequivocally in the presence of components that may be expected to be present.[2]

Swab type and surface type are typically evaluated to determine if interferences are present in the method. Although each of these components is typically examined during method development, they should be included in the validation process and shown, under protocol, to have little or no interference. Swabs and surfaces are prepared as per the method without the introduction of the analyte of interest. Interference from either the swab or surface should be less than 10% of the MCL. Lower limits for specificity may be appropriate depending on the method conditions.

**Limits of Detection and Quantitation:** The limit of detection (LOD) of an individual analytical procedure is the lowest amount of analyte in a sample that can be detected but not necessarily quantitated as an exact value. The limit of quantitation (LOQ) of an individual analytical procedure is the lowest amount of analyte in a sample that can be quantitatively determined with suitable precision and accuracy.[2]

Both the LOD and LOQ should be verified by a suitable number of preparations known to be prepared near the respective limit being evaluated.[4] LOD and LOQ can be estimated using a signal-to-noise approach with typical values of three-to-one for LOD and 10-to-one for LOQ.

During method validation, standard solutions are prepared at the estimated LOD and LOQ (three preparations for LOD and three preparations with duplicate analyses for LOQ). Typical acceptance criteria for LOD require that the analyte be detected in each analysis. For LOQ, the percent recovery is determined for each of the six measurements and should fall between 75% and 125% recovery. The relative standard deviation is also determined for the six measurements and should be less than 25%.

**Robustness–Chromatographic Conditions:** The robustness of an analytical

procedure is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage.[2]

Instrument and reagent variations, for example, may be examined as part of robustness to ensure that the method provides reliable data under varying conditions. Robustness is not a critical validation component according to ICH guidelines, but should be considered on a case-by-case basis. Robustness may be determined during development of the analytical procedure, and if measurements are susceptible to variations in analytical conditions, these should be suitably controlled, or a precautionary statement should be included in the procedure.[3]

**Stability–Stock Standard, Working Standard, Working Swab:** Stability of stock standards, working standards, and working swab or rinseate samples are evaluated as part of the validation. Stability can be evaluated under various conditions such as refrigeration or protection from light, but ambient conditions are preferred. This stability period is necessary to ensure that cleaning validation samples can be collected, shipped to the testing facility, and analyzed. The length of stability is particularly important for cleaning validation sample solutions and should be at least one week old, preferably two weeks.

Table 1 (see previous page) lists a summary of the validation components involved in a typical cleaning validation, along with examples of typical acceptance criteria that can be set for those tests. Please note that the acceptance criteria are listed for informational examples only and that the actual acceptance criteria must be determined on a case-by-case basis, depending on validation specifics.

## Revalidation

Cleaning validation procedures should be revalidated when the equipment train of the manufacturing process is changed. Possible changes in the equipment train include the surface type utilized and/or surface area, which can lead to the establishment of a new MCL. A full validation can usually be avoided, and only certain elements of the cleaning validation need to be revalidated. If the new limit is within the previously established linear range, only surface recoveries (bracketing the new limit) and surface residue specificity need to be revalidated. These same two elements must be revalidated if a surface type is changed.

Cleaning validation procedures should be revalidated when the equipment train of the manufacturing process is changed.

If the new limit is outside the previously established linear range, linearity must be extended above or below the new limit, and swab recovery, surface recovery, and surface residue specificity need to be revalidated. For a new limit below the established linear range, a new standard concentration at this level may be recommended. If the method is not linear through the new level, however, a new standard concentration is necessary. A new standard concentration requires a full revalidation.

Other possible but less likely reasons to revalidate swab recovery, surface recovery, and surface specificity include a change in the type of swab or swabbing pattern. For a change in swab type, swab specificity also needs to be revalidated. For any of the previously listed changes, elements that do not require revalidation are LOD and LOQ.

The prior revalidation discussion assumes that the validated method was for swab samples and not for rinse samples. For rinse samples, validation elements involving swabs and surfaces do not need to be conducted. Additionally, any changes in the synthesis of the drug substance, changes in the composition of the finished product, or changes in the analytical procedure require revalidation according to ICH guidance.[2]

## Correction Factors

Sometimes in cleaning validation studies, it is determined that not all the residue on a surface can be fully recovered, thus producing lower recoveries. In these instances, it may be necessary to apply a recovery factor. If a recovery factor is deemed appropriate, several issues must be considered before it is set:

- Recovery factors are usually not applied if recovery results are above 70%; however, there is no standard limit.

There are a variety of swabs to pick from, but when a change in swab type takes place, swab specificity also needs to be revalidated.

- Recovery factors must be set under sound scientific justification.
- Recovery factors should not be used if recoveries are too low. (For example, if recoveries are consistently around 10%, a 10X factor would not be appropriate.)
- Recovery factors need to be set prior to

No matter which scientific field you are in, the question of how to handle failing data during routine sample testing will arise; the world of cleaning validation is no different.

or during validation, not during routine monitoring.

- All results used to determine the recovery factor need to be consistent and reproducible.

Recovery factors are often seen as a last resort to salvage a mediocre method. Recovery method optimization should always be explored as an alternative prior to using recovery factors.

## Failing Data

No matter which scientific field you are in, the question of how to handle failing data during routine sample testing will arise; the world of cleaning validation is no different. The best way to approach this issue is to address it before it becomes a problem. When developing the cleaning validation master plan or protocol, dedicate a section to appropriate handling of failing results. Here, a step-by-step investigation of the results can be laid out in advance, so that decisions won't be made based on instance-by-instance circumstances. When reviewing data, regulatory agencies like to see that failing results were handled in a consistent and systematic manner.

All data that do not meet protocol or master plan acceptance criteria need to be treated as a deviation. They must be handled by first being verified, resolved, and approved. This may require that samples be retested. Sometimes more samples may need to be collected to verify outlying results. If results indicate that a criterion or limit is not attainable under set conditions, modifications to the method, protocol, standard operating procedure, or master plan may be entertained. Again, all of these scenarios should be investigated during the feasibility/method development/validation stage of the cleaning validation study. ■

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